THE UNIVERSITY *of* EDINBURGH

QUANTITATIVE PLAQUE ANALYSIS

IN CORONARY ARTERY DISEASE

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To Abbu
“If you decide to do something, do it well.”

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i. DECLARATION

This thesis represents research I performed at the Centre for Cardiovascular Sciences at the University of Edinburgh between August 2019 and June 2022. Research conducted in this thesis was supported by the British Heart Foundation (FS/19/46/34445). The DIAMOND study was funded by a Wellcome Trust Senior Investigator Award (WT103782AIA) and an unrestricted educational grant from AstraZeneca. AstraZeneca was not involved with study design or analysis. The PRECISE-CTCA study and DEMAND-MI were funded by the British Heart Foundation (FS/18/25/33454, FS/16/75/32533). The RAPID-CTCA study was funded by The National Institute for Health Research HTA Programme (13/04/108).

With regards to the data included in this thesis, I was involved in the collation and analysis of all CT coronary angiograms and in developing the concept, data analysis and interpretation for all studies. In keeping with the collaborative nature of research, images were provided to me by Professor David Newby, Professor Alasdair Gray and Dr Kuan-Ken Lee. During this time, I was also the Principal Investigator for the SCOTHEART-2 trial between October 2019 and August 2022. Chapter 3 has been published in a peer-reviewed journal and at present Chapters 4, 5 and 6 are currently under peer-review. This thesis has not been accepted in any previous applications for a degree and all sources of information have been acknowledged. The research was undertaken in

accordance with the Declaration of Helsinki and the regulation of various Research Ethics Committees.

Mohammed Nooruddin Meah

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ii. LAY SUMMARY

Blood vessels carry blood to every organ in our body. Coronary artery disease is a condition that occurs over time where the vessels that supply the heart with blood become irritated and 'fur up' with plaque. This process can reduce the amount of blood that reaches the heart muscle. On occasion, regions where the furring is most significant can burst (or rupture), leaking debris into the blood vessel and causing clots to form. This is what we commonly refer to as a heart attack. Heart attacks are the commonest cause of death and disability throughout the world and can lead to symptoms such as chest pain, and breathlessness. Doctors have become very good at treating heart attacks when they are diagnosed but there is still a lot of room to improve the way we identify people who are having or are at risk of a heart attack in the future. CT scans have been used for many years to identify patients with 'stable' coronary artery disease. As technology has improved, we can now not only detect coronary artery disease, but determine how much and how 'irritated' the plaque is. In fact, in patients with angina, this technique of quantifying and characterising plaque has been shown to predict the chances of a heart attack in the future better than current approaches.

CT is rarely used when patients present suddenly to the hospital, and we do not know whether quantifying plaque is possible or useful in this setting. This raises some questions: 1) Can the technique be reliably used in patients who have a lot of plaque? 2) In those who attend hospital where the doctors do not

feel they have had a heart attack, can the technique help determine who would benefit most for treatments? 3) In those who have had a heart attack, can it help tell doctors why it has happened? 4) In those who have attended the hospital with a suspected heart attack, can it predict whether they will have another one in the coming year?

The following body of work seeks to answer these questions. We do this by first showing the technique can be applied accurately in patients with a lot of 'furring up'. Second, we show that there is much more inflamed plaque in patients who have not had a heart attack but have a higher blood level of heart protein called troponin which is known to predict their risk of future heart attacks. Third, we compare the amount of plaque in patients who have had heart attacks because of clots in the artery with those who have had heart attacks for other reasons. We show that there is much more inflamed plaque when heart attack occurs due to plaque rupture and clot formation. Finally, we show that the presence of inflamed plaque on CT in patients who come to the Emergency Department concerned about having a heart attack, predicts their risk of having another heart attack or dying over the next 12 months.

The work we show here highlights new and useful findings that not only improve our understanding of the disease process behind heart attacks but may potentially change the way we assess individual patient's risk of future events. Further studies are now needed to investigate the direct impact of these findings on patient diagnosis and treatment.

iii. ABSTRACT

Background:

Coronary artery disease is the commonest cause of death worldwide and clinicians have struggled to limit the associated inexorable tide of morbidity and mortality over the past few decades. Most often patients only become aware that they have coronary artery disease when they are admitted to hospital with chest pain. Computed tomography coronary angiography has revolutionised our ability to detect even mild coronary artery disease, improving the prognosis of those with symptoms of stable angina. However, its effectiveness is somewhat limited by physician reliance on the singular factor of the severity of coronary artery stenosis. The ability to characterise and to quantify the extent of coronary artery disease can incrementally improve the prognostic capability of coronary computed tomography angiography in patients with stable angina. However, we have yet to determine whether quantifying plaque is of benefit in the more unstable populations of patients who present to the Emergency Department with acute chest pain. Such patients may or may not have suffered a myocardial infarction. Moreover, in those who have myocardial infarction, this may or may not be due to plaque rupture. Computed tomography and quantitative plaque analysis could provide a novel avenue to assist both in the diagnosis and risk stratification of this patient population.

Given this background, there are several questions that we put forward. These include: 1) Can plaque be accurately and reproducibly quantified in patients with a high burden of coronary artery disease? 2) Is there value in quantifying plaque in patients who have had myocardial infarction excluded? 3) In those with myocardial infarction, can quantitative plaque analysis assist in the differentiation between type 1 and type 2 myocardial infarction? 4) Does quantification of plaque burden predict recurrent events and mortality in patients who present with acute chest pain to the Emergency Department?

Methods and results:

In study one, twenty patients with known multivessel disease underwent repeated computed tomography coronary angiography 2 weeks apart. Coronary artery segments were analysed using semi-automated software by two trained observers to determine intraobserver, interobserver and interscan reproducibility. Overall, 149 coronary arterial segments were analysed. There was excellent intraobserver, interobserver and interscan agreement for all plaque volume measurements. There were no substantial interscan differences for measures of plaque burden. Whilst low-attenuation plaque volume had relatively wider 95% limits of agreement, this reflected the lower absolute volumes of low-attenuation plaque in this cohort of patients with advanced coronary disease.

In study two, quantitative plaque analysis was performed on CT coronary angiograms of 242 patients recruited in a single-centre cross-sectional

observational study. Patients with acute chest pain who had had myocardial infarction excluded were dichotomised by plasma high-sensitivity cardiac troponin I concentration into low (<5 ng/L, n=81) and intermediate (≥5 ng/L, n=161) risk groups. There was a higher burden of plaque in the intermediate risk group compared to the low risk group. Moreover, low-attenuation plaque burden was associated with intermediate-risk plasma troponin concentrations after adjustment for clinically relevant characteristics suggesting plaque instability may contribute to the underlying cardiovascular risk of these patients.

In study three, a post-hoc analysis of two prospective clinical studies of patients with acute chest pain was conducted. Patients were classified as type 1 myocardial infarction, type 2 myocardial infarction or chest pain without infarction. The diagnosis of type 2 myocardial infarction was adjudicated by an expert panel due to the inherent difficulties in making this diagnosis. Quantitative plaque analysis was conducted in 155 patients with type 1 myocardial infarction, 36 patients with type 2 myocardial infarction and 136 patients with chest pain without infarction. We showed that patients with type 1 myocardial infarction had a significantly greater burden of total, non-calcified and low-attenuation plaque compared to those with type 2 myocardial infarction. Low-attenuation plaque was an independent predictor of type 1 myocardial infarction and had better discrimination than non-calcified plaque and even severity of coronary artery stenosis. This suggests that quantitative

plaque analysis holds potential to help differentiate between these diagnoses thereby assisting in guiding patient management.

