NOVEL APPROACHES TO THE ASSESSMENT OF PATIENTS WITH CHEST SYMPTOMS IN THE ACUTE MEDICAL AND OUTPATIENT SETTINGS:
the use of multislice computed tomography

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DECLARATION OF ORIGINALITY

I am aware of and understand the University's policy on plagiarism and I certify that this thesis is my own work**,** except where indicated by referencing. The administration of all studies contained herein was performed by me, with the part-time support of a departmental research nurse, who assisted in telephone liaison with study participants and with computer data entry. The studies using computed tomography were all performed in the Radiology Department at Chelsea and Westminster Hospital, where image formatting and analysis was undertaken by specialist radiology colleagues. Other non-invasive and invasive investigations were performed by colleagues as part of standard clinical care. Statistical analyses were performed in collaboration with a professional statistician.

BRIEF ABSTRACT

This thesis evaluated the clinical utility of cardiopulmonary computed tomography (CT) in patients presenting with chest pain and dyspnoea.

Studies within this thesis confirmed the following. Firstly, there is a requirement for improved diagnostic pathways to minimise patients being discharged without a diagnosis, which currently occurs in 30-40% of patients admitted with chest pain and dyspnoea. Historically, CT has been utilised in 32% of admissions with chest pain and 10% of admissions with dyspnoea.

Secondly, challenges exist to the wider adoption of cardiopulmonary CT. These include patient-related factors, institutional capabilities and guideline restrictions. In acute admissions, 11% of patients with dyspnoea and 7% of patients with chest pain and a low to moderate likelihood of CAD are suitable for CT. In the RACPC setting, including patients across the entire spectrum of CAD likelihood, 18% of patients are suitable for CT. NICE CG95 would recommend only 1% of acute chest pain admissions and 2% of RACPC attenders for CT.

Thirdly, NICE CG95 would recommend 51% of acute chest pain admissions and 66% of RACPC attenders for discharge without cardiac investigation. In the RACPC population, significant CAD is identified in 10% of these patients and a major adverse cardiac event in 2%.

Fourthly, in selected patients with suspected cardiac chest pain, cardiac CT has a diagnostic yield of 21% in acute admissions and 13% in RACPC attenders for significant CAD. In acute admissions with dyspnoea, cardiopulmonary CT has a diagnostic yield of 20% for CAD, 20% for pulmonary embolism, nil for aortic dissection and 89% for non-vascular chest pathology.

Fifthly, inclusion of CT in diagnostic pathways for chest pain result in fewer patients discharged without a diagnosis, fewer invasive angiography procedures and reduced diagnostic costs. In patients with dyspnoea, CT provides value to clinicians making diagnoses and supports early discharge without detrimental outcomes.

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LIST OF ABBREVIATIONS

AAU	Acute assessment unit
ACR	American College of Radiology
ACS	Acute coronary syndrome
BMIPP	βmethyl-P-iodophenylpentadecanoic acid
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CCS	Coronary calcium score
CCT	Cardiac computed tomography
CK	Creatine kinase
CMR	Cardiac magnetic resonance
CPCT	Cardiopulmonary computed tomography
CT	Computed tomography
CTA	Computed tomographic angiography
CTP	Computed tomographic perfusion
CTPA	Computed tomographic pulmonary angiography
CWH	Chelsea and Westminster Hospital
CXR	Chest x-ray
ED	Emergency department
ECG	Electrocardiograph
EH	Ealing Hospital
FDG	Fluorodeoxyglucose
FFR-CT	Fractional flow reserve computed tomography
HRCT	High resolution computed tomography
ICRP	International Committee on Radiological Protection

HU	Hounsfield units
IVUS	Intravascular ultrasound
MACE	Major adverse cardiac event
MDCT	Multi-detector computed tomography
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST-segment-elevation myocardial infarction
PE	Pulmonary embolism
PET	Positron emission tomography
RACPC	Rapid access chest pain clinic
RVD	Right ventricular dysfunction
SPECT	Single photon emission computed tomography
STEMI	ST-segment-elevation myocardial infarction
STP	Standard pressure and temperature
TAG	Transluminal contrast attenuation gradient
TN	Troponin
VQ	Ventilation/perfusion

CHAPTER 1: GENERAL INTRODUCTION

1.1 INTRODUCTION

Over 900,000 patients present to emergency departments in England each year with cardiac and respiratory symptoms. Combining emergency and elective admissions, cardio-respiratory disease is thought to account for around two and a half million bed days per annum{HSCIC, 2014}.

Most commonly, cardio-respiratory conditions manifest as chest pain and/or dyspnoea. The symptoms of cardiac and respiratory disease overlap and elucidating the underlying pathology or pathologies in patients presenting to hospital with chest-related symptoms is a recognised diagnostic challenge, particularly when communication may be limited by breathlessness. Chest pain occurs concurrently with dyspnoea in a number of conditions, including acute coronary syndrome (ACS), pneumothorax, and pulmonary embolism (PE). A significant minority of patients with ACS or PE complain of dyspnoea alone.

Evidence suggests that there is a lack of association between clinical history and underlying pathophysiology{Swap, 2005; Lien, 2002}. Diagnosis is even more difficult in older patients with multiple co-morbidities and obesity. This is particularly relevant now almost two thirds (65%) of people admitted to hospital are over 65 years old and those over 85 years old account for 25% of bed days{Cornwell, 2011}

Diagnostic uncertainty contributes to misdiagnosis and delays the initiation of appropriate therapy. Selection of a treatment strategy based on misdiagnosis may even be hazardous to health; for example, β agonist and steroid therapy for suspected chronic obstructive pulmonary disease may be detrimental in decompensated congestive cardiac failure.

In patients admitted to the emergency department, any delay within the department reduces adherence to recognised treatment algorithms{Diercks, 2007} and increases the risk of admission to hospital and short term death{Guttmann, 2011}. Similarly, diagnostic uncertainty, delayed diagnosis and delayed admission has the secondary

effects of increasing in-hospital adverse events{Kline, 2007}, time to discharge and cost of treatment{Huang, 2010}.

Clinical guidelines are increasing in prevalence and have a role in supporting consistent, evidence based and cost effective approaches to diagnosis and management. At present, national and international guidelines exist for the assessment of patients in whom a provisional diagnosis of cardiac chest pain or pulmonary embolism has already been made{Hamm, 2011; Amsterdam, 2014; Konstantinides, 2014}. Algorithms for the assessment of patients with acute dyspnoea are more broad-based and lack focus{NICE, 2010}. Specific guidance relating to acute dyspnoea is currently limited to suspected cardiac failure.

In part, this relative lack of guidance relates to an absence of robust data fully defining the clinical, biochemical and radiological findings of patients presenting with non-specific chest pain and dyspnoea. The result is that diagnosis remains highly dependent on the impression of the admitting physician, based on clinical history and examination.

1.2 CURRENT APPROACH TO THE ASSESMENT OF PATIENTS WITH CHEST PAIN

Coronary artery disease (CAD) accounts for up to one third of hospital admissions in England (around 600,000 admissions per year), while angina affects more than two million individuals in the UK{Shaper, 1984}. Although the most common symptom attributable to CAD is chest pain, chest pain is often non cardiac in origin{Bosner, 2009; Nilsson, 2003}. The prevalence of acute myocardial infarction in patients attending the emergency department with undifferentiated chest pain is as low as 4%. Significant pulmonary disease such as pneumonia accounts for 11%, with pulmonary embolism and aortic dissection diagnosed in around 0.4% and 0.3% of patients with chest pain respectively{Kohn, 2005}.

Table 1.1: Differential diagnoses for acute chest pain{Stillman, 2007}

Life threatening	Non-life threatening
Acute coronary syndrome	Pneumonia/pulmonary parenchymal
Pulmonary embolism	disease
Aortic dissection	Pulmonary, mediastinal, or pleural
Intramural haematoma	neoplasm
Penetrating aortic ulcer	Musculoskeletal injury or inflammation
Aortic aneurysm/rupture	Cholecystitis
Oesophageal rupture	Pancreatitis
Pericardial tamponade	Herpes zoster
Tension pneumothorax	Hiatus hernia/GORD/oesophageal spasm
	Pericarditis/myocarditis
	Simple pneumothorax

Nevertheless, the diagnosis of acute myocardial infarction is missed in between 5 and 10% of patients and these individuals have worse clinical outcomes{Lee, 1987}. Missed diagnoses are more common amongst patients who present atypically; these individuals are more likely to be female, aged less than 55 years, non-white, to report dyspnoea as their primary complaint and to have a non-diagnostic electrocardiograph (ECG){Pope, 2000}. The life threatening nature of myocardial infarction and the time imperative for therapeutic intervention has led to a 'rule out MI' approach.

Traditionally, emergency department algorithms for the management of patients with chest pain risk have risk stratified individuals based on age, symptoms, ECG changes and positive biomarkers of myocardial necrosis{Anderson, 2007}. Those deemed low risk have typically been discharged from hospital while those deemed high risk have proceeded to invasive coronary angiography{Antman, 2000}.

Malpractice fear is a contributing factor for hospitalisation and use of diagnostic tests{Katz, 2005}. Due to the limitations of risk stratification and the potential fatal consequences of missed ACS, up to 60% of patients eligible for emergency department discharge are admitted to hospital for further investigation{Gibbons, 1999}. This perceived "intermediate risk" group utilise significant resources, often with prolonged observation and multiple investigations. The resulting number of potentially

unnecessary hospital days is equal to or greater than 65 per hundred patients{Kaul, 2004}.

Conventional assessment of chest pain includes serial measurement of serum biomarkers, exercise ECG testing, radionuclide perfusion imaging and ultimately invasive coronary angiography. Each of these techniques has recognised limitations.

1.2.1 BIOMARKERS IN ACUTE CHEST PAIN

There is broad consensus that cardiac troponin (Tn) I or T is the preferred biomarker in clinical practice, however, release occurs only slowly from damaged myocytes and peak levels are reached around 12 hours after symptom onset. The need for serial sampling to obtain maximum sensitivity results in delays in triage decision making. Uncertainties remain regarding the value of high-sensitivity Tn assays, including the optimum timings for measurement and the thresholds for normality.

Other markers used in the triage of patients with acute chest pain include copeptin and natriuretic peptides. Some centres continue to rely on less sensitive and less specific markers such as myocardium specific creatine kinase (CK-MB). The triad of myoglobin-CK-MB-Tn I has a sensitivity of 57% for the detection of acute coronary ischaemia, and the combination of ischaemia modified albumin-myoglobin-CK-MB-Tn I increases diagnostic sensitivity to 97%{Anwaruddin, 2005}.

1.2.2 IMAGING IN ACUTE CHEST PAIN

Non-invasive imaging has a role in the risk stratification, prior to discharge, of stable patients who are not selected for urgent cardiac catheterisation. Imaging is often performed as an intermediate step and improves confidence in the safety of emergency department discharge{Andersen, 2007}. There is an additional benefit in identifying patients with latent ischaemia who may benefit from more aggressive revascularisation. Imaging also aids identification of non-coronary causes of chest pain.

Non-invasive cardiac imaging modalities include: chest radiography; multi-detector computed tomography (MDCT) used predominantly for the assessment of anatomic

CAD; single-photon emission computed tomography (SPECT), positron emission tomography (PET) and cardiac magnetic resonance (CMR) used for myocardial perfusion imaging; stress echocardiography and CMR used for stress wall motion imaging.

These imaging modalities have varying combinations of availability, portability, and ease of applicability to the acute setting. Furthermore, a variety of factors impact the quality and breadth of information that the tests provide. Selection of the most appropriate imaging modality depends on patient-related factors (e.g. heart rate control, hemodynamic stability, renal function, contrast allergy) and institutional capabilities (e.g. rapid availability, state-of-the-art technology, and expertise).

1.2.2.1. Chest Radiography

Chest radiography is inadequate for the diagnosis or exclusion of significant CAD. It is primarily used to exclude conditions that mimic myocardial infarction and to identify secondary features such as pulmonary oedema{Buenger, 1988}. In this context, chest radiography is highly useful to exclude pneumothorax, with a sensitivity around 40% and specificity around 99%{Alrajab, 2013}. Cardiovascular diagnoses, including aortic aneurysm, aortic dissection, and pulmonary embolism may be suggested on chest radiography but with far lower sensitivity than other imaging modalities such as CT.

1.2.2.2. Radionuclide Imaging

In patients with ongoing chest pain, no ischaemic changes on ECG and a negative Tn, rest SPECT is useful as a first line investigation{Kontos, 2004; Udelson 2002}. The most commonly used SPECT radionuclides are the technetium-based agents, Tc-99m-sestamibi and Tc-99m-tetrofosmin, and thallium (Tl-201). The absence of a perfusion defect during an acute rest study is associated with a very high negative predictive value for ACS{Heller, 1998; Candell-Rieraa, 2004}. If symptoms have abated, provocative stress testing may be necessary to exclude obstructive CAD. A perfusion defect that becomes apparent or larger during exercise stress or pharmacologic stress SPECT defines myocardial ischaemia. Meta-analysis of 79 studies totalling 8,964

patients showed an overall diagnostic sensitivity and specificity of SPECT myocardial perfusion imaging (MPI) of 86% and 74%, respectively{Underwood, 2004}.

MPI, using dipyridamole and radiolabelled ammonia (13N-NH_3) or rubidium (Rb-82), can also be performed using PET. PET is more costly and less available than SPECT but appears to be superior in image quality, interpretive certainty, and diagnostic accuracy for significant coronary artery stenoses{Bateman, 2006}.

Both SPECT and PET allow metabolic imaging of the myocardium. Altered glucose and fatty acid metabolism in regions of myocardial ischaemia and reperfusion (demonstrating ischaemic memory) are detectable using 18F-fluorodeoxyglucose (18F-FDG) and 123I-βmethyl-P-iodophenylpentadecanoic acid (123I-BMIPP) respectively. Kawai et al. suggest that metabolic imaging may be superior to perfusion imaging for identifying CAD as the cause of chest pain{Kawai, 2001}. In a meta-analysis of 7 studies and 528 patients, the sensitivity of resting BMIPP imaging for significant CAD was 78% with specificity 84%{Inaba, 2008}. Metabolic imaging with FDG and BMIPP has also been used for direct ischaemia detection during stress testing{He, 2003; Dilsizian, 2005}.

The clinical role for integrated radionuclide and CT imaging and image fusion continues to evolve{Flotats, 2010; Dorbala, 2013}.

1.2.2.3. Cardiac Magnetic Resonance

Some centres have adopted CMR for the diagnosis of CAD. Approaches include first-pass gadolinium myocardial enhancement with vasodilator stress and dobutamine stress-induced wall motion studies. The strengths of CMR are high resolution imaging without soft tissue attenuation artefact, the absence of ionising radiation, and the capability to assess valve and ventricular function. Disadvantages include the requirement to transport patients out of acute assessment areas, and incompatibility with implanted cardiac and other metallic devices.

1.2.2.4. Echocardiography

Two-dimensional echocardiography has a high sensitivity for the diagnosis of ACS (91%), and moderate specificity (75%) based on the detection of regional wall dysfunction{Kontos, 1998}. Stress echocardiography, using a pharmacologic agent (e.g. dobutamine) to induce wall motion abnormalities in regions of ischaemia, is equivalent to stress SPECT MPI in the acute setting in low-to-intermediate risk patients{Quinones, 1992}. Based on pooled data, in patients with intermediate-to-high likelihood of CAD, stress echocardiography is equivalent in sensitivity to SPECT but superior in specificity{Fleischmann, 1998}. The often quoted limitations of echocardiography are suboptimal image quality (10-15%), lack of quantitation and poor identification of single vessel or circumflex disease{Senior, 2005}; however, advances in image acquisition, digital display, and the development of harmonic and contrast imaging have reduced variability in study acquisition and increased reliability and reproducibility. Colour kinesis, tissue Doppler, strain and strain rate imaging allow the assessment of segmental arterial function and provide some quantitative analysis of the left ventricular response to stress. Using contrast imaging, myocardial perfusion can be reviewed in parallel with wall motion imaging. The modality also allows detection of left ventricular aneurysms, pseudoaneurysms, effusions, and valvular dysfunction.

1.2.2.5. Computed Tomography (see also section 1.5.1)

Coronary computed tomographic angiography (CTA) offers direct visualisation of the coronary arterial system for the detection of obstructive CAD. The strength of the technique is in the detection of CAD in symptomatic patients with either low-to intermediate CAD risk or equivocal echocardiographic or SPECT results. In a recent European study, the diagnostic accuracy of coronary CTA was significantly greater than that of myocardial perfusion imaging and wall motion imaging for detection of significant CAD defined invasively{Neglia, 2015}. The absence of obstructive CAD in a patient with chest pain is also useful to exclude ACS. Coronary CTA has a very high negative predictive value for the detection of coronary atherosclerosis with or without significant stenosis{Chow, 2009}. Evaluation of patients with coronary CTA may be

limited in patients with high heart rates (>65 beats/min) uncontrolled by beta-blockers or other rate-limiting agents, and in patients with intractable dysrhythmias.

Table 1.2: American College of Radiology appropriateness criteria® for the investigation of chest pain suggestive of acute coronary syndrome{ACR, 2014)

Radiologic Procedure	Rating	Comments	RRL*
SPECT MPI rest and stress	8	This procedure is appropriate for intermediate-to-high likelihood for coronary artery disease. There is abundant literature available on clinical utility.	☢☢☢☢
Arteriography coronary	8	This procedure is the gold standard and is invasive.	☢☢☢
SPECT MPI rest only	7	In the setting of ongoing chest pain, this procedure has a high negative predictive value. Tc-99m is the most commonly used radionuclide agent for this test. RRL may be higher if thallium (Tl-201) used.	☢☢☢
US echocardiography transthoracic stress	7	Consider this procedure when resting echo and cardiac enzymes are normal.	O
US echocardiography transthoracic resting	6	This procedure is primarily used for evaluating wall-motion abnormalities and aortic dissection.	O
CTA coronary arteries with contrast	6	Consider this procedure for those patients with low-to-intermediate likelihood for coronary artery disease, in the absence of cardiac enzyme elevation and ischaemic ST changes.	☢☢☢
X-ray chest	5	This procedure is primarily a survey for non-cardiac aetiologies of chest pain.	☢
CT chest with contrast	5	This procedure is primarily for non-cardiac aetiologies such as pulmonary embolism and aortic dissection.	☢☢☢
MRI heart function with stress without and with contrast	5	For this procedure there is limited experience in the clinical setting and lack of availability.	O
MRI heart function with stress without contrast	4	For this procedure there is limited experience in the clinical setting and lack of availability.	O

Rb-82 PET heart stress	4	For this procedure there is lack of widespread use and availability.	☢☢☢
MRI heart function and morphology without and with contrast	4	This procedure is primarily for the possibility of aortic dissection.	O
CT chest without and with contrast	3		☢☢☢
MRI heart function and morphology without contrast	3	This procedure is primarily for the possibility of aortic dissection.	O
US echocardiography transoesophageal	3	This procedure has a relative contraindication for acute coronary syndrome.	O
CT coronary calcium	2	This procedure is not validated in the acute setting.	☢☢☢
MRA coronary arteries without contrast	2	This procedure is technically challenging, and there is a lack of widespread use as well as protocol availability.	O
MRA coronary arteries without and with contrast	2	This procedure is technically challenging, and there is a lack of widespread use as well as protocol availability.	O
CT chest without contrast	2		☢☢☢

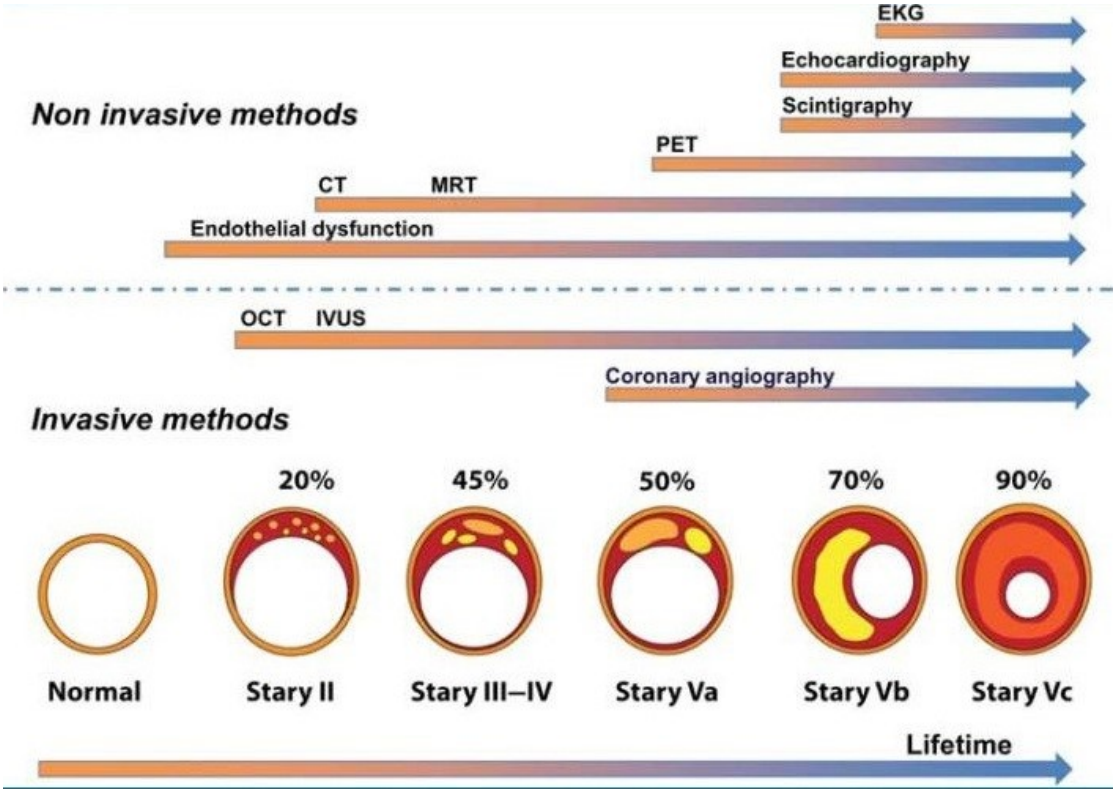
*Relative Radiation Level; Rating scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate

1.2.3 RATIONALE FOR NON-INVASIVE TESTING

A sequence of events, known as the ischaemic cascade, occurs when myocardial oxygen demand exceeds supply. The first detectable abnormality is regional myocardial blood flow heterogeneity between vascular beds supplied by normal and stenosed coronary arteries (manifest as areas of perfusion deficit on MPI). Subsequently, left ventricular relaxation abnormalities manifest as diastolic dysfunction and progress to regional systolic dysfunction (manifest as regional wall motion abnormalities). Chest pain and ECG changes are late features of the cascade. A rest image during symptoms may be adequate to detect or exclude flow heterogeneity (MPI) or regional wall motion abnormalities (echocardiography). If symptoms have resolved, provocative stress testing may be indicated. Since atherosclerosis, the basis for most acute coronary events, presents initially as artery wall thickening and arterial enlargement with luminal narrowing only occurs following

plaque rupture, stress tests may be falsely negative in patients with vulnerable plaque disease.

Figure 1.1: Stages of atherosclerosis detectable by invasive and non-invasive methods{Erbel, 2012}

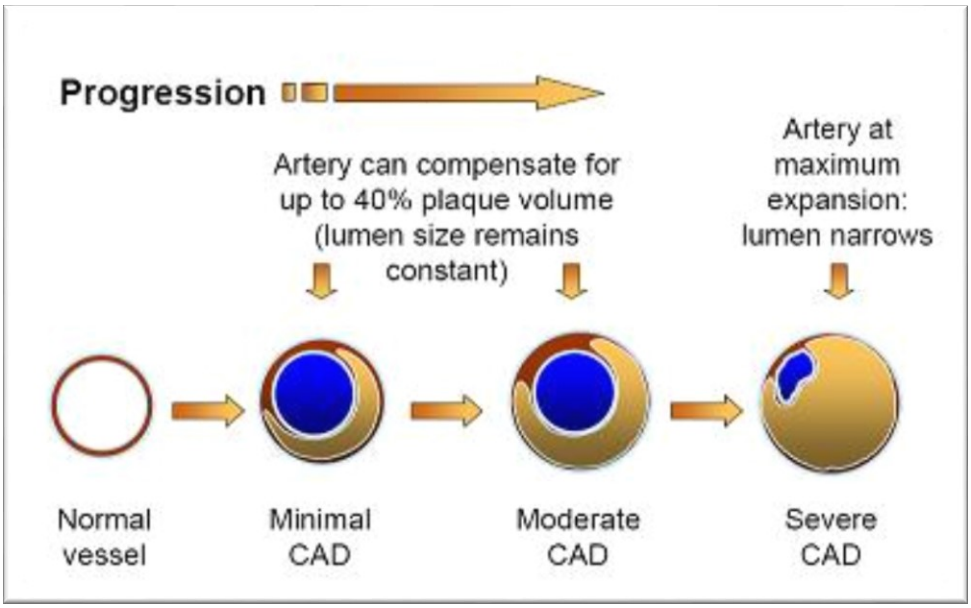


Schematic drawing of the development of coronary arteriosclerosis including positive remodelling during plaque burden increase and the listing of invasive and non-invasive methods concerning their ability to detect signs of atherosclerosis starting with endothelial dysfunction and ending with signs of ischaemia in the ECG

(EKG – electrocardiograph; PET – positron emission tomography; CT – computed tomography; MRT – magnetic resonance tomography; OCT – optical coherence tomography; IVUS – intravascular ultrasound)

Plaque composition and morphology are key determinants for plaque vulnerability and likelihood of rupture. Features of high risk disease include large plaque volume, a lipid-rich core that occupies greater than 40% of the plaque volume, and the presence of positive coronary artery remodelling (Figure 1.2). Furthermore, plaque distribution impacts on an individual's likelihood of death with proximal left anterior descending artery and multi-vessel disease portending the greatest risk{Min, 2007}. Non-invasive detection and analysis of plaques at an early stage, particularly in asymptomatic and low risk patients, has the potential to improve risk stratification without the need for more invasive procedures.

Figure 1.2: Positive remodelling in response to progressive atherosclerosis and plaque formation{Glacov, 1987}



1.2.4 INVASIVE CORONARY ANGIOGRAPHY

Invasive coronary angiography has historically been the 'gold standard' investigation for CAD. Coronary artery luminal diameter, estimated by visual inspection of a radio-opaque lumen during angiography, is used to predict clinical presentation and stress-induced reductions in coronary blood flow. CAD severity assessment can be optimised by the use of quantitative coronary angiography, intravascular ultrasound or the use of fractional flow reserve to assess the haemodynamic effects of individual stenosis. The usefulness of invasive coronary angiography is limited by its inability to demonstrate the nature of atherosclerotic plaques or the presence of coronary artery remodelling (Figure 1.2). Furthermore, the endovascular nature of the test confers a 1.7% risk of major complications including heart attack, stroke and peripheral embolic events and a mortality risk of 0.1%{Scanlon, 1999; Scanlon, 1999}.

1.2.5 NICE CLINICAL GUIDELINE CG95

In March 2010, the National Institute for Health and Care Excellence (NICE) released guidelines for the assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin{NICE, 2010}. NICE CG95 is subdivided into acute and stable chest pain algorithms. The first is intended for patients with acute chest pain who may have an acute coronary syndrome (ACS). In this context, ACS is considered to include unstable angina, non-ST-segment-elevation myocardial infarction (NSTEMI) and ST-segment-elevation myocardial infarction (STEMI). The second is for those with intermittent stable chest pain who may have stable angina.

The acute chest pain algorithm states that initial assessment of patients presenting to hospital with suspected ACS should focus on clinical history, physical examination, resting 12 lead ECG and cardiac biomarker analysis. Patients with findings consistent with STEMI should be managed in accordance with NICE CG167(NICE, 2013} and considered for urgent coronary reperfusion therapy. Patients with findings consistent with unstable angina or NSTEMI should be managed in accordance with NICE CG94{NICE, 2010} and considered for ischaemia testing and/or invasive angiography prior to hospital discharge. Patients in whom ACS is excluded but myocardial ischaemia is still suspected should be investigated according to the stable chest pain algorithm.

Patients admitted to acute assessment units (via referral from general practitioners and the emergency department) with suspected cardiac chest pain are most commonly those pending investigations to confirm/exclude ACS and those in whom ACS has been excluded but a clinical suspicion of CAD persists. Upstream triage means that patients with STEMI or low risk of CAD rarely reach this clinical setting. Thus, assessment of this population may involve either the acute or stable chest pain algorithms of NICE CG95.

Patients with suspected stable angina in whom hospital admission is not immediately warranted are routinely referred to outpatient cardiology services via Rapid Access Chest Pain Clinics (RACPCs). Assessment and investigation of these patients should follow the stable chest pain algorithm of NICE CG95. CCT has been incorporated into

the stable chest pain algorithm, highlighting its increasing role in the acute and outpatient settings.

Figure 1.3: Summary of NICE CG95

Diagnostic approach for patients with 'chest pain of recent onset'
Subdivided into acute and stable chest pain algorithms.

Patients with suspected *stable* CAD are risk stratified using a model which amalgamates modified Diamond-Forrester criteria{Diamond, 1979} and the Duke clinical score{Pryor, 1993}. Patients are assigned within age and sex categories to higher or lower risk according to whether they have any of diabetes, hyperlipidaemia or a history of smoking (Table 1.3).

1) Patients with a history of non-anginal chest pain are not routinely recommended for further cardiac investigation.
2) Patients with a history of atypical or typical cardiac chest pain and a likelihood of CAD between 10% and 90% should be investigated further.
a) CCT for those with a likelihood of CAD 10-29%
b) functional cardiac testing for those with a likelihood of CAD 30–60%
c) invasive coronary angiography for those with a likelihood of CAD 61–90%
3) above 90%, it is recommended that patients are treated for angina without further diagnostic testing.

CCT in this context comprises coronary calcium scoring with progression to CT coronary angiography if calcium score exceeds an absolute total value of 1 and progression directly to invasive coronary angiography if calcium score exceeds an absolute total value of 400.

Exercise ECG should not be used to diagnose or exclude stable angina for those without known CAD.

1.2.5.1. Risk stratification using NICE CG95 criteria

Pre-test likelihood of CAD is determined from the nature of chest pain (Figure 1.4) and the nomogram below (Table 1.3).

Figure 1.4: Clinical classification of chest pain{NICE, 2010}

1. **Sub-sternal chest discomfort of characteristic quality and duration**
2. **Provoked by exertion or emotional stress**
3. **Relieved by rest and/or GTN**

Typical angina (definite) Meets three of the above criteria

Atypical angina (probable) Meets two of the above criteria

Non-anginal chest pain Meets one or none of the above criteria

Table 1.3: Estimated percentage likelihood of CAD{NICE, 2010}

AGE (YEARS)	NON ANGINAL CHEST PAIN				ATYPICAL ANGINA				TYPICAL ANGINA			
	M		F		M		F		M		F	
	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

- For men older than 70 with atypical or typical symptoms, assume an estimate >90%.
- For women older than 70, assume an estimate of 61–90% EXCEPT women at high risk AND with typical symptoms where a risk of >90% should be assumed.
- Values are per cent of people at each mid-decade age with significant coronary artery disease (CAD).
- Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47mmol/litre). Lo = Low risk = none of these three. If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

1.3 CURRENT APPROACH TO THE ASSESMENT OF PATIENTS WITH DYSPNOEA

Dyspnoea is defined by the American Thoracic Society as a 'subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'{Parshall, 2012}.

Dyspnoea is commonly reported by older people in the UK community setting with a prevalence of 32.3%{Ahmed, 2012}. Population sampling across fifteen countries suggests around 27% of the general population report dyspnoea but prevalence is reduced to 16% in those without risk factors or dyspnoea-associated disease. In a community based survey of men in Sweden, dyspnoea was reported in 21% of the total population and in 70% of patients with angina, highlighting the overlap between cardio-respiratory symptoms{Hagman, 1981}. Females report dyspnoea more

frequently than males (odds ratio ≈ 2.1){Nielsen, 2013}. Historically, breathlessness has been reported in around 25% of patients admitted as medical emergencies{Pearson, 1981}.

Breathlessness is associated with poor functional status, reduced physical and mental health. Increasing Medical Research Council (MRC) dyspnoea grade corresponds to 10 year mortality{Ho, 2001; Ahmed, 2012}. After adjustment for age, gender and underlying diseases, dyspnoea is an independent predictor of death{Ahmed, 2012}.

The physiological mechanisms of dyspnoea are poorly understood but are thought to relate to stimulation of respiratory muscle and juxta-capillary mechanoreceptors, central and peripheral chemo-receptors, in response to increased work of breathing, interstitial fluid and hypoxia/hypercarbia. When forced vital capacity is below 60% of predicted, dyspnoea is more likely{Nielsen, 2013}.

The diagnoses that manifest as acute breathlessness are multi-systemic but around two thirds of cases are attributable to cardio-respiratory disease{Gillespie, 1994}. Around 85% of cases are attributed to one or more of chronic obstructive pulmonary disease, pneumonia, ischaemic heart disease, interstitial lung disease or psychogenic manifestation. Acute dyspnoea is multifactorial in up to one third of cases{Michelson, 1999}.

Table 1.4 Differential diagnosis for dyspnoea{Shiber, 2006}

Mechanical interference with ventilation	Abdominal or chest mass
	Asthma, emphysema, bronchitis
	Endobronchial tumour
	Interstitial fibrosis of any cause
	Kyphoscoliosis
	Left ventricular failure
	Lymphangitic tumour
	Obesity
	Obstruction to airflow, central or peripheral
	Pleural thickening
	Resistance to expansion of the chest wall or diaphragm
	Resistance to expansion of the lung
	Thoracic burn with eschar formation
	Tracheal or laryngeal stenosis
Weakness of the respiratory pump	Absolute
	Hyperinflation
	Neuromuscular disease
	Obesity
	Pleural effusion
	Pneumothorax
	Previous poliomyelitis
	Relative
Increased respiratory drive	Decreased cardiac output
	Decreased effective haemoglobin
	Hypoxemia of any cause
	Metabolic acidosis
	Renal disease
	Stimulation of intrapulmonary receptors
Wasted ventilation	Capillary destruction
	Large-vessel obstruction
Psychological dysfunction	Anxiety
	Bodily preoccupation, somatization disorder
	Depression
	Secondary gain, malingering

Traditionally, comprehensive clinical assessment has been the foundation for diagnosis in patients with acute dyspnoea; however, signs and symptoms are often unhelpful{Mueller, 2005} and can lack both sensitivity and specificity, particularly when performed by junior staff in noisy or chaotic environments such the emergency department. In a study of elderly patients with dyspnoea and acute respiratory failure, the accuracy of diagnosis of their admitting emergency department physician ranged from 0.76 for cardiogenic pulmonary oedema to 0.96 for asthma. Inappropriate

treatment was initiated in almost one third of patients, contributing to increased mortality{Ray, 2006}.

1.3.1. IMAGING IN ACUTE DYSPNOEA

Chest radiography is the primary imaging modality for the direct assessment of patients with dyspnoea although CT is widely used to allay diagnostic uncertainty and guide admission decisions{Pandharipande, 2015}. Radionuclide imaging has traditionally been used to evaluate myocardial perfusion and systolic function in suspected CAD and for the inclusion or exclusion of pulmonary embolism. Peripheral ultrasound provides additional information when venous thromboembolism is suspected. Bedside echocardiography and CMR are increasingly popular for non-invasive evaluation of the myocardium, chambers, valves and pericardium when cardiac causes of dyspnoea are suspected.

1.3.1.1. Chest radiography

The use of diagnostic chest radiography is almost universal and the percentage of acute hospital admissions undergoing radiography is often used as a marker of quality of acute care{Malnick, 2010}. This is despite evidence that in acute admissions, the rate of detection of abnormal x-ray features is less than 50%{Malnick, 2010; Sagel, 1974; Verma, 2011} and in the absence of an abnormal chest examination or clinical indication, admission radiographs contribute to management in less than 4% of patients{Malnick, 2010}. The strength of the chest radiograph is its wide availability, low risk and suitability for serial assessment. The UK has a lower frequency of x-ray examination per capita than other developed countries with an estimated 8.3 million chest radiographs performed per annum{DOH, 2002}.

1.3.1.2 Radionuclide imaging

Planar ventilation-perfusion (VQ) scanning has long been established as a robust, safe investigation for the diagnosis of PE. The investigation is based on an intravenous injection of 99m-technetium-labelled albumin particles to allow scintigraphic assessment of lung perfusion. Perfusion scans are combined with ventilation studies,

for which tracers include 133-xenon gas, 99m-technetium-labelled aerosols, and 99m-technetium-labelled carbon microparticles.

Planar VQ has traditionally been limited by challenges in defining the size and precise location of thrombus, the use of probabilistic reporting criteria, and a relatively high indeterminate rate{PIOPED Investigators, 1990}. As a result, CT pulmonary angiography (CTPA), with its binary (positive/negative) reporting approach, has been the preferred imaging technique for suspected thromboembolism.

The use of VQ SPECT imaging techniques, with or without low-dose CT, contributes to fewer non-diagnostic scans{Bajc, 2008}. On pooled analysis of study data, VQ SPECT has higher sensitivity, specificity and accuracy than planar imaging and a lower indeterminate rate{Stein, 2009}. Furthermore, SPECT has superior sensitivity and only mildly inferior specificity to CTPA (0.97/0.91 vs 0.86/0.98 respectively){Reinartz, 2004}. Compared with CTPA, SPECT also offers a lower radiation dose and no contrast-related complications.

SPECT is gaining popularity as the first line imaging technique in patients with suspected PE and a normal chest radiograph. In the future, SPECT may allow the use of automated detection algorithms for PE but large-scale prospective studies are needed to validate such approaches{Konstantinides, 2014}.

1.3.1.3. Computed Tomography (see also section 1.5.2)

Conventional CT, with or without contrast-enhancement, has a role in the detection of pericardial disease and pulmonary causes of dyspnoea (e.g. diffuse parenchymal lung disease){Dyer, 2013}. CT is particularly appropriate in patients for whom clinical, radiographic, and laboratory studies are non-revealing or non-diagnostic. Compared to chest radiography, CT enables more comprehensive assessment of pulmonary vascularity in the context of cardiac failure. In many institutions, CT angiography is the first-line investigation for the assessment of suspected PE and proximal thoracic aortic disease. The strengths of cardiac CT in the dyspnoeic patient are in non-invasively differentiating between ischaemic and non-ischaemic causes of cardiomyopathy and providing supportive information regarding ventricular volumes and function.

Table 1.5: American College of Radiology appropriateness criteria® for the investigation of dyspnoea of suspected cardiac origin{ACR, 2010}

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	8		☢
US echocardiography transthoracic resting	8		O
US echocardiography transthoracic stress	7		O
SPECT MPI rest and stress	7		☢☢☢☢
PET heart stress	7		☢☢☢
MRI heart function and morphology with or without contrast	7		O
CTA coronary arteries	6		☢☢☢☢
CTA coronary arteries with advanced low dose techniques	6		☢☢☢
CTA chest (non-coronary)	6		☢☢☢
Cardiac catheterization with angiocardiography	6		☢☢☢
US echocardiography transoesophageal	5		O
CT chest with or without contrast	5		☢☢☢
Radionuclide ventriculography	4		☢☢☢
Tc-99m V/Q scan lung	3		☢☢☢
CT coronary calcium	3		☢☢☢
Arteriography pulmonary	3		☢☢☢☢

*Relative Radiation Level; Rating scale: 1,2,3 usually not appropriate; 4,5,6 may be appropriate; 7,8,9 usually appropriate

1.3.2 NON-IMAGING TECHNIQUES

Non-imaging techniques are more commonly used to aid diagnosis in patients with chronic rather than acute dyspnoea. Diagnostic accuracy in chronic dyspnoea increases from 55% to 72% when pulmonary function testing is incorporated into an algorithm with history and physical examination{Pratter, 2011}. Pulmonary function

testing and oximetry are particularly important when asthma or chronic obstructive pulmonary disease is suspected. Cardiopulmonary exercise testing, with measurement of peak oxygen uptake, anaerobic threshold and breathing reserve, is useful when combinations of cardiac and respiratory causes are being considered{Maeder, 2009}.