In study four, quantitative plaque analysis was conducted on 404 patients who presented to the Emergency Department with suspected acute coronary syndrome. Patients underwent early coronary CT angiography and were followed up for 12 months. We assessed the association between plaque burden and the primary endpoint of 1-year all cause death or non-fatal myocardial infarction and compared this to traditional markers of risk including the GRACE score and the presence of obstructive coronary disease. Following the index admission, 25 patients went on to have an event. Events were associated with larger burdens of all plaque subtypes. Total, non-calcified and low-attenuation plaque were the strongest predictors of future events, and these associations were independent of GRACE score and presence of obstructive coronary disease. Plaque burden therefore was a major predictor of 1-year death or recurrent myocardial infarction in patients who present to hospital with suspected acute coronary syndrome.

Conclusion:

We have demonstrated that quantitative plaque analysis is a reliable tool and gives precise results even in patients with a large burden of coronary atherosclerosis. This technique can be applied to all patients who attend the hospital and are suspected of having acute coronary syndrome. When troponin concentrations do not reach the threshold to diagnose myocardial infarction

according to the Universal Definition, quantifying the low-attenuation plaque burden of those with an intermediate concentration of troponin is a powerful risk stratification tool that may assist in the decision to pursue more intensive preventative medical therapy. When myocardial infarction is diagnosed but clinicians are not sure if this is due to plaque rupture or a supply and demand mismatch, the burden of low-attenuation plaque can assist in decision making and help guide downstream medical investigation and management. Finally, in all the above situations, the burden of plaque and low-attenuation plaque in particular can identify those patients at highest risk of recurrent cardiovascular events, further risk stratifying patients in the short to medium term. Taken together, these four studies provide major impetus for future prospective clinical trials that could base treatment decisions on the burden of high-risk low-attenuation plaque.

iv. ACKNOWLEDGEMENTS

This research was conducted under the guidance and supervision of Professor David E. Newby and Dr Michelle C. Williams at the University of Edinburgh. They have both provided me with immeasurable support. Professor Newby finds time to talk through problems at a moment's notice. His doors (both physical and electronic) are always open, and few problems seem insurmountable after a 7AM 'chat'! Dr Williams has taught me how to report and interpret computed tomography coronary angiography, a skill I will be able to carry through to clinical practice. Her patience and the time she gave early in my training have been invaluable to my development. My experience in the world of academia was almost interrupted by the COVID-19 pandemic, which dramatically changed the focus of my research. Without the support of these amazing supervisors, I may never have completed this thesis, and I am forever grateful to them.

I would like to thank the British Heart Foundation for their support of my research through the Clinical Research Training Fellowship (FS/19/46/34445). Without their generosity, this thesis would not have been possible. I also wish to acknowledge Dr Damini Dey, at the Cedars-Sinai Medical-Centre (Los Angeles, USA) who not only provided the software to make this research possible but was quick to help with troubleshooting.

During the time spent working on this thesis I have been extremely fortunate to share my journey with several ‘Newbies’ who have shared this experience with me. Trisha, Anda, Evangelos and Kang-Ling amongst others. They have listened to my endless rants, covered my scan lists, shared R code, and proof-read my work. They provided friendship during my time in the ‘Barn’ and it has been a true privilege to learn with them.

Finally, to my family. To my Abbu, who had always wanted to do a PhD but was not afforded the same opportunities I have had, you are my inspiration and drive. To my Ammu, who has checked in every day and driven hundreds of miles for fear I was going “hungry”, you are the reason I have my health. To Nirmol – for stepping up whilst I have been away. And to Debora Moreira Meah, my bedrock of support through these challenging 3 years, I can never thank you enough – here’s to the future!!

1. CHAPTER 1: Introduction

Extracts of this chapter have been published in:

Meah, MN *et al*. Cardiovascular imaging to guide primary prevention. Heart. 2020;106:1267-1275

Meah, MN *et al*. Long term prognostic role of Computed Tomography Coronary Angiography for stable angina. Curr Treat Options Cardio Med. 2020;22(9):22

Meah, MN *et al*. Clinical relevance of coronary computed tomography angiography beyond coronary artery stenosis. ROFO. 2021;193(10):1162-1170

1.1 OVERVIEW

Coronary heart disease is the commonest cause of death across the world. The World Health Organisation estimates it accounts for nearly a third of all global deaths each year and since 1990, more people have died from cardiovascular disease than any other cause.[1] So how can we prevent this inexorable tide of cardiovascular morbidity and mortality?

To improve health and prognosis, one must first make an accurate diagnosis. The term prognosis was coined by Hippocrates, to mean "foreseeing and foretelling".[2] When doctors give a prognostic statement, they predict the future course of an individual's condition. However, to predict the prognosis in any individual, it is vital that an accurate diagnosis is made. A diagnosis traditionally identifies a person as having or not having a disease. An accurate diagnosis and an assessment of the severity of disease are important and can focus treatments on those who stand to gain the most benefit.[3] There is growing interest in how improved diagnosis can positively impact upon prognosis. In those with stable chest pain for example, accurate diagnosis of the presence and severity of coronary atherosclerosis has the potential to alter management and improve outcomes.

Atherosclerosis is the underlying pathogenesis behind most cardiovascular diseases. It is a multifactorial multisystem disease process that begins as a fatty streak made up of mainly of macrophages in the subendothelium which

have become lipid laden. The resultant inflammatory response to oxidised lipid and foam cell accumulation causes proliferation of smooth muscle cells and further accumulation of debris in the form of connective tissue components, leading to the formation of atherosclerotic plaque.[4, 5] Atherosclerotic plaque in coronary arteries can present with stable symptoms of angina or, in cases where the plaque ruptures or erodes, as acute myocardial infarction. In the acute setting, patients are selected for further investigation by measuring high-sensitivity plasma cardiac troponin which when elevated, indicate myocardial injury.

Early descriptions of angina can be found in the Ancient Egyptions text Ebers papyrus which they acknowledged as a life-threatening condition,[6] however the link between angina and coronary disease took many more centuries.[7] Our understanding of the complex interplay between environmental and genetic factors that drive atherosclerosis and subsequent coronary heart disese only began with earnest in the 1950s. Inspired by the death of President Roosevelt in 1945 and on the back of a pandemic of the then “untreatable” cardiovascular disease, the United States of America established the National Heart Lung and Blood Institute whose primary aim was to conduct an epidemiological study of heart disease.[8] The Framingham Heart Study was credited with identifying the importance of blood pressure control in the battle to prevent heart disease. It also popularised the term ‘risk factor’, the articulation of which led to the development of cardiovascular risk scores.[9] Hyperlipidaemia, smoking and

diabetes mellitus (amongst many others) are now established as risk factors which initiate and accelerate the atherosclerotic process.

As a direct result of our improved understanding of the pathophysiology and significant advances in medical and interventional therapies, global trends in cardiovascular death have fallen in many countries where survival rates have improved over the last 30 years. In the United Kingdom alone, cardiovascular death rates have fallen by 52% since the 1990s.[10] Despite this, it remains the primary cause of death not just in the UK but throughout the world, accounting for 45% of all deaths in Europe and a third of all deaths globally.[11, 12]

Traditionally, the burden of atherosclerosis and severity of coronary artery disease has been assessed through invasive angiography. Primarily, this has been through a visual quantification of severity of stenoses on 2-dimentional 'lumenography'. In 1979, Godfrey Hounsfield and Allan Cormack were awarded the Nobel Prize in Physiology and Medicine for the development of computer-assisted tomography. In his Nobel Prize acceptance speech, Godfrey Hounsfield said "*A further promising field may be the detection of the coronary arteries*".[13] In the years that followed, the challenge of capturing the beating heart has driven innovation in the field at a remarkable pace. As life expectancy throughout the world has risen, the global burden of cardiovascular disease has followed suit.[14] It is fitting therefore that computed tomography coronary angiography (CTCA) should advance to face it.

Despite many advances in the field, clinicians often focus on the ability of CTCA to predict the severity of a coronary artery stenosis, perhaps because of its historical significance. However, the totality of CTCA capabilities is numerous. Computational fluid dynamic algorithms enable a functional assessment of stenotic lesions, with the potential to reduce unnecessary invasive angiography.[15] Positron emission tomographic data can be layered over the anatomical data of CTCA to demonstrate lesions at high risk of rupture.[16] In this chapter, we will focus on the ways in which CTCA can evaluate atherosclerotic plaque to provide clinically relevant information, over and above simply answering the question “how narrow is that blood vessel?”

1.2 HISTORICAL PERSPECTIVE ON PLAQUE CHARACTERISATION

Leonardo da Vinci was amongst the first to describe atherosclerotic plaque, describing “vessels in the elderly which restrict the transit of blood through thickening of the tunics”.[17] Clinician efforts in recent history have often focused on lesions that appeared more stenotic partly because early studies on coronary artery bypass grafting appeared to provide prognostic benefit.[18] However post-mortem studies from the 1980s provided crucial observations that form the basis of our understanding today. A description of ‘pre-cursor’ lesions to myocardial infarction was developed. This included a substantial core of lipid and cellular debris with a thin cap of fibrous tissue, heavily infiltrated with foamy macrophages. In almost every post-mortem case, erosion or rupture of this fibrous cap associated with the lipid core had led to coronary thrombosis and myocardial infarction.[19] As such, the idea of the ‘vulnerable’ plaque has gained great popularity. Defined as the direct precursor lesions which give rise to coronary thrombosis and described simply as thin-cap fibroatheroma, physicians have since spent years improving our ability to detect these important lesions.[20]

1.3 CARDIAC TROPONIN

Cardiac troponin is a complex of three regulatory proteins (troponin T, I and C) and forms an integral component of cardiomyocytes contractile apparatus.[21] It is found exclusively within the myocardium bound to the protein tropomyosin, mainly within the sarcomere. When an action potential stimulates the myocyte, calcium released from the sarcoplasmic reticulum binds to troponin causing the sliding of thick and thin filaments and resulting in cell shortening.[22] When myocardial tissues are injured, cardiac troponin is released into the systemic circulation and can be detected using biochemical assays. There are several proposed pathophysiological mechanisms via which cardiac troponin is released into the blood stream. The commonest cause is due to myocardial necrosis as occurs in ischaemic events. However, it can also be caused by increased membrane permeability which happens when cardiomyocytes undergo mechanical stretch in response to pressure or volume loading.[21, 23]

Over the last few years, there have been major improvements in assay technology which has permitted the quantification of very low concentrations of troponin with high precision. In fact, high-sensitivity cardiac troponin I assays have limits of detection that are up to 100 times less than previous generation assays, such that concentrations can be quantified even in healthy individuals.[24] The result has been a revolution in the way in which clinicians diagnose, risk stratify and treat patients suspected of suffering a myocardial infarction.

1.3.1 High-sensitivity cardiac troponin – what is “normal”?

Because of the extremely low concentrations of cardiac troponin high-sensitivity assays can quantify, troponin has become detectable even in individuals who have not suffered any myocardial injury. In a landmark individual patient-level meta-analysis of more than 22,000 patients with suspected acute coronary syndrome, Chapman and colleagues confirmed an extremely high negative predictive value of 99.9% for cardiac death and 99.5% for myocardial infarction or cardiac death with a high-sensitivity cardiac troponin-I concentration of <5 ng/L.[25, 26] Using this very low threshold in clinical practice has proven to miss significantly fewer true myocardial infarctions whilst also safely and robustly ruling out more myocardial infarctions than contemporary pathways, thereby reducing overall hospital admissions and length of stay.[27, 28] As a result, a rule-out pathway incorporating very low concentrations of high-sensitivity troponin was added to international guidelines in the screening and management of acute coronary syndromes (**Figure 1-1**)[29] and it has become widely accepted as the optimal threshold identifying patients at the lowest risk of cardiovascular events.

1.3.2 High-sensitivity cardiac troponin in patients with myocardial infarction

On the other side of the coin, lies the question of what threshold should be used to rule in myocardial infarction, and this is more contentious. Unlike with exclusion of myocardial infarction, there is always tension between sensitivity and specificity when determining a threshold for inclusion in a continuous variable. Most guidelines and manufacturers of high-sensitivity troponin assays recommend thresholds greater than the 99th centile of normal healthy individuals.[24, 30] Importantly, the thresholds are sex-specific, being two-fold higher in men compared to women.[31]

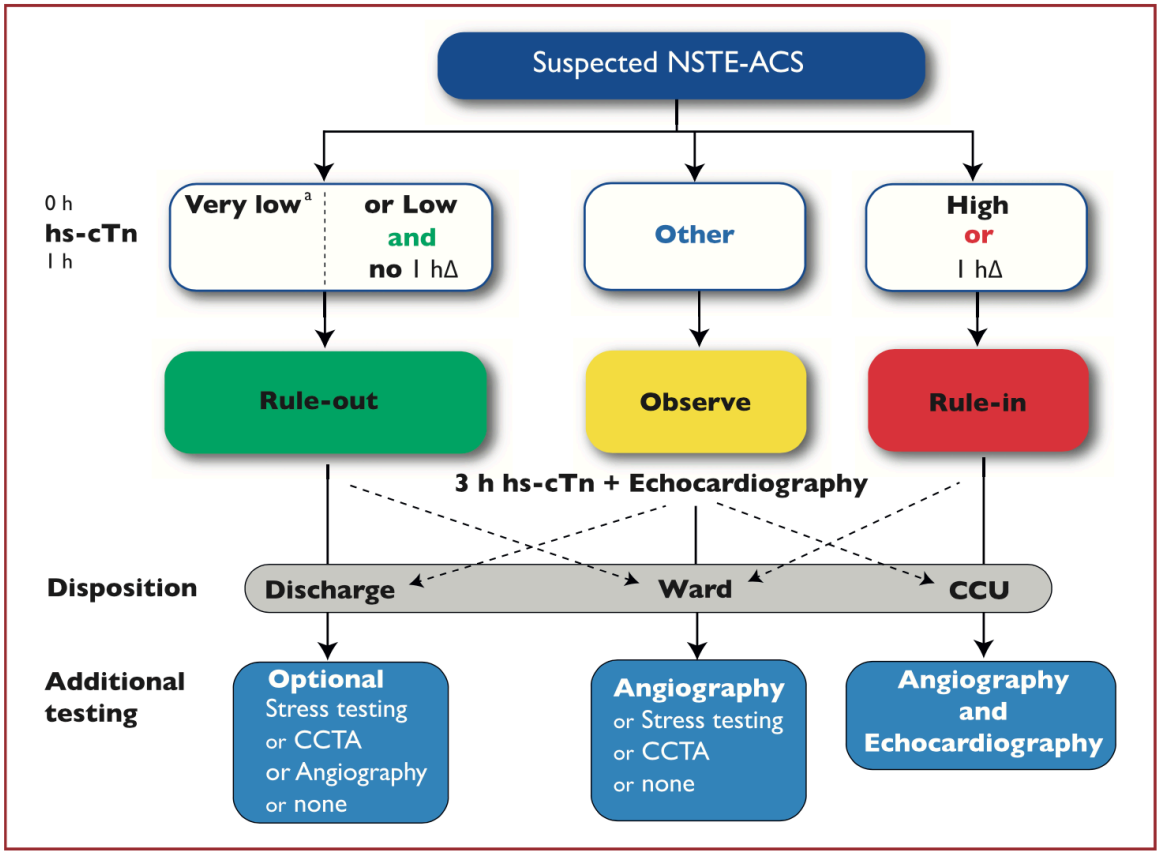

Figure 1-1: European Society of Cardiology 2020 update for the use of high-sensitivity troponin to screen patients with suspected non-ST segment elevation acute coronary syndromes. Reprinted from the ESC guidelines.[29]