1.3.3. BIOMARKERS IN ACUTE DYSPNOEA

Natriuretic peptides are widely used for the diagnosis and exclusion of cardiac failure in patients with acute dyspnoea. BNP has additive diagnostic benefit when combined with clinical judgement{Januzzi, 2005} and rapid BNP testing within triage protocols for acute dyspnoea has been shown to reduce time to diagnosis, length of hospital stay, rehospitalisation rates and total cost of treatment{Mueller, 2006; Breidthardt, 2007; Moe, 2007}.

BNP is also a powerful prognostic indicator in unselected dyspnoea{Christ, 2007}. Increasing levels are associated with intensive care admission in acute exacerbations of COPD{Stolz, 2008} and of treatment failure and death in patients with community acquired pneumonia{Christ-Crain, 2008}. BNP levels correlate with the pneumonia severity index{Christ-Crain, 2008} and, in patients with pulmonary embolism, BNP is a significant predictor of unfavourable outcome{Cavallazzi, 2008; Klok, 2008; Coutance, 2008}. Conversely, BNP has a high negative predictive value for mortality in pulmonary embolism and as such may be used to identify low risk patients{Coutance, 2008; Vuilleumier, 2009}.

Individual and multi-marker combinations have a role in the diagnosis of clinically challenging overlapping disease states{Maisel, 2012}. Pro-calcitonin (PCT) expression in parenchymal tissue is induced by bacterial infection and this biomarker aids the diagnosis of pneumonia, particularly in cases with high diagnostic uncertainty{Maisel A, 2012}. Pro-adrenomedullin (proADM) is a marker of severity assessment and outcome prediction in community acquired pneumonia{Christ-Crain, 2006}. D dimer has traditionally been used to exclude pulmonary embolism but there is increasing evidence for its use in assessing clot burden{Jeebun, 2010; Ghanima, 2007; Hochuli,

2007} and in prognostication{Kline, 2008}. High sensitivity Tn T also correlates with mortality in acute dyspnoea{van Wijk, 2012}.

1.4 COMPUTED TOMOGRAPHY

Computed Tomography (CT) is a radiological investigation which utilises x-rays to generate detailed cross sectional images of the body. CT was first developed in the 1970s by Sir Godfrey Hounsfield and Allan Cormack, who received the 1979 Nobel Prize in Medicine in recognition of their work.

1.4.1 THE PHYSICS OF CT

CT requires an x-ray source rotating within a circular plane and a set of x-ray detectors rotating in synchrony. The source and detector elements are housed in a ring shaped structure, known as a gantry, with the patient on a motorised table between them.

The x-ray source acts as a transmitter and produces a narrow, fan-shaped beam of radiation, perpendicular to the long axis of the body. As the beam passes through tissue, there is variable attenuation along its path, due to absorption and scattering.

The attenuation of a mono-energetic beam through a homogeneous material may be expressed according to Beer's Law (Figure 1.5). The linear attenuation co-efficient is determined by the atomic number and electron density of the tissue through which the beam passes.

Figure 1.5 Beer's Law

$$I = I_0 e^{-\mu d}$$

I = intensity of the transmitted radiation

I_0 = initial radiation intensity

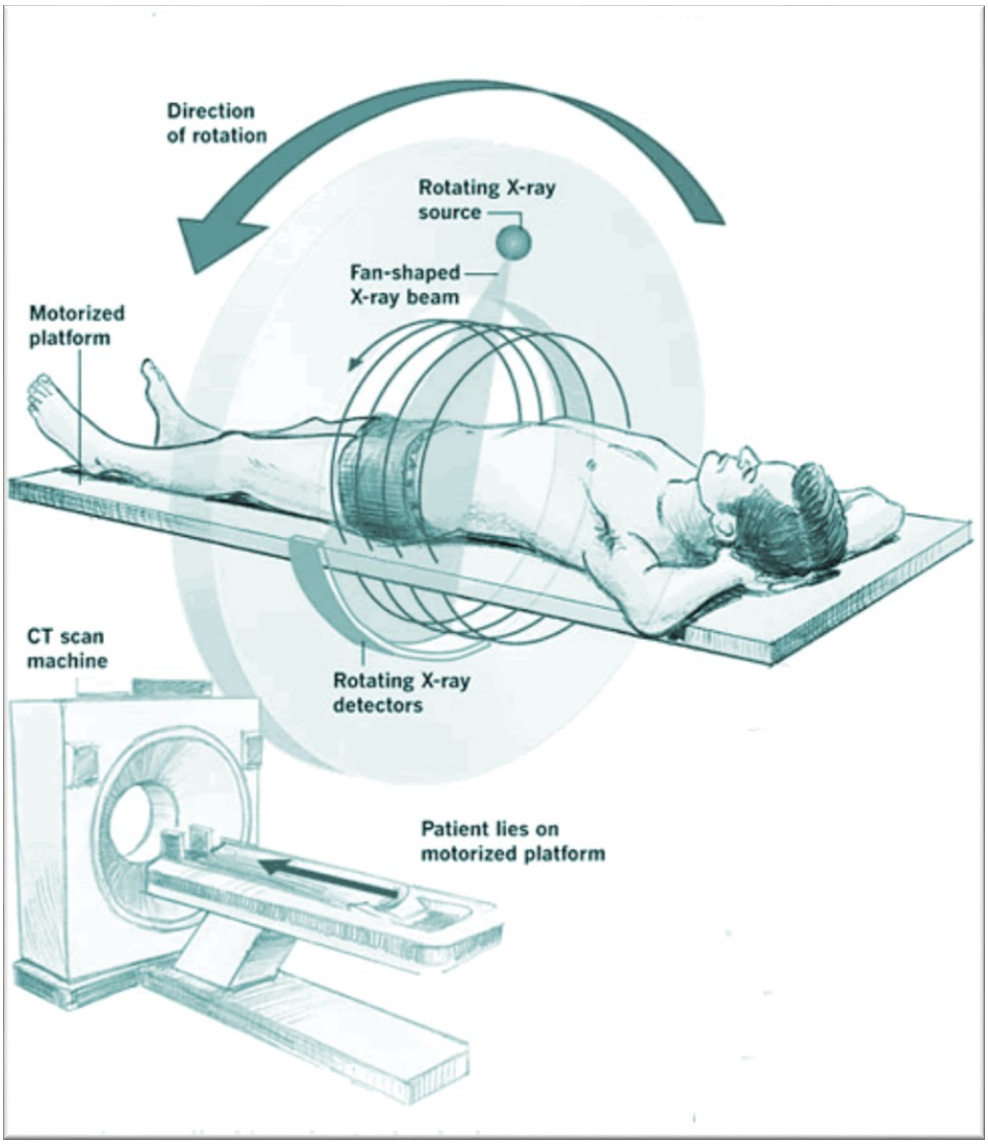
μ = linear attenuation co-efficient of the tissue being scanned

d = distance travelled by the radiation through tissue (i.e. tissue thickness)

The application of Beer's law in CT is somewhat for convenience, as the x-ray beam produced is by no means mono-energetic.

X-ray detectors convert incident x-rays into electrical impulses for transmission to a data acquisition unit. The resulting series of two-dimensional images are digitally reconstructed to produce detailed cross sectional and three-dimensional images of the patient.

Figure 1.6: Diagrammatic representation of a spiral CT scanner



1.4.2 SCANNER TECHNOLOGY

In traditional axial scanning, the x-ray source and detector rotated 360 degrees around the patient with the table being stationary; thereafter the table was advanced for the next slice. If movement occurred during data acquisition, image quality was degraded.

Axial scanning was therefore only appropriate for imaging organs with no automatism function.

In the 1970s, the development of spiral CT scanning facilitated continuous image acquisition as patients advanced through the CT gantry. The gantry performs multiple rotations, tracing a spiral of x-rays around the patient to produce a data volume. Individual slices are reconstructed from a series of overlapping images to reduce the impact of movement artefact seen with traditional axial 'step and shoot' scanners. Spiral scanning can therefore be used to image organs subject to involuntary motion.

In the past two decades, CT scanners with multiple-row detectors have been developed, which allow simultaneous scanning of several slices, reducing overall scanning time. The first multi-slice scanners acquired 4 slices per rotation of the gantry. Modern scanners can acquire up to 640 slices per rotation, in as little as 0.2 seconds. In addition to multiple detectors, scanners have now been developed with dual source capability. These allow a full CT slice to be obtained in a half rotation of the gantry.

Short acquisition times mean a longer spiral scan can be acquired in a given time and a comparable volume can be scanned in less time with the elimination of motion artefact. Through the combination of speed and continuity, complete data sets can be obtained within a single breath-hold for thoracic imaging or within a single heartbeat for cardiac imaging. The speed of acquisition also facilitates dynamic contrast studies. Vessels can be imaged at the point of maximal enhancement and serial images can be taken during a single contrast cycle.

The disadvantage of high speed acquisition is that the quantity of radiation generated per rotation is less, resulting in reduced image quality. Furthermore continuous movement results in increased slice thickness, associated with an increased likelihood of artefact.

1.4.3 DATA ACQUISITION AND IMAGE PROCESSING

Each data volume comprises a number of volume elements known as voxels. Voxels are three dimensional elements of anatomy represented by the two dimensional

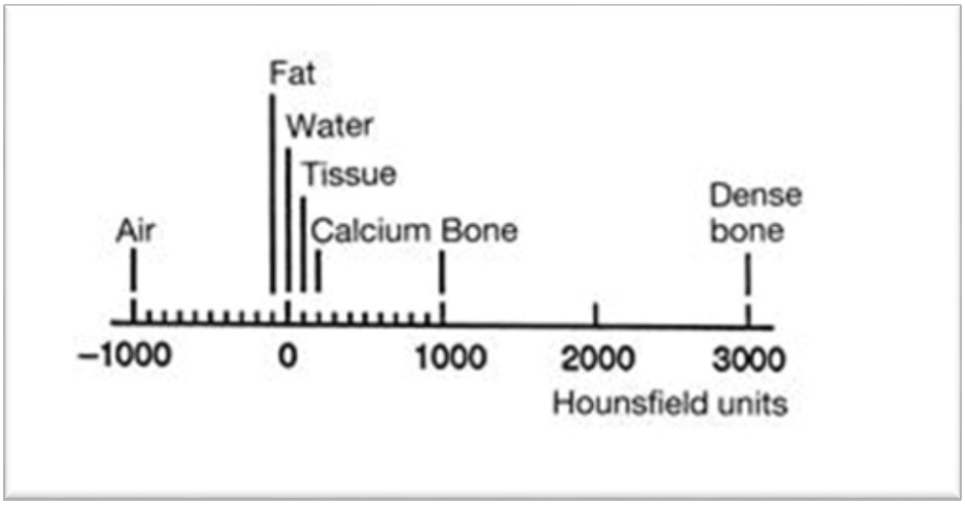
pixels. Pixels are therefore two dimensional picture elements that combine to form the image matrix.

The attenuation in each voxel determines the grey-scale of the corresponding pixel in the final two-dimensional image. Attenuation is measured according to the Hounsfield scale, derived by linear transformation of the linear attenuation co-efficient, in which the radiodensity of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU), and the radiodensity of air at STP is defined as -1000 HU{Brooks, 1977}.

Table 1.6: The Hounsfield Scale

SUBSTANCE	HOUNSFIELD UNITS (HU)
Air	−1000
Lung	−500
Fat	−100 to −50
Water	0
Blood	+30 to +45
Muscle	+10 to +40
Soft Tissue, Contrast	+100 to +300
Bone	+700 (cancellous bone) to +3000 (dense bone)

Figure 1.7: The Hounsfield scale



Partial volume effect occurs when different tissues are contained within the same voxel. Each tissue (e.g. calcified coronary plaque) only partially fills the voxel and is therefore a partial volume. When this occurs, μ is not representative of a single tissue

but instead is a weighted average of the different μ values. The thicker the slice on CT, the greater the averaging that occurs.

Modern scanners allow for volumetric data acquisition with isotropic voxel size resolution in x, y, and z axes, facilitating multi-planar reformations with no limitation to orientation and angulation.

1.4.4 IMAGE QUALITY

There have been recent dramatic advances in imaging software that allow virtual reality and 3D image reconstruction. Detailed images can now be generated with sub-millimetre resolution. Improvements in both spatial and temporal resolution have reduced the impact of respiratory motion, tachycardia and dysrhythmia on image quality. There remains, however, a compromise between spatial resolution and contrast resolution.

Compared with standard x-ray radiography, CT has significantly worse spatial resolution but significantly better contrast resolution. The limiting spatial resolution for standard x-ray is approximately 7lp/mm versus 12-20lp/mm for CT. The contrast resolution of x-ray is approximately 5% versus 0.5% for CT.

1.4.4.1 Spatial resolution

Spatial resolution is a measure of the ability of an imaging system to discriminate between discrete, adjacent structures. Axial spatial resolution (i.e. in the scan plane) is inherent to each CT scanner and depends on the distances between the x ray source, the centre of rotation and the x ray detector, as well as the focal spot size, the detector aperture, and the number of measurements per rotation. Longitudinal spatial resolution (i.e. perpendicular to the scan plane) can be optimised by modification of CT protocols.

In conventional CT, longitudinal spatial resolution is entirely determined by slice thickness. Slice thickness impacts on voxel size; the smaller the voxel size, the greater the spatial resolution. Slice thickness is typically between 5 and 10mm, but may be as thin as 1mm. Reducing slice thickness improves spatial resolution and minimises

partial volume effect but requires a higher radiation dose to maintain image quality. Radiation burden may be a concern if there is a large anatomical area to be scanned, necessitating a high number of slices.

1.4.4.2 Contrast resolution

Contrast resolution indicates the ability of CT to detect differences in image density. It is a measure of the details that are just visible at a given x-ray dose. Increased visual noise reduces the visibility of low-contrast objects. The better the signal to noise ratio, the greater the visibility of detailed structures of a given size and contrast. Image noise results from variation in attenuation coefficients between voxels of identical tissue. Filters selected during the image reconstruction process can be used to control noise.

1.4.4.3 Temporal resolution

Motion free imaging of organs with an automism function requires high temporal resolution, where temporal resolution is effectively the ability of CT to deliver image detail in the smallest 'window' of time. This is particularly relevant for cardiac imaging, for which a temporal resolution of 250ms is required to achieve motion free imaging during diastole. As heart rate increases, so temporal resolution must also increase.

Temporal resolution increases with the number of x-ray detectors present and with increased gantry speed. Temporal resolution can be further enhanced by the use of ECG gated protocols, segmentation and tailored reconstruction algorithms.

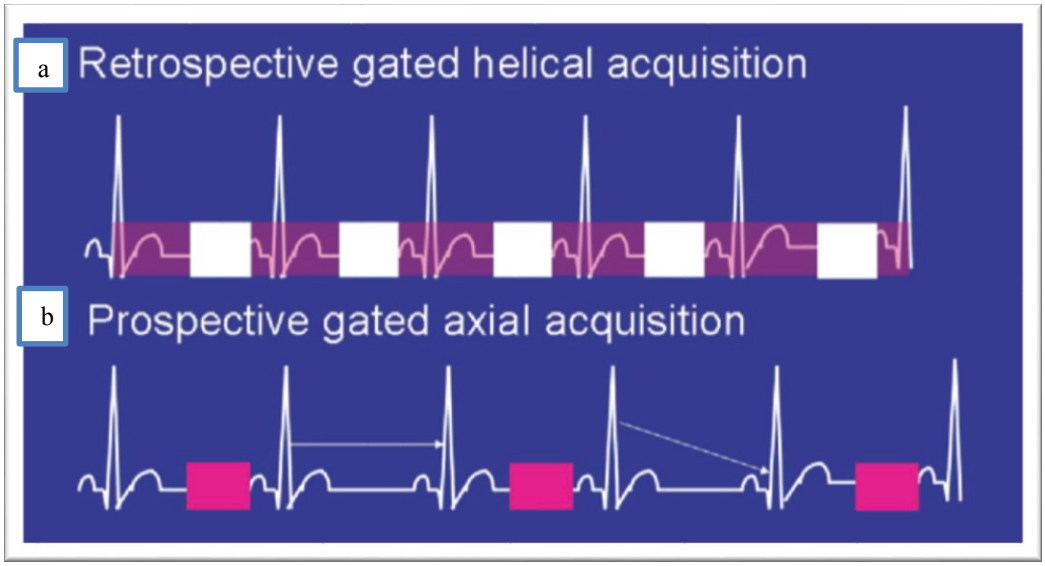
1.4.5 ECG GATED TECHNIQUES

Cardiac motion is at its least during diastole, when passive filling of the ventricles occurs. Cardiac gating is used to optimise imaging during diastole and may be prospectively or retrospectively applied.

In prospective gating, ECG triggering ensures x-ray generation and data acquisition during diastole. The scanner estimates the start of the diastolic phase by analysis of the preceding 3-7 heartbeats. This approach is less useful in patients with tachycardia and dysrhythmia.

In retrospective gating, the CT volume set is acquired simultaneously with a surface ECG recording. X-ray detection must occur from every area of the heart for the duration of the cardiac cycle. Reconstruction algorithms assign data to phases of the cardiac cycle, relative to the R wave. This approach allows faster cardiac volume coverage and functional analysis throughout the cardiac cycle. The trade-off is a higher radiation dose than for prospective gating.

Figure 1.8: Tube current application during retrospective and prospective CT acquisition{Courtesy of Dr. Nadeem Hussain, University of South Alabama}



[a] Retrospective gating; [b] Prospective gating

With prospective gating, the tube current is in force for a predefined portion of the cardiac cycle (shown here as 40%, but can be as short as 10% of the cardiac cycle). Arrows marks 100% of the cardiac cycle.

1.4.6 RADIATION DOSING

Publications in the lay and medical press have raised concerns about the health risks associated with increasing medical radiation exposure, particularly related to cardiovascular imaging{Brenner, 2007}. Data from Europe and the US demonstrated that in 2007 CT scanning constituted 5–10% of all imaging procedures, but contributed 40–67% of the total radiation burden{Sadetzki, 2007}.

The effective dose, expressed in Sieverts (Sv), is a generic estimate of the overall harm to the patient caused by the radiation exposure and allows rough comparison between different CT scenarios. Cardiac CT examinations may deliver effective doses in excess of 20mSv, versus 3-9mSv for other CT examinations of the chest{Mayo,

2009}. The absence of evidence-based standard cardiac acquisition protocols mean there is wide variation in radiation doses for the same examination (5-30mSv){Hausleiter, 2009}. Nevertheless, where CT negates the requirement for additional radiological investigations, such as myocardial perfusion scanning or invasive coronary angiography, the overall patient radiation dose may be reduced.

The relationship between radiation dose and CT tube current in milliamperes (mA) is linear. Methods proposed for achieving radiation dose reduction during cardiac CT include body mass-based modulation of tube current, ECG correlated modulation of tube current during retrospectively gated acquisitions{Jakobs, 2002}, prospective axial gating{Earls, 2008; Maruyama, 2008}, tube voltage reduction{Bischoff, 2009}, reducing scan length/volumes{Gopal, 2009} and combinations of the above{Hausleiter, 2006}. Dose minimisation technologies built into scanning equipment include grids, collimators and filters to shield scattered radiation, define scan slice and absorb low-energy x-rays.

For cardiac imaging, lowering the heart rate by beta-blocker administration not only reduces motion artefacts but also stabilises sinus rhythm to allow consistent use of ECG dependent dose reduction algorithms. The use of high pitch data acquisition (resulting in x-ray tubes and detectors rotating around the patient without overlap) has (to date) been limited to patients with heart rates lower than 65 bpm.

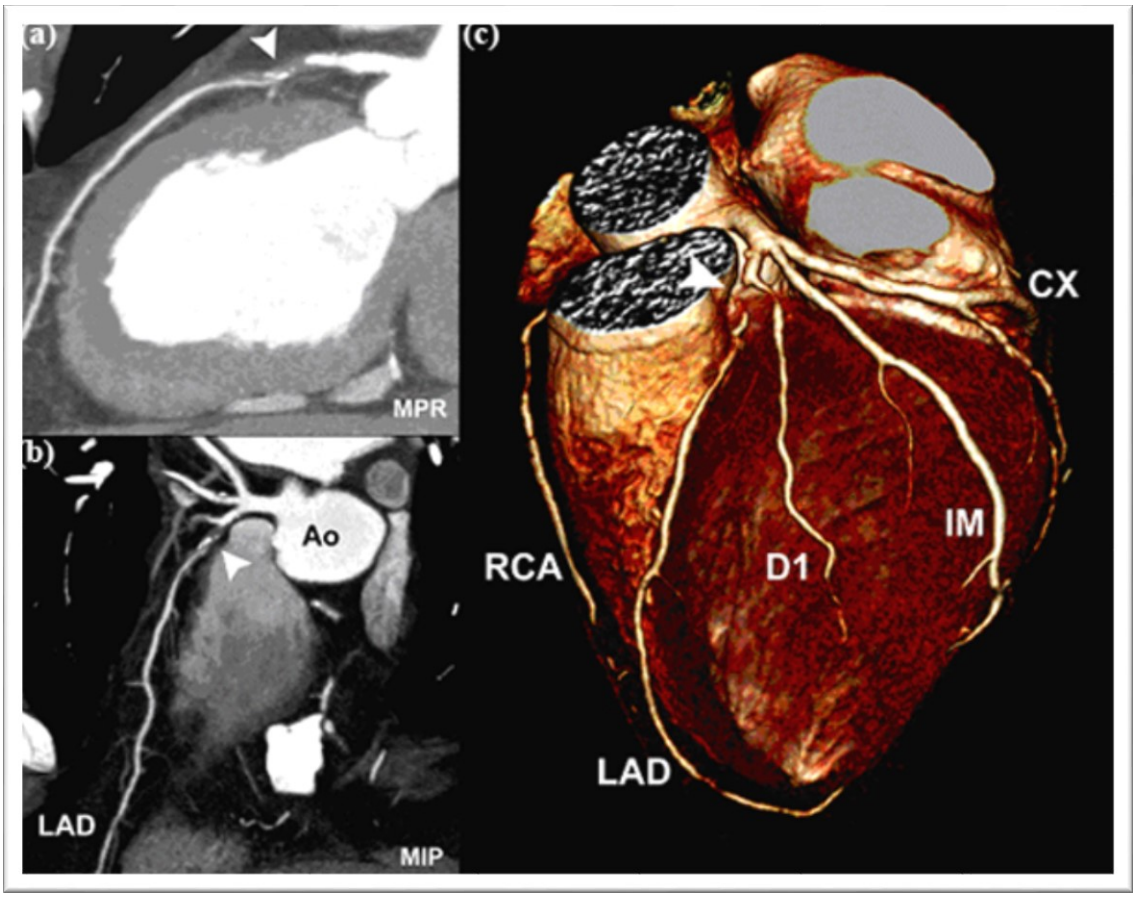
When imaging the lungs, current as low as 40mAs can be used to obtain high resolution images, although higher doses may be required for the assessment of ground glass opacity, sub-pleural lines and in obese patients.

Table 1.7: Typical radiation doses resulting from cardio-pulmonary imaging{IAEA, 2014}

PROCEDURE	EFFECTIVE RADIATION DOSE (mSV)
Background radiation per annum[a]	2.4
Chest radiograph	0.02
MDCT thorax	3-11
CT calcium scoring by MDCT	1-5
CT coronary angiography by MDCT	8-30
Comprehensive cardiopulmonary CT	8-22
Ventilation perfusion scan	7
Invasive coronary angiography	3-10 (up to 22)

[a] global average

Figure 1.9: Radiation exposure using different CCT protocols{Weustink, 2009}



[a] Helical CT coronary angiography (CTA) without ECG tube modulation.

[b] Retrospectively gated helical CTA with ECG tube modulation (10-20mSv; 64-slice CT).

[c] Prospectively gated axial CTCA or step-and-shoot algorithm (2-3mSv; 64-slice CT).

1.5 COMPUTED TOMOGRAPHY IN CLINICAL PRACTICE

Technological advancement, increased availability and the perception that imaging can meaningfully affect medical decision making has resulted in an upsurge in the use of CT. There has been a 140% increase in the number of scans performed in the UK since 1997, with in excess of 3.4 million scans performed per annum{Hart, 2008}.

A significant proportion of these scans relate to the diagnosis and early triage of patients with acute medical conditions and over 31% are lung imaging. Rates of growth in the use of CT are highest for abdominal pain, flank pain, chest pain and shortness of breath. Reports suggest CT use in the emergency department may be increasing at a greater rate than in other clinical areas.

The ability to perform non-invasive angiography is one of the greatest attributes of CT. Like invasive angiography, CT scanning allows direct visualisation of emboli, but is safer and cheaper than invasive angiography, and more widely available.

Advanced computer systems now offer the capability for a growing number of non-invasive virtual endoscopy procedures to be performed. CT virtual endoscopy has been used to evaluate pathologic processes of the nasopharynx, larynx, and tracheobronchial tree{Thomas, 2009}. In comparison with virtual colonoscopy, virtual bronchoscopy requires no prior preparation of the patient and images are generated as part of post-processing, with no additional radiation burden. The advantages of virtual procedures include the capability to access small structures, to view non-traditional perspectives, to provide volumetric analyses and to apply automatic pathology detection software.

In recent years, MDCT has been combined with PET and SPECT in hybrid imaging approaches that assimilate cellular signalling (functional) and anatomical information. The combination of CT calcium scoring and cardiac SPECT with Tl-201 for myocardial viability and Tc-99m-sestamibi for myocardial perfusion is an attractive possibility. SPECT-CT also offers the opportunity to anatomically define the lobes of the lungs so that lobar function can be assessed semi-automatically from V/Q images in patients being considered for lung volume reduction surgery{Beyer, 2011}.

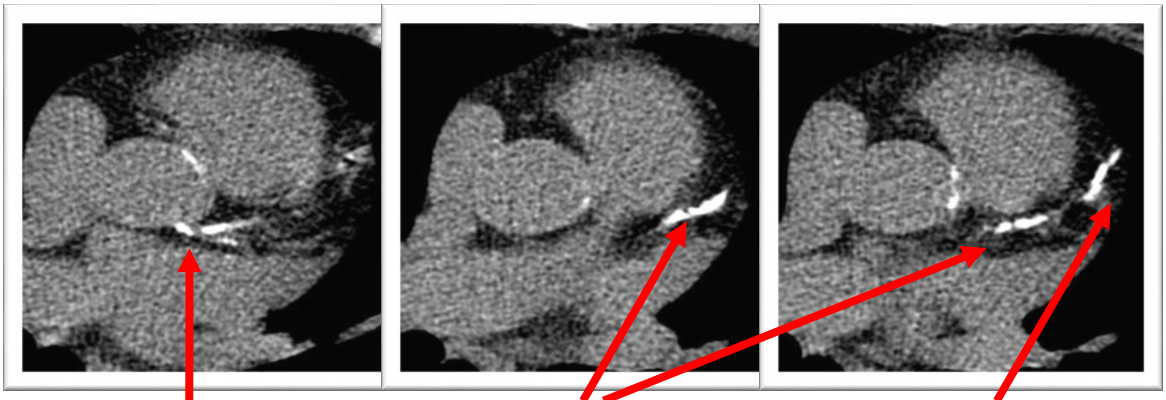
1.5.1 CARDIAC COMPUTED TOMOGRAPHY

The primary indication for cardiac CT (CCT) is in the risk assessment of patients with potential or suspected CAD. The key elements of the investigation are coronary calcium assessment and coronary CT angiography (CTA). CCT may also be used to characterise coronary artery plaque, to evaluate cardiac function, myocardial perfusion, infarction, malignancy, pericardial pathology, and congenital anomalies{Desjardins, 2004}.

1.5.1.1 Coronary calcium scoring

Coronary artery calcification occurs as part of the process of atherosclerosis and is absent in the normal vessel wall{Stary, 1995}. Unenhanced CT is a sensitive method for the detection of coronary calcium{Greenland, 2007; Carr, 2005} and the coronary calcium score (CCS), which quantifies coronary calcification, correlates closely to global atherosclerotic plaque volume on autopsy{Rumberger, 1995}.

Figure 1.10: Example of coronary calcium imaging{Agatston, 1990}



CCS increase with age, reflecting progressive atherosclerosis, and are typically higher in male patients{Hoff, 2001; McClelland, 2006}. Scores are reported as absolute values (Agatston score equivalent) and as percentiles of calcification relative to an age and sex-matched population. Agatston scores are determined from measurements of the area and density of calcified plaque. A typical report provides an Agatston score for each individual coronary artery and a total score.

There is a well-documented association between CCS and the occurrence of cardiovascular events. Similarly, in patients with a CCS of zero, the likelihood of coronary events is low{Shareghi, 2007}. Evidence suggests that CCS is independently predictive of outcome, irrespective of traditional cardiac risk factors{Greenland, 2007}.

Table 1.8: Correlation between coronary calcium score and angiographically documented stenosis in patients with suspected CAD {Haberl, 2001}

TOTAL CORONARY CALCIUM SCORE	DIAGNOSIS	CLINICAL INTERPRETATION
0	No identifiable atherosclerotic plaque	A negative examination. >97% chance of being free from CAD Very low cardiovascular risk.
1-10	Minimal plaque burden	Significant CAD very unlikely
11-100	Mild plaque burden	Likelihood of mild-mod non-obstructive CAD
101-400	Moderate plaque burden	High likelihood of moderate non-obstructive CAD
>400	Extensive plaque burden	High likelihood of at least one significant coronary stenosis

The diagnostic utility of CCS was initially validated using electron beam computed tomography (EBCT){Rumberger, 1995; O'Rourke, 2000}. In more recent years, EBCT and MDCT scanners have been demonstrated to have equivalent reproducibility for measuring coronary artery calcium, supporting the adoption of MDCT in this role{Detrano, 2005}.

In symptomatic patients, CCS <100 are typically associated with a low probability of abnormal perfusion on myocardial perfusion testing (<2%){Berman, 2004} or significant arterial obstruction on invasive coronary angiography (<5%; where significant obstruction is taken as stenosis >50%){Haberl, 2001}. The sensitivity of CCS for significant atherosclerotic obstruction exceeds 95% but specificity is limited.

The strength of CCS is its high negative predictive value (96-100%){Haberl, 2001; Knez, 2004}, meaning the investigation can be used to exclude coronary artery disease with a high level of confidence. A degree of caution is; however, recommended in symptomatic patients in whom 5-15% with a CCS of zero have 1 or more stenoses >50% on CT coronary angiography due to non-calcified lesions{Jarreau, 2007}. In a study of high risk patients with suspected ACS, 39% of patients with CCS zero still had obstructive disease, highlighting the importance of considering pre-test probability{Henneman, 2008}. In symptomatic patients with a CCS of zero, obstructive CAD is associated with an increased incidence of cardiovascular events{Villines, 2011}.

The main limitation of CCS is its inability to detect the location of significant lesions in individuals with a high score or the likelihood of those with a high score having a coronary event. International guidelines discourage the use of CCS for coronary artery disease screening in patients with a high risk profile as these patients should be commenced directly on primary preventive therapy{Greenland, 2007; NICE, 2010}.

Whether a coronary calcium scan can be used alone to exclude ACS reliably or to provide added value to coronary CTA in emergency department patients with acute chest pain remains a subject of debate. In a recent study, a CCS of zero was found not to exclude ACS, nor did a high CCS preclude interpretation of coronary CTA in most patients. The authors concluded that the decision to perform a coronary calcium scan should be balanced against the additional radiation exposure required{Pursnani, 2015}.

1.5.1.2 Coronary CT angiography

ECG gating techniques maximise temporal resolution and minimise imaging artefacts caused by cardiac motion to allow coronary artery visualisation. With newer generations of MDCT scanners the proportion of non-assessable segments has decreased{Vanhoenacker, 2007}. Coronary CTA still does not provide the same degree of image quality or diagnostic accuracy for the quantification of stenosis as invasive coronary angiography but may be superior for identifying cumulative calcified, non-calcified and mixed plaque burden{Butler, 2007}. Sensitivity for the detection of

significant coronary segment stenosis (≥50%) is 90-93% with specificity 93-97%{Vanhoenacker, 2007; Mowatt, 2008}. In pooled study results, the positive predictive value for significant CAD was 93% and negative predictive value 100%{Mowatt, 2008}.

Evidence suggests that CTA performs best in ruling out obstructive CAD in patients with a low likelihood of CAD and a low CCS, and in patients across the range of CAD likelihood with a CCS of zero. Conversely, CTA is less effective for this purpose in patients with a high likelihood of CAD, known CAD or extensive coronary calcification{Arbab-Zadeh, 2012}. CTA does not provide additional relevant diagnostic information in symptomatic patients with a high estimated pre-test probability of CAD {Meijboom, 2007}.

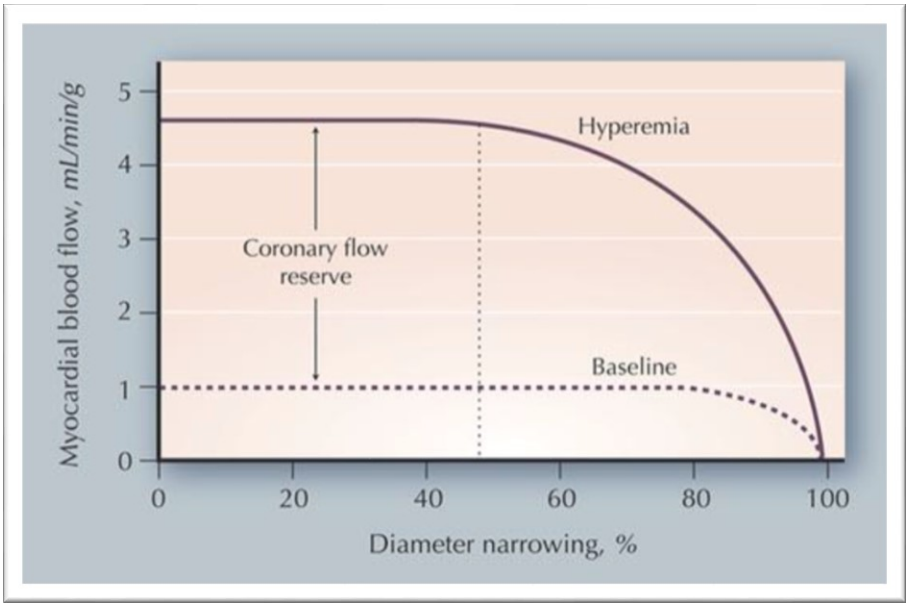
Table 1.9: Pre and post-test probability for a positive CTA based on likelihood of CAD{Adapted from Meijboom, 2007}

	LOW PRE-TEST LIKELIHOOD (<30%)		**INTERMEDIATE PRE-TEST LIKELIHOOD (30-69%)**		**HIGH PRE-TEST LIKELIHOOD (>70%)**	
	CT-Y	CT-N	CT-Y	CT-N	CT-Y	CT-N
Pre-test probability	13		53		87	
Post-test probability	68	0	88	0	96	17

CTA is the only non-invasive investigation to allow detection of vulnerable plaque disease through the characterisation and quantification of coronary plaque. Adverse characteristics detectable using CTA include low attenuation plaque, positive remodelling and spotty calcification{Nakazato, 2013}; proximal left anterior descending artery and multi-vessel involvement also suggest high risk disease{Min, 2007}. Intravascular ultrasound (IVUS) is the standard reference for the assessment of plaque composition/progression and direct comparison of CTA with IVUS suggests non-inferiority of CTA{Voros, 2011; Nakazato, 2013}.

CTA, without adjunctive functional testing, is limited by its inability to identify clinically significant CAD. It is assumed that there is a threshold above which a stenosis causes significant reduction in coronary blood flow but in reality all stenoses are of unknown significance following purely anatomical assessment.

Figure 1.11: Progression of CAD to flow limiting stenosis{Gould, 2009}



More advanced CAD is associated with dense coronary calcification and reduced coronary luminal diameters that have historically been considered detrimental to image interpretation. Similarly, CTA is of limited value in the assessment of in-stent stenosis and coronary artery bypass grafts. Depending on stent type, there is a high variability of artefacts and lumen visibility{Maintz, 2006}. Graft visualisation may be obscured by movement and surgical clip artefacts{Heye, 2014}. In the future CTA may have a role in the non-invasive diagnosis of in-stent restenosis and occlusion{Oncel, 2007} but at present, the strength of the technique is in the exclusion of coronary artery disease where none is present.

CCT can also be used to assess for acute myocardial infarction, detectable as hyper-enhancement on delayed acquisition scanning{Lardo, 2006; Gerber, 2006}. The transmural extent of this hyper-enhancement correlates well with findings on radionuclide imaging{Sato, 2008; Habis, 2007}. Precise and reproducible

measurements of ventricular volumes, wall thickness, and regional contraction abnormalities are achievable but CCT should not be considered a first line investigation for evaluating cardiac function. The technique also provides detailed information on wider cardiovascular and thoracic pathology. Effusions and pericardial calcification are readily detected.

The technique has been used in the acute setting to exclude coronary stenosis in selected patients with chest pain{Vanhoenacker, 2007}, and when the diagnosis remains uncertain despite clinical evaluation and simple non-invasive testing{Hoffmann, 2006}. In symptomatic patients with suspected CAD, CTA adds incremental benefit to CCS for discrimination of individuals at risk of death or MI{Al-Mallah, 2014}.

With appropriate patient selection, CCT has been demonstrated to reduce diagnostic time, costs and requirement for repeat evaluation for recurrent chest pain{Goldstein, 2007}, and has been shown to be more cost effective than exercise testing and stress echocardiography in the triage of emergency department patients with acute chest pain{Khare, 2008}. Furthermore, CCT can preclude the need for invasive angiography{Schroeder, 2005; Dorgelo, 2005}.

The multi-centre PROMISE trial recently confirmed CCT as a viable alternative to functional testing{Douglas, 2015}. In symptomatic patients with suspected CAD, a strategy of initial CTA was associated with fewer catheterisations showing no obstructive CAD and a lower median cumulative radiation exposure per patient. There was no statistically significant difference between the costs of first receiving CCT versus a functional test over three years of follow-up{Douglas, 2015}.

Patients with normal study findings have excellent clinical outcomes and can be safely discharged from hospital{Rubinshtein, 2007; Rubinshtein, 2007; Hollander, 2009; Litt, 2012}. In patients with low-intermediate risk of CAD, negative CCT may be used to support hospital discharge without major adverse cardiac events (MACE) for up to five years {Laudon, 2010; Rubinshtein, 2007; Rubinshtein, 2007; Hollander, 2009}.

1.5.2 THORACIC COMPUTED TOMOGRAPHY

Developments in CT technology, particularly multi-detector CT, now allow coverage of the entire thorax with sub-millimetre resolution, within a single breath-hold (less than 10s). The appearance of most lung diseases on CT has already been described. The advantages of CT over standard chest radiography for diagnosis are widely recognised, and CT is increasingly used for monitoring disease progression.

1.5.2.1 CT pulmonary angiography

CT pulmonary angiography (CTPA) is the initial imaging modality of choice for stable patients with suspected pulmonary embolism{Remy-Jardin, 2007}. Modern CT scanners enable the evaluation of pulmonary vessels down to sixth order branches{Patel, 2003}. The sensitivity of CTPA for pulmonary embolism is around 83% and specificity around 96%{Stein, 2006}. The negative predictive value of a normal CTPA exceeds 98%, regardless of whether there is underlying lung disease{Tillie-Leblond, 2002}. CTPA also allows a quantitative assessment of clot burden, measured by pulmonary artery obstruction index, which correlates with clinical severity{Wu, 2004; van der Meer, 2005}.

Quantitative assessment of ventricular dimensions by CT is also useful as a marker of right ventricular dysfunction (RVD){Becattini, 2011; Bach, 2005}. There is an association between RVD detected by CT and other markers of cardiac dysfunction (elevated serum BNP and Tn I){Jimenez, 2014}. Right to left ventricular dimensional ratio on CT correlates well with echocardiography for the assessment of RVD in patients with acute pulmonary embolism{Becattini, 2011; Henzler, 2012}; however, recent literature does not currently support an association between CT detected RVD and 30 day mortality{Jimenez, 2014}.

By imaging the lung parenchyma, pleura and great vessels, CTPA offers additional information not provided by V/Q scintigraphy or pulmonary angiography. In one study, CTPA identified pleural or parenchymal abnormalities that explained indeterminate defects on V/Q scans in 57% of patients{van Rossum, 1996}. In other studies, alternative intra-thoracic findings were identified in 11% to 85% of patients

undergoing CTPA{Kanne, 2004}. Using CTPA as the primary diagnostic test in suspected pulmonary embolism leads to alternative diagnoses in up to 25% of patients{Van Strijen, 2003}. CTPA can also differentiate causes of pulmonary hypertension such as chronic thromboembolic disease, underlying lung pathology, and their sequelae.