The exquisite sensitivity of these assays is however also a victim of its own success. Shah and colleagues demonstrated that when high-sensitivity cardiac troponin concentrations were measured in an unselected cohort of consecutive patients attending the Emergency Department, concentrations above the 99th centile was a common finding that related in most cases to myocardial injury rather than myocardial infarction.[32] Mariathas et al demonstrated a higher 99th centile in unselected inpatients where there was no indication for cardiac troponin testing (563 ng/L) as compared to the manufacturer's recommended 99th centile (40 ng/L).[33] These studies demonstrate the importance of clinical decision making when selecting patients in whom to check cardiac troponin but also highlight the issues with applying a threshold based on healthy populations to pathological populations. Whilst having a low threshold may improve the number of myocardial infarctions detected, it markedly increases the diagnosis of patients with type 2 myocardial infarction or myocardial injury.[34]

1.3.3 High-sensitivity cardiac troponin- the grey zone

The use of the 99th sex-specific centile as a 'high-risk' threshold to rule in myocardial infarction creates a third group with an "intermediate" concentration of high-sensitivity cardiac troponin (≥5 ng/L but below the 99th centile). These patients do not have myocardial infarction or injury according to the standard criteria.[30] Unless there are other clinical signs, such as persisting chest pain or dynamic changes in electrocardiograms, it is highly likely that these patients will be discharged from hospital with no further investigation. This group is

large, representing a third of patients in whom myocardial infarction has been excluded and crucially they are 10 times more likely to suffer a major cardiovascular event at 1 year when compared to patients with a high-sensitivity troponin concentration of <5 ng/L.[26] The reasons why this would be the case are not entirely clear, although a higher prevalence of coronary artery disease was recently demonstrated in patients who have had myocardial infarction excluded but have a high-sensitivity cardiac troponin concentration ≥5 ng/L when compared to patients with concentrations <5 ng/L.[35]

1.4 MYOCARDIAL INFARCTION

In clinical practice, when myocardial infarction is suspected, it is usually in the context of a patient with symptoms of ischaemia (chest tightness, jaw pain etc) who develop changes in the electrocardiogram (such as ST deviation or T wave inversion). In such circumstances, serum cardiac biomarkers, such as high-sensitivity cardiac troponin, are measured to confirm the clinical suspicion of myocardial infarction. Guidelines suggest that this is sufficient to initiate invasive investigations to determine if a thrombotic event has occurred and to consider coronary revascularisation.[29] However, in some cases, there may not have been an atherothrombotic event. To understand why, we need a better understanding of the differences between myocardial injury and infarction and grasp the underlying mechanisms that can lead to myocardial infarction.

1.4.1 Myocardial injury

Myocardial injury is denoted by the presence of an elevated cardiac troponin above the 99th centile upper reference limit. It is considered acute if there is a rise or fall in cardiac troponin and chronic if persistently elevated.[30] Although elevated cardiac troponin reflects injury to myocardial cells, detection does not give any indication of the underlying pathological mechanism of which there are many. These can range from physiological stresses applied to an otherwise normal heart or pathological causes of cellular degradation and structural protein release such as apoptosis or myocyte necrosis.[36] Advances

in assay technology have improved our ability to detect these biomarkers and in doing so, increased the sensitivity with which clinicians can identify myocardial injury and by proxy, myocardial infarction.

1.4.2 Defining myocardial infarction

Myocardial infarction encompasses a group of acute clinical events diagnosed when a patient has evidence of myocardial injury in the context of myocardial ischaemia. Once again, cardiac biomarkers are central to the diagnosis and a rise and/or fall in cardiac troponin is necessary.[30] The commonest clinical presentation is chest pain,[37] and when a change in cardiac troponin is detected, most clinicians treat with atherothrombotic therapies and refer for coronary revascularisation. However, as with myocardial injury, diagnosing myocardial infarction does not necessarily define the underlying pathology.

Patients presenting with myocardial infarction form a heterogenous group with a multitude of potential pathological causes, and treatment strategies differ significantly depending on this. As a result, myocardial infarction must be further subdivided into clear diagnoses based on pathophysiology. Type 1 myocardial infarction is precipitated by atherosclerotic plaque disruption and thrombotic obstruction of the coronary artery. Type 2 myocardial infarction on the other hand occurs when there is myocardial oxygen supply and demand mismatch, and this can occur in the presence or absence of coronary artery disease. There are many proposed stressors that can lead to oxygen supply and demand mismatch including sustained tachycardias, hypotension, shock,

hypoxaemia, and anaemia (**Table 1-1**). Type 3 myocardial infarction is a pathological diagnosis made in patients with symptoms of myocardial ischaemia who die before serum troponin measurement was possible. Type 4 and 5 myocardial infarctions are those associated with percutaneous coronary intervention and coronary artery bypass grafting respectively.

Table 1-1: Summary of classifications of myocardial injury and infarction

Raised cardiac biomarker >99th centile	Evidence of ischaemia?	Classification	Example underlying aetiologies
Stable elevation	**No**	**Chronic myocardial injury**	**Structural heart disease, such as HCM** **Chronic kidney disease**
Dynamic rise and/or fall	**No**	**Acute myocardial injury**	**Acute heart failure** **Myocarditis**
	Yes	**Atherothrombosis Type 1 MI**	**Plaque rupture** **Plaque erosion**
	Yes	**Oxygen supply demand mismatch Type 2 MI**	**Coronary:** - **Vasospasm** - **Dissection** - **Embolism** **Arrhythmia:** - **Tachycardic** - **Bradycardic** **Systemic:** - **Anaemia** - **Hypoxaemia** - **Severe hypertension** - **Hypotension (shock)**

MI – myocardial infarction, HCM – hypertrophic cardiomyopathy

1.4.3 Distinguishing between type 1 and type 2 myocardial infarction

Determining the difference between type 1 and type 2 myocardial infarction is a common clinical conundrum that can be difficult to resolve. This is particularly the case as both types of myocardial infarction can occur with or without obstructive coronary artery disease.[38] However, differentiating between these conditions is important because the treatment varies significantly. For example, in type 1 myocardial infarction, antiplatelet, anticoagulant and fibrinolytic therapies may be required along with subsequent preventative therapies. With type 2 myocardial infarction, treatments will be dependent on the underlying cause: antibiotics for septic shock, rate control or cardioversion for tachyarrhythmias, and blood transfusion for anaemia. An incorrect diagnosis can lead to poor outcomes,[39] such as with a patient who is anaemic due to gastrointestinal blood loss being given antithrombotic medication. Currently, the only way to differentiate between type 1 and type 2 myocardial infarction is with invasive angiography (**Figure 1-2**) which is not without its own limitations.[40] Whilst invasive intracoronary imaging such as optical coherence tomography or intravascular ultrasound can help in unclear cases, the cost and practical limitations can present a barrier to routine adoption.[41] There is growing interest in whether computed tomography coronary angiography may be able to provide an avenue of diagnostic evaluation.