1.5.2.2 Conventional CT chest

Conventional chest CT provides continuous axial cross-sectional imaging in a cranio-caudal direction. The image window extends from the lung apices to costophrenic angles. With current MDCT technology, slices are usually reconstructed at 2.5–5mm. Thinner reconstructions can be used to evaluate fine morphological detail such as the lung parenchyma. Contrast enhanced images are acquired in a similar manner to non-enhanced images but follow the administration of intravenous iodinated contrast medium.

Selection of different processing algorithms generates mediastinal and lung windows. Mediastinal windows are used to assess the chest wall, pleura and mediastinal structures, usually with intravenous contrast so that vascular structures in the mediastinum can be differentiated from enlarged lymph nodes or other masses. Lung windows allow the pulmonary parenchyma and vasculature to be seen in detail, while the mediastinal and chest wall structures are essentially obscured.

1.5.2.3 High resolution CT chest

HRCT images were traditionally acquired as non-contiguous 1–2mm slices, 20–30mm apart. MDCT offers the capability to reconstruct the entire chest into contiguous 1mm slices and therefore HRCT is often no longer performed as a separate investigation. Continuous, helical MDCT detects significantly more pulmonary abnormalities and has better inter-observer agreement than conventional interrupted (axial) HRCT{Dodd, 2008; Dodd, 2006}.

The use of high spatial resolution reconstruction algorithms enhance the detection of small structures and subtle pathological changes. The smallest anatomic unit

detectable on HRCT is the secondary pulmonary lobule{Murata, 1986; Webb, 1988}. Inter-lobular septae are not usually seen unless their diameter exceeds 0.2mm. Intra-lobular acinar arteries have a diameter of 0.5mm and are highly visible, as are the pulmonary arteries supplying each lobule with a diameter of 1mm. Bronchi are usually visible, but bronchioles, which have a wall diameter of 0.15mm, are at the limit of CT resolution and are rarely seen{Webb, 1988}.

HRCT images are used to demonstrate the lung parenchyma. The clinical indications for HRCT are to detect and evaluate bronchiectasis, to evaluate suspected interstitial lung disease when standard chest radiography is unremarkable, to delineate abnormalities identified on standard chest radiography to aid diagnosis, to evaluate disease activity, to predict treatment response and to guide interventional procedures (e.g. biopsy){Kazerooni, 2001}

Diagnoses with pathognomonic features on HRCT include bronchiectasis, emphysema, Langerhan's cell histiocytosis, lymphangioleiomyomatosis, idiopathic interstitial pneumonias, lymphangitis carcinomatosis, pneumoconiosis and sarcoidosis. Thus, CT may obviate the need for a histological diagnosis. The role of HRCT imaging in the emergency setting is limited but may be useful to help assess the cause of pulmonary consolidation.

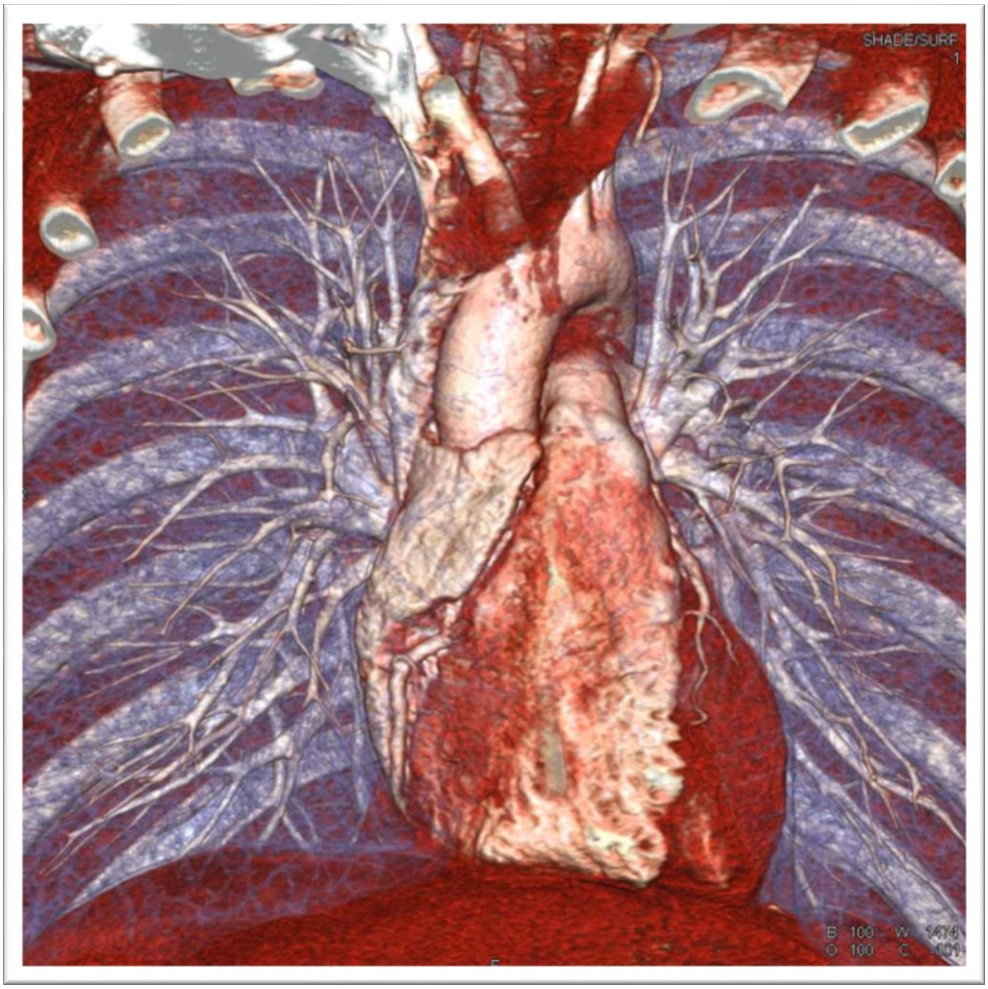
1.5.3 COMPREHENSIVE CARDIO-PULMONARY COMPUTED TOMOGRAPHY (CPCT)

CT angiography of the coronary arteries, pulmonary arteries, and thoracic aorta are increasingly used in the non-invasive workup of suspected low to intermediate-risk CAD, pulmonary embolism, and thoracic aortic disease associated with aortic valve dysfunction, respectively.

Dedicated coronary CT protocols allow excellent assessment of the coronary arteries and proximal ascending aorta but are less suitable for assessment of the pulmonary vasculature, and should not be used to exclude pulmonary embolism{Dodd, 2008 }. By contrast, the main differential diagnoses for pulmonary embolism, namely aortic aneurysm/dissection and coronary artery disease manifest on thoracic CT.

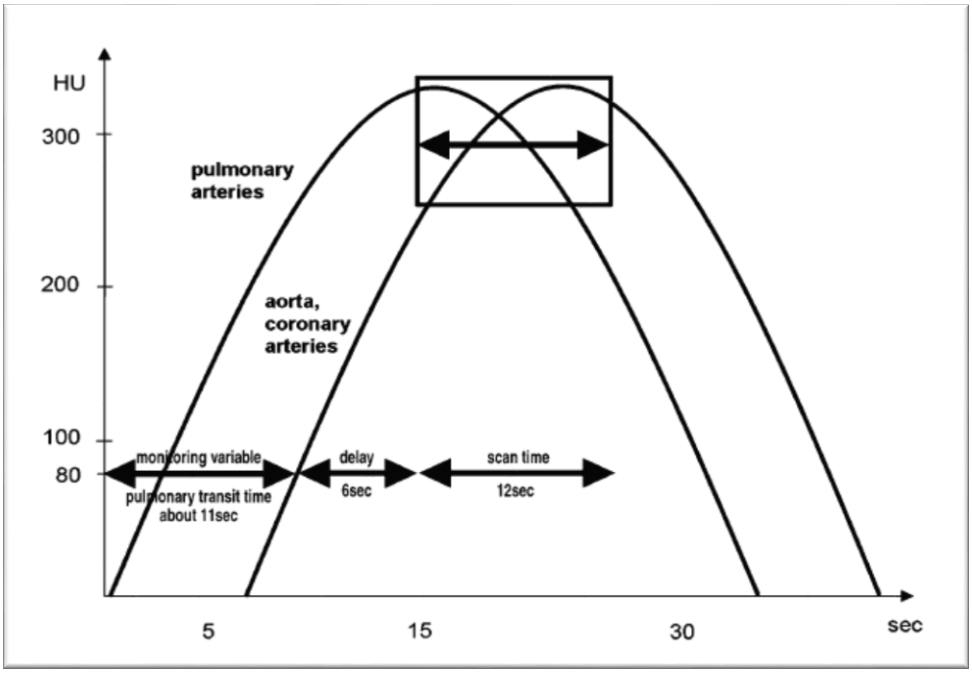
Comprehensive cardio-pulmonary CT (CPCT) protocols for the complete assessment of thoracic vessels and adjacent intra-thoracic structures, aim to opacify the pulmonary and coronary arteries and the aorta during a single breath-hold acquisition. These so called 'triple rule out' protocols are currently being used predominantly in the assessment of patients presenting with acute chest pain to the emergency department, although there are concerns about excess radiation and contrast burden relative to dedicated angiographic protocols{Ayaram, 2013}.

Figure 1.12: Example of an image generated using a CPCT protocol



The challenge of CPCT is in achieving 3 separate diagnostic quality examinations in a single CT, with peak contrast enhancement 10-12 seconds apart for the pulmonary arteries (>200HU) and aorta/coronary arteries (>300HU). One method is to increase the volume of intravenous contrast administered and CPCT requires larger contrast volumes than CTPA. Split bolus protocols have also been trialled.

Figure 1.13: Peak arterial enhancement using a CPCT contrast protocol{Frauenfelder, 2009}



CPCT requires simultaneous, homogenous, and high contrast attenuation (>250 HU) of the pulmonary arteries, the aorta, and the coronary arteries. Dedicated contrast-medium application protocols must take into account the transit time between the pulmonary and aortic/coronary opacification (typical duration 11s)

The literature suggests diagnostic enhancement of the pulmonary arteries is more easily achieved than for the coronary arteries{Halpern, 2009}, nevertheless, with ECG gating, coronary artery images are comparable in quality to dedicated cardiac studies{Halpern, 2009}. Simultaneous evaluation of coronary arteries in high-pitch dual-source CT of the thorax for non-cardiac purposes is consistently diagnostic in patients with low heart rates and heart rate variability (such as can be achieved with β-blockade){Scharf, 2011}.

CPCT protocols make use of a larger field of view than cardiac protocols. Causes of chest pain which manifest in this wider view include pneumonia, pleural effusion, intra-thoracic masses, pericardial effusion, pericarditis, hiatus hernia, oesophageal rupture, pancreatitis and bone fractures{Thoongsuwan, 2002}. The sensitivity of comprehensive CPCT for identifying the cause of chest pain is estimated between 93%{Johnson, 2007} and 87%, with a specificity of 96%{White, 2005}.

The larger volume of anatomy to scan for CPCT necessitates a longer breath hold and an increased radiation burden. The increase in tube current necessary for coronary artery imaging and use of retrospective ECG gating mean the effective dose with CPCT is higher than for examination of the pulmonary arteries or thoracic aorta alone. The effective dose for CPCT is around 50% greater than for cardiac CT.

The role for CPCT in the emergency department remains controversial. Supporting the finding that CCT may increase diagnostic sensitivity and specificity in patients presenting with acute chest pain{Rubinshtein, 2007}, Takakuwa et al. found that CPCT eliminated the need for further diagnostic testing in over 75% of low to moderate risk patients{Takakuwa, 2008}. By contrast, Madder et al. found CPCT resulted in higher radiation exposure than CCT, but was not associated with improved yield, reduced clinical events, or diminished downstream resource use. The composite diagnostic yield was 14% with CPCT, and 16% with CCT. CPCT patients had a 50% higher effective dose, a higher incidence of subsequent emergency attendance, and more downstream CTPA scans{Madder, 2011}.

The application of CPCT in patients with acute dyspnoea has yet to be fully evaluated, despite the fact that many of the pathologies causing dyspnoea are common with those that cause chest pain. A single study by Rogers et al. looked at efficiency of comprehensive CT examination in patients presenting to the emergency department with undifferentiated chest pain/discomfort, or dyspnoea. Patients were randomised to receive CPCT or a dedicated CCT. While CPCT was feasible, with similar diagnostic yield to CCT, it did not reduce length of stay, rates of subsequent testing or cost. The authors concluded that CPCT may be helpful in the evaluation of select patients{Rogers, 2011}.

To date, the consensus appears to be that CPCT can be useful and potentially cost-effective when used appropriately, but further clarity is required regarding protocols to avoid overuse of this technique.

1.6 AIMS OF THESIS

This aims of this thesis were:

- To evaluate the characteristics of patients attending hospital with undifferentiated chest pain and dyspnoea
- To evaluate the role for cardiopulmonary computed tomography in the diagnosis and prognostication of these patients
- To review the use of this imaging modality within the framework of existing UK guidance

CHAPTER 2: GENERAL METHODOLOGY

During the course of this thesis, I personally undertook the duties of study design, ethical approval and funding acquisition, patient identification, recruitment, preparation for CT scanning (including relevant phlebotomy, cannulation and administration of beta-blockade), follow-up, data entry and analysis.

I was supported by a team including clinicians (study design and image interpretation), research nurse specialists (patient identification, follow-up and data entry), data analysts (power analyses and statistical outcome analyses) and the Chelsea and Westminster Research and Development (R&D) Support Office.

2.1 PATIENT SELECTION FOR CT SCANNING INVOLVING CARDIAC PROTOCOLS:

Inclusion criteria for each of the studies in this thesis are detailed in their respective chapters. The exclusion criteria were, however, universal for all studies involving CCT and are listed below.

Table 2.1: Exclusion criteria for cardiac CT protocols

CRITERIA	DETAILED DEFINITION
Age <40years	
Features of acute myocardial infarction	• Consistent ECG: ST elevation/new left bundle branch block • Ongoing chest pain with dynamic ECG changes • Elevated serum troponin I: ≥3µg/ml
Haemodynamic or respiratory instability	• Systolic blood pressure ≤90mmHg • SpO2 ≤92% on supplemental oxygen
Previous percutaneous coronary intervention	• Coronary arerty stent or bypass grafting
Resting heart rate >70bpm	• Including after pharmacologic treatment
Contraindication to negative chronotropic agents if resting HR >70bpm	• Allergy or previous intolerance • Established on verapamil • Sick sinus syndrome, 2^{nd}/3^{rd} degree heart block, history of transient loss of consciousness • Severe aortic stenosis • Restrictive cardiomyopathy
Contraindication to contrast enhanced CT	• Allergy or previous intolerance of iodinated contrast • Renal dysfunction: serum creatinine >150 µmol/l • Pregnancy or childbearing potential
Inability/disinclination to provide written informed consent	

2.2. MDCT SCANNING PROTOCOLS

All CT scans undertaken for this thesis were performed using a 128-slice, single source scanner (Somatom Definition AS+, Siemens Healthcare, Germany). The features of this specific scanner are a gantry rotation of 0.3s, temporal resolution 150ms and spatial resolution 0.33mm for each individual image. A 2m (whole body) scan can be achieved in around 10s.

Three acquisition protocols were used; coronary calcium acquisition, coronary CTA and a combined CPCT acquisition. Scan parameters are detailed in Table 2.2. All scans were performed during inspiratory breath hold. Patients were familiarised with the breath-holding technique prior to scanning.

2.2.1 CORONARY CALCIUM PROTOCOL

Coronary calcium acquisition was undertaken using prospective ECG gating and an unenhanced CT protocol. ECG pulsing interval was at 70% of the R-R interval.

2.2.2 CORONARY CT ANGIOGRAPHY PROTOCOL

Coronary CTA was undertaken using retrospective ECG gating. Images were acquired from the level of the carina to just inferior to the diaphragm.

Angiography was preceded by coronary calcium acquisition for all patients undergoing CTA. Thus, patients underwent an initial scan without contrast and a further scan following triple phase intravenous contrast injection.

Acquisition delay time was determined by the injection of a 15ml test-bolus of contrast at 6ml/sec followed by 40ml saline chaser at 6ml/sec. The time to peak test-bolus enhancement plus three seconds was used as scan delay time. A non-ionic contrast medium (Omnipaque 350; GE Healthcare) was infused via an ante-cubital intravenous catheter at rates as per Table 2.2.

Patients with a heart rate exceeding 70 bpm and no contraindications to beta-blockers received metoprolol tartrate on the scanner table. A starting dose of 5mg was administered by intravenous injection over one minute, followed by a saline flush, with re-administration of the same dose every 2-5 minutes until heart rate was controlled (≤65bpm) or a total dose of 30mg was reached. Heart rate was monitored continuously via an ECG on the CT scanner console. Blood pressure was recorded before and after the administration of beta-blockers and at 15 minute intervals thereafter.

Although rate control agents other than beta-blockers exist, neither calcium channel blockers nor ivabradine were used in the course of the studies in this thesis, in accordance with national guidance{RCP/BSCI/RCR, 2014}.

2.2.3 COMPREHENSIVE CARDIOPULMONARY CT PROTOCOL

CPCT was undertaken using retrospective ECG gating. The protocol differed from the CTA protocol, having a larger field of view to include the entire chest and scanning in a caudal-cranial direction to ensure prompt imaging of the heart post intravenous contrast.

The contrast protocol dispensed with the injection of the contrast-saline mixture used for coronary CTA to avoid dilution of contrast in the right heart for optimum pulmonary arterial opacification.

As per coronary CTA, patients with a heart rate exceeding 70bpm and no contraindications to beta-blockers received metoprolol prior to scanning. Up to six 5mg doses were administered by intravenous injection.

Table 2.2: Scanning parameters for coronary calcium acquisition, CTA and CPCT

CT PARAMETER	CCS	CTA ONLY	CPCT
Tube voltage (kV)	120	120	120
Tube current (mA)	30	500	600
Field of view (mm)	400/250	250	400/250
Collimation (mm)	60x0.6mm	0.60x0.6mm	60x0.6mm
Direction	Cranial-caudal	Cranial-caudal	Caudal-cranial
Time (sec)		8-12	14-15
Test bolus injection	N/A	15ml contrast @ 6ml/sec 40ml saline @ 6ml/sec	15ml contrast @ 6ml/sec 40ml saline @ 6ml/sec
Contrast: Scan acquisition injection protocol	N/A	65ml contrast @ 6ml/sec 40 ml saline @ 6ml/sec	85ml contrast @ 6ml/sec 60 ml saline @ 6ml/sec

2.2.4 RADIATION DOSE REDUCTION STRATEGIES

When possible, prospective ECG gating was used. Dose modulation outside of the acquisition window was adopted for retrospectively gated scanning. Scan ranges were tailored to patient dimensions.

2.2.5 DATA ACQUISITION

All CT data sets were transferred to a dedicated workstation. Images for coronary calcium scoring were reconstructed as 3mm contiguous slices. Images were

reconstructed at an effective thickness of 0.6mm every 0.5mm for CTA and 0.75mm x 0.5mm for CPCT. Using retrospective analysis of R wave timing, scanning phases were reconstructed to allow coronary assessment in the phase of minimal cardiac motion. Phases were reconstructed at 10% increments throughout the cardiac cycle (from 10%-90% of the R-R interval). The best mid-late systolic (20-40% of R-R interval) or mid-late diastolic (50-70% of R-R interval) data set was chosen for final image interpretation.

2.2.6 IMAGE ANALYSIS

All images were analysed and processed by two experienced radiologists in consensus. Any disagreements were settled by consensus, with a third experienced clinician mediating.

2.2.6.1 Coronary artery image analysis

Images of the heart and coronary arteries were reconstructed with a small field of view (120-190 mm), and a medium-smooth convolution kernel (B 26f).

Coronary calcification was identified using a 130 Hounsfield Unit threshold and calculated as an Agatston Score Equivalent. All calcific lesions with an area greater than $1mm^2$ were considered significant for scoring purposes. Total coronary calcium scores were recorded as absolute values and as categories (ASE 0; 1-100; 101-400; >400).

Coronary CTA analysis was performed using a cardiac software package (Syngo.via; Siemens Healthcare, Germany). Axial data sets were supplemented by 3D volume-rendered images, maximum intensity projection, curved multi-planar formats and automated lumen detection algorithms, as indicated.

Coronary anatomy was divided into 16 segments, using a modified version of the traditional 15 segment model{Austen, 1975}, to allow for separate assessment of the intermediate coronary artery, should it exist. Coronary segments were reported as

having no stenosis, non-significant stenosis (<50% luminal narrowing) or significant stenosis (>50% luminal narrowing).

Coronary artery stenosis >50% was chosen as a diagnostic threshold because patients with this degree of obstruction on CT are generally referred for non-invasive or invasive testing to characterise their disease further.

2.2.6.2 Extra-cardiac image analysis

For the evaluation of extra-cardiac pathology, images were reconstructed with a large field of view (>300 mm). Images were reviewed in axial, coronal, and sagittal planes, using a mediastinal window (width: 400, level: 40), lung window (width: 1,500, level: -500), and bone window (width: 3,700, level: 700) for all examinations.

Based on existing models {Kirsch, 2007; Lazoura 2010}, extra-cardiac findings were classified as benign, indeterminate or of clinical significance at the time of image evaluation. Benign findings were those of minimal clinical significance requiring no follow-up. Indeterminate findings were those of potential clinical significance, requiring correlation with the patient's history or a follow-up study. Clinically significant findings were those requiring immediate clinical assessment or intervention. Findings of clinical significance were classified according to ICD-10.

Recognised criteria were used for the assessment of specific extra-cardiac findings. Pulmonary nodules were classified according to Fleischner Society criteria published at the time{MacMahon, 2005}. We accept the limitations of these guidelines in the consideration of sub-solid nodules, both solitary and multiple, which have been addressed in a more recent Statement of the Fleischner Society{Naidich, 2013}. Nodules of less than 8mm diameter with features concerning for malignancy were also considered clinically significant.

Low attenuation areas were labelled as emphysema, while high attenuation areas were labelled as ground glass opacification or consolidation. Interstitial lung disease was characterised by interlobular septal thickening in the absence of evidence of congestive cardiac failure. Pulmonary embolism was characterised by one or more

filling defects in the pulmonary arterial system and a diagnosis of pulmonary hypertension was made if there was dilatation of a main pulmonary artery to a diameter of ≥29mm.

Aortic aneurysm was defined by the diameter of the ascending aorta exceeding 4cm or the diameter of the abdominal aorta exceeding 3.5cm. Lymphadenopathy was considered significant if a node measured ≥1cm in diameter in its short axis. Liver lesions were labelled as cysts if they were smooth and non-enhancing, with the attenuation of water. Nodular, peripherally enhancing liver lesions were labelled as haemangiomas.

2.3 STATISTICAL ANALYSIS

Statistical analysis was performed using Graphpad Software (Prism 6, Instat, StatMate: GraphPad Software, Inc., La Jolla, California USA).

2.3.1 ASSESMENT OF NORMAL DISTRIBUTION (D'Agostino-Pearson test)

There are multiple tests for normal distribution, including the D'Agostino-Pearson test, the Shapiro Wilk test, the Kolmogorov-Smirnov test and the Chi-squared goodness-of-fit test. In this thesis, the D'Agostino-Pearson test was used to compute a single P-value for the combination of the coefficients of Skewness and Kurtosis. D'Agostino developed several normality tests. The one used by Graphpad Prism is the Omnibus K2 test.

2.3.2 TESTS OF DIFFERENCE/MEASUREMENT OF AGREEMENT

For parametric data, the T-test was used to compare mean values for two independent groups or against hypothesised values and analysis of variance (ANOVA) was used to compare means for multiple groups.

For non-parametric data, the Mann Whitney U test was used to compare the median values for two independent groups (e.g. the distribution of CAD likelihood categories between two groups) and the Wilcoxon signed rank test was used for discrete, paired data as the non-parametric analog to the paired t-test. The Chi square test was used to test goodness of fit to a hypothesis or to determine the relationship between

categorical variables (e.g. gender, frequency of cardiac risk factors, nature of chest pain, likelihood of CAD, and frequency of MACE). Fisher's exact test was used instead of the Chi square test when one or more cells had an expected frequency of ≤5.

2.3.3 SIGNIFICANCE TESTING

The P value represents the probability of getting the results obtained, in the event of the null hypothesis being true. Conventional significance is taken as $P<0.05$ and for the purpose of this thesis $P<0.05$ was deemed statistically significant. The P value does not measure the measure the importance of an effect; therefore in large studies a small P value may occur in the context of a minimally significant clinical effect, while in small studies, P may not reach significance even for clinically relevant effects.

2.4 ETHICAL CONSIDERATIONS

All patients involved in prospective research were required to give written informed consent to participate.

As the benefits of CT in patients presenting with acute chest symptoms are not fully known, and there are appreciable risks with regard to radiation and intravenous contrast exposure, age criteria were used to exclude patients from undergoing CT scanning where the technique was less likely to be useful. The incidence of COPD, lung malignancy and coronary artery disease all rise above the age of forty years; aged less than forty these conditions are rare{Chaitman, 1981; Raherison, 2009; ONS 2013}. Patients aged less than forty years were therefore excluded from undergoing CT.

Recently published data suggests that around 1 in 20 patients aged under 45 years undergoing cardiac CT for the investigation of suspected CAD have evidence of obstructive disease{Otaki, 2015}. Whilst the nature of disease in this sub-population, and pathways for appropriate investigation and management warrant further investigation, this was not within the remit of this thesis.

All female patients aged forty to sixty years were required to give the date of their last menstrual period. If uncertain, a urinary pregnancy test was carried out and the result documented in writing.

2.4.1 EFFECTIVE RADIATION DOSE

There is considerable debate regarding the significance of repeated low-level radiation exposure. Stochastic risks of radiation-induced malignancy and heritable genetic disease are the principal concerns. With increasing radiation doses, acute tissue reactions (deterministic effects) become more important.

At a cellular level, exposure to ionising radiation results in the formation of free radicals with the potential to cause chemical damage to DNA. Cells respond by undergoing cell cycle arrest to allow DNA repair. A single unrepaired or misrepaired double strand break can result in DNA mutation or cell death via necrosis or apoptosis. Reactive oxygen species and reactive nitric oxide species also induce cellular stress responses and inflammation with the release of cytokines, growth factors and chemokines. These responses are thought to account for damage occurring in cells not directly irradiated, the so-called 'bystander effect'.

It has been proposed that radiation-induced DNA repair, apoptosis, terminal cell differentiation and immune activation may be adaptive responses to reduce genomic instability and the number of mutated cells in tissues; however, adaptive protection diminishes at radiation doses above 100-200mGy and is not observed following acute exposures in excess of 500mGy{Feinendegen, 2005}. Where radiogenic damage induction occurs unchecked there is increased susceptibility to malignancy, supporting a threshold or hormesis for cancer risk.

There is a paucity of epidemiological data demonstrating excess cancer risk below 100mSv. Since the effective dose from a single cardio-pulmonary CT is lower than this, the potential risk can only be estimated by assuming a dose-response relationship.

The International Committee on Radiological Protection (ICRP) estimates that the radiogenic fatal cancer risk for an adult population is about 5%/Sv or (by using the linear non-threshold dose-response hypothesis) 0.005%/mSv (Table 2.3). Potential radiation risks can be compared to the spontaneous fatal cancer risk (about 20%) and the spontaneous cancer incidence (about 40%). With modern scanners, the

theoretical risk of radiation-induced cancer is therefore low compared with the intrinsic risk of developing cancer{Perisinakis, 2012}.

Table 2.3: Estimation of cancer risk based on radiation exposure{IAEA, 2012}

APPROXIMATE EFFECTIVE DOSE(MSV)	APPROXIMATE RISK PER SCAN OF FATAL RADIOGENIC CANCER[A]
1 mSv	0.005%
2 mSv	0.01%
3-5 mSv	0.015-0.025%
10 mSv	0.05%
25 mSv	0. 125%

[a]Radiogenic cancer incidence is approximately twice the fatal risk.

It is implicit that every possible effort should be made to use low radiation dose protocols. Retrospectively gated CTA is associated with a radiation dose not greater than 15mSv. Prospectively gated late pass acquisition typically delivers a radiation dose around 4mSv. Non-cardiac images acquired simultaneously with cardiac images do not contribute further radiation. The maximum total radiation exposure for patients enrolled in CT studies within this thesis was therefore predicted to be 19mSv.

In actuality, the effective dose for CCT performed at Chelsea and Westminster Hospital was found to be in the range 4-6mSv. Using the accepted ICRP risk factor of 0.005% per mSv for risk of fatal cancer induction{ICRP, 1991}, the maximum excess risk of fatal cancer induction was 0.03% (1 in 3,333), increasing the risk of fatal cancer from 1 in 4.000 to 1 in 3.998.

In the course of studies for this thesis the risk of radiation-induced tissue reactions (e.g. acute radiation syndrome, reproductive impairment, dermatologic lesions, cardiovascular and cerebrovascular disease, and cataract formation) was judged to be negligible as the IRCP have concluded there is no convincing evidence of their occurrence at the effective doses detailed above{ICRP, 2012}.

2.4.1.1 Radiation dose for CPCT versus dedicated angiographic protocols

Although radiation and contrast exposure with CPCT exceed dedicated CT angiographic studies (mean difference in radiation 4.84mSv (95% CI 1.65-8.04mSv)

and contrast 38.0 mL (95% CI 28.1-48.0 mL)){Ayaram, 2013}, CPCT offers additional diagnostic information in patients with symptoms concerning for ACS, acute aortic syndrome and PE and may reduce total radiation burden by reducing the requirement for serial investigations{Halpern, 2009}.

In patients with acute dyspnoea, CPCT was hypothesised to facilitate more rapid detection or exclusion of significant pathology, reduce time to diagnosis, initiation of appropriate treatment and hospital discharge; also to reduce re-admission rates and improve long-term mortality by facilitating targeted treatment of underlying disease. In the context of falling radiation doses with advances in CPCT technology and practice{Takakuwa, 2009}, the overall risk:benefit ratio of CPCT was judged likely to be favourable.

2.4.2 INTRAVENOUS CONTRAST ADMINISTRATION

Omnipaque (350) or an equivalent intravenous contrast medium was used for vascular delineation during CT scanning. As with all contrast media, Omnipaque may be associated with serious, life threatening, anaphylactoid or cardiovascular reactions. Literature produced by GE Healthcare, the manufacturer of Omnipaque, states that approximately 95% of adverse reactions are mild to moderate in degree. Incidence of shock is estimated at one per twenty thousand patients (0.05%) and incidence of death is reported as less than one per ten thousand patients (less than 0.01%).

2.4.3 INCIDENTAL FINDINGS

Clinically significant non-cardiac incidental findings are detected in between 2.8%{Hunold, 2001} and 45.6%{Cademartiri, 2007} of patients undergoing CCT. In one of the largest studies (n = 503), Onuma et al. identified 31 cases of pneumonia, 7 aortic aneurysms, 1 aortic dissection, 2 lung cancers, and 2 breast cancers{Onuma, 2006}. The detection rate is higher for a large field of view, encompassing the entire thorax, versus a small ‘cardiac’ field of view.

CTPAs requested for the exclusion of pulmonary embolism have a high yield of cardiac abnormalities{Foley, 2010}. Few reports of non-coronary findings are available for

CPCT. In a study of 69 patients investigated with CPCT, relevant non-coronary diagnoses were found in three patients, including pericarditis, pneumonia, and pulmonary embolism{White, 2005}. More recently, CPCT evaluation of low to moderate risk ACS patients presenting to the emergency department identified a non-coronary diagnosis that explained the presenting complaint in 11% of patients{Takakuwa, 2008}. All patients undergoing CT during the studies detailed in this thesis were informed that further investigation and follow-up of incidental findings may be required.

2.4.4 ETHICAL APPROVAL

All studies within this thesis went through a process of local review and internal authorisation via the Chelsea and Westminster R&D Support Office and the Trust acted as the Sponsor for all studies.

Research Ethic Committee approval was required and successfully obtained for the following studies:

- Prospective assessment of the utility of CCT in patients admitted with chest pain to the acute medical setting (Chapter 4)
    - Cambridgeshire 1 REC: reference number 09/H0304/64
- Prospective assessment of the utility of CCT in patients presenting with chest pain to the cardiac outpatient setting (Chapter 6)
    - North London REC 1: reference number 10/H0717/33
- Prospective assessment of the utility of CPCT in patients admitted with dyspnoea to the acute medical setting (Chapter 9)
    - North West London REC 1: reference number 10/H0722/12

2.5 FUNDING CONSIDERATIONS

My salary throughout the duration of this thesis was funded by a Research Fellowship Award from the Defence Postgraduate Medical Deanery. In addition, I obtained funding to the total value of £63,600 through a Joint Research Committee Fellowship Award, a Joint Research Committee Small Grant and a Special Award from the Chelsea

and Westminster Health Charity. These funds financed my research activities (including radiology costs) and covered the cost of employing a research nurse specialist for a period of two years.

CHAPTER 3: DEMOGRAPHIC ANALYSIS OF PATIENTS ADMITTED TO HOSPITAL WITH UNDIFFERENTIATED CHEST PAIN AND DYSPNOEA

3.1. INTRODUCTION

With the increasing economic pressures in healthcare, there is a drive to improve the efficiency of care for patients with chest pain and dyspnoea, to minimise delays in targeted therapy, to avoid unwarranted hospital admission or inappropriate discharge and to reduce total costs. Any measures to streamline the patient journey must take into account the prevalence of underlying disease, patient characteristics and the nature of existing clinical practice{Solinas, 2003}.

One of the recognised challenges in generating robust diagnostic algorithms for patients admitted with undifferentiated chest pain and dyspnoea is an absence of information delineating the demographic, biochemical and radiological characteristics of these populations. Furthermore, there is a lack of available information regarding the investigations undertaken and the ultimate diagnoses of these patients. Medical literature tends to focus on definitive diagnosis of patients in whom a preliminary diagnosis or series of differentials has already been proposed.

3.1.1 CHEST PAIN

Chest pain accounts for approximately 1% of general practice attendances{Bosner, 2009}, 6% of emergency department attendances (around 700,000 patient attendances per annum in the UK){Goodacre, 2005} and 20–30% of emergency medical admissions.

Gastrointestinal causes of pain, musculoskeletal problems and psychopathology are identified more frequently in general practice{Klinkman, 1994}; and serious lung diseases and cardiovascular diseases in the hospital attenders{Buntinx, 2001}. Compared with patients with cardiac chest pain, patients with non-cardiac pain are usually younger, less likely to have typical symptoms and more likely to have a normal resting ECG{Sekhri, 2007}.

3.1.2 DYSPNOEA

Studies have documented the prevalence of dyspnoea in different settings with widely variable results. In the community prevalence ranges from 3-25%, in general practice consultations 4%, in medical outpatient clinics 4%, in the emergency department 3%-4% and in acute hospital admissions 15-25%{Mulrow, 1993}. Factors associated with increased prevalence include increasing age, raised body mass index, smoking history and lower socio-economic status{Mulrow, 1993}.

Across the various medical settings, the most common causes of dyspnoea are cardiac or pulmonary in origin{Gillespie, 1994}. In elderly patients presenting to the emergency department, congestive cardiac failure (43%), community-acquired pneumonia (35%), exacerbation of chronic respiratory disease (32%), pulmonary embolism (18%) and acute asthma (3%) are the leading diagnoses{Ray, 2006}. A study of 599 patients attending the emergency department found 209 (35%) had a final diagnosis of cardiac failure, 31 (5%) had an ACS and amongst patients with acute cardiac failure, 12 (6%) had a concomitant acute myocardial infarction{Januzzi, 2005}.

Up to one third of patients have more than one aetiology underlying their breathlessness. Pulmonary dysfunction, particularly COPD, and the use of pulmonary medication often coincides with unrecognised heart failure{McCullough, 2003; Rutten, 2005}

3.1.3 CLINICAL CODING AT CHELSEA AND WESTMINSTER HOSPITAL

The hospital employs non-medical staff to undertake centralised clinical coding duties. The coding team includes 6 qualified and non-qualified clinical coding officers and 2 qualified clinical coding trainers/auditors. Each coding officer is expected to code for multiple, random medical and surgical specialties.

Coding officers use alpha-numeric codes, known as Read Codes, to record clinical conditions and procedures for finished consultant episodes in the emergency department and in-patient admissions. Code selection is based on information from the Full Medical Record (hard copy) and Electronic Patient Record (EPR). A number of

separate systems are accessible to coding staff including radiology, laboratory and endoscopy systems{Chelwest, 2014}.

Accurate maintenance of the Full Medical Record and EPR is the responsibility of medical, nursing and allied health professionals. Within the EPR, medical staff are expected to record working diagnoses for patients admitted via the emergency department and final diagnoses for patients discharged from hospital.

Clinical coding data are validated by regular internal audit and the Payment by Results data assurance framework.

3.2. AIMS

This aims of this study were to:

- Identify the frequency of admissions to Chelsea and Westminster Hospital with undifferentiated chest pain or dyspnoea
- Review the investigative pathways, length of stay and final diagnoses for these patients

3.3 PATIENTS AND METHODS

Chelsea and Westminster Hospital coding data were analysed for the 5 years preceding February 2012. All patients aged over eighteen years admitted to hospital via the emergency department with a primary diagnosis of non-specific chest pain or dyspnoea were identified. Diagnosis was determined according to the Read codes detailed in Table 3.1.

Table 3.1: Read codes for patients with undifferentiated dyspnoea and chest pain

	DESCRIPTOR	READ CODE	ICD CODE
CHEST PAIN	retrosternal chest pain	R065011	R074
	chest discomfort	R065600	R073
	chest pain NOS	R065Z00	R074
	chest pain, unspecified	R065000	R074
	chest tightness	R065800	R073
	pleuritic pain	R065400	R073
	other chest pain	RYU0460	R073
DYSPNOEA	breathlessness	R060D00	R068
	dyspnoea	R060A00	R060
	shortness of breath	R060800	R060

When it became apparent that the number of patients admitted with non-specific dyspnoea was significantly lower than predicted, a second survey was undertaken to identify all patients discharged over the same five year period with discharge Read codes compatible with respiratory disease and/or symptoms of acute dyspnoea (>500 Read codes; Appendix – Tables 1 and 2).

The medical records of all patients admitted with non-specific dyspnoea were reviewed. Data were collated regarding the diagnostic investigations performed during the index admission, hospital length of stay and primary discharge diagnosis for each patient. Discharge diagnoses recorded by hospital coding (Read codes) were compared with those entered by the responsible clinician in the EPR.

A sample of patients with non-specific chest pain, randomly selected using a computerised number generator, and equal in number to the number of patients with non-specific dyspnoea, was compared with the dyspnoea group.

3.4 STATISTICAL ANALYSES

This study was conceived as a scoping exercise in advance of studies detailed later in this thesis. As such, it was not powered to achieve statistical significance.

Patients with chest pain and dyspnoea were compared using descriptive analyses. Clinical and demographic characteristics were summarised as frequency distributions (absolute and as percentages). Comparisons between the groups were performed for

age and length of stay using the independent samples t-test following assessment for normality by the D'Agostino-Pearson test. Gender and frequency of investigations were compared using Chi-square or Fisher's exact tests as appropriate. Length of stay was compared using the Mann Whitney U test.

3.5 RESULTS

According to primary diagnosis coding in the emergency department, a total of 3,907 patients were admitted to Chelsea and Westminster Hospital with undifferentiated chest pain and 38 patients were admitted with undifferentiated dyspnoea over a five year period (Table 3.2). Analysis of discharge coding over the same period demonstrated in excess of 4,600 patients with symptoms of dyspnoea, diagnoses or radiological features with the potential to cause dyspnoea.