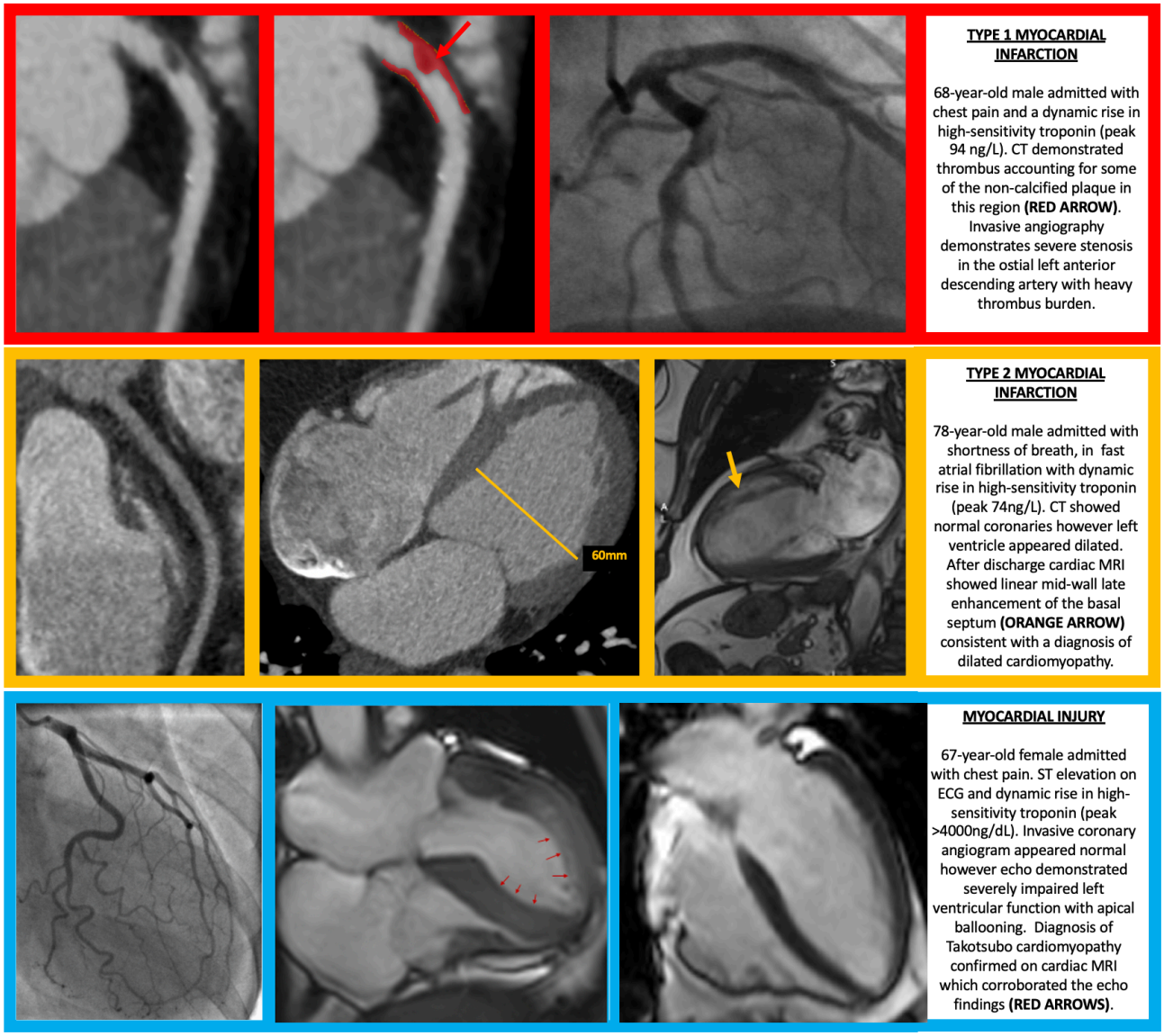

Figure 1-2: Case panel delineating difference between type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury.

1.5 COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY

CTCA is a well-established imaging modality and annually tens of thousands are performed in the United Kingdom. Greater row detector numbers, rapid gantry rotation and enhanced reconstruction algorithms have facilitated our ability to capture detailed images of the cardiac vasculature in a few heartbeats.[42]

Accurately identifying the presence of coronary artery disease has the potential to alter diagnoses, and subsequently management. Registry studies have established the ability of CTCA to reclassify patients compared to clinical risk scores in up to two thirds of cases.[43] In the Scottish Computed Tomography of the HEART (SCOT-HEART) trial,[44] a large multicentre randomised study assessing the use of CTCA in patients presenting to the rapid access chest pain clinic, CTCA clarified the diagnosis in 1 in 4 patients.[45] This was further corroborated by Foy and colleagues in their meta-analysis which found that in comparison to functional testing, CTCA led to an increase in coronary artery disease diagnosis and initiation of preventative medications.[46] A further meta-analysis has demonstrated the greater ability of CTCA to exclude atherosclerosis compared to stress testing.[46] By contrast, a negative functional test does not mean the patient is free from non-obstructive coronary artery disease. CTCA therefore not only clarifies the diagnosis, but

also identifies those with sub-clinical disease who may benefit from preventive therapies.

The 5-year outcomes of the SCOT-HEART trial provided the first evidence that management based on CTCA findings could improve clinical outcomes.[47] Here, 4146 patients with stable chest pain were randomised to either undergo CTCA or standard care **(Table 1-2)**. At 5 years there was a marked reduction in the occurrence of fatal or non-fatal myocardial infarction in patients whose management was guided by CTCA (HR 0.59; 95% confidence interval 0.41 to 0.84; p=0.004). The improved prognosis did not appear to be driven by increased revascularisation, but rather the impact of increased medical therapy, particularly in the group with non-obstructive coronary artery disease.[48] These findings have been replicated in a real world setting from a national Danish registry.[49] Amongst 32,961 patients who underwent CTCA there was increased use of preventative medical therapy and a lower risk of myocardial infarction (HR 0.71; 95% CI 0.61 to 0.82).[49] Interestingly, in the Prospective Multicentre Imaging Study for Evaluation of Chest Pain (PROMISE), which compared CTCA with functional testing, although there was no difference in the primary composite outcome (death, myocardial infarction, hospitalisation for unstable angina or major procedural complication) between the two approaches, there was a reduction in death or myocardial infarction with CTCA at one year.[50, 51]

An early criticism of CTCA was the potential to increase the use of invasive coronary angiography. In the PROMISE trial, rates of referral for invasive coronary angiography were higher in patients undergoing CTCA compared to functional imaging, but those undergoing CTCA were less likely to have normal coronary arteries.[50] Moreover, the 5-year results of SCOT-HEART demonstrated that with time, the rate of referral for invasive coronary angiography actually reduced over time when compared with patients who did not undergo CTCA.[47, 52] Thus, CTCA can be used to guide more appropriate and timely use of invasive coronary angiography.

Table 1-2: Outcomes from randomised controlled trials comparing an initial strategy of CCTA in patients with stable angina.

Trial	N	Follow-up	Comparison	Outcome
Randomised Pilot Trial Min et al, 2012 [53]	180	3-month	Myocardial perfusion imaging vs CCTA	• Equivalent improvements in quality of life • Increase incidence of aspirin (22% vs 8%, p=0.04) and statin (7% vs -3.5%, p=0.03) prescription with CCTA • Lower total cost ($781.08 vs $1214.58, p<0.001) and radiation (7.4 mSv vs 13.3 mSv, p<0.001) with CCTA
CAPP Donnelly et al, 2015 [54]	500	1-year	Exercise ECG vs CCTA	• Improved control of angina symptoms • Fewer patients required further investigations (72 vs 128, p≤0.0001) with CCTA • Increased revascularisation and preventative medication with CCTA • Reduced hospital re-attendance (0.8% vs 5.2%, p=0.009)

PROMISE Douglas et al, 2015 [50]	10,003	2-year	Functional test vs CCTA initially	• No difference in primary outcome of major adverse cardiovascular event (3.3% vs 3.0%, p=0.75) at 2 years
				• Increase in invasive angiography
				  ○ Less likely to be normal (3.4% vs 4.3%, p=0.02)
				  ○ More likely to lead to revascularisation (3.2% vs 6.2%, p<0.0001)

SCOT-HEART Newby et al, 2018 [47]	4,146	5-year	Standard care vs CCTA	• Significant difference in primary outcome of cardiac death or non-fatal myocardial infarction (2.3% vs 3.9%, p=0.004). • Equivalent rates of invasive angiography and revascularisation by 5 years. • Increased incidence of preventive and anti-anginal therapies.

CCTA, Cardiac Computed Tomography Angiography; mSv, millisievert.