Table 3.2: Number of patients admitted with undifferentiated dyspnoea and chest pain (Feb 2008 - Feb 2012)

	DESCRIPTOR	READ CODE	NUMBER OF PATIENTS (% of total)
DYSPNOEA (n =38)	breathlessness	R060D00	4 (10.5)
	dyspnoea	R060A00	5 (13.2)
	shortness of breath	R060800	29 (76.3)
CHEST PAIN (n = 3097)	retrosternal chest pain	R065011	1 (0.03)
	chest discomfort	R065600	1 (0.03)
	chest pain NOS	R065Z00	3085 (99.6)
	chest pain, unspecified	R065000	6 (0.19)
	chest tightness	R065800	2 (0.06)
	pleuritic pain	R065400	1 (0.03)
	other chest pain	Ryu0460	1 (0.03)

Demographic and clinical information for all patients with dyspnoea and a randomised sample of patients with chest pain is shown in Table 3.3. Although no statistically significant differences were found in the age, gender and length of stay of patients in the two groups, patients with dyspnoea were, on average, older than those with chest pain, with a mean difference of 7.11 years (95% CI -1.172 to 15.382 years; P=0.091) and remained in hospital for longer with a mean difference 3.63 days (95% CI -6.7 to -

0.56 days; P=0.066; skewed by 7 patients with dyspnoea who remained in hospital for >15 days).

Table 3.3: Study population characteristics (n=76)

CHARACTERISTIC		DYSPNOEA (%)	CHEST PAIN (%)	P VALUE
No. of patients		38 (100.0)	38 (100.0)	
Gender	Male	18 (47.4)	22 (57.9)	0.491
	Female	20 (52.5)	16 (42.1)	
Age (years)	Mean ± s.d.	63.9 ± 19.2	56.8 ± 16.9	0.091
	Median	68	57	
	Range	22-96	25-94	
Length of stay (days)	Mean ± s.d.	5.4 ± 9.0	1.8 ± 2.9	0.066
	Median	1	1	
	Range	0-33	0-15	

Investigation profiles for both groups are shown in Table 3.4. Routine blood tests (full blood count, renal function and liver function) were performed in over 95% of all patients. There was no statistical difference between the use of D dimer in the two groups (P=0.100) but troponin and CK were measured more frequently in the chest pain group ($p \leq 0.001$ for both). 76% of patients with dyspnoea and 97% of patients with chest pain underwent biomarker analysis for at least one of D dimer, troponin or CK. Imaging with chest radiography was performed in over 90% of patients but CT was used significantly more often in the dyspnoea group (32% vs 11%; P=0.047).

Table 3.4: Diagnostic investigations performed during index admission (n=76)

CHARACTERISTIC		DYSPNOEA (%)	CHEST PAIN (%)	P VALUE
No. of patients		38 (100.0)	38 (100.0)	
LABORATORY	FBC	37 (97.4)	38 (100.0)	1.000
	U&E	37 (97.4)	38 (100.0)	1.000
	LFT	37 (97.4)	37 (97.4)	1.000
	CRP	34 (89.5)	33 (86.9)	1.000
	ESR	2 (5.3)	1 (2.6)	1.000
	D Dimer	19 (50.0)	11 (28.9)	0.0997
	BNP	0 (0)	0 (0)	1.000
	Troponin	14 (36.8)	32 (84.2)	**<0.001**
	CK	7 (18.4)	24 (63.2)	**<0.001**
	GLU	9 (23.7)	16 (42.1)	0.142
	Lipid profile	1 (2.6)	7 (18.4)	0.056
	ANY LABORATORY	37 (97.4)	38 (100)	1.000
BLOOD GAS	Arterial	9 (23.7)	1 (2.6)	0.007
MICROBIOLOGY	Sputum culture	6 (15.8)	1 (2.6)	0.108
	Pleural fluid culture	1 (2.6)	0 (0)	1.000
	Blood culture	2 (5.3)	1 (2.6)	1.000
	Viral screen	1 (2.6)	2 (5.3)	1.000
	TB screen	1 (2.6)	0 (0)	1.000
	Atypical pneumonia screen	3 (7.9)	1 (2.6)	0.615
	ANY MICROBIOLOGY	10 (26.3)	5 (13.2)	0.249
CARDIOLOGY	ECG	16 (42.1)	32 (84.2)	**<0.001**
	ETT	0 (0)	2 (5.3)	0.493
	ECHO	9 (23.7)	6 (15.8)	0.566
	Functional testing	2 (5.3)	1 (2.6)	1.000
	Angiography	0 (0)	1 (2.6)	1.000
	ANY CARDIOLOGY	22 (57.9)	32 (84.2)	**0.022**
RESPIRATORY	Lung function	0 (0)	0 (0)	1.000
	Bronchoscopy	0 (0)	0 (0)	1.000
	ANY RESPIRATORY	0 (0)	0 (0)	1.000
OTHER	OGD	0 (0)	0 (0)	1.000
IMAGING	CXR	35 (92.1)	36 (94.7)	1.000
	CT	12 (31.6)	4 (10.5)	**0.047**
	VQ scan	0 (0)	1 (2.6)	1.000
	MRI	0 (0)	2 (5.3)	0.493
	Doppler	2 (5.3)	0 (0)	0.493
	USS other	2 (5.3)	1 (2.6)	1.000
	ANY OTHER IMAGING	35 (92.1)	36 (94.7)	1.000

Based on discharge coding, no diagnosis was recorded for 63% of patients admitted with chest pain (Table 3.5); the most common diagnoses were coronary artery disease (16%) and musculoskeletal pain (5%). Similarly, in patients admitted with dyspnoea, no diagnosis was recorded for 32% (Table 3.6); the most common diagnoses were

respiratory tract infection (24%), cardiac failure (18%), asthma (5%) and pulmonary embolism (5%). Based on the EPR, 32% of patients with chest pain and 39% of patients with dyspnoea were discharged without a formal diagnosis.

Compared with coding records, the EPR documented a statistically greater proportion of patients as having 'nil abnormal detected' (dyspnoea P=0.025, chest pain P=0.025) but was also more likely to make no attempt to define the reason for admission (dyspnoea P=0.001, chest pain P=0.113). Coding records were more likely to document symptoms without attributing them to a diagnosis (dyspnoea P=0.014, chest pain P<0.001).

Table 3.5: Discharge diagnoses for patients with undifferentiated chest pain (n=38)

DISCHARGE DIAGNOSIS		READ CODE	EPR	P VALUE
Cardiac disorders	Angina	2 (5.3)	8 (21.1)	
	Acute coronary syndrome	4 (10.5)	0 (0)	
	NSTEMI	0 (0)	1 (2.6)	
	Drug induced coronary spasm	0 (0)	1 (2.6)	
	Pericarditis	1 (2.6)	0 (0)	
	Cardiac failure	0 (0)	2 (5.3)	
Musculoskeletal disorders		2 (5.3)	2 (5.3)	
Respiratory disorders	Respiratory tract infection	1 (2.6)	3 (7.9)	
	Asthma/bronchospasm	0 (0)	0 (0)	
	COPD	1 (2.6)	0 (0)	
	Bronchiectasis	1 (2.6)	0 (0)	
	Pulmonary embolism	0 (0)	1 (2.6)	
GI disorders	GORD	1 (2.6)	0 (0)	
	Oesophagitis	0 (0)	1 (2.6)	
	GI malignancy	1 (2.6)	0 (0)	
	Hepatitis	0 (0)	1 (2.6)	
No diagnosis	Symptoms not attributed to disease process	21 (55.3)	3 (7.9)	**<0.001**
	No entry recorded	3 (7.9)	9 (23.7)	0.113
Nil abnormal detected		0 (0)	6 (15.8)	**0.025**

Figure 3.1: Discharge diagnoses for patients with undifferentiated chest pain (n=38)

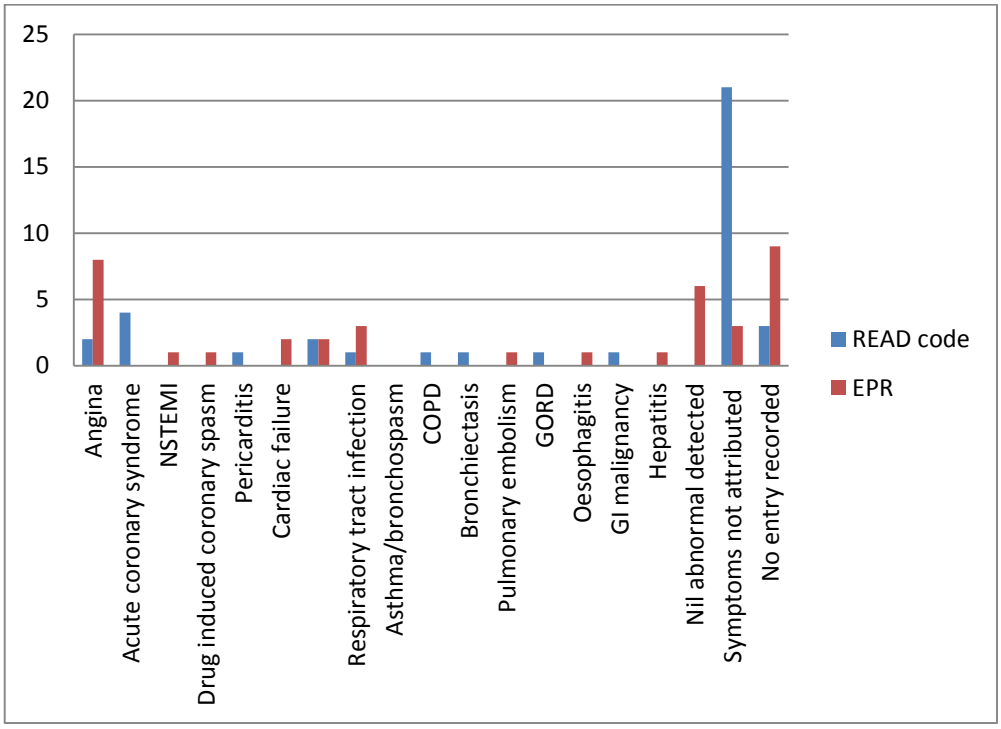
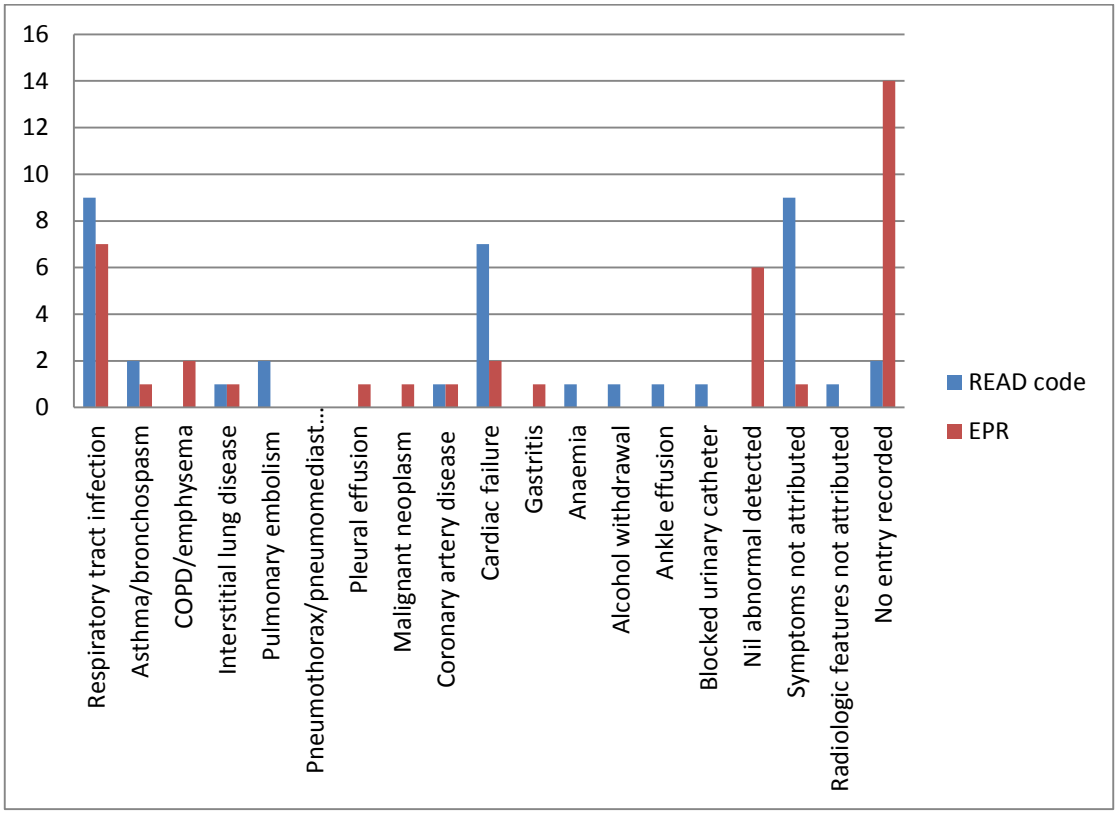


Table 3.6 Discharge diagnoses for patients with undifferentiated dyspnoea (n=38)

DISCHARGE DIAGNOSIS		READ CODE	EPR	P VALUE
Respiratory disorders	Respiratory tract infection	9 (23.7)	7 (18.4)	
	Asthma/bronchospasm	2 (5.3)	1 (2.6)	
	COPD/emphysema	0 (0)	2 (5.3)	
	Interstitial lung disease	1 (2.6)	1 (2.6)	
	Pulmonary embolism	2 (5.3)	0 (0)	
	Pneumothorax/pneumomediastinum	0 (0)	0 (0)	
	Pleural effusion	0 (0)	1 (2.6)	
Thoracic oncology	Malignant neoplasm	0 (0)	1 (2.6)	
Cardiac disorders	Coronary artery disease	1 (2.6)	1 (2.6)	
	Cardiac failure	7 (18.4)	2 (5.3)	
GI disorders	Gastritis	0 (0)	1 (2.6)	
Other	Anaemia	1 (2.6)	0 (0)	
	Alcohol withdrawal	1 (2.6)	0 (0)	
	Ankle effusion	1 (2.6)	0 (0)	
	Blocked urinary catheter	1 (2.6)	0 (0)	
No diagnosis	Symptoms not attributed to disease process	9 (23.7)	1 (2.6)	**0.014**
	Radiologic features not attributed to disease process	1 (2.6)	0 (0)	1.000
	No entry recorded	2 (5.3)	14 (36.8)	**0.001**
Nil abnormal detected		0 (0)	6 (15.8)	**0.025**

Figure 3.2: Discharge diagnoses for patients with undifferentiated dyspnoea (n=38)



3.6 DISCUSSION

This analysis of historical trends in the admission and assessment pathways of patients with undifferentiated chest pain and dyspnoea confirms the routine application of biomarker profiling, x-ray imaging and to a lesser extent CT imaging. Although disparities exist between clinical coding and discharge summary records, this study suggests at least 30-40% of patients with chest pain and dyspnoea are discharged without a formal diagnosis.

In Chelsea and Westminster Hospital, around 52 patients per month (12 patients per week) were admitted via the emergency department with chest pain and no working diagnosis. Despite evidence suggesting that the prevalence of dyspnoea in acute medical admissions is around half that of chest pain{Mulrow, 1993; Skinner 2010}, this study identified fewer than 1 patient per month admitted via the emergency department with undifferentiated dyspnoea. Review of medical discharge coding records suggested the low number of documented admissions was not a true

reflection of clinical practice, given that around 77 patients per month were discharged from hospital with symptoms, radiological features or diagnoses compatible with dyspnoea.

The results indicate a greater tendency for treating clinicians to commit to an early working diagnosis for patients with dyspnoea than for those with chest pain (i.e. before transfer from the emergency department). This is interesting given the potentially life threatening outcomes of incorrect diagnoses in both groups and may reflect the so called 'rule out MI' approach to chest pain, which commonly results in a period of up to twelve hours surveillance with serial ECGs and Tn testing before differential diagnoses are considered.

Analysis of the investigations performed suggests that baseline haematology and biochemistry testing were almost universal. Although diagnosis appeared to occur at an earlier stage for patients with dyspnoea, there was still a reliance on biomarkers to support diagnosis with CRP, D dimer and troponin performed in 90%, 50% and 37% of dyspnoeic patients respectively. Given the evidence supporting the use of BNP in the evaluation of dyspnoea (and the prognostication of ACS and PE){Davis, 1994; Januzzi, 2005; Maisel, 2004}, it was perhaps surprising that BNP was not requested for any patients with undifferentiated dyspnoea. This may reflect the high cost and prolonged laboratory turnaround time when the test was introduced, limiting its role in the acute setting.

Recognising the role of biomarkers to complement clinical assessment and ECG in the diagnosis, risk stratification, triage, and management of patients with suspected ACS{Mueller, 2014}, this study confirmed a high frequency of Tn in use the chest pain group (performed in 84%). The lesser uptake of Tn and ECG testing in the dyspnoea group raises concern for missed CAD, as the EuroHeart data set indicates up to 26% of patients with ACS report predominant breathlessness{Hamaad, 2004} and in a large series of patients referred for evaluation of dyspnoea, 42% of those with dyspnoea alone had ischaemia on stress echocardiography versus 19% of those with chest pain{Bergeron, 2004}.

Given the importance of rapid diagnosis and treatment for conditions such as myocardial infarction, prompt availability of investigation results impacts upon patient satisfaction but also patient safety{Dierks, 2007; Kline, 2007; Guttman, 2011}. The reliance on biomarkers in this study highlights a potential role for bedside biomarker analysis to aid prompt acquisition of results. The Biosite ProfilER (Biosite INC, USA) shortness of breath multi-marker panel is an example of the commercially available options and is used to measure levels of BNP, troponin I, CK-MB, myoglobin and D dimer.

In this study, patients with dyspnoea were more likely to undergo CT during their acute admission than patients with chest pain (P=0.047). The lower use of CT in the chest pain group is likely to reflect the era in which these patients were admitted, when CCT was in its infancy. Nevertheless, the small numbers of patients with chest pain undergoing exercise testing, functional cardiac testing and invasive angiography suggests acute admission episodes were used to risk stratify patients safe for discharge to the community rather than to complete full inpatient cardiac workup. NICE CG95 supports this practice of risk stratification based on Bayesian analysis, while recognising an increasing role for CCT.

Comparison between patient outcomes based on Read codes and EPR discharge summaries demonstrated discrepancies between the two data sets. A recent report on the quality of clinical coding in the NHS highlighted tight deadlines, vacant posts and inexperienced staff as potential causes of coding error that impact on the accuracy of data capture{Capita, 2014}. Our experience was that non-medical coding staff appeared reticent to attribute disease causality. Errors in coding definitive diagnoses may also arise when the quality of source documentation is poor{Capita, 2014} and in this study around one quarter of EPR discharge summary entries were inadequately completed. The implication is that neither method in isolation provided an accurate overview of diagnoses in the study population.

The high proportion of study patients discharged without a diagnosis mirrors recent European findings that one quarter of acute medical admissions leave hospital without the cause of their symptoms being identified{Vest-Hansen, 2014}. If extrapolated to

the 700,000 emergency department admissions for chest pain and approximately 350,000 admissions for dyspnoea, failure to diagnose even one third of these individuals would equate to 346,500 patients per annum at risk of anxiety, delayed or inappropriate investigation and management, hospital re-presentation and ultimately, increased mortality{Pope, 2000; Ray, 2006}.

Evidence-based assessment algorithms have a role in minimising potential harms{Woolf, 1999}. Deficiencies in existing coding systems go part way to explaining the current lack of large scale epidemiological data to support the development and optimisation of algorithms for undifferentiated chest pain and dyspnoea to date. It is important that the NHS continues to improve the quality of its data in a way that benefits patients and improves patient care.

3.7 LIMITATIONS

This study was performed at a single site over a period during which there were significant advances in biomarker and imaging technology, plus the publication of National guidance for the assessment and management of suspected CAD{NICE, 2010}. Furthermore, the number of cases reviewed was small and the dyspnoea cases were non-randomised. While the number of cases of undifferentiated dyspnoea is likely to be underestimated, the number of patients with undifferentiated chest pain may be an over-estimate given the tendency of coding to under-attribute causality. Extrapolation of the results should therefore be with caution.

3.8 LEARNING POINTS

- Over 95% of patients with chest pain and over 75% of patients with dyspnoea undergo biomarker profiling which could be performed using a bedside multi-marker panel. Bedside biomarker analysis may support more rapid diagnosis and treatment in these patients.
- Computed tomography is integral to the assessment of patients with undifferentiated dyspnoea, being performed in around one third of patients.

- Computed tomography is performed in around ten percent of patients assessed for undifferentiated chest pain. This figure may increase with advances in CCT technology and the support of NICE CG95.
- Challenges with the accuracy of medical coding currently limit the role of Hospital Episode Statistics in supporting the development and optimisation of assessment algorithms for patients with undifferentiated chest pain and dyspnoea.

CHAPTER 4: PROSPECTIVE ASSESMENT OF THE UTILITY OF CARDIAC CT IN PATIENTS ADMITTED WITH CHEST PAIN TO THE ACUTE MEDICAL SETTING

4.1 INTRODUCTION

In the past twenty five years the number of general and acute medical beds has fallen by a third{Imison, 2012} while the last decade alone has seen a 37% increase in emergency admissions{HES, 2012}. Hospitals have coped with this increase by reducing average lengths of stay. High event rates and finite facilities for the invasive management of ACS emphasise the clinical and logistical importance of risk stratification in selecting patients safe for discharge.

At present, patients presenting to hospital with chest pain with low likelihood of CAD are often discharged without further investigation while those with high likelihood often proceed directly to invasive coronary angiography. Stratification of patients with intermediate likelihood of CAD remains an important clinical issue as these individuals are at greatest risk of diagnostic uncertainty which may lead to inappropriate discharge or investigation .

CCT is a non-invasive diagnostic test with the ability to detect CAD quickly and accurately{Hamon, 2007, Mowatt 2008, Miller 2008}. A potential role for CCT has been identified in the risk stratification of patients presenting to hospital with chest pain. To date, evidence supporting the early use of CCT has been largely based on studies undertaken in emergency departments in the American healthcare system{Goldstein 2007; Rubinshtein, 2007; Hoffman, 2009; Hoffman, 2012}.

At the time of this study, the value of CCT in acute chest pain was unexplored in the UK setting, where patients with suspected CAD are often managed in acute assessment units whose referrals originate from both general practitioners and emergency departments.

4.2 AIMS

This prospective pilot study was undertaken to assess the feasibility and clinical utility of CCT as an early triage tool in patients admitted to an acute assessment unit with suspected cardiac chest pain and low-intermediate likelihood of CAD.

Specific aims of the study were to:

- Assess the practical challenges of incorporating early CCT into routine care for the target population.
- Assess the impact of CCT-based assessment, relative to standard assessment, on
    - Diagnosis or exclusion of clinically significant CAD
    - Downstream cardiac investigation burden (inpatient and outpatient)
    - Hospital attendances and admissions with chest pain
    - Incidence of major adverse cardiovascular events (MACE)[a]

[a] Major Adverse Cardiac Events defined as any of unstable angina, acute myocardial infarction, urgent coronary revascularisation, life threatening dysrhythmia, stroke, and cardiac death

4.3 PATIENTS AND METHODS

Patients who presented to the acute assessment unit of Chelsea and Westminster Hospital with suspected cardiac chest pain over a four month period from November 2009 were screened for entry to the study.

Chest pain was categorised as non-anginal, atypical or typical for angina (see Chapter 2). Pre-test likelihood of CAD was determined using a nomogram based on modified Diamond-Forrester criteria (Table 4.1){Diamond, 1979}. Low pre-test likelihood was defined as <10%, intermediate 10-90% and high likelihood >90%, in accordance with the ACC/AHA 2002 Guideline Update for Exercise Testing{Gibbons, 2006}. Patients with a high likelihood of CAD or Tn I ≥3μg/ml at 12 hours were excluded from the study.

Table 4.1: Percentage likelihood of CAD according to modified Diamond-Forrester criteria{Diamond, 1979}

	TYPICAL ANGINA		ATYPICAL ANGINA		NON-ANGINAL	
Age (years)	**male**	**female**	**male**	**female**	**male**	**Female**
30–39	67	26	22	4	5	1
40–49	87	55	46	13	14	3
50–59	92	80	59	32	22	8
60–69	94	91	67	54	28	19

Additional standard exclusion criteria for studies including CCT are detailed in Chapter 2. Patients were also excluded if CCT could not occur within 24 hours of admission. Thus, recruitment was based on a convenience sample of patients admitted between 10am on Sunday and 4pm on Friday each week.

Eligible patients were discussed with the cardiology team and excluded from scanning if CCT was felt not to be in the patients' best interests (e.g. patients with non-cardiac chest pain or a high risk of CAD based on the cardiologist's clinical impression). Enrolled patients underwent CCT, comprising CCS and CTA, according to the protocol detailed in Chapter 2. CCT results were made available to the cardiology team, who were solely responsible for further management.

An age and sex-matched historical cohort was selected from patients attending the acute assessment unit with suspected cardiac chest pain and no history of percutaneous cardiac intervention in the year prior to the study, for whom investigation did not include CCT. Where there was no exact age match, a patient as close as possible in age was selected.

The two cohorts were classified as CCT-Y (patients who underwent CCT) and CCT-N (the historical cohort).

Data relating to clinical presentation, demographics, risk factor profiles (i.e. diabetes mellitus, smoking history, hyperlipidaemia and hypertension) and clinical course were collated for all patients. Medical records were reviewed to obtain results of all diagnostic tests performed during the hospital admission and in the 3 months post admission. Downstream investigations were defined as all cardiac tests occurring from admission to completion of follow-up.

Final diagnosis and diagnosis of MACE was based on the judgment of 2 clinicians with access to all clinical and laboratory data, including the results of conventional serial troponin measurements, stress tests and invasive angiography, through 3 months of follow-up.

Following publication of NICE CG95 in March 2010, post-hoc risk stratification was performed for all patients to determine likelihood of CAD based on NICE criteria.

4.4 STATISTICAL ANALYSIS

The study was conceived as a feasibility study and was therefore not powered to achieve statistical significance. It was intended that the study would recruit 20 patients over a three month period. Although the recruitment period was extended to four months, the recruitment target was not met.

The two cohorts were compared using descriptive analyses. Clinical and demographic characteristics were summarised as frequency distributions (absolute and as percentages). Following assessment for normality by the D'Agostino-Pearson test, comparisons between the two groups were performed for age using the independent samples t-test. Gender, nature of chest pain, likelihood of CAD, frequency of cardiac risk factors, and frequency of cardiac investigations and MACE were compared using Chi-square or Fisher's exact tests as appropriate. Additionally, the overall distribution of the CAD likelihood categories between the two groups and length of stay were compared using the Mann-Whitney U test.

4.5 RESULTS

4.5.1. Patient population

A total of 198 patients with suspected cardiac chest pain were screened during the enrolment period (Table 4.2). Exclusion criteria were identified in 106 (54%). A further 78 patients (39%) were either selected to pursue standard clinical care by the cardiology team (n=37), declined to participate (n=18), or could not complete the CCT examination (n=23). Ultimately, 14 patients (7%) were scanned.

Table 4.2: Recruitment analysis (n=198)

Number of patients screened (% of total)	**198 (100.0)**
Number of patients found to be ineligible (% of total)	**106 (53.5)**
Reasons for ineligibility[a] (% of total)	
age <40yrs	12 (6.1)
likelihood of CAD >90%	33 (16.7)
features of AMI	20 (10.1)
haemodynamic/respiratory instability	4 (2.0)
previous coronary intervention	44 (22.2)
resting heart rate >70bpm	9 (4.5)
allergy/intolerance of iodinated contrast	3 (1.5)
renal dysfunction	7 (3.5)
pregnancy	4 (2.0)
unable to provide written consent	16 (8.1)
Number of potentially eligible patients not scanned (% of total)	**78 (39.4)**
Reasons for non-scanning (% of total)	
excluded by cardiologist	37 (18.7)
CCT not possible within 24 hours/prior to discharge	23 (11.6)
declined written consent	18 (9.1)
Number of patients recruited (% of total)	**14 (7.1)**

[a] often more than one factor per patient - 42 patients with >1 exclusion criteria

Reasons for exclusion by the cardiology team were a clinical diagnosis of non-cardiac chest pain (n=24) or a perceived high risk of significant CAD (n=13) warranting invasive angiography as first line management, based on clinical acumen.

Reasons for declined consent were self-discharge from hospital (n=7), unwillingness to undertake inpatient investigations (n=5), inability to decide whether to have CCT (n=2), and concerns regarding radiation (n=3) and intravenous contrast exposure (n=1).

13 patients were discharged from hospital before they could undergo CCT and scanning was not possible within 24 hours of admission for a further 10 patients. The limitations to scanning within 24 hours included delays in troponin result availability, delays in the availability of past medical records and CCT scanner non-availability. The mean time from admission to CCT was 1218 ± 249mins (20hrs 18min; range 815-1623mins).

Demographic information for the CCT-Y and CCT-N cohorts is detailed in Table 4.3. There were no statistical differences between the cohorts with respect to age, gender,

risk factor profiles or likelihood of CAD (measured by both Diamond-Forrester and NICE criteria).

Table 4.3: Study population characteristics (n=28)

CHARACTERISTIC		TOTAL	CCT-Y	CCT-N	P VALUE
No. of patients		28 (100.0)	14 (100.0)	14 (100.0)	
Gender	Male	16 (57.1)	8 (57.1)	8 (57.1)	1.000
	Female	12 (42.9)	6 (42.9)	6 (42.9)	
Age	Mean ± s.d.	63.5 ± 12.03	63.5 ± 12.28	63.5 ± 12.23	1.000
	Median	62.5	62.5	62.5	
	Range	42-85	42-85	42-85	
Cardiac risk factors	NICE risk factors[a]	25 (89.3)	12 (85.7)	13 (92.9)	1.000
	Hypertension	19 (67.9)	9 (64.3)	10 (71.4)	1.000
	Reported CAD	4 (14.3)	3 (21.4)	1 (7.1)	0.596
	Family history of CAD	12 (42.9)	6 (42.9)	6 (42.9)	1.000
Nature of chest pain	Non-anginal	12 (42.9)	4 (28.6)	8 (57.1)	0.252
	Atypical angina	14 (50.0)	10 (71.4)	4 (28.6)	0.057
	Typical angina	2 (7.1)	0 (0.0)	2 (14.3)	0.482
Likelihood of CAD – Diamond-Forrester (%)	<10	2 (7.1)	1 (7.1)	1 (7.1)	1.000
	10-90	24 (85.7)	13 (92.9)	11 (78.6)	0.596
	>90	2 (7.1)	0 (0.0)	2 (14.3)	0.482
Likelihood of CAD - NICE (%)	10-29	3 (10.7)	2 (14.3)	1 (7.1)	1.000
	30-60	10 (35.7)	5 (35.7)	5 (35.7)	1.000
	61-90	13 (46.4)	5 (35.7)	8 (57.1)	0.450
	>90	2 (7.1)	2 (14.3)	0 (0.0)	0.482
Length of stay (hrs)	Mean ± s.d.	63.32 ± 80.0	73.5 ± 101.4	53.14 ± 52.23	
	Median	31	29	32	0.944
	Range	0-388	16-388	0-186	
Downstream investigations	ETT	3	0	3	0.222
	CCS	14	14	0	**<0.001**
	CTA	13	13[b]	0	**<0.001**
	Functional	2	2	0	0.482
	IC A	9	3	6	0.420

	Total	41	32	9	**<0.001**
0-3 months post admission	Re-presentation to ED with chest pain	4	2	2 [c]	1.000
	Re-admission with chest pain	3	2	1	1.000
	MACE	0	0	0	1.00
Adjudicated diagnosis	CAD diagnosed	7 (25.0)	4 (28.6)	3 (21.4)	1.00
	CAD excluded	18 (64.3)	10 (71.4)	8 (57.1)	0.694
	Inconclusive	3 (10.7)	0 (0.0)	3 (21.4)	0.222

[a]Cardiac risk factors used to define patients at high risk for CAD using the NICE algorithm are any one of diabetes mellitus, smoking or hyperlipidaemia (total cholesterol >6.47mmol/l).

[b] One patient underwent CCS without CTA; decision undertaken by radiologist based on elevated CCS. All scans were of diagnostic quality.

[c] One patient attended the emergency department on two occasions

4.5.2 Clinical outcomes

CAD was diagnosed in 29% (n=4) and excluded in 71% (n=10) of the CCT-Y cohort. 75% of patients with clinically significant CAD had abnormal findings on CCT. The diagnostic yield with CCT was 21%. Imaging demonstrated 29% (n=4) had no evidence of CAD, 43% (n=6) had mild plaque burden but no significant stenosis, 14% (n=2) had mild plaque burden with significant stenosis, and 7% (n=1) had significant plaque burden with significant stenosis (one patient with significant plaque did not complete CTA).

CAD was diagnosed in 21% (n=3) and excluded in 57% (n=8) of patients investigated without CCT, leaving 21% (n=3) without a definitive diagnosis. Statistical analysis demonstrated no difference in the diagnostic ability of CCT-based assessment, relative to standard assessment (P=0.222).

Over the three month follow-up period, no patients suffered a MACE.

Figure 4.1: Incidental clinical findings (ICFs) identified on CCT

- 2 ICFs identified in a single patient undergoing CCT (n=1/14; 7%)
- chronic unilateral pleural effusion: no action required
- calcified pulmonary nodule: no action required

4.5.3 Resource utilisation

Downstream investigations are detailed for each cohort in Tables 4.4 and 4.5. None of the CCT-Y cohort underwent ETT versus 21% of the CCT-N cohort (P=0.222). Half as many patients in the CCT-Y cohort underwent invasive angiography as in the CCT-N cohort (21% versus 43%; P=0.420). Both these difference were non-significant.

Table 4.4: Individual demographics, investigations and diagnostic outcomes for CCT-Y cohort (n=14)

Patient No	Age	Gender	Likelihood of CAD	CCS	CTA	In-patient ix	Discharge diagnosis	Out-patient Ix	Final diagnosis
1	42	M	14	0	NAD	-	Non-CAD	-	Non-CAD
2	47	F	3	0	NAD	-	Non-CAD	-	Non-CAD
3	52	M	59	3.9	NAD	-	Inconclusive	Functional	Non-CAD
4	57	M	22	3.4	NAD	-	Non-CAD	-	Non-CAD
5	59	M	22	1	NAD	-	Non-CAD	-	Non-CAD
6	60	M	67	114	Significant	-	CAD	ICA	CAD
7	62	F	54	6.1	NAD	-	Non-CAD	-	Non-CAD
8	63	M	67	36.4	NAD	ICA	CAD	-	CAD
9	65	F	54	0	NAD	-	Non-CAD	-	Non-CAD
10	69	F	54	0	NAD	-	Non-CAD	-	Non-CAD
11	70	F	>54	9	Non-Significant	-	Non-CAD	-	Non-CAD
12	79	F	>54	45	Significant	ICA	CAD	-	CAD
13	79	M	>67	946	-	-	Inconclusive	Functional	Non-CAD
14	85	M	>67	3847	Significant	-	CAD	-	CAD

(Ix – investigations; CCS - coronary calcium score; CTA – CT angiography; ETT – exercise tolerance test; ICA – invasive coronary angiography)

Table 4.5: Individual demographics, investigations and diagnostic outcomes for CCT-N cohort (n=14)

Patient	Age	Gender	Likelihood of CAD	In-patient ix	Discharge diagnosis	Out-patient Ix	Final diagnosis
1	42	M	14	ICA	CAD	-	CAD
2	48	F	3	-	Inconclusive	-	Inconclusive
3	51	M	59	ETT + ICA	Non-CAD	-	Non-CAD
4	57	M	22	ETT	Non-CAD	-	Non-CAD
5	59	M	22	ICA	CAD	-	CAD
6	60	M	28	ETT	Non-CAD	-	Non-CAD
7	62	F	91	-	Inconclusive	-	Inconclusive
8	63	M	28	-	Non-CAD	-	Non-CAD
9	65	F	54	ICA	CAD	-	CAD
10	68	F	91	-	Inconclusive	ICA	Non-CAD
11	72	F	>54	ICA	Non-CAD	-	Non-CAD
12	79	F	>54	-	Non-CAD	-	Non-CAD
13	78	M	>28	-	Inconclusive	-	Inconclusive
14	85	M	>28	-	Non-CAD	-	Non-CAD

(Ix – investigations; ETT – exercise tolerance test; ICA – invasive coronary angiography)

Despite significantly fewer investigations performed overall in the CCT-N cohort ($P<0.001$), the high cost of invasive angiography meant investigation costs per capita were higher in this cohort. The relative decrease in cost using a CCT approach was 14% (Table 4.6).

Table 4.6: Investigation costs per capita{NICE, 2010}

INVESTIGATIONS	TOTAL POPULATION (cost £)	CCT-Y (cost £)	CCT-N (cost £)
ETT (£66)	198	0	198
Ca SCORE (£103)[a]	1442	1442	0
Functional (£293)	586	586	0
ICA (£850)	7650	2550	5100
Total cost	9876	4578	5298
Cost per capita	**352.71**	**327.00**	**378.43**

[a] counting either or both of CCS and CTA as single entity

The use of early CCT neither prolonged nor reduced length of stay significantly. Mean length of stay appeared longer for the CCT-Y cohort but median values for the two cohorts were comparable, highlighting the impact of a single patient who remained in hospital for 388hrs on the CCT-Y mean.

There was no significant difference between the two cohorts regarding the frequency of subsequent emergency department attendance (P=1.000) or admission with chest pain (P=1.000).

4.6 DISCUSSION

This small scale pilot study highlighted clinical and logistical challenges to the introduction of CCT in the acute medical setting. Although the study did not demonstrate a statistically significant clinical or resource benefit to the use of early CCT, clinically relevant CAD was ultimately diagnosed or excluded in a greater proportion of patients undergoing CCT. There was increased diagnostic testing amongst the CCT cohort but costs were less than for standard assessment. These results were achieved without a detected increase in MACE.

Despite broad study inclusion criteria, around half of patients presenting to the acute assessment unit were ineligible for CCT and fewer than 10% reached the scanner. The most common reasons for ineligibility were a history of known CAD with previous coronary intervention (22%), a high pre-test likelihood of CAD (>90% likelihood based on modified Diamond-Forrester criteria) (17%), or features of acute myocardial infarction (10%). The findings suggest a degree of risk stratification occurred upstream of the acute assessment unit (i.e. in the emergency department) and that patients who were admitted were those at higher risk of significant cardiac pathology. There may also have been some misjudgement of risk using the Diamond-Forrester model which overestimates the prevalence of CCT-detectable disease in European populations, especially in women{Cheng, 2011; Genders, 2011}.

Traditionally, patients with likelihood of CAD 0-90% have been considered low-intermediate risk and there are data to support the use of CCT to triage these patients{Athappan, 2010; Singer, 2012; Samad, 2012}; however, NICE CG95 concludes there is insufficient evidence to recommend CCT for the intermediate population over better established functional testing methods and invasive coronary angiography. While adoption of NICE CG95 may have the beneficial effect of minimising diagnostic test selection based on clinical acumen and personal preference, the proportion of

patients eligible for CCT using NICE criteria may be even lower than this study would suggest.

Logistic barriers to the introduction of CCT in acute admissions, highlighted in this study, may be overcome by allowing patients unkeen for inpatient investigations, discharged from hospital or unable to be scanned within 24 hours to return for outpatient scanning within a limited time period. In the emergency department setting, CCT within 72 hours of discharge has been shown to be safe{Raju, 2014}. In a non-research context, a CCT service may also have dedicated time slots available for acute admissions, to facilitate timely scanning of these patients.

Tackling CCT non-availability is an important challenge. Although CCT services are becoming more widespread, they are by no means universal and tend not to be operational outside working hours. A recent emergency department study, performed in a unit with standard business hours CCT availability, demonstrated CCT was associated with shorter length of stay amongst low-risk chest pain patients ($p < 0.0001$) but only for patients presenting to hospital between 8 and 12 am{Mahler, 2013}. Thus, CCT availability may impact on the clinical utility of the investigation.

In our study population, compared with standard care, a diagnostic approach incorporating CCT resulted in a greater proportion of patients for whom CAD was either diagnosed or excluded (100% versus 79%; P=0.222). The strength of CCT appeared to be in the exclusion of CAD, although this was not confirmed statistically (P=0.694). The findings suggest clinicians acknowledged the strong negative predictive value of CCT but were less inclined to exclude CAD on the basis of standard assessment, potentially due to concerns regarding the specificity of traditional investigations or the fear of under treatment.

Prior to recent advances in CCT technology, including the development of CT myocardial perfusion imaging and CT fractional flow reserve, CCT was limited to providing anatomical but not functional assessment; however, information on the presence of anatomical CAD is still relevant to clinical decision making about invasive angiography{Shreibati, 2011; Hoffman, 2012, Douglas, 2015}. This study

demonstrated a non-significant reduction in invasive angiography following CCT but an increased frequency of functional imaging, potentially reflecting clinician uncertainty in the hemodynamic significance of a positive CCT result. Consistent with published data suggesting early CCT leads to increased downstream testing{Hoffman, 2012}, a greater total number of investigations were performed in the CCT cohort; however, fewer invasive angiography procedures resulted in lower cardiac investigation costs per capita (16% decrease; £327.00 versus £378.43).