Whilst the ability of CTCA to reduce cardiovascular death and non-fatal myocardial infarction has been discussed, one of CTCA's greatest strengths is the ability to identify patients with normal coronary arteries. An interesting finding from the SCOT-HEART study was that the greatest quality of life improvements were seen in the cohort of patients who had normal coronary arteries and did not require lifelong medical therapy.[48] The chest pain guideline from the United Kingdom's National Institute for health and Care Excellence (NICE) is currently the only guideline to recommend CTCA as first line assessment in patients with possible angina, doing away with pre-test probability calculations **(Table 1-3)**.[55-57] A recent study by Houssany-Pissot and colleagues lends weight to this approach. They assessed nearly 5000 patients who underwent invasive coronary angiography, and found that CTCA was better than functional testing regardless of pre-test probability, limiting unnecessary downstream testing without missing abnormal invasive angiograms.[58]

Table 1-3: Comparison of guideline recommendations for non-invasive investigation of stable chest pain.

	NICE (2016) [55]	ESC (2019) [56]	ACC/AHA (2021) [57, 59, 60]
Initial assessment	Assessment based on clinical likelihood. Heavy reliance on typicality of chest pain.	Assessment based on pre-test probability and clinical likelihood	Assessment based on pre-test likelihood of coronary artery disease and local availability of non-invasive tests.
First-line	Offer 64-slice CT coronary angiography if pain typical/atypical, or non-cardiac with abnormal ECG.	If likelihood of CAD low-intermediate, suggests CT. If likelihood intermediate/ high, suggests non-invasive functional imaging.	If likelihood of CAD intermediate-high and patient <65 years or low suspicion for obstructive CAD suggest CT. If >65 years or high suspicion for obstructive CAD, functional imaging favoured.
Second-line	If CT results are of uncertain significance or non-diagnostic offer non-invasive functional imaging.	If first line investigation results are of uncertain significance, consider alternative depending on what is available locally.	Recommends CT/ functional imaging if prior test inconclusive.
Previous history of CAD	In cases with known CAD and worsening symptoms offer non-invasive functional testing if there is uncertainty about symptom aetiology.	In cases with known CAD and worsening symptoms offer exercise ECG or non-invasive functional imaging.	In cases with known CAD and worsening symptoms offer exercise ECG or non-invasive functional imaging.

NICE; National Institute for health and Care Excellence, ESC; European Society of Cardiology, ACC/AHA; American College of Cardiology/American Heart Association, CAD; Coronary artery disease,
Non-invasive functional imaging refers to stress echocardiography, myocardial perfusion scanning and stress perfusion cardiac magnetic resonance imaging.

1.5.1 Qualitative assessment

Early angiographic studies demonstrated that culprit lesions in myocardial infarction were often not associated with severe stenosis.[61] Visual assessment of the coronary arteries requires more than just an assessment of the severity of stenosis. As such, along with describing the distribution of disease, a central goal of basic visual assessment is to determine the composition of the coronary plaque, as this contributes to plaque vulnerability.

On CTCA, atherosclerotic plaques can be classified as calcified, non-calcified or mixed. While calcified plaque has always been easy to detect, detecting non-calcified plaque accurately has only been possible in the era of multi-slice CT scanning.[62, 63] Kopp *et al* were the first to demonstrate the ability of CT to characterise non-invasively lesion morphology and composition.[64] Multiple studies since have demonstrated the excellent correlation between CT attenuation density and plaque characterisation as determined by intravascular ultrasound.[65, 66] Culprit lesions in acute coronary syndromes are more likely to be non-calcified than calcified.[67] There are also interesting sex differences in plaque type with women having more non-calcified plaques than men.[68, 69] However, the prognostic implications of basic plaque classification are less certain. In 458 patients presenting with acute chest pain but without an acute coronary syndrome, Nance *et al* found that the occurrence of major adverse cardiovascular events (MACE) at 13 months was higher in those with mixed plaques rather than non-calcified or calcified plaques.[70] However, in 1584 patients undergoing CTCA for suspected coronary artery disease,

Hadamitzky *et al* found that plaque classification as non-calcified, calcified or mixed, did not improve risk stratification over assessment of stenosis severity.[71] One of the important limiting factors of this form of plaque assessment is that observer variability for visual plaque analysis has been shown to be poor.[72] Moreover, this basic assessment does not allow for the quantification of the extent of disease.

1.5.2 Semi-quantitative assessment

A distinct advantage of CTCA over other non-invasive imaging modalities is its ability to derive a measure of atherosclerotic burden throughout the coronary tree. This is particularly important as Maddox *et al* found that those with multi-vessel non-obstructive disease have a similar prognosis to those with single-vessel obstructive disease.[73] A variety of semi-quantitative scores have been proposed which aim to summarise the results of CTCA into a single metric that accounts for plaque burden **(Table 1-4).**[74]

The 'Segment Involved Score' (SIS) is a semi-quantitative measure of the extent of coronary artery disease throughout the coronary tree. Here segments are scored 0 or 1 based on the presence or absence of plaque, irrespective of the degree of stenosis. Meta-analyses have established extent of disease as determined by the SIS is a strong and independent predictor of cardiovascular mortality.[75] Moreover, recent results from the Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicentre (CONFIRM) registry suggest that an SIS > 5 provides more prognostic information than

traditional cardiovascular risk factors such as hypertension or diabetes mellitus.[76] Despite this, the SIS is limited due to the lack of consideration given to stenosis severity. Recently, more comprehensive scores, such as the CT-adapted Leaman score, have been developed to improve prognostic stratification. The CT-adapted Leaman score accounts for lesion locale, plaque composition and degree of stenosis, and performs considerably better than SIS.[77] However, these scores do not account for more advanced visual assessment of high-risk plaque and only provide an estimate, as 'lumenology' cannot truly quantify plaque burden with the coronary artery wall.

Table 1-4: Comparison of Semiquantitative score progression		
Score	Explanation	Example Case: Patient with one 70% lesion in the left main stem.
Coronary Artery Disease – Reporting and Data System (CADS-RADS)	Score 0-5 depending on the severity of the worst stenosis: 0 – 0%, No CAD 1 – 1-24%, Minimal non-obstructive 2 – 25-49%, Mild non-obstructive 3 – 50-69%, Moderate stenosis 4 – 70-99%, Severe stenosis A – >50% LMS B – 3-vessel ≥ 70% 5 – 100%, Total coronary occlusion	**CAD-RADS Score**: 4
Segment Involved Score (SIS)	Score depending on the number of segments with any disease based on the 17-segment coronary tree model. 0 – No coronary artery disease 1 – Coronary plaque present Continuous score, range: 0-16.	**SIS Score**: 1
Segment Stenosis Score (SSS)	Score depending on severity of stenosis in each segment based on the 17-segment coronary tree model. 0 – No coronary artery disease 1 – Mild plaque 2 – Moderate plaque 3 – Severe plaque Continuous score, range: 0-48.	**SSS Score**: 3
CT-adapted Leaman Score (CT-LeSc)	Weighted score based on: 1. Location of coronary plaque - 5.0-6.0 for LMS depending on dominance - 1.0-3.5 for LAD segments and branches depending on dominance - 0.5-2.5 for LCx segments depending on dominance - 0.5-1.0 for RCA segments depending on dominance 2. Severity of stenosis - Multiply score by 1 for obstructive - Multiply score by 0.615 for non-obstructive 3. Coronary plaque composition - Multiply score by 1.5 for non-calcified or mixed plaque - Multiply score by 1.0 for calcified plaque	**CT-LeSc Score if right dominant**: 5 if calcified 7.5 if non-calcified **CT-LeSc Score of left dominant:** 6 if calcified 9 if non-calcified
CAD- coronary artery disease, LMS- left main stem, LAD- left anterior descending artery, LCx- left circumflex artery, RCA- right coronary artery.		

1.5.3 Visual assessment of high-risk plaque

Whilst the extent of disease and severity of stenosis are undoubtedly important, they do not provide any information on the vulnerability of a plaque to rupture. CTCA markers of high-risk plaque include positive remodelling (a positive change in vessel diameter at the plaque site compared to a normal-appearing proximal segment), low-attenuation plaque (<30 Hounsfield units), spotty calcification (calcification <3 mm in size) and the 'napkin-ring sign' **(Figure 1-2)**. These features have been established by correlating CTCA findings to intravascular ultrasound (IVUS) and optical coherence tomography (OCT) findings.[78, 79] Early work by Motoyama *et al* demonstrated the association between positive remodelling, low-attenuation plaque and spotty calcification, to plaque rupture events in patients who had suffered an acute coronary syndrome.[80] Moreover, in their follow-up study, they demonstrated that positively remodelled segments with low-attenuation plaque were more likely to result in acute coronary syndromes.[81, 82] As an individual plaque feature, the 'napkin-ring sign' correlates with histological findings of central necrotic lipid cores surrounded by fibrous tissue [83] and demonstrated excellent specificity in identifying advanced lesions.[84]

Several studies have subsequently built on these findings (**Table 1-5**). The Incident COroNary Syndromes Identified by Computed tomography (ICONIC) case-control sub-study of the CONFIRM registry found that high-risk plaque features predict future acute coronary syndromes independent of, and better than, atherosclerotic plaque burden and the number of obstructed vessels.[85]

The Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT-2) trial found in troponin and electrocardiogram negative patients presenting with chest pain to the Emergency Department, the presence of high-risk plaque on CTCA increased the likelihood of myocardial infarction independent of clinical risk assessment and extent of coronary disease.[86] In the PROMISE trial, 15% of the 4415 patients with stable chest pain who underwent CTCA had high-risk plaques.[87] Patients with high-risk plaques had an increased risk of MACE (hazard ratio 2.73, 95% confidence interval, 1.89 to 3.93), which was independent of cardiovascular risk score and the presence of obstructive coronary artery disease. Interestingly, the presence of high-risk plaque was a more important predictor of events in women and younger patients. In a prospective cohort study of 1469 patients, Feuchtner *et al* found that the strongest predictors of cardiovascular events over an 8-year period were low-attenuation plaque and the napkin-ring sign.[88] Together these studies show that high-risk plaque features provide important prognostic information, over and above traditional assessments, and they are now part of the Society of Cardiovascular Computed Tomography CAD-RADS reporting guidelines.[89]

The inter-observer repeatability for the identification of high-risk plaque features is modest which limits its use in clinical practice.[72] In the SCOT-HEART trial, patients with positive remodelling or visually assessed low-attenuation plaque had a three-fold increase in the rate of fatal or non-fatal myocardial infarction (hazard ratio 3.01, 95% confidence interval 1.61 to 5.63,

p=0.001).[90] However, this was not independent of the coronary artery calcium score, a surrogate marker of the overall plaque burden. In addition, these high-risk plaques are common on CTCA, occurring in between 15 to 50% of patients depending on their presenting symptoms.[85, 87, 90] The importance of visually assessed high-risk plaque is limited by its poor positive predictive value which in PROMISE was as low as 6.4% for major adverse cardiovascular events.[91]

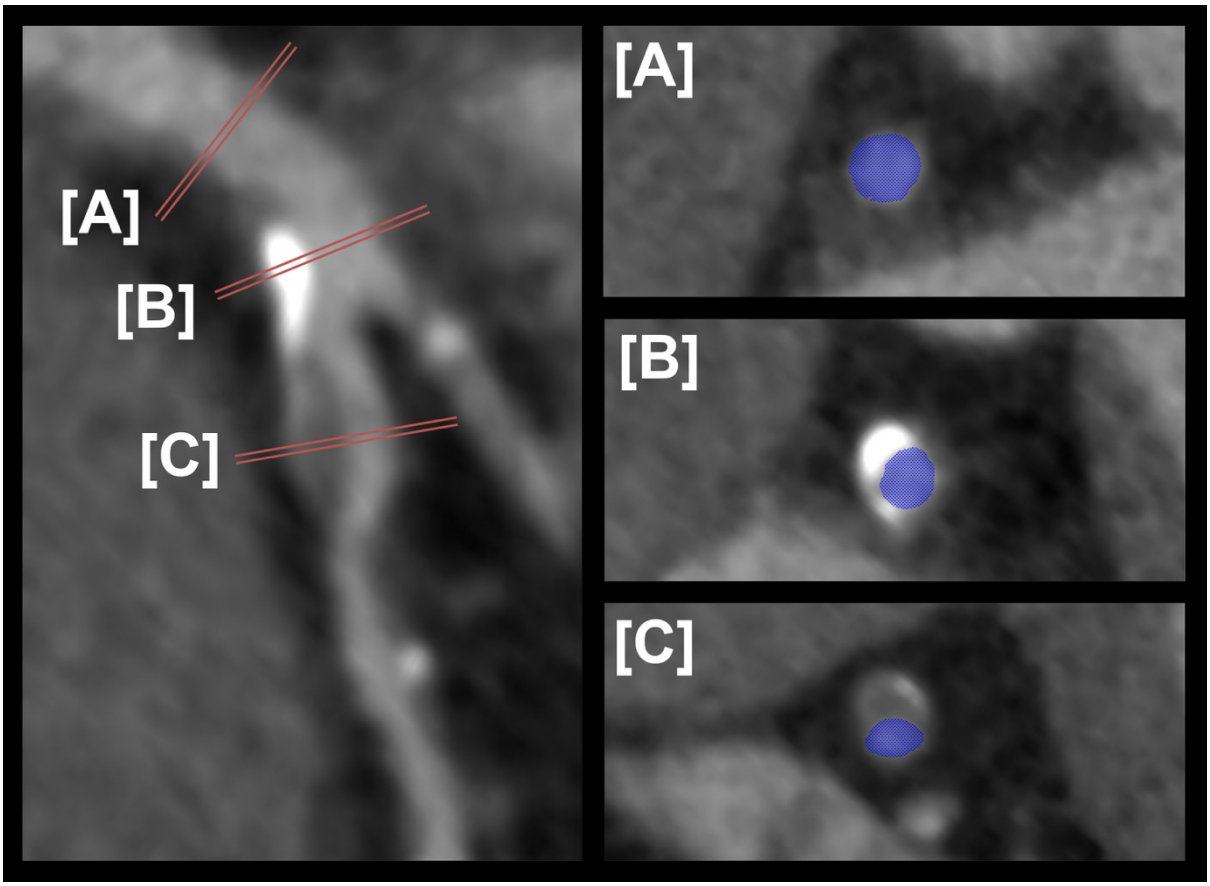

Figure 1-2: CT coronary angiogram of diseased coronary artery
Lumen highlighted in blue. **[A]** normal proximal left main stem measuring 5.1mm x 5.4mm. **[B]** Calcified lesion distal to the left main stem, positively remodeled, measuring 6.5mm x 5.8mm. **[C]** High-risk plaque (napkin-ring sign) in the proximal left anterior descending artery, vessel measuring 6.2mm x 5.7mm.

Table 1-5: Key studies assessing quantitative and qualitative plaque on CTCA.			
Visual assessment of high-risk plaques		**Quantitative assessment of plaque**	
Author, date	**Findings**	**Author, date**	**Findings**
Motoyama *et al*, 2007 [80]	HRP is an independent predictor of acute coronary syndrome	ROMICAT, 2012 [92]	ACS patients have a higher volume of plaque with low CT density (< 90 HU).
ROMICAT-2, 2014 [86]	HRP in troponin negative and ECG indeterminate patients with chest pain increased likelihood of MI independent of clinical risk assessment and atherosclerotic plaque burden.	ROMICAT II, 2015 [93]	ACS patients have a higher volume of plaque with low CT density (< 30HU and <60 HU)
Motoyama *et al*, 2015 [82]	HRP is an independent predictor of acute coronary syndrome at 4 years. Plaque progression by serial CTCA is an independent predictor of acute coronary syndrome.	Nadjiri et al, 2016 [94]	Non-calcified plaque volume and low-attenuation plaque volume are predictive of MACE at 5 years.
Feuchtner *et al*, 2017 [88]	High-risk low-attenuation plaque and the napkin-ring sign are the most powerful predictors of MACE over long-term follow-up (8 years).	ICONIC, 2018 [85]	Cross sectional plaque burden, fibro-fatty and necrotic core volumes were higher in ACS patients than controls. All three were significant predictors of ACS.
PROMISE, 2018 [91]	HRP is associated with increased risk of MACE after adjustment for cardiovascular risk and presence of significant stenoses	PARADIGM, 2018 [95]	Progression of atherosclerosis is slowed by statin therapy. Females are more responsive to statin compared to men.
ICONIC, 2018 [85]	HRP predicted future ACS independent of and better than number of obstructive vessel and atherosclerotic plaque burden	de Knegt, 2019 [96]	ACS patients have higher plaque volume, with more fibro-fatty plaque and less densely calcified plaque
SCOT-HEART, 2019 [90]	HRP is associated with worse prognosis but not independent of coronary calcium score	SCOT-HEART, 2020 [97]	Low-attenuation plaque burden is the strongest predictor of fatal or non-fatal myocardial infarction.
ACS, acute coronary syndrome; ECG, electrocardiogram; HRP, high risk plaque; MACE, major adverse cardiovascular event; MI, myocardial infarction.			