Average length of stay appeared greater in the CCT cohort but median length of stay was comparable for the two approaches, highlighting the impact of a single patient in the CCT cohort who remained in hospital for a prolonged period. The absolute rate of MACE in the study population, over a three month period of follow-up, was zero, suggesting patients managed with a CCT approach were no more likely to experience MACE than those receiving standard care. Similarly, there were very few hospital re-attendances or re-admissions with chest pain meaning the study did not have the statistical power to support the conclusion that hospital readmission may be reduced after CCT-based evaluation.

Finally, this study was conceived and completed prior to the release of NICE CG95. A separate study, based on the same, well-defined population, was subsequently performed to evaluate the consequences of adopting NICE CG95 on the uptake of CCT in acute cardiac admissions (Chapter 5).

4.7 LIMITATIONS

The primary limitation of this study was that it analysed a small patient population in a single centre using a convenience sample. In part, this reflects its origins as a feasibility study but also, obstacles to recruitment which led to termination of the study before the intended number of patients were recruited.

Furthermore, CCT enrolment occurred only during weekday daytime hours when all imaging testing was available, with radiographers and readers on site, to allow rapid reporting and triage decision making. In reality, testing and interpretation are not

accessible around the clock and there is likely to be a resultant impact on the timing of decisions to discharge patients.

As such, caution is advised when considering the generalisability of the results to similar care settings. Large scale diagnostic studies are needed to provide a definitive answer as to whether CCT has a role within an integrated diagnostic strategy for patients admitted acutely to hospital with chest pain and the health economic implications of such a strategy. Extending the period of study follow-up beyond early discharge and more broadly exploring the downstream effects of CCT (e.g. the composite financial contribution of evaluation, monitoring, full investigation and therapy and the impact on quality-adjusted-life-years) is necessary to recognise scenarios in which CCT does, and does not, add 'value'.

Given the limitations of the Diamond-Forrester model of risk stratification, future studies may be better served using the extended predictive models of Genders et al.{Genders, 2011} or the assessment and early management models proposed by NICE CG95 and the European Society of Cardiology{Montalescot, 2013}. The adoption of such evidence-based models may also serve to minimise bias arising from variation in practice between individual cardiologists, encourage clinicians to keep patients in hospital to undergo CCT where indicated and encourage patients to undergo recommended investigations, avoiding the high rates of drop out seen in this study.

Restrictions on local recruitment may be addressed through engagement in multi-centre trials.

4.8 LEARNING POINTS

- Up to 50% of patients admitted to the acute assessment unit with low-intermediate likelihood of CAD are potentially eligible for CCT.
- For CCT to add incremental benefit to the data available to clinicians, investment to provide a 24 hour a day, seven day a week scanning and interpretation service should be considered, even though the number of patients scanned may be relatively small.

- CCT within 72 hours post discharge may negate logistical issues surrounding inpatient scanning.
- A diagnostic algorithm incorporating CCT may enhance the ability of clinicians to diagnose or exclude CAD relative to standard assessment.
- A diagnostic algorithm incorporating CCT may lead to increased diagnostic testing but without an associated increase in cost.
- Locally agreed, evidence-based protocols will minimise under- and over-utilisation of the technique. In the future, it is likely these protocols will be based around NICE guidance.

CHAPTER 5 RETROSPECTIVE ANALYSIS OF THE UTILITY OF CARDIAC CT IN THE ACUTE MEDICAL SETTING IN ACCORDANCE WITH NICE GUIDELINE CG95

5.1 INTRODUCTION

Chapter 4 elaborated upon the potential benefits and challenges of adopting CCT in the UK acute medical setting, based upon a broad inclusion policy with patient selection guided by the acumen of cardiologists on the ground. NICE CG95, published in March 2010 sought to formalise the risk stratification of patients with suspected CAD, to support a unified cost-effective and evidence-based approach to investigation, incorporating CCT for selected patients.

NICE CG95 is primarily intended for the management of patients with suspected CAD in the outpatient setting but is also applicable to patients with acute chest pain in whom ACS is excluded but myocardial ischaemia is still suspected (a common scenario on the acute assessment unit). The guideline is subdivided into acute and stable chest pain algorithms.

NICE CG95 advocates risk stratification of patients with suspected *stable* CAD using an amalgamation of the modified Diamond-Forrester (DF) criteria described previously and the Duke clinical score that incorporates the presence of diabetes mellitus, smoking history and hyperlipidaemia.

Patients with a history of non-anginal chest pain are not routinely recommended for further cardiac investigation. Those with a history of atypical or typical cardiac chest pain and a likelihood of CAD between 10 and 90% should be investigated further.

CCT is recommended for a patients with a likelihood of CAD in the range 10-29%; effectively 1) men aged 40-49 years with atypical angina and no cardiac risk factors, 2) women aged 50-69 years with atypical angina and no cardiac risk factors, or 3) women aged less than 50 years with typical angina and no cardiac risk factors. CCT in this context comprises CCS with progression to CTA if there is a significant calcified plaque burden.

At the time of this study, there were no published data regarding the impact of the NICE CG95 on acute cardiac investigation services and the requirement for acute CCT provision to meet NICE CG95 was unproven.

5.2 AIMS

This retrospective study reviewed the demographic and clinical characteristics of patients admitted to the acute assessment unit with suspected cardiac chest pain, to evaluate the impact of NICE CG95 on our local population.

Specific aims of the study were to:

- Determine the distribution of CAD likelihood amongst acute medical admissions with suspected cardiac chest pain, according to NICE CG95 criteria.
- Review the investigation burden on inpatient cardiac services if NICE CG95 were applied to this population.

5.3 PATIENTS AND METHODS

Patients who presented to the acute assessment unit of Chelsea and Westminster Hospital with suspected cardiac chest pain over a four month period from November 2009 were screened as detailed in Chapter 4.

Data relating to clinical presentation, demographics, risk factor profiles (i.e. diabetes mellitus, smoking history, hyperlipidaemia and hypertension) and clinical course were collated for all screened patients. The data set was used as the basis of analysis for the current study, in which NICE CG95 was applied retrospectively to the population.

Patients with evidence of ACS (positive troponin I, ischaemic ECG changes) or a history of known CAD with previous coronary intervention were excluded from further analysis.

Chest pain was categorised as non-anginal, atypical or typical for angina. Pre-test likelihood of CAD was determined using a nomogram based on NICE CG95. Patients were deemed eligible for investigation if they had typical or atypical anginal chest pain and a likelihood of CAD in the range 10-90%; those in the range 10-29% (i.e. low risk)

were eligible for CCT; those in the range 30-60% (i.e. intermediate risk) were eligible for functional testing and those in the range 61-90% (i.e. high risk) were eligible for invasive coronary angiography in accordance with NICE CG95.

5.4 STATISTICAL ANALYSES

Clinical and demographic characteristics were summarised as frequency distributions (absolute and as percentages).

5.5 RESULTS

A total of 198 patients with suspected cardiac chest pain (median age 63 years, range 21-96 years, male: female ratio 1.3:1) were screened over the four-month period. Demographic and clinical information is shown in Table 5.1. The distribution of CAD likelihood according to nature of chest pain, gender, risk and age is shown in Table 5.2.

Table 5.1: Study population characteristics (n=198)

CHARACTERISTIC		TOTAL
No. of patients		198 (100)
Gender	Male	113 (57.1)
	Female	85 (42.9)
Age	Mean ± s.d.	63.54 ± 16.52
	Median	63
	Range	21-96
Cardiac risk factors	NICE risk factors[a]	155 (78.3)
	Hypertension	119 (60.1)
	Reported CAD	91 (46.0)
	Family history of CAD	47 (23.7)
Nature of chest pain	Non-anginal	100 (50.5)
	Atypical angina	55 (27.8)
	Typical angina	43 (21.7)
Likelihood of CAD – NICE (%)	<10	21 (10.6)
	10-29	27 (13.6)
	30-60	52 (26.3)
	61-90	55 (27.8)
	>90	43 (21.7)
Recommended cardiac investigations - NICE	No investigation	144 (72.2)
	ETT	0 (0.0)
	CCS/CTA	2 (1.0)
	Functional	12 (6.1)
	IC A	17 (8.6)

[a] Cardiac risk factors used to define patients at high risk for CAD using the NICE algorithm are any one of diabetes mellitus, smoking or hyperlipidaemia (total cholesterol >6.47mmol/l).

Table 5.2: Distribution of study population according to age, sex and nature of chest pain (n=198)

Age (years)	Non Anginal				Atypical				Typical			
	M		F		M		F		M		F	
	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
<30	2	3	1	-	-	1	-	-	-	-	-	-
30-39	2	3	-	-	-	-	-	-	-	-	-	-
40-49	3	10	4	2	1	2	1	-	-	6	-	-
50-59	4	11	1	2	1	4	1	5	1	5	2	2
60-69	1	3	4	8	1	6	-	7	-	9	1	3
>70	6	12	7	11	1	10	3	11	1	4	2	7

White: Not routinely recommended for further investigation

Dark grey: Likelihood of CAD 10-29% - recommended for CCT

Mid grey: Likelihood of CAD 30-60% - recommended for functional cardiac testing

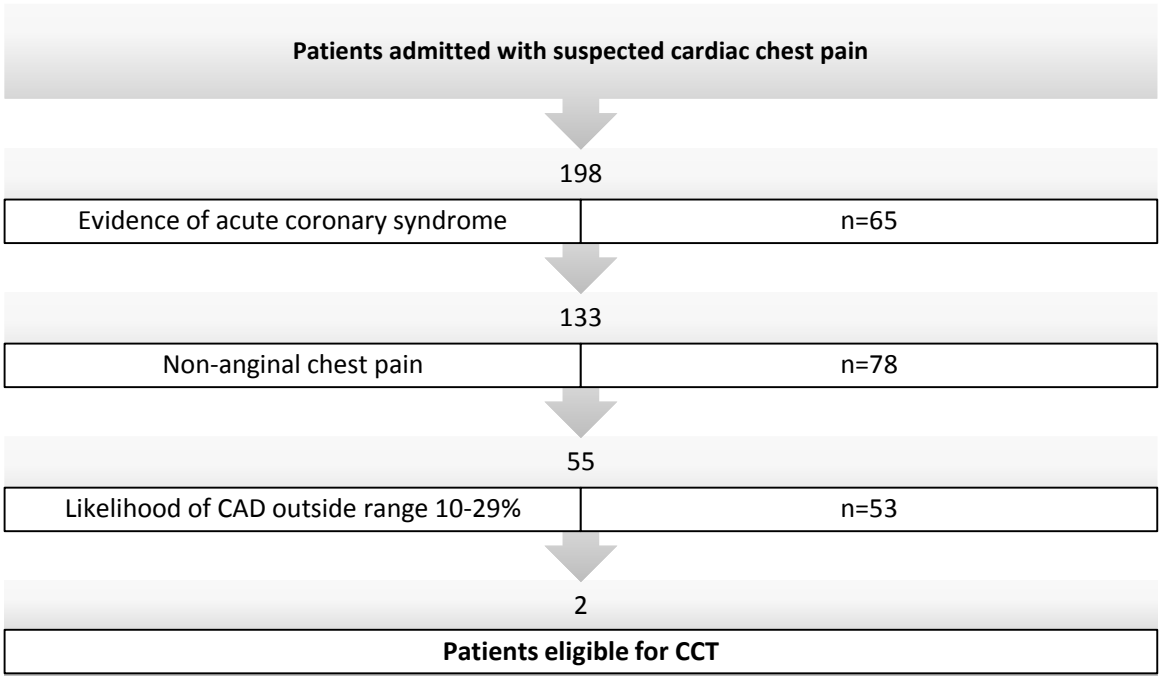
Light grey: Likelihood of CAD 61-90% - recommended for invasive angiography

33% (n=65) would have been excluded from the NICE stable chest pain algorithm by a raised troponin I or ischaemic ECG changes. A further 22% (n=44) would have been excluded as a result of previous coronary intervention.

51% (n=101) of patients would have been recommended for no routine cardiac investigation based on pain classified as non-anginal (n=80), a likelihood of CAD <10% (n=1) or both (n=20). 21.7% (n=43) would have proceeded directly to treatment without investigation, based on a likelihood of CAD >90%.

1% (n=2) of patients would have been recommended for CCT (Figure 5.1), 6% (n=12) for functional cardiac testing and 9% (n=17) for invasive coronary angiography. If the criteria for CCT had been broadened to include patients at intermediate risk of CAD, with a likelihood 10–60%, 7% (n=14) of patients admitted would have been eligible for the investigation.

Figure 5.1: Eligibility for CCT in patients admitted with suspected cardiac chest pain



5.5 DISCUSSION

NICE CG95 currently recommends CCT only for those patients with atypical or typical angina and a low risk of CAD with pre-test likelihood in the range 10-29%. These criteria alone would have excluded over 95% of patients admitted with suspected cardiac chest pain and potentially undervalued CCT as a diagnostic tool. Although there is evidence to support the broadening of CCT inclusion criteria to include patients at intermediate risk of coronary artery disease{van Werkhoven, 2009; Gopal, 2009}, NICE favour functional testing and invasive coronary angiography. In our local population, uptake of functional cardiac testing would have been around six times higher and invasive coronary angiography around nine times higher than for CCT.

NICE CG95 predicts that 'around' 29% of patients have a likelihood of CAD <10%, 11-17% have a likelihood 10-29%, 17-18% have a likelihood 30-60%, 15% have a likelihood 60-90% and 6-9% have a likelihood >90%{NICE, 2010}. These figures are based on outpatient data and it is unsurprising that they underestimated the risk of CAD in our population of acute medical patients. Almost half of patients in this study had a likelihood of CAD exceeding 60%, indicating a high risk of significant CAD and

corroborating the observation in Chapter 4 that triage occurs upstream of acute assessment units .

Over three quarters of patients admitted had at least one cardiac risk factor recognised by NICE (i.e. diabetes mellitus, smoking or hyperlipidaemia), almost half reported a history of previously diagnosed CAD and one fifth had a history of revascularisation. Nevertheless, over half of patients admitted to the acute assessment unit had chest pain categorised as non-anginal. The high percentage of patients with non-anginal symptoms despite clinically suspected ischaemia highlights the challenge of diagnosis in the acute medical population, who are often elderly with multiple co-morbidities{Cornwell, 2011}.

NICE CG95 recommends patients with non-anginal pain should not routinely undergo cardiac investigation. Exercise ECG testing is widely used in this population at present but is not supported by NICE{Timmis, 2010}. There is apprehension that the NICE model focusses on anatomical diagnosis at the expense of functional assessment{Underwood, 2010} and it remains to be seen whether UK cardiologists will persist in using exercise ECG testing, including in place of anatomical imaging such as CCT.

In total, 51% of patients admitted with suspected cardiac chest pain would have been excluded from further cardiac testing on the basis of NICE criteria, raising concern for missed cardiac diagnoses and implicit mortality risk{Pope, 2000}. 1% of the study population would have been recommended for CCT, 6% for functional cardiac testing and 9% for invasive coronary angiography. If the criteria for CCT had been broadened to include patients at intermediate risk of CAD, 7% of patients admitted would have been eligible for the investigation. NICE have requested further cost-effectiveness studies before reviewing their current guideline for amendments.

Differences between the proportion of patients predicted to fall into each CAD likelihood category and the proportion of patients ultimately recommended for each investigation further highlights the hazard of cardiac service development based exclusively on the NICE CG95 predictions.

Computed tomography is universally available in NHS hospitals that admit acute medical patients and, with appropriate software and training, a CCT service can be established to provide rapid diagnostic assessment of patients with suspected CAD. By comparison, functional and invasive cardiac testing are less available. Increasing the number of patients requiring these services is likely to result in delays to diagnosis and increased duration of hospital admission with resultant cost implications. Investment may be better justified in functional and invasive cardiac testing than in the development of CCT services for acute medical admissions, to meet NICE CG95 demands.

5.7 LIMITATIONS

Due to the retrospective nature of this study, typicality of chest pain was judged from notes review, and observer interpretation of the nature of chest pain may have skewed the likelihood of CAD. Retrospectively confirming a history of CAD was another challenge. Traditionally, significant CAD has been defined by a history of myocardial infarction, 'positive' angiography or coronary revascularisation. For the purposes of risk stratification, all patients were considered to have undifferentiated chest pain unless there was a history of coronary revascularisation. This approach more realistically reflects the situation facing acute physicians meeting patients for the first time, especially in London, where inter-hospital mobility of patients adds to the difficulty of maintaining complete records of hospital admissions and cardiac investigations.

5.8 LEARNING POINTS

- NICE CG95 recommends CCT only for use in patients with atypical or typical angina and a low likelihood of CAD (range 10-29%).
- Adoption of NICE CG95 in the acute medical setting may result in fewer than five percent of patients admitted with suspected cardiac chest pain being recommended for CCT.
- Adoption of NICE CG95 is likely to result in a greater number of patients undergoing functional and invasive testing than CCT.

- The results do not support large scale investment in CCT services within the acute medical setting to meet NICE CG95.
- Investment may be more appropriate if NICE broaden the criteria for CCT eligibility to include patients with an intermediate likelihood of CAD.

CHAPTER 6: PROSPECTIVE ASSESMENT OF THE UTILITY OF CARDIAC CT IN PATIENTS PRESENTING WITH CHEST PAIN TO THE CARDIAC OUTPATIENT SETTING

6.1 INTRODUCTION

Rapid access chest pain clinics (RACPCs) have been established in the majority of hospitals across the UK, in accordance with the National Service Framework for coronary heart disease{DOH, 2000}. Their aim is to provide out-patients with suspected cardiac chest pain with prompt investigation and targeted management. Referrals come from general practitioners, consultant cardiologists (when new patients meet the referral criteria) and emergency departments (when patients present with typical symptoms but ECGs and troponin levels do not suggest an acute coronary event).

RACPCs have proven successful in identifying high risk patients with coronary heart disease; however, coronary heart disease continues to be under-diagnosed and patients judged to have non-cardiac pain are not immune from major adverse cardiac events{Sekhri, 2007}. There is a requirement for better diagnostic accuracy and risk stratification in patients attending RACPCS, particularly amongst patients aged <65 years{Boyle, 2007}.

A diagnosis of angina pectoris due to coronary heart disease requires a history consistent with angina and the presence of obstructive CAD. The strength of CCT is in the detection or exclusion of CAD but the technology has yet to be fully evaluated in its application to stable outpatients attending RACPCs. A health technology assessment, including a systematic review of 64-slice CTA, has identified a requirement for research into the usefulness of CTA in patients with suspected CAD{Mowatt, 2008}. Subsequently, as part of NICE CG95, NICE have called for research into the clinical and cost-effectiveness of CTA compared with functional testing in the diagnosis of angina.

Although recently published studies have gone some way to addressing these research questions{Yerramasu, 2014; SCOT-HEART Investigators, 2015; Douglas, 2015}, the benefits of using CCT to diagnose patients with new-onset stable angina and the

effects of CCT use on subsequent management and clinical outcomes remained unexplored in the UK setting at the time of this study.

6.2 AIMS

This prospective pilot study was undertaken to assess the feasibility and clinical utility of early CCT as a diagnostic tool in patients referred to a RACPC with suspected cardiac chest pain.

Specific aims of the study were to:

- Assess the practical challenges of incorporating early CCT into routine care for the target population.
- Assess the impact of CCT-based assessment, relative to standard assessment, on
    - Diagnosis or exclusion of clinically significant CAD
    - Downstream cardiac investigation burden (inpatient and outpatient)
    - Outpatient clinic reviews prior to discharge
    - Hospital attendances and admissions with chest pain
    - Incidence of major adverse cardiovascular events (MACE)[a]

[a] Major Adverse Cardiac Events defined as any of unstable angina, acute myocardial infarction, urgent coronary revascularisation, life threatening dysrhythmia, stroke, and cardiac death

6.3 PATIENTS AND METHODS

Consecutive patients referred to the RACPC at Chelsea and Westminster Hospital, with chest pain of suspected cardiac origin over a twelve month period from November 2010 were screened for entry to the study. Standard exclusion criteria for studies including CCT are detailed in Chapter 2.

Enrolled patients were randomised (1:1) to undergo early CCT or to continue with standard practice, using a statistician-designed randomisation tool. For patients randomised to CCT, an outpatient scan comprising CCS and CTA, (according to the protocol detailed in Chapter 2) was arranged within one week of receipt of referral,

prior to scheduled RACPC review. CCT results were made available to clinicians in the RACPC, who were solely responsible for further management.

Data relating to clinical presentation, demographics, risk factor profiles and clinical course were collated for all patients. Medical records were reviewed to obtain results of all diagnostic tests performed in the six months post RACPC referral. Downstream investigations were defined as all cardiac tests occurring from referral to completion of follow-up. Data were corroborated by a standardised telephone survey of patients and their general practitioners at six months.

Final diagnosis and diagnosis of MACE was based on the judgment of two clinicians with access to all clinical and laboratory data, including the results of conventional serial troponin measurements, stress tests and invasive angiography, through six months of follow-up.

Post-hoc risk stratification was performed for all patients to determine likelihood of CAD based on NICE criteria.

6.4 STATISTICAL ANALYSES

Based on audit data collated from the RACPC in the preceding twelve months, the total sample size required to achieve power of 0.80 at statistical significance level 0.05 was calculated as n=75 patients{Zhao, 2008}. A calculation of sample size using the relative asymptotic efficiency of Wilcoxon-Mann-Whitney test with respect to Student's t test gave a consistent result. A sample size of 100 patients was selected to enable the detection of smaller, but relevant, differences between the distributions.

Comparisons between the two cohorts were performed for age and number of outpatient clinic appointments using the independent samples t-test following assessment for normality by the D'Agostino-Pearson test. Gender, frequency of cardiac risk factors, nature of chest pain, subsequent hospital attendances/admissions with angina, likelihood of CAD, and frequency of MACE were compared using Chi-square or Fisher's exact tests as appropriate. Additionally, the overall distribution of

the CAD likelihood categories between the two cohorts was compared using the Mann-Whitney U test.

All analyses were intention to treat, and patients were analysed in the group they were allocated to, irrespective of compliance with scanning.

6.5 RESULTS

6.5.1. Patient population

A total of 484 patients with suspected cardiac chest pain were screened during the enrolment period (Table 6.1). Exclusion criteria were identified in 399 (82%). Ultimately, 85 patients were recruited to the study (median age 59 years, range 40-92 years, male: female ratio 0.85:1).

Table 6.1: Recruitment analysis (n=484)

Number of patients screened (% of total)	**484 (100.0)**
Number of patients screened but not recruited (% of total)	**399 (82.4)**
Number of patients recruited (% of total)	**85 (17.6)**
Reasons for non-recruitment (% of total)	
age <40yrs	59 (12.2)
no history of chest pain	8 (16.5)
features of AMI	1 (0.2)
haemodynamic/respiratory instability	4 (0.8)
previous coronary intervention	21 (4.3)
resting heart rate >70bpm	-
allergy/intolerance of iodinated contrast	-
renal dysfunction	5 (1.0)
pregnancy	-
unable to provide written consent	38 (7.9)
Language barrier	28
psychiatric disturbance/confusion	8
Hearing impairment	2
declined written consent	50 (10.3)
Lack of time	25
Concerns regarding radiation	6
Contrast	1
Other	18
CCT not possible prior to OPD appointment	147 (30.4)
Patient non-response	61 (12.6)
Cardiac CT within preceding 3 months	4 (0.8)
Enrolled in parallel study	1 (0.2)

[a] i.e. last minute booking into clinic slot, CT scanner non-availability, recruitment team non-availability

40 patients were randomised to undergo early CCT, of whom 9 did not complete the scan (withdrawal of consent (n=4), failure to attend (n=2), acute illness (n=1), elevated creatinine (n=1), logistical issues (n=1)). The remaining 45 patients were randomised to standard practice. Demographic information for the early CCT and standard care cohorts is detailed in Table 6.2. Patients randomised to early CCT were, on average, significantly younger, with a mean difference of 5.08 years (95% CI 9.78 to -0.38; P=0.034). There were no significant differences between the cohorts in their gender distribution, frequency of cardiac risk factors or likelihood of CAD (P=0.271).

Table 6.2: Study population characteristics (n=85)

Characteristic	TOTAL (%)	EARLY CCT (%)	STD PRACTICE (%)	P VALUE
No. of patients	85	40 (47.1)	45 (52.9)	
Gender				
Male	39 (45.9)	17 (42.5)	22 (48.9)	0.664
Female	46 (54.1)	23 (57.5)	23 (51.1)	
Age				
Mean ± s.d.	59.16 ± 11.10	56.48 ± 9.83	61.56 ± 11.72	0.034
Median	59	57	61	
Range	40 - 92	40 - 79	40 - 92	
Cardiac risk factors				
NICE risk factors[a]	66 (77.6)	29 (72.5)	37 (82.2)	0.309
Hypertension	34 (40.0)	20 (50.0)	14 (31.1)	0.120
Reported CAD	4 (4.7)	2 (5.0)	2 (4.4)	1.000
Family history of CAD	50 (58.8)	27 (67.5)	23 (51.1)	0.185
Nature of chest pain				
Non-anginal	40 (47.1)	16 (40.0)	24 (53.3)	0.278
Atypical angina	26 (30.6)	13 (32.5)	13 (28.9)	0.815
Typical angina	19 (22.4)	11 (27.5)	8 (17.8)	0.309
Likelihood of CAD - NICE (%)[a]				
<10	7 (8.2)	5 (12.5)	2 (4.4)	0.250
10-29	17 (20.0)	7 (17.5)	10 (22.2)	0.787
30-60	23 (27.1)	11 (27.5)	12 (26.7)	1.000
61-90	28 (32.9)	14 (35.0)	14 (31.1)	0.818
>90	10 (11.8)	3 (7.5)	7 (15.6)	0.322
Downstream investigations				
ETT	32	9	23	**0.008**
CCS[b]	48	31	17	**<0.001**

CTA[b]	44	31	13	**<0.001**
Functional	24	9	15	0.337
ICA	14	6	8	0.777
Total	162	86	76	0.057
Number of clinic attendances[c]				
Mean ± s.d.	1.47 ± 0.72	1.33 ± 0.76	1.60 ± 0.65	0.077
Median	1	1	2	
Range	0 - 4	0 – 4	1 - 3	
Presentation to ED with chest pain	3	1	2	1.000
Admission with chest pain	3	1	2	1.000
MACE[d]				
Total no. of cases	3 (3.5)	1 (2.5)	2 (4.4)	1.000
MI	2 (2.4)	1 (2.5)	1 (2.2)	
CVA	0	0	0	
Emergency revascularisation	3 (3.5)	1 (2.5)	2 (4.4)	
Death	0	0	0	
Adjudicated diagnosis				
CAD diagnosed	18 (21.2)	8 (20.0)	10 (22.2)	1.000
CAD excluded	61 (71.8)	31 (77.5)	30 (66.7)	0.337
Inconclusive	6 (7.1)	1 (2.5)	5 (11.1)	0.207

[a]Cardiac risk factors used to define patients at high risk for CAD using the NICE algorithm are any one of diabetes mellitus, smoking or hyperlipidaemia (total cholesterol >6.47mmol/l).

[b*] 9 patients in the early CCT cohort did not complete CCT

[c] 2 patients in the early CCT cohort were not seen in clinic (DNA n=1; direct admission from CCT n=1)

[d] Two of the three patients who underwent emergency revascularisation also had another MACE (MI)

6.5.2 Clinical outcomes

The distribution of disease identified on CCT, for both cohorts, is detailed in Table 6.3. Although CTA appeared more sensitive than CCS for the detection of significant CAD, this was not confirmed statistically (P=0.110).

Table 6.3: Distribution of CCT outcomes

CALCIUM SCORE:	TOTAL (%) n=48	EARLY CCT (%) n=31	STD PRACTICE (%) n=17
Zero	26 (54.2)	17 (54.8)	9 (69.2)
1-400	19 (39.6)	13 (41.9)	6 (35.3)
>400	3 (6.3)	1 (3.2)	2 (11.8)
OCCLUSIVE CAD ON CTA:	**TOTAL (%) n=44**	**EARLY CCT (%) n=31**	**STD PRACTICE (%) n=13**
Normal appearance	13 (29.5)	9 (29.0)	4 (30.8)
Non-occlusive CAD (<50% stenosis)	23 (52.3)	18 (58.1)	5 (38.5)
Occlusive CAD (≥50% stenosis)	8 (18.2)	4 (12.9)	4 (30.8)

Early CCT did not statistically increase the likelihood of a subsequent positive cardiac investigation (Table 6.4), even when patients in the early CCT cohort who failed to complete CCT were excluded from analysis (Table 6.5).

Table 6.4: Likelihood of a positive test result

INVESTIGATIONS	TOTAL		EARLY CCT		STD PRACTICE		P VALUE
	Number	+ result (% +)	Number	+ result (% +)	Number	+ result (% +)	
ETT	32	7 (21.2)	9	1 (11.1)	23	6 (26.1)	0.640
CCS[a]	48	3 (6.3)	31	1 (3.2)	17	2 (11.8)	0.283
CTA[b]	44	8 (18.2)	31	4 (12.9)	13	4 (30.8)	0.711
Functional[c]	24	10 (41.7)	9	3 (33.3)	15	7 (46.7)	0.679
ICA[d]	14	11 (73.3)	6	5 (83.3)	8	6 (75.0)	1.000

[a] Taken as ASE >400, [b] Taken as >50% stenosis, [c] Taken as presence of inducible ischaemia, [d] Taken as ≥ 70% stenosis on ICA

Table 6.5: Likelihood of a positive result excluding patients randomised to early CCT who did not undergo CCT

INVESTIGATIONS	EARLY CCT		STD PRACTICE		P VALUE
	Number	+ result (% +)	Number	+ result (% +)	
ETT	5	0 (0)	23	6 (26.1)	0.553
CCS[a]	31	1 (3.2)	17	2 (11.8)	0.283
CTA[b]	31	4 (12.9)	13	4 (30.8)	0.711
Functional[c]	5	2 (40.0)	15	7 (46.7)	1.000
ICA[d]	4	3 (75.0)	8	6 (75.0)	1.000

[a] Taken as ASE >400, [b] Taken as >50% stenosis, [c] Taken as presence of inducible ischaemia, [d] Taken as ≥ 70% stenosis on ICA

Statistical analysis demonstrated no difference in the diagnostic ability of an early CCT approach, relative to standard practice (P=0.207). Clinically significant CAD was diagnosed in 20% (n=8) and excluded in 78% (n=31) of the early CCT cohort leaving 3% (n=1) without a definitive diagnosis. CAD was diagnosed in 22% (n=10) and excluded

in 67% (n=30) of patients in the standard practice cohort, leaving 11% (n=5) without a definitive diagnosis.

Over the six month follow-up period, 3 patients suffered a MACE (event rate 3.5%). All episodes of MACE occurred in patients with functional imaging or invasive coronary angiography indicative of occlusive CAD. None of these patients had undergone prior CCT.

Figure 6.1: Incidental clinical findings identified on CCT

- ICFs identified in 16 patients in CCT cohort and 5 patients in the standard practice cohort who underwent CCT (i.e. 21 of 48 scanned; 44%)
- Mean ICFs per patient 1.38 ± 0.80; median 1; range 1-4.
- 14 patients with thoracic ICFs, 3 with abdominal ICFs and 4 with both
- ICFs include: emphysema (4 patients), pulmonary nodules (9 patients), bronchiectasis (1 patient), chest wall lesion (1 patient), hiatus hernia (2 patients), renal lesions (1 patient), liver lesions (4 patients), polysplenia (1 patient), dextrocardia (1 patient), suspected VSD (1 patient), aortic valve calcification (1 patient), aberrant RCA (1 patient)

6.5.3 Resource utilisation

Reflecting routine practice at the time, patients in the standard practice cohort were significantly more likely to undergo ETT (P=0.008) and significantly less likely to undergo CCT (both CCS and CTA) (P<0.001). Although fewer patients in the CCT cohort underwent functional imaging (-48%) and invasive coronary angiography (-19%), these findings were not statistically significant.

Patients randomised to early CCT underwent a greater total number of investigations (P=0.057), but their investigation costs per capita were lower (£288.10 versus £321.42, relative reduction 10.4%).

Table 6.6: Investigation costs per capita{NICE, 2010}

INVESTIGATIONS:	TOTAL COHORT (COST £)	CCT (COST £)	STD PRACTICE (COST £)
ETT (£66)	2,112	594	1,518
Ca SCORE (£103)[a]	4,944	3,193	1,751
Functional (£293)	7,032	2,637	4,395
ICA (£850)	11,900	5,100	6,800
Total cost	25,988	11,524	14,464
Cost per capita	305.74	288.10	321.42

[a] counting either or both of CCS and CTA as single entity

Patients randomised to early CCT attended fewer clinics, on average, than those randomised to standard practice although the difference was not statistically significant (P=0.077). There was no significant difference in the number of emergency department attendances or hospital admissions with chest pain between the two cohorts over a six month period.

6.6 DISCUSSION

This pilot study was the first to explore the use of CCT in the RACPC setting. The study highlighted clinical and logistical challenges to the introduction of early CCT into assessment pathways. Although the study did not demonstrate a statistically significant clinical or resource benefit to the use of early CCT, clinically relevant CAD was ultimately diagnosed or excluded in a greater proportion of patients undergoing the investigation. Incorporation of early CCT into patient assessment led to increased diagnostic testing but a tendency towards a reduction in functional imaging and invasive angiography, resulting in lower investigation costs and a reduced number of outpatient review appointments. These results were achieved without a detected increase in MACE.

A strength of this study was that it included patients representative of the spectrum of individuals referred to the RACPC, with no limitations based on patient body mass index, atrial fibrillation, pre-test likelihood of CAD or the presence of elevated coronary calcium scores, as has been the case with previous studies of CCT. Furthermore, the study did not dictate the use or withholding of cardiac investigations in either cohort (including CCT (CCS and CTA)), allowing the triage potential of early CCT to be explored, rather than adopting a head to head analysis of CCT versus other diagnostic modalities. Finally, the study focussed on patient and clinician centred outcomes, rather than the diagnostic accuracy of CCT, which has already been extensively reported in the literature.

Fewer than 20% of the screened population were recruited. The primary limitations to recruitment were logistic, relating to CCT or patient non-availability prior to RACPC attendance (43%). In an established RACPC-CCT service logistic concerns may be less

relevant if scanning and reporting can be facilitated on the day of RACPC attendance. Secondary limitations were patient factors including an absence of a history of chest pain (17%) and age less than forty years, highlighting inappropriate RACPC referrals exploiting the prompt availability of a cardiology opinion for patients in whom angina was clinically unlikely.

Nevertheless, 45% of the recruited study population had a likelihood of CAD exceeding 60%, suggesting a high risk of CAD amongst patients referred to RACPCs. 21% of the study population were subsequently diagnosed with clinically significant CAD, supporting published data that the NICE CG95 nomogram may overestimate risk in outpatients{Khan, 2014}. The frequency of CAD diagnosis was not affected by the incorporation of early CCT into patient assessment but the frequency of CAD exclusion increased, resulting in fewer patients with inconclusive outcomes.

Prior to recent advances in CCT technology, including the development of CT myocardial perfusion imaging and CT fractional flow reserve, CCT was limited to providing anatomical but not functional assessment. Thus, patients 'diagnosed' with obstructive disease on CCT have often required further investigation. A role for CCT has been proposed in targeting these investigations{Chow, 2009; SCOT-HEART Investigators, 2015}. This study demonstrated a trend towards a reduction in both functional imaging and invasive angiography following early CCT but failed to demonstrate a statistically significant reduction in the proportion of negative functional studies or catheterisations. The results contrast with published data, suggesting a greater number of invasive procedures are performed after CCT than after standard evaluation or an initial functional imaging approach{Shreibati, 2011; Douglas, 2015}.

The early CCT approach resulted in a greater number of diagnostic investigations per capita but investigation costs were 10% lower than with standard practice (£288.10 versus £321.42). The trend towards fewer clinic follow-up appointments with early CCT also supported the finding that an early CCT approach may be cost effective in RACPCs, particularly when extrapolated to the 500,000 NHS outpatient appointments for CAD per annum {Stewart, 2003}.

The absolute rate of MACE in the study population, over a six month period of follow-up, was low at less than 4%. The results suggest that patients randomised to early CCT were no more likely to experience MACE and the trend towards earlier clinic discharge did not result in missed diagnoses. Similarly, there were very few hospital attendances or admissions with chest pain, and it was not possible to comment on whether hospital attendance may be affected by uncertainty regarding the presence of CAD.

A recent study prospectively evaluated the role of CCT in the RACPC setting, narrowing the eligible population to include only those with patients' pre-assessed as having stable chest pain symptoms and a low likelihood (10-29%) of underlying obstructive CAD, as per NICE CG95{Yerramasu, 2014}. In the immediate future, it is likely that CCT will be targeted to this population.

6.7 LIMITATIONS

Recruitment to this study was a significantly greater challenge than was initially predicted. Despite the recruitment of sufficient patients to achieve statistical power, patient factors including acute illness, deranged biochemistry and study withdrawal meant that around one quarter of patients randomised to undergo early CCT did not undergo either CCS or CTA. Analyses were performed on an intention to treat basis. While this situation may reflect 'real life' uptake of early CCT if this becomes incorporated into routine clinical practice, it means the clinical and financial impact of early CCT is likely to have been underestimated in this study.

Inherent in the study design was a lack of blinding to the intervention, with consequent bias in decision making towards earlier clinic discharge in the CCT group. For both cohorts of patients, however, clinical decision making was the responsibility of experienced clinicians not directly associated with the study whose decisions were subject to the same imperatives to provide high-quality, personalised care.

Although this study provided outcome information for a period of six months post RACPC referral, a prolonged period of follow-up with a wider exploration of patient and economic outcomes (e.g. the composite financial contribution of evaluation,

monitoring, full investigation and therapy and the impact on quality-adjusted-life-years) may have facilitated greater understanding of the risks and benefits of an early CCT strategy, relative to standard practice.

6.8 LEARNING POINTS:

- At the time of this study, standard RACPC assessment was based around exercise tolerance testing as the first line investigation and CCT was less commonly performed.
- Early CCT may improve clinical decision making for patients presenting to RACPCs with suspected cardiac chest pain, resulting in fewer patients in whom CAD is neither diagnosed nor excluded.
- Early CCT may result in an increase in diagnostic testing but a decrease in the total cost of investigations.
- Early CCT may result in the need for fewer outpatient clinic appointments.
- An assessment pathway incorporating early CCT does not appear to have any detrimental effects on cardiovascular outcomes.
- In the immediate future, the use of CCT is RACPCs is likely to be in accordance with NICE CG95.

CHAPTER 7: RETROSPECTIVE ANALYSIS OF THE UTILITY OF CARDIAC CT IN THE CARDIAC OUTPATIENT SETTING IN ACCORDANCE WITH NICE GUIDELINE CG95

7.1 INTRODUCTION

Chapter 6 prospectively evaluated the logistical, clinical and financial implications of a model incorporating early CCT into the assessment of RACPC patients, based upon a broad inclusion policy.

In NICE CG95, NICE propose their own model for the risk stratification and investigation of patients with suspected CAD, with the intention of supporting a unified cost effective and evidence-based approach to investigation. The target audience for NICE CG95 are general practitioners and cardiology specialists in RACPCs.

NICE CG95 uses the nature of a patient's chest pain and their pre-test likelihood of CAD to guide recommendations for further investigation. NICE have predicted the distribution of patients across a spectrum of CAD likelihood, based upon personal communication from two of their authors and detailed in Chapter 5{Skinner, 2010}.

Study findings from Chapter 5 and the published literature suggest NICE underestimate the proportion of higher risk patients presenting to RACPCs, emergency departments and acute assessment units{Fox, 2010} and taking the NICE predictions on trust may lead to inaccurate estimates of the cardiac investigation burden and inadequate resourcing of cardiac services to meet the demands of the population at risk.

At the time of this study, there were no published data regarding the impact of the NICE CG95 on outpatient cardiac investigation services and the requirement for outpatient CCT provision was unproven.

7.2 AIMS

This retrospective study reviewed the demographic and clinical characteristics of patients referred to the RACPCs of two London hospitals with suspected cardiac chest pain, to evaluate the impact of NICE CG95 on our local population.

Specific aims of the study were to:

- Determine the distribution of CAD likelihood in patients attending RACPCs with suspected cardiac chest pain, according to NICE criteria.
- Review the investigation burden on cardiac services if NICE CG95 were applied to this population.

7.3 PATIENTS AND METHODS

Consecutive patients attending RACPCs at Chelsea and Westminster Hospital (CWH) and Ealing Hospital (EH) over a six month period from September 2009 were identified using audit databases at both institutions.

Using information obtained from medical records, data relating to clinical presentation, demographics, risk factor profiles, cardiac investigations and clinical course were collated for all patients. NICE CG95 was applied retrospectively to the population.

Chest pain was categorised as non-anginal, atypical or typical for angina. Chest pain typicality was recorded at the time of consultation for EH patients but determined retrospectively by consensus of two researchers for CWH patients.

Pre-test likelihood of CAD was determined using a nomogram based on NICE CG95. Patients were deemed eligible for investigation if they had typical or atypical anginal chest pain and a likelihood of CAD in the range 10-90%; those in the range 10-29% (i.e. low risk) were eligible for CCT; those in the range 30-60% (i.e. intermediate risk) were eligible for functional testing and those in the range 61-90% (i.e. high risk) were eligible for invasive coronary angiography in accordance with NICE CG95.

Cardiac investigations recommended by NICE were compared with those undertaken in the study population in accordance with standard practice. It should be noted that CCT was not available as part of standard practice at EH at the time of this study. The relative costs of the investigations recommended/undertaken were calculated from values published in NICE CG95.

7.4 STATISTICAL ANALYSIS

The study sample size was determined using the power calculation method of Nisen and Schwertman and the null hypothesis 'no difference exists between the distributions of investigations undertaken in the combined hospitals versus those recommended by NICE{Nisen, 2008}. To achieve a power of 80% required a sample size of 575 patients.

Comparisons between the CWH and EH cohorts were performed for age using the independent samples t-test following assessment for normality by the D'Agostino-Pearson test. Gender, frequency of cardiac risk factors, nature of chest pain and likelihood of CAD and frequency of investigations were compared using Chi-square or Fisher's exact tests as appropriate. Additionally, the overall distribution of the CAD likelihood categories between the two cohorts was compared using the Mann Whitney U test.

7.5 RESULTS

A total of 595 patients (median age 55 years, range 22-94 years, male: female ratio 1:1) attended the RACPCs at EH (n=300) and CWH (n=295) over the six month period. Demographic and clinical information is shown in Table 7.1. There were no significant differences between the cohorts in their age, gender distribution, frequency of cardiac risk factors; however, the CWH cohort were significantly more likely to have non-anginal pain ($P<0.001$) and had a lower likelihood of CAD ($P=0.008$).

Table 7.1: Population characteristics for patients attending CWH and EH RACPCs (n=595)

CHARACTERISTIC	TOTAL COHORT (%)	CWH (%)	EH (%)	P VALUE
No. of patients	595	295	300	
Gender				
Male	302 (51%)	151 (52%)	151 (50%)	0.450
Female	293 (49%)	144 (49%)	149 (50%)	
Age				
Mean ± s.d.	55.39 ± 13.17	54.54 ± 13.14	56.23 ± 13.16	0.125
Median	55	54	57	
Range	22-94	24-94	22-87	
Cardiac risk factors				
NICE risk factors[a]	411 (69%)	203 (69%)	208 (69%)	0.481
Nature of chest pain				
Non-anginal	381 (64%)	220 (75%)	161 (54%)	**<0.001**
Atypical angina	162 (27%)	57 (19%)	105 (35%)	**<0.001**
Typical angina	52 (9%)	18 (6%)	34 (11%)	**0.029**
Likelihood of CAD - NICE (%)				
<10	106 (18%)	56 (19%)	50 (17%)	0.521
10-29	123 (21%)	71 (24%)	52 (17%)	**0.044**
30-60	175 (29%)	88 (30%)	87 (29%)	0.857
61-90	141 (24%)	62 (21%)	79 (26%)	0.148
>90	50 (8%)	18 (6%)	32 (11%)	0.054
Recommended investigations - NICE				
No investigation	443 (74%)	244 (83%)	199 (66%)	**<0.001**
Exercise ECG	0 (0%)	0 (0%)	0 (0%)	1.000
CCT	10 (2%)	4 (14%)	6 (2%)	0.752
Functional testing	69 (12%)	23 (8%)	46 (15%)	**0.005**
Invasive angiography	73 (12%)	24 (8%)	49 (16%)	**0.003**

[a]Cardiac risk factors used to define patients at high risk for CAD using the NICE algorithm are any one of diabetes mellitus, smoking or hyperlipidaemia (total cholesterol >6.47mmol/l).

The distribution of CAD likelihood according to nature of chest pain, gender, risk and age is shown in Table 7.2.

Table 7.2: Distribution of combined CWH and EH RACPC populations according to age, sex and nature of chest pain (n=595)

AGE (YEARS)	NON ANGINAL CHEST PAIN				ATYPICAL ANGINA				TYPICAL ANGINA			
	M		F		M		F		M		F	
	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI
<30	3	5	1	1	2	-	-	1	-	-	-	-
30-39	9	17	11	8	2	4	4	4	-	2	-	1
40-49	13	42	25	19	4	11	4	5	2	3	1	1
50-59	14	32	21	36	10	14	2	20	1	6	1	4
60-69	7	25	11	34	1	18	3	19	2	6	3	4
≥70	4	18	8	17	3	15	11	5	1	6	-	8

White: Not routinely recommended for further investigation

Dark grey: Likelihood of CAD 10-29% - recommended for CCT

Mid grey: Likelihood of CAD 30-60% - recommended for functional cardiac testing

Light grey: Likelihood of CAD 61-90% - recommended for invasive angiography if clinically indicated

Across all categories of CAD likelihood in the range 10-90%, the proportions of patients were higher than predicted by NICE CG95. As a result, the distribution of recommended cardiac investigations would have differed significantly from that predicted by NICE for EH, CWH and the combined population (P<0.001). The distribution of recommended cardiac investigations would also have differed significantly between the two cohorts (P<0.001).

66% (n=393) of the total population would have been recommended for no routine cardiac investigation based pain classified as non-anginal (n=287), a likelihood of CAD <10% (n=12), or both (n=94). 8% (n=50) would have proceeded directly to treatment without further investigation, based on a likelihood of CAD >90%.

No patients would have been recommended for ETT. 2% (n=10) of patients would have been recommended for CCT, 12% (n=69) for functional cardiac testing and 12% (n=73) for invasive coronary angiography.

Relative to standard practice, applying NICE CG95 would have resulted in increased CCT testing (+43%; P=0.436), reduced functional cardiac testing (-24%, P=0.060) and a significant increase in invasive coronary angiography (+508%; P<0.001) (Figure 7.1).

The total number of investigations would have been reduced by 73% (P<0.001), predominantly due to the exclusion of ETT.

Applying NICE CG95 would have resulted in a 36% reduction in investigation costs at CWH, a 127% increase in investigation costs at EH and a 24% increase across the two cohorts combined.

Table 7.3: Cardiac investigations actually undertaken compared with those recommended by NICE CG95 (n=595)

	INVESTIGATION	ACTUAL	RECOMMENDED	% CHANGE	P VALUE
CWH	None	16	244	+1425	**<0.001**
	Exercise ECG	195	0	-100	**<0.001**
	CCT	7	4	-43	0.361
	Functional testing	65	23	-65	**<0.001**
	ICA	12	24	+100	**0.040**
	Total number	279	51	-82	**<0.001**
EH	None	17	199	+1071	**<0.001**
	Exercise ECG	257	0	-100	**<0.001**
	CCT	0	6	∞	**0.031**
	Functional testing	26	46	+77	**0.012**
	ICA	0	49	∞	**<0.001**
	Total number	283	101	-64	**<0.001**
CWH & EH	None	33	443	+1242	**<0.001**
	Exercise ECG	452	0	-100	**<0.001**
	CCT	7	10	+43	0.436
	Functional testing	91	69	-24	0.060
	ICA	12	73	+508	**<0.001**
	Total number	562	152	-77	**<0.001**

Figure 7.1: Cardiac investigations actually undertaken compared with those recommended by NICE CG95 (n=595)

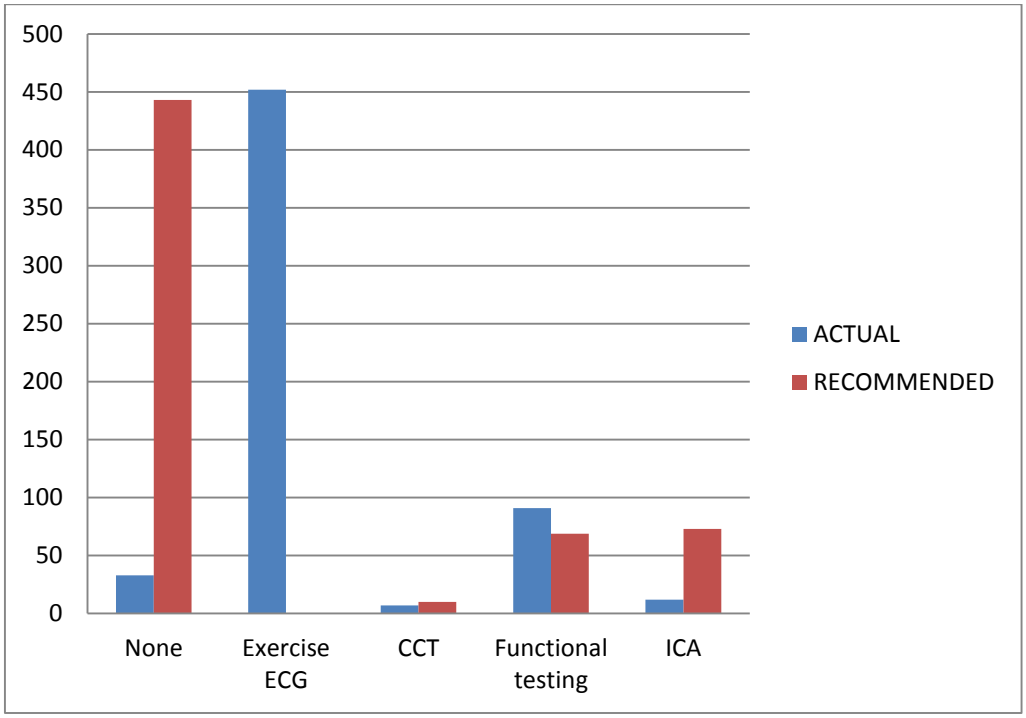


Table 7.4: Comparison of actual investigation costs and costs based on NICE CG95 recommendations{NICE, 2010}

	INVESTIGATION	ACTUAL (COST £)	RECOMMENDED (COST £)	% CHANGE
CWH	Exercise ECG	12870	0	
	CCT	721	412	
	Functional testing	19045	6739	
	ICA	10200	20400	
	Total cost	42836	27551	
	Cost per capita	145.21	93.39	-35.7
EH	Exercise ECG	16962	0	
	CCT	0	618	
	Functional testing	7618	13478	
	ICA	0	41650	
	Total cost	24580	55746	
	Cost per capita	81.93	185.82	+126.8
CWH & EH	Exercise ECG	29832	0	
	CCT	721	1030	
	Functional testing	26663	20217	
	ICA	10200	62050	
	Total cost	67416	83297	
	Cost per capita	113.30	139.99	+23.6

[a] counting either or both of CCS and CTA as single entity

7.6 DISCUSSION

In our dual-site study population, NICE CG95 would have recommended no investigation for around two thirds of RACPC attenders. CCT would have been recommended for 2% of patients while functional cardiac testing and invasive coronary angiography would have been recommended for 12%. There would have been an overall reduction in the number of investigations performed but an increase in the cost of these investigations, relative to standard practice.

Based on the distribution of CAD likelihood amongst the study population, it appears NICE may have underestimated the impact of NICE CG95 on RACPC service provision. Compared with predictions, a larger proportion of patients would have fallen within the boundaries of 10-90% likelihood of CAD and therefore been potentially eligible for investigation. Furthermore, the distribution was skewed towards a higher likelihood of CAD than predicted by NICE, suggesting a requirement for functional cardiac testing and invasive coronary angiography greater than predicted.

Importantly, the study also demonstrated how subtle demographic differences between RACPC populations can result in markedly different patterns of referral for cardiac investigations to meet NICE CG95. EH and CWH both serve patients within a limited geographic area and their RACPC patients are similar in number, age, gender and risk factor profiles, yet NICE CG95 would have necessitated significantly different service provision for the two RACPCs ($P<0.001$). Differences in practice between clinicians categorising the nature of chest pain may also have contributed to variations in scoring the likelihood of CAD and thus recommended investigations. The higher proportion of patients with non-anginal pain in the CWH cohort would have resulted in more discharges without investigation. By contrast, the EH cohort, having a higher likelihood of CAD would have been more likely to be recommended for invasive angiography.

Application of NICE CG95 would have resulted in the discharge without further cardiac investigation of two thirds of the study population, with pain categorised as non-anginal or a likelihood of CAD <10%. This equates to a greater than 1000% increase in

discharge without investigation, relative to standard practice. Despite the recognised validity of pre-test probability scoring in the prediction of CAD{Pryor, 1993}, a large, multi-centre RACPC study has demonstrated nearly one-third of significant cardiac events occur in patients diagnosed with non-cardiac chest pain, raising concern for potential missed diagnoses{Sekhri, 2007}. Clinicians may be justifiably unkeen to discharge without investigation a patient whom another clinician has deemed at risk, and consultation without progression to investigation may also do little to reassure patients who have been informed they are at risk of CAD{Fox, 2009}.

In the study population, exercise ECG testing was performed as a preliminary investigation in around 85% of EH patients and 65% of CWH patients but would have been recommended for none based on NICE CG95. NICE CG95 excludes exercise ECG testing as a first line investigation based upon its relative lack of sensitivity and specificity and the superior cost-effectiveness of imaging, an approach which differs significantly from standard UK practice and European guidance{Montalescot, 2013}. There is concern that cardiology services may struggle to divert resources from the 'ubiquitous' treadmill to the various forms of cardiac imaging in which equipment and expertise is less common{Ranjani, 2011} and this readily available, inexpensive test is likely to continue to play a role in risk stratification.

NICE CG95 would have recommended CCT for 2% of the study population. Despite a 43% increase in CCT relative to standard practice, the numbers would have remained small. 12% of the study population would have been recommended for functional cardiac testing, a 24% drop relative to standard practice. Referrals for invasive angiography would have increased significantly, by over 500%.This may be an over-estimation as NICE CG95 recommends angiography with the caveat that it should be limited to patients for whom revascularisation is a consideration and for whom the procedure is clinically appropriate and personally acceptable. As it stands; however, NICE CG95 appears to overcommit to the use of invasive angiography, which will impact upon catheter lab workload, consultant availability and costs{Khan, 2014; Cubukcu, 2015}.

Based on our study findings, implementation of NICE CG95 appears likely to result in a reduction in the total number of patients referred for cardiac investigation relative to standard practice, however, costs are likely to increase due to increased reliance on more expensive investigations such as invasive coronary angiography over non-invasive and less expensive tests such as exercise ECG testing and CCT.

When considering service development to meet the demands of NICE CG95, it is noteworthy that a number of the diagnostic investigations recommended by NICE are not widely available across the NHS. While the majority of NHS hospitals with RACPCs have access to a CT scanner, developing a CCT service (using a minimum 64-detector scanner), enhancing a local functional imaging service (using stress echocardiography, myocardial perfusion scintigraphy or perfusion cardiac MRI) or expanding invasive angiographic services requires significant investment in equipment, personnel and training{Ranjani, 2010}. Hospitals may elect to send patients to specialist hubs for these investigations, delaying time to definitive diagnosis and targeted management.

Since the primary determinant of costs is local demographic equivalence to the NICE CG95 model, it would appear prudent that individual hospitals audit their RACPC populations before investing in cardiac services to meet the guideline. Recent studies suggest this is now occurring across the UK {Garg, 2011; Athauda-Arachchi, 2013}. In hospitals where cardiac services are currently insufficient to meet NICE CG95 requirements, the costs of establishing the pre-requisite infrastructure will have to be justified economically based upon predicted uptake of investigations.

7.7 LIMITATIONS

While the study was designed to provide a representative sample of UK RACPC attendances, the findings were limited by the fact that the study occurred within a limited geographical area and data were collected retrospectively, therefore the results should be generalised with caution.

The study only analysed the impact of NICE CG95 on preliminary cardiac investigations and not on subsequent investigations or patient outcomes. Extrapolation of the data

to predict overall costs from first patient contact to discharge were therefore not possible. The methodology of the study reflects NICE guidelines, which are focussed on diagnosis rather than resultant management. Likewise, NICE economic analyses do not take infrastructure costs into account.

7.8 LEARNING POINTS

- Patients attending RACPC appear to have a greater likelihood of CAD than predicted by NICE CG95.
- Adoption of NICE CG95 may result in:
    - Up to two thirds of RACPC patients recommended for discharge without further cardiac investigation.
    - Fewer than five percent of patients admitted with suspected cardiac chest pain being recommended for CCT
    - A significant increase in the proportion of RACPC patients referred for invasive angiography.
- Despite fewer referrals for cardiac investigations, bias towards invasive angiography may result in up to a 24% increase in the average cost of investigation per patient with NICE CG95.
- Differences between recommended investigations and existing practice should guide investment in local cardiac services.

CHAPTER 8: RETROSPECTIVE ANALYSIS OF CLINICAL OUTCOMES OF CARDIAC OUTPATIENTS NOT INDICATED FOR FURTHER INVESTIGATION IN ACCORDANCE WITH NICE GUIDELINE CG95

8.1 INTRODUCTION

In accordance with the National Service Framework for coronary heart disease{DOH, 2000}, RACPCs have been established across the UK to provide one stop cardiological assessment of patients with suspected angina. Implicit in the provision of these clinics is that they not only diagnose patients with CAD accurately and promptly, but that they also identify patients at low risk of CAD, who can be discharged without further investigation or treatment.

NICE CG95 gives significant diagnostic weight to comprehensive clinical assessment of the patient with chest pain with a view to avoiding progression to unwarranted investigation. Patients with non-anginal pain, and those with atypical/typical anginal pain but a likelihood of CAD <10% are considered at low risk and recommended for discharge from care without anatomical or functional cardiac testing.

Despite widespread awareness of the potential implications of missed CAD{Lee, 1987}, patients continue to be misdiagnosed with non-cardiac chest pain and, in the outpatient setting, up to one-third of significant cardiac events occur in patients previously diagnosed with non-cardiac chest pain{Sekhri, 2007}.

Studies detailed in Chapters 5 and 7 suggest a high proportion of patients with suspected cardiac chest pain are recommended for discharge without investigation based on the application of NICE CG95 to our local acute assessment unit and RACPC populations.

At the time of this study, the impact of NICE CG95 on patient outcomes and potential missed diagnoses had not been evaluated in the outpatient (or more specifically RACPC) setting.

8.2 AIMS

This aims of this study were to:

- Compare the clinical outcomes of RACPC patients for whom NICE CG95 would have recommended further investigation with those for whom NICE CG95 would not recommend further investigation.

8.3 PATIENTS AND METHODS

Consecutive patients attending RACPCs at Chelsea and Westminster Hospital (CWH) and Ealing Hospital (EH) over a six month period from September 2009 were identified using audit databases at both institutions.

Using information obtained from medical records, data relating to clinical presentation, demographics, risk factor profiles, cardiac investigations and clinical course were collated for all patients, as per Chapter 7. Patients were excluded from further analysis if their full medical notes were not available for review. NICE CG95 was applied retrospectively to the population.

Chest pain was categorised as non-anginal, atypical or typical for angina. Pre-test likelihood of CAD was determined using a nomogram based on NICE CG95. Patients were deemed eligible for investigation if they had typical or atypical anginal chest pain and a likelihood of CAD in the range 10-90%; those in the range 10-29% (i.e. low risk) were eligible for CCT; those in the range 30-60% (i.e. intermediate risk) were eligible for functional testing and those in the range 61-90% (i.e. high risk) were eligible for invasive coronary angiography in accordance with NICE CG95.

Following risk stratification, patients were classified into two cohorts: NICE-Y (patients for whom the NICE guideline recommended further investigation) and NICE-N (patients not routinely recommended for cardiac investigation by NICE; i.e. those with non-anginal chest pain or a likelihood of CAD <10%).

For each group, subsequent admissions with angina were recorded, and information from cardiac investigations, clinic letters and discharge summaries used to ascertain if

significant CAD had been diagnosed, excluded, or if investigations were inconclusive over a six month period. The reference diagnosis was based on the judgment of 2 physicians with access to all clinical and laboratory data, through 6 months of follow-up.

Major adverse cardiac events (MACE) were determined from the RACPC databases at six months from the time of presentation and were defined as myocardial infarction (MI), cerebrovascular accident (CVA), emergency revascularisation (ER) and cardiac-related death.

The frequencies of MACE according to the likelihood of CAD and according to the nature of chest pain were calculated. A descriptive analysis was also performed for the sub-group of patients in the NICE-N group with no previous CAD diagnosis.

8.4 STATISTICAL ANALYSES

Comparisons between the two groups were performed for age using the independent samples t-test following assessment for normality by the D'Agostino-Pearson test. Gender, frequency of cardiac risk factors, nature of chest pain, subsequent admissions with angina, likelihood of CAD, and frequency of MACE were compared using Chi-square or Fisher's exact tests as appropriate. Additionally, the overall distribution of the CAD likelihood categories between the two groups was compared using the Mann Whitney U test.

8.5 RESULTS

8.5.1 Patient population

A total of 557 patients (median age 55 years, range 22-94 years, male: female ratio 1:1) attending the RACPCs at CWH (n=263) and EH (n=294) over the six-month period were reviewed.

Following risk stratification according to the NICE guidelines, 187 of the 557 patients (33.6%) comprised the NICE-Y group, while 370 (66%) comprised the NICE-N group and would have been excluded from further cardiac investigation.

The vast majority of the NICE-N group would have been excluded due to non-anginal chest pain (360/370 patients, 97 %), with the remainder (10/370 (3%)) excluded due to a CAD likelihood of <10% on risk stratification, despite presenting with atypical angina.

Demographic and clinical information is shown in Table 8.1. Patients in the NICE-N group were, on average, significantly younger than those in the NICE-Y group, with a mean difference of 6.1 years (95% CI 3.8 to 8.4 years, P<0.0001), and were less likely to have risk factors for cardiac disease (67% versus 78%, P=0.007). There were 5% and 17% of patients who had a previous history of CAD in the NICE-N and NICE-Y groups, respectively.

Table 8.1: Study population characteristics (n=557)

CHARACTERISTIC	TOTAL COHORT (%)	NICE-Y (%)	NICE-N (%)	P VALUE
No. of patients	557 (100.0)	187 (100.0)	370 (100.0)	
Gender				
Male	281 (50.4)	99 (52.9)	182 (49.2)	0.462
Female	276 (49.6)	88 (47.1)	188 (50.8)	
Age				
Mean ± s.d.	55.4 ± 13.3	59.5 ± 11.9	53.4 ± 13.6	**<0.001**
Median	55	60	52	
Range	22 - 94	23 - 87	22 - 94	
Cardiac risk factors				
NICE risk factors[a]	396 (71.1)	147 (78.6)	249 (67.3)	**0.007**
Hypertension	253 (45.4)	111 (59.4)	142 (38.4)	**<0.001**
Reported CAD	50 (9.0)	31 (16.6)	19 (5.1)	**<0.001**
Family history of CAD	213 (38.2)	71 (38.0)	142 (38.4)	0.999
Nature of chest pain				
Non-anginal	360 (64.6)	0 (0)	360 (97.3)	**<0.001**
Atypical angina	148 (26.6)	138 (73.8)	10 (2.7)	**<0.001**
Typical angina	49 (8.8)	49 (26.2)	0 (0)	**<0.001**
Likelihood of CAD (%)				

<10	97 (17.4)	0 (0)	97 (26.2)	**<0.001**
10-29	112 (20.1)	8 (4.3)	104 (28.1)	**<0.001**
30-60	168 (30.2)	66 (35.3)	102 (27.6)	0.064
61-90	130 (23.3)	63 (33.7)	67 (18.1)	**<0.001**
>90	50 (9.0)	50 (26.7)	0 (0)	**<0.001**
Admissions with chest pain	24 (4.3)	10 (5.3)	14 (3.8)	0.385
MACE				
Total no. of cases	11 (2.0)	4 (2.1)	7 (1.9)	1.000
MI	6 (1.1)	3 (1.6)	3 (0.8)	0.409
CVA	3 (0.5)	1 (0.5)	2 (0.5)	1.000
ER	4[b] (0.7)	4 (2.1)	0 (0)	0.012
Death	2 (0.4)	0 (0)	2 (0.5)	0.553
Adjudicated diagnosis				
CAD diagnosed	92 (16.5)	57 (30.5)	35 (9.5)	<0.001
CAD excluded	405 (72.7)	107 (57.2)	298 (80.5)	<0.001
Inconclusive	54 (9.7)	22 (11.8)	32 (8.6)	0.292
No follow-up data	6 (1.1)	1 (0.5)	5 (1.4)	0.669

[a]Cardiac risk factors used to define patients at high risk for CAD using the NICE algorithm are any one of diabetes mellitus, smoking or hyperlipidaemia (total cholesterol >6.47mmol/l).

[b]All four patients who underwent emergency revascularisation also had another MACE; three had an MI, and one had a CVA.

The distribution of CAD likelihood according to nature of chest pain, gender, risk and age is shown in Table 8.2. Although no statistical difference was found between the proportions of patients in both groups that had a CAD likelihood of 30-60%, overall the NICE-N group had a significantly higher proportion of patients with lower likelihoods of CAD compared to the NICE-Y group (median CAD likelihood 10-29% versus 61-90% respectively, P<0.001), as would be expected.

Table 8.2: Distribution of RACPC population according to age, sex and nature of chest pain (n=557).

AGE (YEARS)	NON ANGINAL CHEST PAIN				ATYPICAL ANGINA				TYPICAL ANGINA			
	M		F		M		F		M		F	
	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI	LO	HI
<30	3	5	1	1	2	0	0	1	0	0	0	0
30-39	9	17	10	6	1	5	4	4	0	2	0	1
40-49	13	38	20	21	3	11	3	5	2	3	1	1
50-59	10	35	18	35	8	11	2	20	1	6	1	3
60-69	4	26	13	31	1	15	4	14	0	7	4	3
≥70	3	16	7	18	3	15	10	6	0	6	0	8

White: Not routinely recommended for further investigation

Dark grey: Likelihood of CAD 10-29% - recommended for CCT

Mid grey: Likelihood of CAD 30-60% - recommended for functional cardiac testing

Light grey: Likelihood of CAD 61-90% - recommended for invasive angiography

8.5.2 Clinical outcomes

The frequency of subsequent admissions with angina between the two groups was not significantly different (Table 8.3). 17% of the total cohort (n=92) were subsequently diagnosed with significant CAD, of whom over one-third were from the NICE-N group. 10% (n=35) of patients who would have been excluded from further cardiac investigation were subsequently diagnosed with significant CAD within six months.

In total, 11 patients (2%) experienced at least one MACE. Seven patients (64%) who experienced a MACE were from the NICE-N group and all had clinical events (MI, CVA or death) rather than revascularisation; nearly 2% of all patients who would have been denied cardiac investigation using the NICE criteria experienced a MACE. All seven patients had presented with non-anginal chest pain; one was subsequently diagnosed with significant CAD, whereas significant CAD had been excluded in four patients and investigations were inconclusive in the remaining two. As depicted in Table 8.1, the frequencies of MACE were not significantly different between the two groups. The distribution of MACE according to CAD likelihood is illustrated in Table 8.3.

Table 8.3: Distribution of patients with at least one MACE according to CAD likelihood (n=11).

LIKELIHOOD OF CAD (%)	NO. OF PATIENTS WITH AT LEAST ONE MACE (%)
<10	1 (9.1)
10-29	3 (27.3)
30-60	2 (18.2)
61-90	3 (27.3)
>90	2 (18.2)

19 patients in the NICE-N group had a history of known CAD. Even if these patients were excluded, 24/351 remaining patients (7%) would subsequently have been diagnosed with significant CAD, and with a similar frequency of MACE (Table 8.4).

Table 8.4: Comparison of characteristics of patients in the NICE-N group when patients with a history of known CAD were included, versus when such patients were excluded.

CHARACTERISTIC	NICE-N EXCLUDING PATIENTS WITH KNOWN CAD (%)	NICE-N INCLUDING PATIENTS WITH KNOWN CAD (%)
No. of patients	351 (100.0)	370 (100.0)
Gender		
Male	169 (48.1)	182 (49.2)
Female	182 (51.9)	188 (50.8)
Age		
Mean ± s.d.	52.8 ± 13.3	53.4 ± 13.6
Median	51	52
Range	22-94	22 – 94
NICE risk factors	230 (65.5)	249 (67.3)
Nature of chest pain		
Non-anginal	341 (97.2)	360 (97.3)
Atypical angina	10 (2.8)	10 (2.7)
Typical angina	0 (0)	0 (0)
Likelihood of CAD (%)		
<10	97 (27.6)	97 (26.2)
10-29	101 (28.8)	104 (28.1)
30-60	96 (27.4)	102 (27.6)
61-90	57 (16.2)	67 (18.1)
>90	0 (0)	0 (0)
Admissions with chest pain	11 (3.1)	14 (3.8)

MACE		
Total no. of cases	6 (1.7)	7 (1.9)
MI	2 (0.6)	3 (0.8)
CVA	2 (0.6)	2 (0.5)
ER	0 (0)	0 (0)
Death	2 (0.6)	2 (0.5)
Adjudicated diagnosis		
CAD diagnosed	24 (6.8)	35 (9.5)
CAD excluded	292 (83.1)	298 (80.5)
Inconclusive	30 (8.5)	32 (8.6)
No follow-up data	5 (1.4)	5 (1.4)

8.6 DISCUSSION

The results of this study suggest that, in a population of patients attending RACPCs, application of NICE CG95 would result in two-thirds of patients being excluded from further cardiac investigations, primarily due to non-anginal chest pain. A diagnosis of significant CAD will subsequently be made in 10% of these patients, while a MACE will occur in 2%.

The Diamond-Forrester risk stratification model is based on Bayesian analysis that emphasises the importance of age, gender and nature of chest pain. It has been validated against invasive coronary angiography for the diagnosis of obstructive CAD, and confirmed in multiple prospective studies{Chaitman, 1981; Genders, 2011}. Further risk stratification models have been developed that take into account other cardiovascular risk factors (including the Duke clinical score that incorporates the presence of diabetes mellitus, hyperlipidaemia and smoking history) while reiterating the strength of clinical assessment{Pryor, 1993}. In NICE CG95, NICE have essentially amalgamated the Diamond-Forrester and Duke models.

NICE have acknowledged that their model may over-estimate the likelihood of CAD in (lower-risk) community populations, but may simultaneously also underestimate the likelihood of angina as a cause of chest pain (in part because it does not account for the cumulative effect of cardiac risk factors and ignores the risks attributable to history

of established CAD, history of other cardiovascular disease, hypertension and family history of premature CAD). A further important caveat of the model is that it is based on data validated for obstructive, but not non-obstructive CAD.

Recent multicentre trial evidence reinforces the idea that CAD (whether non-obstructive or obstructive) is prevalent amongst stable patients even when no modifiable risk factors are present and that an increasing burden of CAD in such patients is predictive of MACE{Leipsic, 2013}. These limitations may help explain why 10% of the population excluded from further investigation in our study had a subsequent diagnosis of significant CAD.

In clinical reality, RACPC patients with a prior history of known CAD (whether substantiated or not) would undergo further investigation even if they were categorised as low-risk according to NICE CG95. The guideline does make provision for such an approach, stating that clinical suspicion could be raised 'based on other aspects of the history and risk factors'{NICE, 2010}. To test this argument, the analysis was repeated, excluding those with a history of known CAD. The results demonstrate that even allowing for this more liberal application of NICE CG95, the frequency of subsequent CAD diagnosis and MACE remained essentially unchanged.

Studies documenting MACE frequency{Jespersen, 2012; Six, 2013; Body, 2014; Kelly, 2013} have varied with respect to the type of populations studied, the durations of follow-up, and their clinical settings. As such, the definition of an 'acceptable' MACE rate is still a subject of debate{Brace-McDonnell, 2014}. While a 2% risk of MACE appears low, the financial implications of the study findings are not inconsiderable. If extrapolated to the 700,000 annual ED admissions for chest pain, a 2% risk of MACE may translate into 14,000 patients per year experiencing a major cardiac event within six months of presentation and up to 70,000 subsequently being diagnosed with significant CAD. Not investigating these patients deemed at low risk of CAD may, in fact, result in patients re-presenting with cardiac events that are significantly more resource intensive and expensive to manage.

One method of improving the performance of the NICE CG95 model may be to allow provision for clinical assessment to be combined with one more non-invasive tests, even in patients with non-cardiac chest pain. Comprehensive clinical risk scores incorporating a demographic, clinical and diagnostic testing offer prognostic information in the evaluation of ACS, but have yet to be widely validated or adopted in the evaluation of the patient presenting with recent-onset chest pain{Morrow, 2010}. Non-invasive functional tests provide vital information on reversible disease, but are not quick to perform. CT coronary angiography and coronary calcium scoring, with their high sensitivity for CAD{Mowatt, 2008}, are another alternative especially as ever improving radiation dose reduction strategies in CCT become available.

Evidence suggests that a stepwise approach, combining an extended version of the Duke clinical score with coronary calcium scoring, improves the predicted probability of disease in lower risk populations{Genders, 2012). NICE CG95 currently recommends CT calcium scoring in patients with a low (10-29%) likelihood of CAD. There is emerging evidence that extending CT calcium scoring to patients with low and intermediate pre-test probability of CAD, in addition to (but not in place of) clinical assessment could also improve CAD prediction{Genders, 2010; Mouden, 2013}.

Coronary CTA measures of CAD severity have independent prognostic value{Chow, 2011} and a prognostic score incorporating plaque burden and stenosis may have merit for risk prediction beyond clinical risk scores alone{Hadamitzky, 2013}. Biomarker measurement (e.g. highly sensitive Tn assays) is also showing increasing promise as a risk prediction tool for cardiovascular events and mortality for patients with stable chest pain{Omland, 2013; Lyngback 2013}, but has yet to be incorporated into guidelines on the diagnosis of patients with stable CAD.

8.7 LIMITATIONS

Due to its retrospective nature, typicality of chest pain had to be estimated from note review, and variable interpretations of the nature of chest pain could have resulted in some patients in the excluded group (particularly in the small number of patients with a history of known CAD) actually being recommended for further investigation.

The absolute number of MACE was also small, and comparisons between rates in the excluded and included groups should be viewed with caution, as should their extrapolation. The use of medical records to determine the occurrence of MACE in this study may have contributed to the true incidence being underestimated. Options to minimise this bias in future studies include corroboration via patients' general practitioners or patient status tracking via the Office of National Statistics.

Extending the period of study follow-up beyond six months may also facilitate greater understanding of the risks of adopting the NICE CG95 in the RACPC setting.

8.8 LEARNING POINTS

- Application of NICE CG95 to a RACPC population may result in up to two-thirds of patients being excluded from further cardiac investigation.
- Up to 10% of patients excluded from further cardiac investigation are subsequently diagnosed with significant coronary artery disease, and 2% experience a major adverse cardiac event within six months of presentation.
- Up to two-thirds of all major adverse cardiac events may occur in patients diagnosed with non-cardiac chest pain on the basis of history.
- Information offered by the addition of an anatomical test, such as CCT, or cardiac-specific biomarkers (as these are increasingly validated) may allow more robust risk stratification and appropriate reassurance to those with normal or minor CAD.
- Adherence to the NICE algorithm alone should not be used to justify excluding patients from further investigation if CAD is clinically suspected.
- The results are also a reminder that guidelines are not edicts{Rastogi, 2014} and should not be used as a substitute for clinical judgement or experience in the assessment of chest pain.

CHAPTER 9: PROSPECTIVE ASSESSEMENT OF THE UTILITY OF CARDIOPULMONARY CT IN PATIENTS ADMITTED WITH DYSPNOEA TO THE ACUTE MEDICAL SETTING

9.1 INTRODUCTION

Dyspnoea, the subjective sensation of breathlessness, is among the most common causes of presentation to the acute medical services. Breathlessness may result from a number of independent or concurrent pathologies, most commonly respiratory or cardiac in origin. Evidence suggests that a proportion of diagnoses are missed by treating clinicians using existing assessment algorithms{Stevenson, 1989; Remes, 1991; Pope, 2000; Mascarenhas, 2010}.

CT is already extensively used in the investigation of suspected lung disease. Over the past decade there has been mounting evidence that CT may also be used to provide accurate, reproducible assessment of cardiac pathology, and specifically CAD. Technological advances in cardiac CT and intravenous contrast injection protocols have enabled the development of CPCT protocols that simultaneously image the coronary, pulmonary and aortic beds, allowing the diagnosis or exclusion of CAD, pulmonary embolism, aortic dissection and other clinically significant intra-thoracic disease. In the past, the prolonged period of breath-holding required for image acquisition limited the utility of CPCT in breathless patients; however, high resolution images can be now obtained in a single, short, breath-hold.

The potential of CPCT as a fast and all-inclusive diagnostic study is appealing for clinical practice. Further to evidence that the use of CCT may increase diagnostic sensitivity and specificity in patients presenting to the emergency department with acute chest pain{Rubinshtein, 2007}, CPCT has been shown to eliminate the need for further diagnostic testing in over 75% of patients{Takakuwa, 2008}. In particular, CPCT has proven utility in the triage of patients safe for early discharge from hospital{Henzler, 2013}.

One small survey reported that 18% of radiology departments have protocols for CPCT{Thomas, 2008}. CCT and CPCT are becoming increasingly important for the clinical risk stratification of patients presenting to hospital with stable chest pain and

suspected ACS. However, studies that have considered the role of CPCT in patients with acute dyspnoea are lacking. To date, there is only one study looking into the utility of CPCT in acutely breathless patients, and this study is in the context of suspected CAD{Rogers, 2011}. The broad overlap between the conditions causing chest pain and dyspnoea would suggest CPCT may also be diagnostically useful, improve the efficiency and downstream clinical outcomes of acute dyspnoea evaluations.

9.2 AIMS

This aims of this study were to:

- Evaluate the spectrum, prevalence and significance of radiological findings in patients attending Chelsea and Westminster Acute Assessment Unit with symptoms of acute dyspnoea.
- Describe the diagnostic yield, clinical outcomes and downstream resource use of patients undergoing CPCT in clinical practice.

9.3 PATIENTS AND METHODS

Consecutive patients who presented to the acute assessment unit of Chelsea and Westminster Hospital with the primary complaint of new or worsening dyspnoea, over a fourteen month period from July 2010, were screened for entry to the study. Exclusion criteria, common to other studies involving CT in this thesis, are detailed in Chapter 2.

Enrolled patients underwent a structured history and physical examination at admission. CPCT was performed once optimal heart rate had been achieved according to the protocol detailed in Chapter 2. CT scans were assessed by a trained clinician for CCS, the presence/absence of coronary artery stenoses, mediastinal, pulmonary vascular and pulmonary parenchymal pathology. Where the field of view permitted, review of the upper abdominal organs also occurred. Radiological findings were classified according to location and clinical importance, as detailed in Chapter 2. CT

reports were made available to the treating clinicians, who were solely responsible for further management.

Two sub-groups were identified; those patients who achieved a diagnostic quality CPCT (CPCT-Y) and those patients who did not achieve a diagnostic quality CPCT (CPCT-N).

Data relating to clinical presentation, demographics, risk factor profiles (i.e. diabetes mellitus, smoking history, hyperlipidaemia and hypertension) and clinical course were collated for all patients. Medical records were reviewed to obtain results of all diagnostic tests performed during the hospital admission and in the 6 months post admission. Downstream investigations were defined as all cardiac and respiratory tests occurring from admission to completion of follow-up. Data were corroborated by telephone survey of patients and their general practitioners at 6 months.

Diagnoses documented in the medical notes at initial clerking and consultant review and in the EPR discharge summary were collated. The diagnostic performance of CPCT was assessed using adjudicated discharge diagnoses as reference standards. Diagnosis of MACE was based on the judgment of a clinician with access to all clinical and laboratory data, and test results through 6 months of follow-up.

A descriptive analysis was also performed for the sub-group of patients in the CPCT-Y group with a previous COPD diagnosis.

9.4 STATISTICAL ANALYSES

Using evidence that 35% of asymptomatic patients have evidence of pulmonary pathology on CT{Gil, 2007}, we performed a calculation using the one-sample z test for population proportion. This indicated that a sample size of 250 would yield a 95% confidence interval of width 13% in the prevalence of clinically significant pathology.

Outcome data were analysed using descriptive statistics. Continuous variables were expressed as mean values with standard deviations, ranges and median values where appropriate. For non-continuous variables, counts and % frequencies were used. Categorical variables were compared using Chi-square or Fisher's exact tests and the

Mann Whitney U test was used for the analysis of non-normally distributed continuous variables. Additionally, the distributions of CAD likelihood and clinical risk scores for patients in the CPCT-Y and CPCT-N groups were compared using the Mann Whitney U test.

9.5 RESULTS

9.5.1 Patient population

A total of 530 patients attending the acute assessment unit at Chelsea and Westminster Hospital, with symptoms of dyspnoea, were screened during the enrolment period. It was apparent from early in the recruitment phase that the target of 250 study participants was unlikely to be achieved based on high exclusion rates. Exclusion criteria were identified in 89% (n=474). The reasons for exclusion are detailed in Table 9.1.

Table 9.1: Recruitment analysis

Number of patients screened	**530 (100.0)**
Number of patients recruited	**56 (10.6)**
Number of patients screened but not recruited	**474 (89.4)**
Reasons for non-recruitment:	
Age <40 years	73 (13.8)
Acutely unwell/unstable	48 (9.1)
Previous coronary intervention	16 (3.0)
Resting HR >70pbm	27 (5.1)
Poorly controlled asthma	0 (0.0)
Cardiac CT within preceding 3 months	28 (5.3)
CI to contrast including CKD	20 (3.8)
Palliative care	20 (3.8)
Enrolled in parallel study	6 (1.1)
Unable to provide written consent	65 (12.3)
Declined written consent	78 (14.7)
Lack of time	10
Concerns regarding radiation	23
Contrast	0
Medical advice	2
Other	43
Logistical issues	49 (9.2)
Discharged from hospital	44 (8.3)

56 patients (median age 68 years, range 41-90 years, male: female ratio 1:1.5) were recruited to the study. 43 patients completed CPCT imaging, resulting in 35 scans of diagnostic quality (Figure 9.1). Thus, the CPCT-Y group comprised 35 patients and the CPCT-N comprised the remaining 21 patients. Demographic and clinical information for both groups is detailed in Table 9.2.

Figure 9.1: Scanning profiles for recruited patients (n=56)

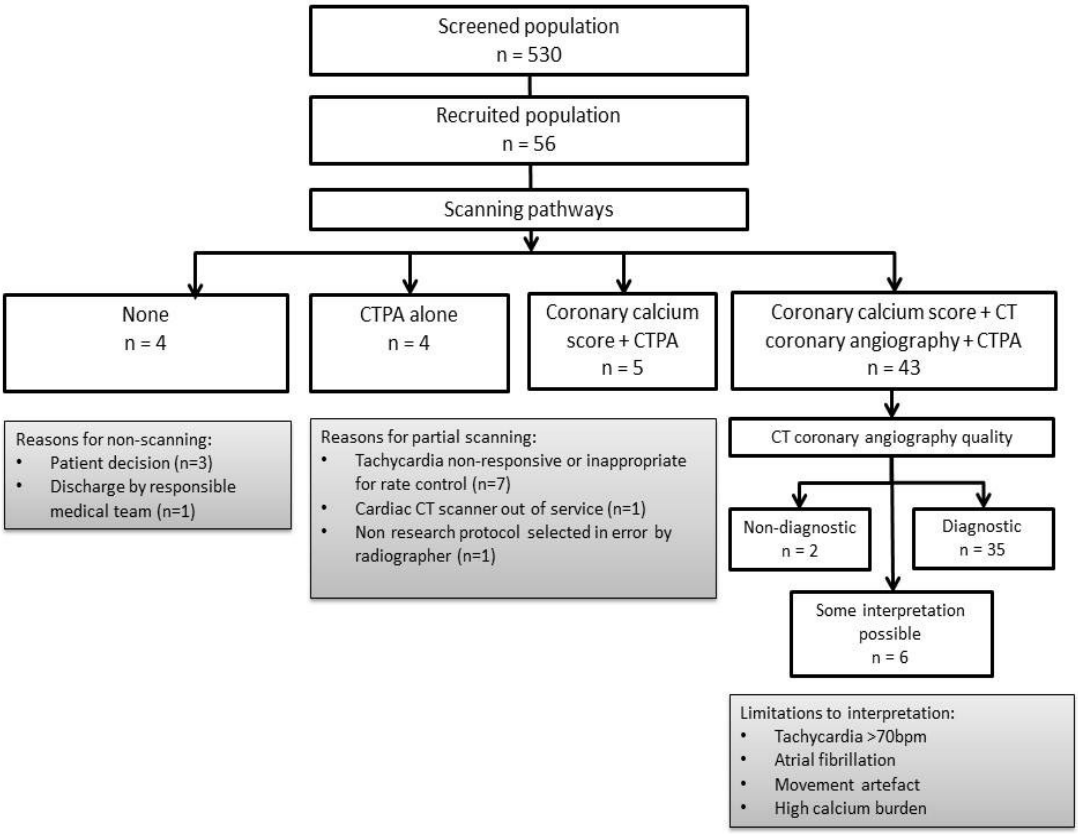


Table 9.2: Study population characteristics (n=56)

CHARACTERISTIC		TOTAL (%)	CPCT-Y (%)	CPCT-N (%)	P VALUE
No. of patients		56 (100.0)	35 (100.0)	21 (100.0)	
Gender					
	Male	23	15 (42.9)	8 (38.1)	0.785
	Female	33	20	13	
Age					
	Mean ± s.d.	68.80 ± 13.93	67.94 ± 13.19	70.24 ± 15.31	0.571
	Median	68	66	72	
	Range	40-97	40-90	41-97	

Cardiac risk factors					
	NICE risk factors[a]	43 (76.79)	27 (77.1)	16 (76.2)	1.000
	Hypertension	26	17	9	0.785
	Reported CAD	4	1	3	0.143
	Family history of CAD	10	7	3	0.727
Pack year smoking history					
	Mean ± s.d.	22.95 ± 28.86	26.77 ± 31.57	16.57 ± 22.96	
	Median	11.25	20	5	0.180
	Range	0-140	0-140	0-80	
NYHA					
	Mean ± s.d.	2.18 ± 0.92	2.00 ± 0.94	2.48 ± 0.81	0.051
	Median	2	2	2	
	Range	1-4	1-4	1-4	
TIMI score[a]					
	Mean ± s.d.	1.25 ± 0.98	1.03 ± 0.82	1.62 ± 1.12	
	Median	1	1	1	0.0615
	Range	0-4	0-3	0-4	
Wells Score[b]					
	Mean ± s.d.	2.03 ± 2.18	2.01 ± 2.33	2.05 ± 1.97	
	Median	1.5	1.5	1.5	0.741
	Range	0 -10.5	0 -10.5	0 - 7	
Length of stay					
	Mean ± s.d.	4.67 ± 5.04	3.61 ± 3.51	6.44 ± 6.61	
	Median	2.60	2.24	2.87	0.112
	Range	0.32-24.13	0.32-15.13	0.97-24.13	
Downstream investigations					
	CXR	56	35	21	1.000
	ECHO	22	11	11	0.161
	Exercise ECG	1	1	0	1.000
	Functional imaging	11	7	4	1.000
	Invasive angiography	0	0	0	1.000
	Doppler uss	1	1	0	1.000
	VQ scan	0	0	0	1.000
	CPCT	35	35	0	**<0.001**
	Non-CPCT protocol CT	21	4	17	**<0.001**
	Bronchoscopy	4	2	2	0.626
	Pulmonary function test	0	0	0	1.000
	TOTAL	151	96	55	0.773
OPD clinic appointments					
	Respiratory				

	Mean	0.80 ± 1.34	0.86 ± 1.48	0.71 ± 1.10	0.682
	Median	0	0	0	
	Range	0-7	0-7	0-3	
Cardiology					
	Mean	0.52 ± 0.89	0.46 ± 0.89	0.62 ± 0.92	0.522
	Median	0	0	0	
	Range	0-3	0-3	0-3	
General Medicine					
	Mean	0.34 ± 0.75	0.40 ± 0.88	0.24 ± 0.44	0.364
	Median	0	0	0	
	Range	0-3	0-3	0-1	
TOTAL		230	149	81	0.741
Re-presentation to ED with dyspnoea		17	7	10	**0.039**
Re-admission with dyspnoea		15	8	7	0.534
MACE		0	0	0	1.000

[a]Reference: Antman, 2000

[b]Reference: Wells, 2000

There were no statistical differences between the groups with respect to age, gender, cardiac risk factor profiles or smoking history, although the CPCT-Y group tended towards a greater pack-year smoking history (P=0.180).

9.5.2 Clinical outcomes (for the CPCT-Y group, n=35)

In the CPCT-Y group, CPCT was unremarkable in 9% (n=3) of patients scanned. Abnormalities on CPCT were identified in 91.4% (n=32). In 65.7% (n=23), multiple abnormalities were identified, and in 60% (n=21), findings were defined as significant. A total of 120 abnormal findings were identified. Of these, 24 were classified as benign, 70 as indeterminate and 26 as significant (Table 9.3).

Table 9.3: Benign, intermediate and significant findings on CPCT (n= 35)

CLINICAL SIGNIFICANCE	SYSTEM	FINDING	NUMBER	% OF TOTAL
SIGNIFICANT	**CARDIAC**	CAD >50%	7	20.0
		Intra-cardiac thrombus	1	2.9
	PULMONARY	Pulmonary embolism	7	20.0
		Pulmonary nodule >3cm or lesion with malignant characteristics	3	8.6
		Pleural lesion with malignant characteristics	1	2.9
		Unilateral pleural effusion	2	5.7
		Pneumothorax	1	2.9
	MEDIASTINAL	Aortic aneurysm with mural thrombus	1	2.9
	OTHER	Bone lesion with malignant characteristics	1	2.9
INTERMEDIATE	**CARDIAC**	CAD <50%	15	42.9
		Valve calcification	3	8.6
		Poorly enhancing myocardium	1	2.9
		Pericardial effusion	1	2.9
	PULMONARY	Pulmonary nodule >0.8 and <3cm	8	22.9
		Atelectasis	10	28.6
		Ground glass change/consolidation	12	34.3
		Pulmonary fibrosis	2	5.7
		Pleural thickening	1	2.9
		Bilateral pleural effusion	2	5.7
	MEDIASTINAL	Mediastinal mass lesion	1	2.9
		Thyroid mass lesion/enlargement	2	5.7
		Lymphadenopathy	6	17.1
	OTHER	Hepatic lesion/cyst	3	8.6
		Renal lesion/cyst	2	5.7
		Axillary fluid collection	1	2.9
BENIGN	**CARDIAC**	Left ventricular hypertrophy	1	2.9
	PULMONARY	Emphysema	6	17.1
		Bronchiectasis	4	11.4
	OTHER	Hiatus hernia	5	14.3
		Spinal degeneration	5	14.3
		Bone haemangioma	1	2.9
		Bone fracture	3	8.6
		Small volume kidneys	1	2.9

9.5.2.1 Cardiovascular outcomes

Mean CCS was 206.25 (s.d. ± 399.88; median 2; range 0-1693). 46% (n=16) of patients scanned had a score of zero, 40% (n=14) had a score <400 and14% (n=5) had a score

>400. On CTA, 37.1% (n=13) had no evidence of CAD, 43% (n=15) had non-significant stenosis and 20% (n=7) had significant stenosis, based on luminal obstruction >50%.

In patients with known COPD (n=10), 60% (n=6) had non-significant stenosis and 20% (n=2) had significant stenosis on CTA.

9.5.2.2 Pulmonary vascular outcomes

Pulmonary embolism was detected in 20% (n=7) of patients scanned. In five patients the emboli were acute and two were chronic. Emboli were distributed in the main pulmonary artery (n=2), the lobar arteries (n=1), the segmental arteries (n=2) and the sub segmental arteries (n=2). Emboli were identified in 20% (n=2) of the 10 patients with known COPD.

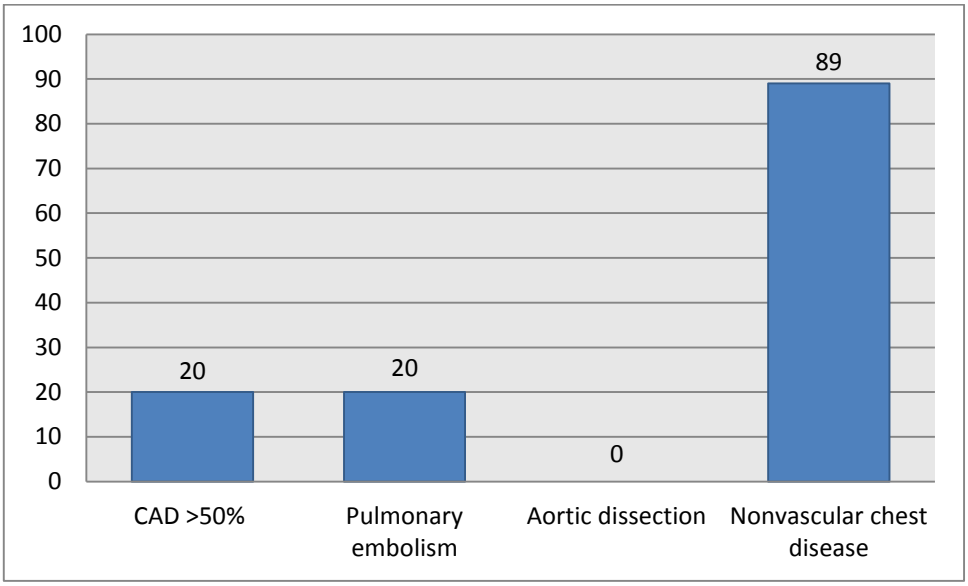
9.5.2.3 Aortic outcomes

No patients were found to have aortic dissection.

9.5.2.4 Non-vascular chest outcomes

Non-vascular chest disease was identified in 89% (n=31) of patients scanned. As detailed in Table 9.3, the most commonly identified non-vascular pathologies were consolidation (identified in 34%), atelectasis (29%), emphysema (17%), lymphadenopathy (17%) and hiatus hernia (14%).

Figure 9.2: Diagnostic yield with CPCT (%)



9.5.2.5 Impact of CPCT on diagnosis

A radiological diagnosis for dyspnoea was identified in 94% (n=33) of patients scanned; either pulmonary (54%; n=19), cardiac (20%; n=7) or both (20%; n=7). No extra-thoracic causes of dyspnoea were identified.

Inclusion of CPCT in the diagnostic pathway resulted in a refined diagnosis (i.e. modified during the course of admission in light of CPCT findings) for 49% (n=17) of patients scanned.

9.5.2.6 Adverse events

One patient undergoing CPCT experienced bronchoconstriction in response to intravenous contrast. All participants survived to hospital discharge and mortality was nil for the following six months with no major adverse cardiac events.

9.5.3 Resource utilisation

Over the 6 month follow-up period, there was a tendency towards an increased frequency of cardiopulmonary investigations in the CPCT-Y group but this was not statistically significant (P=0.773).

CPCT resulted in a reduced frequency of non-cardiopulmonary investigations (P=0.383). Investigations performed in the CPCT-Y cohort were abdominal uss (n=4), abdominal MRI (n=1), thyroid uss (n=1), bone studies (n=2) and GI endoscopy (n=2). Investigations performed in the CPCT-N cohort were abdominal uss (n=1), abdominal MRI (n=1), bone studies (n=3) and GI endoscopy (n=2).

Although mean and median length of stay were lower in the CPCT-Y group, the difference was not statistically significant (P=0.112). 14 patients represented to the emergency department and/or were readmitted with dyspnoea on at least one occasion. Patients in the CPCT-Y group were significantly less likely to represent (P=0.039) but there was no significant difference in the likelihood of patients being re-admitted between the two groups (P=0.534).

9.6 DISCUSSION

This pilot study highlighted clinical and logistical challenges to the introduction of CPCT in the acute medical setting. In those patients for whom a diagnostic CPCT was achieved, a radiological diagnosis for dyspnoea was identified in 94% and inclusion of CPCT in the diagnostic pathway impacted upon the diagnoses made by treating clinicians in 49% of patients scanned. CPCT also revealed incidental pathology ranging from clinically significant to benign in 89% of patients scanned. The CPCT approach resulted in increased diagnostic testing but reduced hospital length of stay and re-presentation to the emergency department without a detected increase in MACE.

In this selected population of patients presenting with dyspnoea, the diagnostic yield with CPCT was equal for coronary artery disease and pulmonary embolism. No patients were diagnosed with aortic dissection, making it impossible to estimate the performance characteristics of CPCT for this condition. The results highlight a difference between patients undergoing CPCT for dyspnoea and chest pain. In the emergency department setting, the majority of the pathology yield in patients with chest pain is from CAD, with a trivial contribution from new pulmonary embolism{Feldmann, 2013}.

20% of patients undergoing diagnostic CPCT demonstrated at least 50% diameter coronary artery stenosis, warranting further workup. The results raise concern that standard assessment for acute breathlessness, which does not include dedicated cardiac assessment, may lead to the under-diagnosis of clinically significant CAD in up to one fifth of patients presenting to acute assessment units.

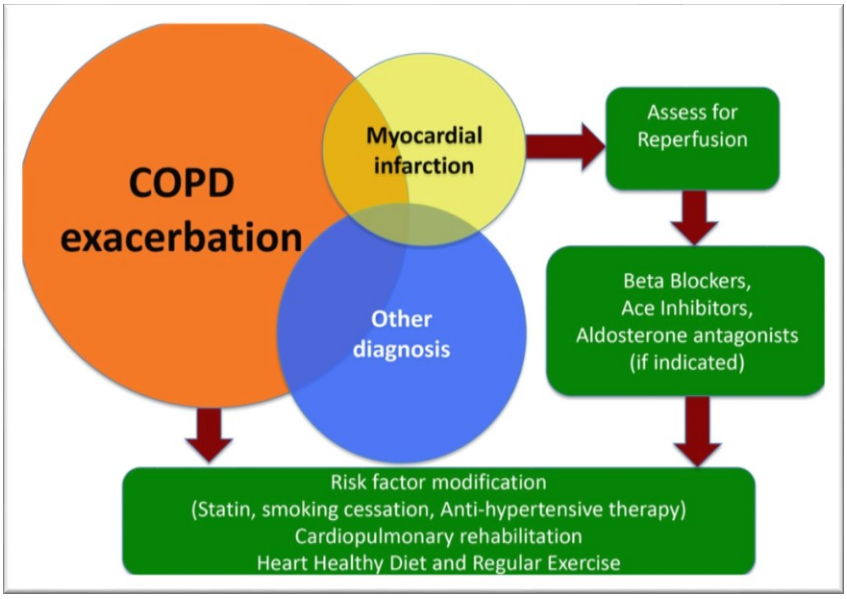
Dyspnoea as a marker of myocardial ischaemia was first described in 1968, when Phibbs identified dyspnoea alone in 26% of patients at the time of a positive exercise test{Phibbs, 1968}. Data from the GRACE study suggest 8% of patients with ACS present without chest pain{Brieger, 2004} and the EuroHeart data set has shown around one quarter present with breathlessness at rest{Hamaad, 2004}. A missed diagnosis of CAD in patients with dyspnoea or another painless presentation of unstable angina increases the likelihood of poor outcome in a population already recognised to have greater morbidity and higher mortality than patients with typical symptoms{Brieger, 2004; Steg, 2004}. Thus, CPCT assessment of selected breathless patients may be particularly useful in atypical presentations of CAD.

Where CPCT may have the greatest potential is in the exclusion of CAD in patients with COPD. In this study 80% of patients scanned with COPD had evidence of CAD. COPD is recognised as an independent risk factor for CAD, increasing the odds of disease by a factor of 2.7{Finkelstein, 2009}. One-third of deaths in patients with COPD are attributable to cardiovascular disease and cardiovascular mortality increases by 28% for every 10% decrement in FEV1{Anthonisen, 2002}. Patients with COPD commonly exhibit an atypical presentation, reporting dyspnoea more frequently and chest pain less frequently than patients without COPD{Andell, 2014}. Patients with COPD are more likely to be misdiagnosed and undertreated, contributing to excess mortality in this group{Andell, 2014}.

It has been suggested that myocardial ischaemia should be considered in every patient presenting an exacerbation of COPD, recognising that an ACS may coexist with another acute illness (Figure9.3). There is some reticence to use beta-blockers in COPD patients which may limit the application of CPCT in this context (although rate control will become less important with advances in CT technology), despite increasing evidence

that beta-blockers are safe and can actually be beneficial in patients with COPD{Quint, 2013}.

Figure 9.3: A suggested approach to patients with COPD presenting with dyspnoea{Sinha, 2014}



An atypical presentation of myocardial infarction (MI) should be considered in every patient presenting with COPD exacerbation. Patients with COPD and MI should be urgently assessed for revascularisation and started on guideline-based therapy. Any hospitalisation in a patient with COPD, even in the absence of an MI, should be considered an opportunity to assess and optimise their coronary risk factors.

In a previous study of patients undergoing CPCT for suspected ACS, a 1.5% prevalence of pulmonary embolism was detected{Takakuwa, 2008}. Based on pilot data, detailed in Chapter 1, we predicted a less than three percent prevalence of pulmonary embolism in patients admitted with acute dyspnoea. By contrast, this study identified pulmonary embolism in 20% of patients undergoing a diagnostic CPCT. Our figures correlate with the 'acceptable' yield of 9-19% reported with dedicated CT pulmonary angiography protocols{Anderson, 2007; Constantino, 2008} and with Schertler et al. who identified acute PE in 21% patients with suspected PE using CPCT{Schertler, 2009}.

Our results also correlate with studies in COPD that have shown up to twenty five percent of patients with an exacerbation of unknown origin have pulmonary embolism on CT{Rizkallah, 2009; Tillie-Leblond, 2006}, further supporting a role for CPCT in this

population. Identifying PE in patients with COPD is of vital importance due to the increased relative risk of death at one year when the conditions occur concurrently (RR 1.94 versus RR 1.14 with PE alone){Carson, 1996}.

Published data suggest around 7.7% of COPD patients have aneurysmal changes of the aorta{Lindholt, 1998}. Genetic susceptibility to extracellular matrix degradation and secondary inflammation are proposed as common mechanisms in both COPD and aneurysm formation{Ramnath, 2014}. Although it is rare for aortic rupture to present with dyspnoea, there are case reports of painless left sided haemothorax with non-catastrophic events{Poondru, 2014}. Given the low prevalence of aortic dissection in patients presenting with chest pain {Ayaram, 2013} and the absence of dissection amongst our study population of patients with dyspnoea, CPCT may not be justified in the diagnosis of this condition.

Data from chest pain studies suggest that CPCT detects up to a 45% prevalence of undiagnosed non-cardiac pathology{Lehman, 2009; Machaalany, 2009; Burt, 2008}, although not all pathology is of clinical significance. In a study of 197 patients at low to moderate risk of ACS, CPCT provided a non-coronary diagnosis in 11% of patients{Takakuwa, 2007}. In our study population we identified non-vascular chest disease in 89% of patients undergoing a diagnostic CPCT, which explained breathlessness in 49% of patients scanned. The CT findings were predominantly consolidation and atelectasis, which it may be argued can be diagnosed by x-ray with a lower radiation dose; however, around one in five patients were noted to have pulmonary nodularity that would not have been detected by x-ray and one patient was diagnosed with new lung adenocarcinoma as a result.

In the absence of guidelines constraining the tendency to follow-up incidental non-coronary findings, the use of CPCT may increase costs for the work-up of individual patients and lead to patient anxiety without proven benefit{Budoff, 2007}. However, early identification of some incidental findings may allow early intervention, improve health outcomes and reduce overall costs for the treatment of more advanced disease{Gruettner, 2013}. In this study, assessment involving CPCT resulted in an

increased frequency of diagnostic testing but fewer non-cardiopulmonary investigations, indicating CPCT may have facilitated more targeted test selection.

In contrast to CPCT performed to investigate chest pain{Rogers, 2011}, this study suggested the use of CPCT reduced length of stay in patients presenting with undifferentiated dyspnoea. This is particularly relevant give our observation in Chapter 3 that patients with undifferentiated dyspnoea remain in hospital for around three days longer than those with chest pain. The effect is likely to have been underestimated as not all CCT reports were available to responsible clinicians prior to patient discharge (whereas pulmonary imaging was reported directly). Early discharge following CPCT occurred without an increase in MACE, suggesting there were no significant missed diagnoses as a result.

Although this study supports the use of CPCT to facilitate early discharge in patients with acute dyspnoea, there is justifiable concern regarding high exposure to ionising radiation and intravenous contrast, exceeding that for dedicated pulmonary and cardiac angiographic protocols. Furthermore, the incidence of poor/uninterpretable image quality, noted in around one fifth of scans performed in this study, has been found to be greater with CPCT (CPCT 10% vs. coronary CTA 8%, $P<0.01$){Burris, 2013}.

It has been proposed that dedicated angiographic protocols should be performed as a first line when there is a significant pre-test likelihood of CAD/ PE/aortic dissection. Where there is diagnostic uncertainty, particularly amongst groups at increased risk of atypical presentation, this study confirms a high diagnostic yield using CPCT. Given the low frequency of findings in aortic dissection, CPCT may be best utilised for patients with suspected pulmonary embolism{Schertler, 2009} or in COPD where it is important to exclude CAD and occult PE. CPCT should ideally be reserved for older patients who have relatively lower risk of lifelong radiation-induced cancer.

9.7 LIMITATIONS

The relatively small study population limits the significance of the data; however, this is the first study that has specifically addressed the role of CPCT in dyspnoeic patients and it provides a baseline for further prospective, potentially multi-centre, trials.

Larger studies may also allow comparison of risk scores (e.g. NYHA, TIMI, Wells) and/or smoking history with radiographic findings.

In the course of this study, cardiac CT reports were not always available for the treating clinicians prior to discharge although they received the results at a later point. This limits the impact of the investigation on hospital length of stay and may have contributed to the relatively low levels of downstream functional cardiac testing and invasive coronary angiography despite a 20% prevalence of significant CAD on CPCT. Failure of timely reporting is also likely to have minimised differences between the CPCT-Y and CPCT-N groups and therefore underplayed the impact of CPCT on outcomes and downstream resource use.

Extending the period of study follow-up beyond six months and more broadly exploring the downstream effects of CPCT (e.g. the composite financial contribution of evaluation, monitoring, full investigation and therapy and the impact on quality-adjusted-life-years) may have facilitated greater understanding of the risks and benefits of CPCT and the recognition of scenarios in which CPCT does, and does not, add 'value'.

9.8 LEARNING POINTS

- CPCT is feasible in selected patients presenting with acute dyspnoea and reveals a wide range of vascular and non-vascular chest disease.
- 20% of patients with undifferentiated dyspnoea have evidence of CAD on CPCT; in those patients with known COPD the prevalence is 80%
- 20% of patients with undifferentiated dyspnoea have pulmonary embolism; prevalence is the same in patients with known COPD
- Inclusion of CPCT in the diagnostic pathway of patients with undifferentiated dyspnoea results in a refined diagnosis for up to half of those scanned.
- The use of CPCT does not result in increased adverse patient events, suggesting the technique may be useful to aid early discharge of patients presenting with undifferentiated dyspnoea.

- CPCT reduces re-presentation to the emergency department with acute dyspnoea and with improved and prompt diagnosis, may contribute to reduced risk of hospital readmission.

CHAPTER 10: CONCLUSION

10.1 REVIEW OF FINDINGS

The studies within this thesis sought to explore a potential role for cardiopulmonary assessment with multi-detector CT and provide insights into the potential clinical role for this evolving new technology.

At the inception of this thesis, there was a body of evidence demonstrating good to excellent diagnostic accuracy of cardiac CT for the non-invasive visualisation of coronary arteries {Meijer, 2008} with high negative predictive values for the presence of stenotic disease{Mowatt, 2008; Marano, 2009}. From 2008 onwards, there was also increasing evidence to support the diagnostic utility of comprehensive CPCT in patients with acute chest pain, via the simultaneous evaluation of the coronary arteries, pulmonary arteries, thoracic aorta and other intra-thoracic structures{Rubinshtein, 2007; Gallagher, 2008}.

Where the evidence was more sparse was in the clinical utility of these techniques, particularly outside the emergency department setting e.g. in acute medical admissions and rapid access chest pain clinics. At the time, there was debate regarding whether cardiac CT should be limited to patients with chest pain at low risk of CAD {NICE, 2010} and CPCT was being evaluated in patients at low-intermediate risk of CAD with possible aortic/pulmonary arterial pathology{Halpern, 2009}. Until this thesis, the concept of using CPCT in patients presenting with acute dyspnoea had not been introduced.

10.1.1 Chapter 3

The inadequacy of existing diagnostic pathways for undifferentiated chest pain and dyspnoea were highlighted in this retrospective survey of patients admitted to Chelsea and Westminster Hospital over a 5 year period. Of these patients, between 30% and 40% of patients were discharged without a documented diagnosis. Considering the potential of cardiopulmonary CT as a rapid, all-inclusive diagnostic test, we identified that CT was performed in only 10% of patients admitted with acute chest pain, although uptake was higher in patients admitted with acute dyspnoea(32%; P=0.047).

10.1.2 Chapter 4

This prospective pilot study assessing the feasibility and clinical utility of cardiac CT within a diagnostic pathway for acute medical admissions with symptoms of chest pain highlighted clinical and logistical challenges.

Despite broad inclusion criteria to recruit patients with low to moderate risk of CAD (likelihood 10-90%), the study recruitment rate was less than 10%. Over 50% of individuals screened were ineligible for CCT due to clinical reasons (i.e. known CAD with previous intervention, high likelihood of CAD, features of acute myocardial infarction). The proportion of ineligible patients would have been still higher if NICE CG95 criteria, which restrict CCT to low risk patients, been applied.

There was patient reticence to undergo CCT. One third of patients offered CCT declined the investigation. Although radiation and contrast burden were contributing factors, most patients declined CCT to expedite hospital discharge. The non-availability of CCT outside routine working hours limited our ability to scan patients within 24 hours of admission and for CCT to add benefit to the data available to clinicians, investment to provide an out of hours service should be considered.

In the recruited cohort of 14 patients, diagnostic yield for significant CAD was 21%. Compared with standard practice in a historical cohort, a diagnostic pathway involving CCT resulted in a greater proportion of patients for whom CAD was diagnosed or excluded (100% versus 79%; P=0.222). Following CCT there was a 100% increase in functional imaging but a 100% decrease in invasive angiography (although absolute numbers were small and should be extrapolated with caution). Despite a greater number of investigations performed in patients undergoing CCT, costs per capita were 13.6% lower than with standard care.

Inclusion of CCT in the diagnostic pathway for acute chest pain admissions had no significant impact on hospital length of stay, hospital re-attendance or re-admission with chest pain over a three month follow-up but an absolute rate of MACE of zero confirmed no detrimental cardiovascular effects with the CCT pathway.

10.1.3 Chapter 5

In the future, it is likely that the diagnostic investigations undertaken for medical admissions with suspected cardiac chest pain will be aligned to those recommended by NICE CG95. This retrospective study analysed the impact of NICE CG95 on referrals for cardiac investigation for the population of medical admissions with acute chest pain described in Chapter 4.

Using NICE criteria, 51% of study population would have been excluded from further cardiac testing based on pain deemed non-anginal or a likelihood of CAD <10%. Exercise ECG would not have been recommended in this context. 1% of the study population would have been recommended for CCT, 6 % for functional testing and 9% for invasive coronary angiography. Based on NICE criteria, all patients aged 70 years or older with typical or atypical angina symptoms would have been assigned a likelihood of CAD whereby they would have been referred for angiography or presumed to have angina.

The results raise concern that adoption of NICE CG95 may result in missed cardiac diagnoses and therefore increase mortality risk. NICE CG95 also appears to undervalue CCT despite favouring anatomical diagnosis over functional assessment.

Overall, the results do not support local investment in inpatient CCT services to meet NICE CG95 and resources may be better directed towards functional and invasive coronary angiography facilities. If NICE expand their recommendations for CCT to include patients at intermediate risk of CAD, investment may be better justified.

10.1.4 Chapter 6

Prior to this thesis, there was no literature evidence to support the use of CCT in the risk stratification of outpatients with stable chest pain. This prospective pilot study assessed the feasibility and clinical utility of cardiac CT within a diagnostic pathway for RACPC patients with suspected CAD.

The study recruitment rate was less than 20%. The main barriers to recruitment were logistic, relating to CCT or patient non-availability prior to RACPC attendance

compounded by a short turn-around time between RACPC referrals being accepted and seen.

In the cohort of 40 patients randomised to CCT, diagnostic yield for significant CAD was 13%. Compared with a cohort of 45 patients randomised to standard practice, a diagnostic pathway involving CCT resulted in a greater proportion of patients for whom CAD was diagnosed or excluded (97% versus 89%; P=0.207).

Following CCT there were decreases in functional imaging (48%) and in invasive angiography (19%) but disappointingly, no significant reduction in the proportion of negative functional studies or catheterisations. Despite a greater number of investigations performed in patients undergoing CCT, costs per capita were 10% lower than with standard care. Inclusion of CCT in the diagnostic pathway for RACPC patients resulted in fewer clinic follow-up appointments, further supporting the potential of CCT to be a cost effective addition to the RACPC diagnostic armamentarium.

A low absolute rate of MACE across the entire study population suggests patient randomised to CCT were no more likely to experience detrimental cardiovascular effects and the trend towards earlier discharge did not result in missed diagnoses. CCT had no significant impact on the frequency of hospital attendance or admission with chest pain over a six month follow-up.

10.1.5 Chapter 7

In the future, it is likely that the diagnostic investigations undertaken in RACPCs will be aligned to those recommended by NICE CG95. This retrospective study analysed the impact of NICE CG95 on referrals for cardiac investigation, relative to existing practice, for patients attending the RACPCs of two central London district general hospitals (Chelsea and Westminster Hospital and Ealing Hospital).

Using NICE criteria, 66% of study population would have been excluded from further cardiac testing based on pain deemed non-anginal or a likelihood of CAD <10%. Exercise ECG would not have been recommended in this context. 2% of the study population would have been recommended for CCT, 12% for functional testing and 12% for invasive coronary angiography. All patients aged 70 years or older with typical

or atypical angina symptoms would have been referred for angiography or presumed to have angina.

Relative to existing practice, there would have been a >1000% increase in discharge without investigation, a 43% increase in CCT, a 24% decrease in functional cardiac testing and a 500% increase in invasive coronary angiography. The results raise concern that NICE CG95 appears to place unprecedented diagnostic weight on clinical assessment yet also overcommit to invasive angiography. As noted in acute admissions (Chapter 5), CCT and functional testing appear to have been undervalued as first line investigations.

Despite fewer patients undergoing investigation, the bias towards more expensive investigations such as invasive angiography over non-invasive and less expensive tests such as exercise ECG testing and CCT means that adoption of NICE CG95 would have resulted in a 24% increase in the cost of investigation per capita.

Differences in population demographics, existing and recommended practice at the two RACPC sites highlight the risks of service development without prior evaluation of NICE compliant local practice.

10.1.6 Chapter 8

The high proportion of patients identified for discharge without further cardiac investigation in accordance with NICE CG95 (Chapters 5 and 7) prompted analysis of the clinical outcomes in these individuals against the outcomes of patients recommended for further investigation. This retrospective study compared the outcomes for a subgroup of the population attending the RACPCs of two central London district general hospitals, described in Chapter 7.

Amongst the patients recommended for discharge without investigation, a diagnosis of significant CAD was subsequently made in 10%, and a MACE occurred within six months of presentation in 2%. Two thirds of MACE occurred in patients diagnosed with non-anginal chest pain on the basis of history.

The results highlight the risk of deferring investigation in accordance with NICE CG95, leading to potential missed diagnoses and a significant proportion of patients likely to re-present with hard cardiac events (i.e. more resource intensive and expensive to manage).

10.1.7 Chapter 9

This prospective pilot study assessed the feasibility and clinical utility of CPCT within a diagnostic pathway for acute medical admissions with symptoms of dyspnoea.

The recruitment rate for the study was 11%, due a combination of logistic and clinical challenges. 23% of the 56 patients recruited failed to complete scanning and 14% of scans were partially or non-diagnostic.

Amongst the 35 patients for whom a diagnostic CPCT was achieved, a radiological diagnosis for dyspnoea was identified in 94%. The diagnostic yield of CPCT was 20% for significant CAD, 20% for pulmonary embolism, zero for aortic dissection and 89% for non-vascular chest disease. CPCT also revealed incidental pathology ranging from clinically significant to benign in 89% of patients scanned.

For the subset of patients achieving a diagnostic CPCT with a history of COPD, 80% had evidence of significant CAD and 20% had evidence of pulmonary embolism on CPCT.

Inclusion of CPCT in the diagnostic pathway impacted upon the diagnoses made by treating clinicians in 49% of patients scanned. The CPCT approach resulted in increased diagnostic testing but reduced hospital length of stay and re-presentation to the emergency department, without a detected increase in MACE.

The potential strength of CPCT in the diagnosis of patients with acute dyspnoea for whom there is diagnostic uncertainty, or amongst groups with an increased likelihood of atypical presentation such as those with COPD, in whom CAD and occult PE are often overlooked.

10.1.8 Summary overview

Overall, these studies suggest that there are significant obstacles to the widespread adoption of CCT and CPCT in the acute and outpatient settings. A number of these are logistical and may be remedied by investment in infrastructure, personnel and training to provide an accessible and responsive CT service if the financial implications can be justified. Patient factors, particularly in the acute setting where tachycardia, orthopnoea and renal impairment are more prevalent, also limit uptake of the technology at present.

Inclusion of CCT in diagnostic pathways in both acute medical admissions and RACPC attenders with chest pain appears to result in fewer patients discharged without a diagnosis, fewer invasive angiography procedures and reduced diagnostic costs relative to standard practice, suggesting CCT may be a clinically and cost-effective addition to the diagnostic investigations currently available.

In acute medical admissions with dyspnoea, CPCT demonstrates relevant cardiac, pulmonary and incidental pathology and provides value to clinicians making diagnoses. The strength of the technique is likely to be in the assessment of patients in whom there is diagnostic uncertainty. Prompt diagnosis will allow timely initiation of targeted management and CCT appears to support early discharge without detrimental outcomes.

Ultimately, the idea that CT may provide a one stop diagnostic capability for all patients with acute chest pain and dyspnoea is contrary to the increasing trend for personalised medicine. Appropriate patient selection for CCT and CPCT is key to achieving both a diagnostic result and one which can be interpreted in the context of pre-test probability. In the future, it is likely that CCT will be targeted to patients with chest pain in the narrow cohorts recommended by NICE CG95, despite the fact that the strict criteria imposed by NICE potentially undervalue the investigation in both the inpatient and outpatient settings.

10.2 THE FUTURE

Significant advances in CT technology have occurred during the period of investigation for this thesis. Multi-detector computed tomography (MDCT) has rapidly evolved from 4-detector row systems in 1998 to 320 and 640-detector row CT systems in clinical use today. Wide-area detector coverage and dual-source acquisition strategies have further contributed to dramatic reductions in temporal resolution and there is now the option for simultaneous dual-energy investigation in a single study. Future innovations focused on faster gantry rotation speeds and reductions in radiation dosing will facilitate greater spatial resolution, allowing CT to match invasive angiography.

At present, CCT is the only non-invasive investigation able to evaluate robustly the presence and extent of CAD, the anatomical severity of CAD, coronary plaque characteristics and global atherosclerotic burden but the investigation has recognised limitations in its ability to predict the functional relevance of stenoses. Methods are emerging to estimate the functional significance of CAD using CCT. The first, CT perfusion (CTP), allows evaluation of myocardial ischaemia induced by pharmacological stress, but is disadvantaged by its requirement for contrast, radiation, and image acquisition beyond standard CCT. The second, transluminal contrast attenuation gradient (TAG), identifies lesion-specific ischaemia using manual or semi-automated techniques to measure a falloff in contrast in the coronary vessel corresponding to coronary blood flow. The third, CT fractional flow reserve (FFR-CT), uses anatomic and physiologic data combined with fluid dynamics observed on CCT to identify lesion-specific ischaemia. Published data suggest that CT perfusion and FFR-CT improve accuracy and discrimination versus CT alone for the diagnosis of hemodynamically significant CAD{Rocha-Filho, 2010; Min, 2012}. The incremental diagnostic value of TAG is less clear{Stuijfzand, 2014}. The potential to provide non-invasive anatomic and functional assessment in a single scan is likely to enhance the clinical utility of CCT and improve the yield of invasive angiography.

Technological advances to date have prompted stepwise phases of research with an academic focus on validation of the technology rather than its potential capability.

Seeking to address the following research questions, including those raised by Hoffman in 2009{Hoffman, 2009}, will inform future debate regarding the appropriate use of CCT and CPCT.

1. Can a combination of clinical assessment and CCT enhance the diagnosis of patients at low risk of CAD?
2. Can CCT replace functional testing as the initial diagnostic investigation for suspected CAD, with or without the addition of CTP, TAG or FFR-CT?
3. Will CCT lead to an increase in percutaneous intervention on lesions that would not have been detected as physiologically significant on functional imaging studies?
4. Will the detection of non-obstructive plaque on CCT prompt medical therapy and result in a decrease in future MACE?
5. Can CPCT reduce the incidence of missed diagnoses in patients with unexplained dyspnoea, particularly amongst those patients at risk of atypical presentation of CAD?
6. Will the detection of incidental findings in the CCT or CPCT field of view result in increased diagnostic testing and will the benefits of these investigations outweigh the risks?
7. Is there a minimal event rate that justifies the use of CCT or CPCT?
8. Will advances in MRI offer comparable outcomes to CT angiography and perfusion imaging, without the associated radiation burden?

Further, larger, longer term, outcome studies are necessary to delineate the roles for both CCT and CPCT, to optimise clinical and cost-effectiveness, and to allow the generation of robust national and international guidance.

CHAPTER 11: PUBLICATIONS AND ABSTRACTS

11.1 PUBLICATIONS ARISING FROM THIS WORK

11.1.1 PEER REVIEWED PAPERS

1 Patterson CM, Nair A, Ahmed N, Bryan L, Bell D, Nicol ED. Clinical outcomes when applying NICE guidance for the investigation of recent-onset chest pain to a rapid-access chest pain clinic population. *Heart* 2015 Jan;101(2):113-8

2 Patterson C, Padley S. Advances in Chest Imaging in Acute Medicine. *Medicine* 2013 Mar;41(3):142-146

3 Patterson C, Bryan L, Duncan M, Collinson J, Padley S. The feasibility of nurse-led assessment in acute chest pain admissions by means of coronary computed tomography. *Eur J Cardiovasc Nurs* 2013 Feb;12(1):25-32.

4 Patterson C, Nicol E, Bryan L, Woodcock T, Collinson J, Padley S, Bell D. The effect of applying NICE guidelines for the investigation of stable chest pain on outpatient cardiac services in the UK. *QJM* 2011 Jul;104(7):581-8.

5 Patterson C, Bryan L, Nicol E, Duncan M, Bell D, Padley S. The consequences of applying NICE chest pain guidelines to an acute medical population: a role for cardiac computed tomography. *QJM* 2010 Dec;103(12):959-63.

11.1.2 PUBLISHED ABSTRACTS

1 Patterson C, Ahmed N, Nicol E, Bryan L, Bell D. Clinical outcomes of patients excluded from cardiac investigation in the NICE Guidelines for chest pain of recent onset. British Cardiovascular Society Annual Conference; 2012 May 28-30; Manchester. Abstract 139

2 Patterson C, Curran J, Weldring T, Davies G, Bell D, Padley S. The challenges to using early comprehensive cardio-pulmonary computed tomography in the assessment of acute dyspnoea. European Society of Radiology Annual Conference; 2012 Mar 1-5; Vienna. Scientific Paper Control Number 2265

3 Patterson C, Nicol E, Bryan L, Woodcock T, Padley S, Bell D. The impact of NICE guidelines for the investigation of chest pain on outpatient cardiology services in the UK. British Cardiovascular Society Annual Conference; 2011 Jun 13-15; Manchester. Abstract 126

4 Bryan L, Patterson C, Duncan M, Collinson J, Padley S. Cardiac computed tomography as part of nurse-led assessment in acute medical admissions in the UK. European Society of Cardiology 11th Annual Spring Meeting on Cardiovascular Nursing; 2011 Apr 1-2; Brussels. Abstract 90119

5 Patterson C, Bryan L, Nicol E, Collinson J, Bell D. The impact of NICE guidelines on acute cardiac services. Society for Acute Medicine 4th International Conference; 2010 Oct 7-8; Edinburgh. Abstract SD25

11.1.3 ORAL PRESENTATIONS

1 Patterson C, Ahmed N, Nicol E, Bryan L, Bell D. Do current United Kingdom guidelines for the assessment of suspected angina underestimate the prevalence of coronary artery disease? European Society of Cardiology Congress; 2012 Aug 25-29; Munich. Abstract no 85499

2 Patterson C, Nicol E, Bryan L, Bell D, Padley S. The impact of NICE guidelines for the investigation of stable chest pain on radiology services. UK Radiological Congress; 2011 Jun 6-8; Manchester. Abstract 271

3 Patterson C, Nicol E, Bryan L, Woodcock T, Bell D, Padley S. The impact of NICE guidelines for the investigation of chest pain on outpatient radiology services in the UK. European Society of Radiology Annual Conference; 2011 Mar 3-7; Vienna. Scientific Paper Control Number 2150

CHAPTER 12: REFERENCES

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APPENDIX

Table App 1.2: Read codes compatible with symptoms of dyspnoea[a]

READ CODE	ICD 10	TEXT
R0606	R060	[D]RESPIRATORY DISTRESS
R060600	R060	[D]RESPIRATORY DISTRESS
R0608	R060	[D]SHORTNESS OF BREATH
R060800	R060	[D]SHORTNESS OF BREATH
R060A	R060	[D]DYSPNOEA
R060A00	R060	[D]DYSPNOEA
R061.	R061	[D]STRIDOR
R061.00	R061	[D]STRIDOR
R0609	R062	[D]WHEEZING
R060900	R062	[D]WHEEZING
R060E00	R062	[D]MILD WHEEZE
R060F00	R062	[D]MODERATE WHEEZE
R0605	R063	[D]CHEYNE-STOKES RESPIRATION
R0601	R064	[D]HYPERVENTILATION
R060100	R064	[D]HYPERVENTILATION
R04z2	R065	[D]MOUTH BREATHING
R04z200	R065	[D]MOUTH BREATHING
R060B	R065	[D]SNORING
R060B00	R065	[D]SNORING
R068.00	R066	[D]HICCOUGH
R04z0	R068	[D]CHOKING SENSATION
R04z000	R068	[D]CHOKING SENSATION
R0603	R068	[D]TACHYPNOEA
R060300	R068	[D]TACHYPNOEA
R0604	R068	[D]APNOEA
R060400	R068	[D]APNOEA
R0607	R068	[D]RESPIRATORY INSUFFICIENCY
R060700	R068	[D]RESPIRATORY INSUFFICIENCY
R060D	R068	[D]BREATHLESSNESS
R060D00	R068	[D]BREATHLESSNESS
R060z	R068	#MULTIVALUE
R060z00	R068	[D]RESPIRATORY ABNORMALITIES NOS
R060z11	R068	[D]MOUTH BREATHER
R06z.	R068	[D]OTHER RESPIRATORY SYSTEM AND CHEST SYMPTOMS

R06z0	R068	[D]BREATH-HOLDING SPELL
R06z.00	R068	[D]OTHER RESPIRATORY SYSTEM AND CHEST SYMPTOMS
R06z000	R068	[D]BREATH-HOLDING SPELL
R06zz00	R068	[D]RESPIRATORY SYSTEM AND CHEST SYMPTOMS NOS
Ryu03	R068	[X]OTHER AND UNSPECIFIED ABNORMALITIES OF BREATHING
Ryu0300	R068	[X]OTHER AND UNSPECIFIED ABNORMALITIES OF BREATHING
R041.00	R070	[D]THROAT PAIN
R041.11	R070	[D]THROAT DISCOMFORT
R065300	R071	[D]PAINFUL RESPIRATION NOS
H00..	J00X	#MULTIVALUE
H00..11	J00X	COMMON COLD
H00..12	J00X	CORYZA - ACUTE
H00..13	J00X	FEBRILE COLD
H00..15	J00X	PYREXIAL COLD
H00..16	J00X	RHINITIS - ACUTE
H010.00	J010	ACUTE MAXILLARY SINUSITIS
H010.11	J010	ANTRITIS - ACUTE
H011.	J011	ACUTE FRONTAL SINUSITIS
H011.00	J011	ACUTE FRONTAL SINUSITIS
H013.00	J013	ACUTE SPHENOIDAL SINUSITIS
H01y.00	J018	OTHER ACUTE SINUSITIS
H01yz00	J018	OTHER ACUTE SINUSITIS NOS
H01z.	J019	ACUTE SINUSITIS NOS
H01z.00	J019	ACUTE SINUSITIS NOS
H01..	J01X	#MULTIVALUE
H01..11	J01X	SINUSITIS
A340.	J020	STREPTOCOCCAL SORE THROAT
A340.00	J020	STREPTOCOCCAL SORE THROAT
A3402	J020	STREPTOCOCCAL PHARYNGITIS
A340200	J020	STREPTOCOCCAL PHARYNGITIS
A340z	J020	STREPTOCOCCAL SORE THROAT NOS
A340z00	J020	STREPTOCOCCAL SORE THROAT NOS
H024.	J028	ACUTE VIRAL PHARYNGITIS
H024.00	J028	ACUTE VIRAL PHARYNGITIS
H022.00	J029	ACUTE ULCERATIVE PHARYNGITIS
H023z00	J029	ACUTE BACTERIAL PHARYNGITIS NOS
H02z.	J029	ACUTE PHARYNGITIS NOS
H02z.00	J029	ACUTE PHARYNGITIS NOS

H02..	J02X	#MULTIVALUE
H02..11	J02X	SORE THROAT NOS
A3403	J030	STREPTOCOCCAL TONSILLITIS
A340300	J030	STREPTOCOCCAL TONSILLITIS
H035z00	J038	ACUTE BACTERIAL TONSILLITIS NOS
H030.00	J039	ACUTE ERYTHEMATOUS TONSILLITIS
H031.	J039	ACUTE FOLLICULAR TONSILLITIS
H031.00	J039	ACUTE FOLLICULAR TONSILLITIS
H03..11	J039	THROAT INFECTION - TONSILLITIS
H03..12	J039	TONSILLITIS
H036.	J039	ACUTE VIRAL TONSILLITIS
H036.00	J039	ACUTE VIRAL TONSILLITIS
H037.	J039	RECURRENT ACUTE TONSILLITIS
H037.00	J039	RECURRENT ACUTE TONSILLITIS
H03z.	J039	ACUTE TONSILLITIS NOS
H03z.00	J039	ACUTE TONSILLITIS NOS
H03..	J03X	#MULTIVALUE
H040.	J040	ACUTE LARYNGITIS
H040w	J040	ACUTE VIRAL LARYNGITIS UNSPECIFIED
H040w00	J040	ACUTE VIRAL LARYNGITIS UNSPECIFIED
H041.	J041	ACUTE TRACHEITIS
H041z00	J041	ACUTE TRACHEITIS NOS
H042z	J042	ACUTE LARYNGOTRACHEITIS NOS
H043211	J050	CROUP
H044.	J050	CROUP
H044.00	J050	CROUP
H0430	J051	ACUTE EPIGLOTTITIS WITHOUT OBSTRUCTION
H043100	J051	ACUTE EPIGLOTTITIS WITH OBSTRUCTION
H043z00	J051	ACUTE EPIGLOTTITIS NOS
H05..00	J068	OTHER ACUTE UPPER RESPIRATORY INFECTIONS
H051.	J069	ACUTE UPPER RESPIRATORY TRACT INFECTION
H051.00	J069	ACUTE UPPER RESPIRATORY TRACT INFECTION
H05z.	J069	#MULTIVALUE
H05z.00	J069	UPPER RESPIRATORY INFECTION NOS
H05z.11	J069	UPPER RESPIRATORY TRACT INFECTION NOS
H05z.12	J069	VIRAL UPPER RESPIRATORY TRACT INFECTION NOS
H270100	J100	INFLUENZA WITH PNEUMONIA, INFLUENZA VIRUS IDENTIFIED
Hyu04	J101	[X]FLU+OTH RESPIRATORY MANIFESTATIONS,'FLU VIRUS IDENTIFIED

Hyu0400	J101	[X]FLU+OTH RESPIRATORY MANIFESTATIONS,'FLU VIRUS IDENTIFIED
Hyu0500	J108	[X]INFLUENZA+OTHER MANIFESTATIONS,INFLUENZA VIRUS IDENTIFIED
H270.00	J110	INFLUENZA WITH PNEUMONIA
H270z00	J110	INFLUENZA WITH PNEUMONIA NOS
H27..	J111	INFLUENZA
H27..00	J111	INFLUENZA
H271.	J111	INFLUENZA WITH OTHER RESPIRATORY MANIFESTATION
H27z.	J111	#MULTIVALUE
H27z.00	J111	INFLUENZA NOS
H27z.11	J111	FLU LIKE ILLNESS
Hyu0600	J111	[X]INFLUENZA+OTH RESPIRATORY MANIFESTATNS,VIRUS NOT IDENTIFD
Hyu0700	J118	[X]INFLUENZA+OTHER MANIFESTATIONS, VIRUS NOT IDENTIFIED
H200.00	J120	PNEUMONIA DUE TO ADENOVIRUS
H201.00	J121	PNEUMONIA DUE TO RESPIRATORY SYNCYTIAL VIRUS
H202.	J122	PNEUMONIA DUE TO PARAINFLUENZA VIRUS
H202.00	J122	PNEUMONIA DUE TO PARAINFLUENZA VIRUS
H20y.00	J128	VIRAL PNEUMONIA NEC
H20..00	J129	VIRAL PNEUMONIA
H20..11	J129	CHEST INFECTION - VIRAL PNEUMONIA
H20z.	J129	VIRAL PNEUMONIA NOS
H20z.00	J129	VIRAL PNEUMONIA NOS
H21..	J13X	#MULTIVALUE
H21..00	J13X	LOBAR (PNEUMOCOCCAL) PNEUMONIA
H21..11	J13X	CHEST INFECTION - PNEUMOCOCCAL PNEUMONIA
H222.	J14X	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
H222.00	J14X	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
H222.11	J14X	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
H220.00	J150	PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
H221.	J151	PNEUMONIA DUE TO PSEUDOMONAS
H221.00	J151	PNEUMONIA DUE TO PSEUDOMONAS
H224.	J152	PNEUMONIA DUE TO STAPHYLOCOCCUS
H224.00	J152	PNEUMONIA DUE TO STAPHYLOCOCCUS
H223000	J153	PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
H223.	J154	PNEUMONIA DUE TO STREPTOCOCCUS
H223.00	J154	PNEUMONIA DUE TO STREPTOCOCCUS
H22y000	J155	PNEUMONIA DUE TO ESCHERICHIA COLI

H22y011	J155	E.COLI PNEUMONIA
H22yX00	J156	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
Hyu0900	J156	[X]PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
H231.	J157	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
H231.00	J157	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
H28..	J157	ATYPICAL PNEUMONIA
H28..00	J157	ATYPICAL PNEUMONIA
H22..00	J158	OTHER BACTERIAL PNEUMONIA
H22..11	J158	CHEST INFECTION - OTHER BACTERIAL PNEUMONIA
H22y.	J158	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
H22y.00	J158	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
Hyu0A	J158	[X]OTHER BACTERIAL PNEUMONIA
Hyu0A00	J158	[X]OTHER BACTERIAL PNEUMONIA
H22yz	J159	PNEUMONIA DUE TO BACTERIA NOS
H22yz00	J159	PNEUMONIA DUE TO BACTERIA NOS
H22z.	J159	BACTERIAL PNEUMONIA NOS
H22z.00	J159	BACTERIAL PNEUMONIA NOS
H23..11	J168	CHEST INFECTION - PNEUMONIA ORGANISM OS
H23z.00	J168	PNEUMONIA DUE TO SPECIFIED ORGANISM NOS
Hyu0B00	J168	[X]PNEUMONIA DUE TO OTHER SPECIFIED INFECTIOUS ORGANISMS
Hyu0F	J173*	[X]PNEUMONIA IN PARASITIC DISEASES CLASSIFIED ELSEWHERE
H25..	J180	#MULTIVALUE
H25..00	J180	BRONCHOPNEUMONIA DUE TO UNSPECIFIED ORGANISM
H25..11	J180	CHEST INFECTION - UNSPECIFIED BRONCHOPNEUMONIA
H260.	J181	LOBAR PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H260.00	J181	LOBAR PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H260000	J181	LUNG CONSOLIDATION
H261.	J181	BASAL PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H261.00	J181	BASAL PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H5400	J182	HYPOSTATIC PNEUMONIA
Hyu0H00	J188	[X]OTHER PNEUMONIA, ORGANISM UNSPECIFIED
H26..	J189	#MULTIVALUE
H26..00	J189	PNEUMONIA DUE TO UNSPECIFIED ORGANISM
H26..11	J189	CHEST INFECTION - PNEMONIA DUE TO UNSPECIFIED ORGANISM
H262.00	J189	POSTOPERATIVE PNEUMONIA
H263.00	J189	PNEUMONITIS, UNSPECIFIED
H060800	J201	ACUTE HAEMOPHILUS INFLUENZAE BRONCHITIS
H060C	J204	ACUTE BRONCHITIS DUE TO PARAINFLUENZA VIRUS

H060C00	J204	ACUTE BRONCHITIS DUE TO PARAINFLUENZA VIRUS
H060D00	J205	ACUTE BRONCHITIS DUE TO RESPIRATORY SYNCYTIAL VIRUS
H060E00	J206	ACUTE BRONCHITIS DUE TO RHINOVIRUS
H0605	J209	ACUTE TRACHEOBRONCHITIS
H060w00	J209	ACUTE VIRAL BRONCHITIS UNSPECIFIED
H060z	J209	ACUTE BRONCHITIS NOS
H060z00	J209	ACUTE BRONCHITIS NOS
H060.	J20X	#MULTIVALUE
H060.00	J20X	ACUTE BRONCHITIS
H0615	J210	ACUTE BRONCHIOLITIS DUE TO RESPIRATORY SYNCYTIAL VIRUS
H061500	J210	ACUTE BRONCHIOLITIS DUE TO RESPIRATORY SYNCYTIAL VIRUS
H061600	J218	ACUTE BRONCHIOLITIS DUE TO OTHER SPECIFIED ORGANISMS
Hyu1100	J218	[X]ACUTE BRONCHIOLITIS DUE TO OTHER SPECIFIED ORGANISMS
H061.00	J219	ACUTE BRONCHIOLITIS
H061000	J219	ACUTE CAPILLARY BRONCHIOLITIS
H061100	J219	ACUTE OBLITERATING BRONCHIOLITIS
H061z	J219	ACUTE BRONCHIOLITIS NOS
H061z00	J219	ACUTE BRONCHIOLITIS NOS
H061.	J21X	ACUTE BRONCHIOLITIS
H062.	J22X	ACUTE LOWER RESPIRATORY TRACT INFECTION
H062.00	J22X	ACUTE LOWER RESPIRATORY TRACT INFECTION
H06z0	J22X	#MULTIVALUE
H06z000	J22X	CHEST INFECTION NOS
H06z011	J22X	CHEST INFECTION
H06z1	J22X	#MULTIVALUE
H06z100	J22X	LOWER RESP TRACT INFECTION
H06z111	J22X	RESPIRATORY TRACT INFECTION
H06z112	J22X	ACUTE LOWER RESPIRATORY TRACT INFECTION
H06z200	J22X	RECURRENT CHEST INFECTION
H0z..00	J22X	ACUTE RESPIRATORY INFECTION NOS
SP132	J22X	POST OPERATIVE CHEST INFECTION
SP13200	J22X	POST OPERATIVE CHEST INFECTION
H172.11	J304	HAY FEVER - UNSPECIFIED ALLERGEN
H17z.	J304	ALLERGIC RHINITIS NOS
H17z.00	J304	ALLERGIC RHINITIS NOS
H120.	J310	#MULTIVALUE
H120.00	J310	CHRONIC RHINITIS
H120300	J310	CHRONIC ATROPHIC RHINITIS

H120z	J310	CHRONIC RHINITIS NOS
H120z00	J310	CHRONIC RHINITIS NOS
H121.	J312	#MULTIVALUE
H121.11	J312	SORE THROAT - CHRONIC
H130.	J320	#MULTIVALUE
H1y8.	J393	UPPER RESPIRATORY TRACT HYPERSENSITIVITY REACTION NOS
H1y8.00	J393	UPPER RESPIRATORY TRACT HYPERSENSITIVITY REACTION NOS
H5y12	J398	STENOSIS OF TRACHEA
H5y1200	J398	STENOSIS OF TRACHEA
Hyu2A00	J398	[X]OTHER SPECIFIED DISEASES OF UPPER RESPIRATORY TRACT
H3...	J40X	#MULTIVALUE
H30..	J40X	#MULTIVALUE
H3...00	J40X	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H300.	J40X	TRACHEOBRONCHITIS NOS
H30..00	J40X	BRONCHITIS UNSPECIFIED
H300.00	J40X	TRACHEOBRONCHITIS NOS
H301.	J40X	LARYNGOTRACHEOBRONCHITIS
H30..12	J40X	RECURRENT WHEEZY BRONCHITIS
H302.00	J40X	WHEEZY BRONCHITIS
H30z.	J40X	BRONCHITIS NOS
H30z.00	J40X	BRONCHITIS NOS
H310.	J410	SIMPLE CHRONIC BRONCHITIS
H31..	J42X	CHRONIC BRONCHITIS
H31..00	J42X	CHRONIC BRONCHITIS
H31z.	J42X	CHRONIC BRONCHITIS NOS
H31z.00	J42X	CHRONIC BRONCHITIS NOS
H321.00	J431	PANLOBULAR EMPHYSEMA
H322.00	J432	CENTRILOBULAR EMPHYSEMA
Hyu3000	J438	[X]OTHER EMPHYSEMA
H32..	J439	EMPHYSEMA
H32..00	J439	EMPHYSEMA
H32z.	J439	EMPHYSEMA NOS
H32z.00	J439	EMPHYSEMA NOS
H3y0.00	J440	CHRONIC OBSTRUCT PULMONARY DIS WITH ACUTE LOWER RESP INFECTN
H3122	J441	ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H312200	J441	ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

H3y1.	J441	CHRON OBSTRUCT PULMONARY DIS WTH ACUTE EXACERBATION, UNSPEC
H3y1.00	J441	CHRON OBSTRUCT PULMONARY DIS WTH ACUTE EXACERBATION, UNSPEC
H061400	J448	OBLITERATING FIBROUS BRONCHIOLITIS
H312.	J448	OBSTRUCTIVE CHRONIC BRONCHITIS
H3120	J448	#MULTIVALUE
H312.00	J448	OBSTRUCTIVE CHRONIC BRONCHITIS
H312000	J448	CHRONIC ASTHMATIC BRONCHITIS
Hyu3100	J448	[X]OTHER SPECIFIED CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H36..00	J449	MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H38..00	J449	SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H39..00	J449	VERY SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
H3z..	J449	#MULTIVALUE
H3z..00	J449	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE NOS
H3z..11	J449	CHRONIC OBSTRUCTIVE PULMONARY DISEASE NOS
H3y..	J44X	#MULTIVALUE
H3y..00	J44X	OTHER SPECIFIED CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
H330.	J450	#MULTIVALUE
H33..00	J450	ASTHMA
H3300	J450	#MULTIVALUE
H330.00	J450	EXTRINSIC (ATOPIC) ASTHMA
H330011	J450	HAY FEVER WITH ASTHMA
H330.11	J450	ALLERGIC ASTHMA
H330.12	J450	CHILDHOOD ASTHMA
H330.13	J450	HAY FEVER WITH ASTHMA
H330z	J450	EXTRINSIC ASTHMA NOS
H330z00	J450	EXTRINSIC ASTHMA NOS
H331.	J451	#MULTIVALUE
H331.11	J451	LATE ONSET ASTHMA
H331z	J451	INTRINSIC ASTHMA NOS
H333.	J459	ACUTE EXACERBATION OF ASTHMA
H333.00	J459	ACUTE EXACERBATION OF ASTHMA
H334.00	J459	BRITTLE ASTHMA
H33z.	J459	#MULTIVALUE
H33z.00	J459	ASTHMA UNSPECIFIED
H33z1	J459	#MULTIVALUE
H33z100	J459	ASTHMA ATTACK

H33z111	J459	ASTHMA ATTACK NOS
H33z200	J459	LATE-ONSET ASTHMA
H33zz	J459	#MULTIVALUE
H33zz00	J459	ASTHMA NOS
H33zz12	J459	ALLERGIC ASTHMA NEC
H33zz13	J459	ALLERGIC BRONCHITIS NEC
H330100	J46X	EXTRINSIC ASTHMA WITH STATUS ASTHMATICUS
H331100	J46X	INTRINSIC ASTHMA WITH STATUS ASTHMATICUS
H33z0	J46X	#MULTIVALUE
H33z000	J46X	STATUS ASTHMATICUS NOS
H33z011	J46X	SEVERE ASTHMA ATTACK
H34..	J47X	BRONCHIECTASIS
H34..00	J47X	BRONCHIECTASIS
H340.00	J47X	RECURRENT BRONCHIECTASIS
H34z.	J47X	BRONCHIECTASIS NOS
H34z.00	J47X	BRONCHIECTASIS NOS
H41..	J61X	ASBESTOSIS
H41..00	J61X	ASBESTOSIS
H41z.	J61X	ASBESTOSIS NOS
H41z.00	J61X	ASBESTOSIS NOS
H434.00	J634	SIDEROSIS
H45..00	J64X	PNEUMOCONIOSIS NOS
H357.00	J677	"VENTILATION" PNEUMONITIS
H35..	J679	EXTRINSIC ALLERGIC ALVEOLITIS
H35..00	J679	EXTRINSIC ALLERGIC ALVEOLITIS
H35z100	J679	HYPERSENSITIVITY PNEUMONITIS NOS
H460.00	J680	BRONCHITIS AND PNEUMONITIS DUE TO CHEMICAL FUMES
H460100	J680	ACUTE PNEUMONITIS DUE TO CHEMICAL FUMES
H462.	J682	UPPER RESPIRATORY INFLAMMATION DUE TO CHEMICAL FUMES
H470.	J690	#MULTIVALUE
H470.00	J690	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS
H470000	J690	PNEUMONITIS DUE TO INHALATION OF REGURGITATED FOOD
H470100	J690	PNEUMONITIS DUE TO INHALATION OF GASTRIC SECRETIONS
H470.11	J690	ASPIRATION PNEUMONIA
H4702	J690	#MULTIVALUE
H4703	J690	#MULTIVALUE
H470311	J690	VOMIT INHALATION PNEUMONITIS
H470312	J690	ASPIRATION PNEUMONIA DUE TO VOMIT

H470z	J690	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS NOS
H470z00	J690	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS NOS
H47..	J698	#MULTIVALUE
H47..00	J698	PNEUMONITIS DUE TO INHALATION OF SOLIDS OR LIQUIDS
H47..11	J698	ASPIRATION PNEUMONITIS
H47y.00	J698	PNEUMONITIS DUE TO INHALATION OF OTHER SOLID OR LIQUID
H47yz	J698	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS
H47yz00	J698	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS
H47z.	J698	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS
H47z.00	J698	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS
Hyu4700	J698	[X]PNEUMONITIS DUE TO INHALATION OF OTHER SOLIDS AND LIQUIDS
H4y0.00	J700	ACUTE PULMONARY RADIATION DISEASE
H4y10	J701	CHRONIC PULMONARY FIBROSIS FOLLOWING RADIATION
H4y1.00	J701	CHRONIC PULMONARY RADIATION DISEASE
H5850	J80X	PULMONARY INSUFFICIENCY FOLLOWING SHOCK
H5853	J80X	ADULT RESPIRATORY DISTRESS SYNDROME
H585300	J80X	ADULT RESPIRATORY DISTRESS SYNDROME
H585z	J80X	TRAUMA AND POST-OPERATIVE PULMONARY INSUFFICIENCY NOS
H54..	J81X	PULMONARY CONGESTION AND HYPOSTASIS
H54..00	J81X	PULMONARY CONGESTION AND HYPOSTASIS
H541000	J81X	CHRONIC PULMONARY OEDEMA
H541z	J81X	PULMONARY OEDEMA NOS
H541z00	J81X	PULMONARY OEDEMA NOS
H584.	J81X	#MULTIVALUE
H5840	J81X	POSTOPERATIVE PULMONARY OEDEMA
H584.00	J81X	ACUTE PULMONARY OEDEMA UNSPECIFIED
H584000	J81X	POSTOPERATIVE PULMONARY OEDEMA
H584.11	J81X	ACUTE OEDEMA OF LUNG, UNSPECIFIED
H584z	J81X	ACUTE PULMONARY OEDEMA NOS
H584z00	J81X	ACUTE PULMONARY OEDEMA NOS
H583.	J82X	PULMONARY EOSINOPHILIA
H583.00	J82X	PULMONARY EOSINOPHILIA
H5831	J82X	TROPICAL EOSINOPHILIA
H583z00	J82X	PULMONARY EOSINOPHILIA NOS
H562.00	J840	PULMONARY ALVEOLAR MICROLITHIASIS
H55..11	J841	CIRRHOSIS OF LUNG
H563.	J841	#MULTIVALUE

H563.00	J841	IDIOPATHIC FIBROSING ALVEOLITIS
H5631	J841	DIFFUSE PULMONARY FIBROSIS
H563100	J841	DIFFUSE PULMONARY FIBROSIS
H563.12	J841	CRYPTOGENIC FIBROSING ALVEOLITIS
H563z00	J841	IDIOPATHIC FIBROSING ALVEOLITIS NOS
Hyu50	J841	[X]OTHER INTERSTITIAL PULMONARY DISEASES WITH FIBROSIS
Hyu5000	J841	[X]OTHER INTERSTITIAL PULMONARY DISEASES WITH FIBROSIS
H58y3	J848	INTERSTITIAL LUNG DISEASE NEC
H58y300	J848	INTERSTITIAL LUNG DISEASE NEC
Hyu51	J848	[X]OTHER SPECIFIED INTERSTITIAL PULMONARY DISEASES
Hyu5100	J848	[X]OTHER SPECIFIED INTERSTITIAL PULMONARY DISEASES
H56y1	J849	INTERSTITIAL PNEUMONIA
H56y100	J849	INTERSTITIAL PNEUMONIA
H530200	J850	GANGRENOUS PNEUMONIA
H5303	J851	ABSCESS OF LUNG WITH PNEUMONIA
H530.	J852	ABSCESS OF LUNG
H530.00	J852	ABSCESS OF LUNG
H530100	J852	MULTIPLE LUNG ABSCESS
H530z00	J852	ABSCESS OF LUNG NOS
H531.00	J853	ABSCESS OF MEDIASTINUM
H5000	J860	EMPYEMA WITH BRONCHOCUTANEOUS FISTULA
H500.00	J860	EMPYEMA WITH FISTULA
H500z00	J860	EMPYEMA WITH FISTULA NOS
J10y2	J860	TRACHEO-OESOPHAGEAL FISTULA
J10y200	J860	TRACHEO-OESOPHAGEAL FISTULA
H50..	J869	EMPYEMA
H50..00	J869	EMPYEMA
H501100	J869	THORAX ABSCESS NOS
H5012	J869	PLEURAL EMPYEMA
H501200	J869	PLEURAL EMPYEMA
H5013	J869	LUNG EMPYEMA NOS
H5016	J869	PYOTHORAX
H501600	J869	PYOTHORAX
H50z.	J869	EMPYEMA NOS
H50z.00	J869	EMPYEMA NOS
H5109	J90X	PNEUMOCOCCAL PLEURISY
H511.00	J90X	BACTERIAL PLEURISY WITH EFFUSION
H51y.00	J90X	OTHER PLEURAL EFFUSION EXCLUDING MENTION OF TUBERCULOSIS

H51yz	J90X	OTHER PLEURAL EFFUSION
H51z.	J90X	PLEURAL EFFUSION NOS
H51z.00	J90X	PLEURAL EFFUSION NOS
H51zz	J90X	PLEURAL EFFUSION NOS
H51zz00	J90X	PLEURAL EFFUSION NOS
H410.00	J920	PLEURAL PLAQUE DISEASE DUE TO ASBESTOSIS
H510100	J929	THICKENING OF PLEURA
H520.	J930	SPONTANEOUS TENSION PNEUMOTHORAX
H520.00	J930	SPONTANEOUS TENSION PNEUMOTHORAX
H52y.00	J931	OTHER SPONTANEOUS PNEUMOTHORAX
H52yz	J931	#MULTIVALUE
H52yz00	J931	OTHER SPONTANEOUS PNEUMOTHORAX NOS
H52yz11	J931	SPONTANEOUS PNEUMOTHORAX NOS
Hyu7100	J931	[X]OTHER SPONTANEOUS PNEUMOTHORAX
H52y000	J938	ACUTE PNEUMOTHORAX NOS
Hyu7200	J938	[X]OTHER PNEUMOTHORAX
H52..	J939	PNEUMOTHORAX
H52..00	J939	PNEUMOTHORAX
H52z.	J939	PNEUMOTHORAX NOS
H52z.00	J939	PNEUMOTHORAX NOS
H51y500	J940	CHYLOUS EFFUSION
H51y1	J942	HAEMOPNEUMOTHORAX
H51y100	J942	HAEMOPNEUMOTHORAX
H51y200	J942	HAEMOTHORAX
H510200	J948	CALCIFICATION OF PLEURA
H51y000	J948	ENCYSTED PLEURISY
H51y300	J948	HYDROPNEUMOTHORAX
H51y400	J948	HYDROTHORAX
H5X..	J949	PLEURAL CONDITION, UNSPECIFIED
H5y0.00	J950	TRACHEOSTOMY COMPLICATION
H5y0000	J950	TRACHEOSTOMY HAEMORRHAGE
H5y0300	J950	TRACHEOSTOMY OBSTRUCTION
H5y0z00	J950	TRACHEOSTOMY COMPLICATION NOS
H5851	J952	PULMONARY INSUFFICIENCY FOLLOWING SURGERY
Hy03.00	J955	POSTPROCEDURAL SUBGLOTTIC STENOSIS
Hy04.00	J958	POSTPROCEDURAL RESPIRATORY FAILURE
Hyu8000	J958	[X]OTHER POSTPROCEDURAL RESPIRATORY DISORDERS
SP131	J958	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF CARE

SP13100	J958	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF CARE
SP13.	J959	RESPIRATORY COMPLICATIONS OF CARE
SP13.00	J959	RESPIRATORY COMPLICATIONS OF CARE
SP13z	J959	RESPIRATORY COMPLICATION OF CARE NOS
SP13z00	J959	RESPIRATORY COMPLICATION OF CARE NOS
H590.	J960	ACUTE RESPIRATORY FAILURE
H590.00	J960	ACUTE RESPIRATORY FAILURE
H591.00	J961	CHRONIC RESPIRATORY FAILURE
H593.00	J961	CHRONIC TYPE 2 RESPIRATORY FAILURE
H59..	J969	RESPIRATORY FAILURE
H59..00	J969	RESPIRATORY FAILURE
R2y1.	J969	[D]RESPIRATORY FAILURE
R2y1.00	J969	[D]RESPIRATORY FAILURE
R2y1z	J969	[D]RESPIRATORY FAILURE NOS
R2y1z00	J969	[D]RESPIRATORY FAILURE NOS
H58y.	J980	OTHER LUNG DISEASE NEC
H58y0	J980	BRONCHOLITHIASIS
H5y1.	J980	#MULTIVALUE
H5y1.00	J980	OTHER DISEASES OF TRACHEA AND BRONCHUS NEC
H5y1100	J980	CALCIFICATION OF BRONCHUS
H5y1.11	J980	OTHER BRONCHUS DISEASE
H5y1300	J980	STENOSIS OF BRONCHUS
H5y1600	J980	BRONCHOSPASM
H5y1z	J980	DISEASES OF TRACHEA AND BRONCHUS NEC NOS
H5y1z00	J980	DISEASES OF TRACHEA AND BRONCHUS NEC NOS
H580.	J981	#MULTIVALUE
H5800	J981	POST OPERATIVE ATELECTASIS
H580.00	J981	PULMONARY COLLAPSE WITH ATELECTASIS
H580000	J981	POST OPERATIVE ATELECTASIS
H580.11	J981	ATELECTASIS
H580.12	J981	COLLAPSE OF LUNG
H581.	J982	#MULTIVALUE
H581.11	J982	PNEUMOMEDIASTINUM
H58..	J984	OTHER DISEASES OF LUNG
H58..00	J984	OTHER DISEASES OF LUNG
H58yz00	J984	OTHER LUNG DISEASE NEC NOS
H58z.	J984	LUNG DISEASE NOS
H58z.00	J984	LUNG DISEASE NOS

Hyu8100	J984	[X]OTHER DISORDERS OF LUNG
H5y2.00	J985	MEDIASTINITIS
H5y3.00	J985	OTHER DISEASES OF MEDIASTINUM, NEC
H5y3z00	J985	DISEASES OF MEDIASTINUM, NEC NOS
H5y4.00	J986	DISORDERS OF DIAPHRAGM
H5y4000	J986	DIAPHRAGMATITIS
H5y41	J986	PARALYSIS OF DIAPHRAGM
H5y4z00	J986	DISORDERS OF DIAPHRAGM NOS
H5C..	J988	CHOKING DUE TO AIRWAYS OBSTRUCTION
H5C..00	J988	CHOKING DUE TO AIRWAYS OBSTRUCTION
H5y..	J988	OTHER SPECIFIED DISEASES OF RESPIRATORY SYSTEM
H5y..00	J988	OTHER SPECIFIED DISEASES OF RESPIRATORY SYSTEM
H5yy.	J988	#MULTIVALUE
H5yy.00	J988	OTHER DISEASES OF RESPIRATORY SYSTEM NEC
H5yy.11	J988	RESPIRATORY INFECTION NOS
Hyu82	J988	[X]OTHER SPECIFIED RESPIRATORY DISORDERS
Hyu8200	J988	[X]OTHER SPECIFIED RESPIRATORY DISORDERS
H5yz.	J989	OTHER DISEASES OF RESPIRATORY SYSTEM NOS
H5yz.00	J989	OTHER DISEASES OF RESPIRATORY SYSTEM NOS
H5z..00	J989	RESPIRATORY SYSTEM DISEASES NOS

[a]No cases of cardiac failure, PE or malignancy recorded

Table App 1.2: Number of patients discharged with respiratory diagnoses (Feb 2008 - Feb 2012; n=4600)

	DESCRIPTOR	NUMBER OF PATIENTS (% OF TOTAL)
Infection	Upper respiratory tract infection	178 (3.9)
	Chest/Lower respiratory tract infection	838 (18.2)
	Pneumonia	1134 (24.7)
	Aspiration pneumonia/pneumonitis	204 (4.3)
	Lung abscess	2 (0.04)
	Viral infection	59 (1.3)
	Respiratory infection NOS	24 (0.5)
Atopic disease	Hay fever/rhinitis	3 (0.07)
Obstructive lung disease	Upper airway obstruction	2 (0.04)
	Bronchitis	15 (0.3)
	Asthma/bronchospasm	441 (9.6)
	COPD/emphysema	985 (21.4)
Bronchiectasis	Bronchiectasis	34 (0.7)
Interstitial lung disease	Interstitial lung disease/radiation associated	36 (0.8)
Pulmonary vascular disease	Pulmonary embolism	0 (0.0)
	Pulmonary oedema	39 (0.9)
Disorders of the mediastinum and pleura	Pneumothorax/pneumomediastinum	130 (2.8)
	Pleural effusion	126 (2.7)
	Empyema	10 (0.2)
Respiratory failure	Respiratory failure	124 (2.7)
Other	Symptoms not attributed to disease process	168 (3.7)
	Radiologic features not attributed to disease process	39 (0.9)
	Unspecified respiratory disease	9 (0.2)
Total		**4600 (100)**