1.6 QUANTITATIVE ASSESSMENT

1.6.1 Development of quantitative plaque analysis

Whilst semi-quantitative scores provide important prognostic information, they remain a surrogate for actual measurements of plaque volume and burden. With advances in computing technology, we are now able to assess quantitatively plaque subtypes on CTCA based on their attenuation density. There are several software options that automatically detect the boundary between coronary lumen and vessel wall (including the surface of atherosclerotic plaque). Once detected, and if required, these segments can be manually adjusted by a trained reader who ensures the boundaries are accurately selected. Automated algorithms then measure total plaque volume well as volumes of plaque subtypes including calcified and noncalcified (fibrous, fibro-fatty, and low-attenuation) volumes. These volumetric measurements (in cubic millimetres; mm^3) can be measured at a lesion, segment, vessel, and patient level. Measurements are often presented as a percentage of the overall vessel volume, referred to as plaque burden, with the denominator being total vessel volume analysed. However to date, there are no standardised normative values.[98] This technique can be used to identify patients with an increased burden of plaque and an increased burden of the high-risk, low-attenuation plaque subtype (**Figure 1-3**).

Early iterations of plaque quantification software were time-consuming manual processes that could not differentiate between low-attenuation and non-calcified plaque.[99] Accordingly, semi-automated software was developed that substantially reduced the time taken to quantify plaque burden. They demonstrate improved repeatability and reproducibility over manual quantification, especially in patients with low to intermediate disease burden.[100, 101] Moreover, improved algorithms allow for a more precise description of low-attenuation plaque burden which correlate better with intravascular ultrasound.[40, 102] These advances have streamlined our ability to measure plaque burden and progression on serial imaging.

1.6.2 Validation and variability of quantitative plaque analysis

Quantitative plaque analysis has been extensively compared with invasive measures of plaque quantification by intravascular ultrasound (IVUS) or optical coherence tomography (OCT). One of the most frequently cited software is Autoplaque (Cedars-Sinai Medical Centre, Los Angeles, CA). Dey *et al* found excellent correlation between plaque volumes quantified by Autoplaque on CT and those quantified by intravascular ultrasound ($r=0.94$, $p<0.001$).[103] This was particularly the case for total, non-calcified and calcified plaque subtypes. However, early versions of the software had difficulties automatically calculating the volume of low-attenuation plaque. This was primarily due to the presence of low-attenuation adipose tissue that surrounds coronary arteries. To account for this, skilled readers were required to trace coronary artery plaque to avoid over-estimation, adding to the manual effort required and

thereby limiting widescale applicability. Matsumoto *et al* refined and automated this technique by creating a "low-attenuation plaque" editing software, which allows the exclusion of voxels adjacent to the vessel wall.[40]

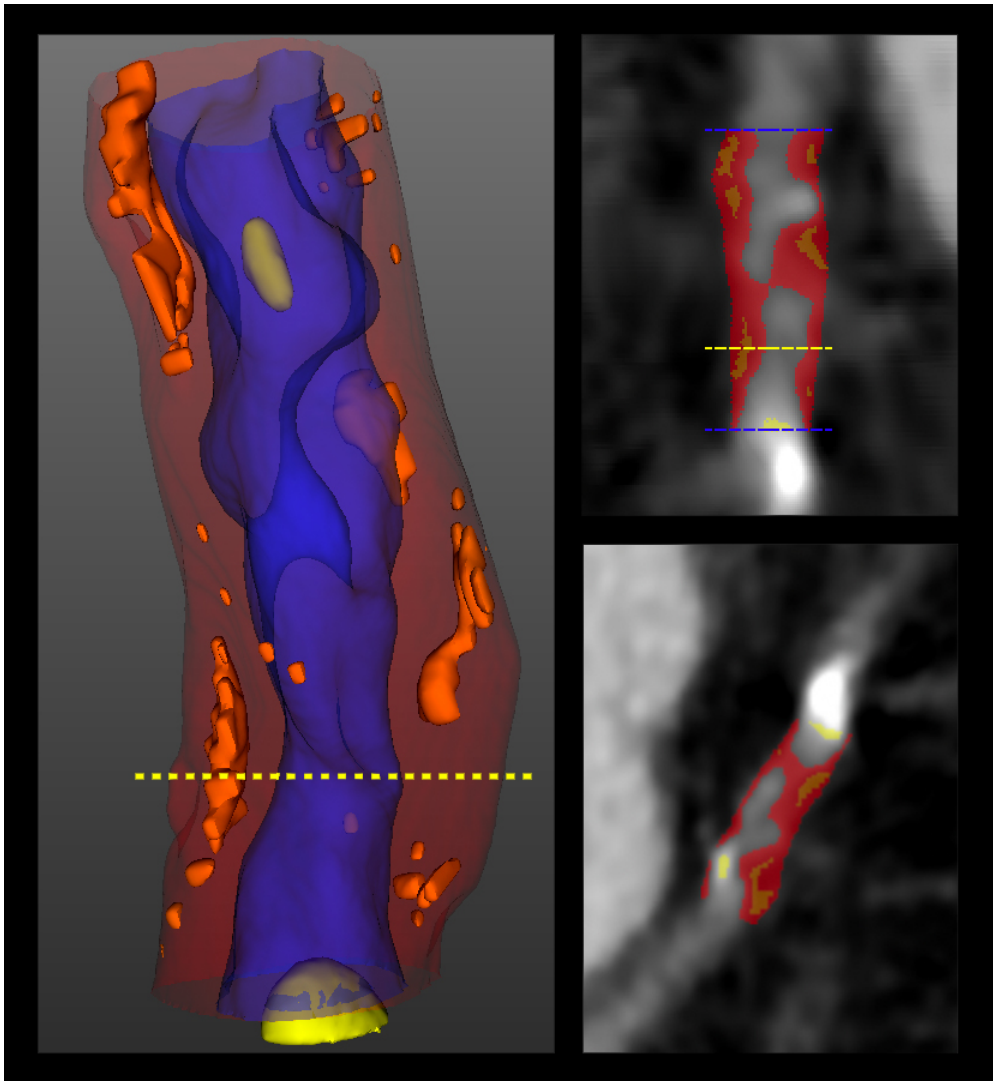

Figure 1-3: Quantitative plaque assessment of a stenotic mid left anterior descending artery.
Blue represents the lumen, calcified plaque volume (highlighted in yellow) 3.0 mm^3, non-calcified plaque volume (highlighted in red) 154.3 mm^3, low-attenuation plaque volume (highlighted in orange) 8.0 mm^3.

The reproducibility of quantitative plaque analysis has been assessed. Using Autoplaque, Cheng *et al* demonstrated the excellent intra-observer and inter-observer agreement for normal segments (100%), and strong correlations for total, non-calcified and calcified plaque burdens in diseased segments (r=0.81-0.96, p<0.001).[99] As algorithms improved and automated components were added to the software, further reproducibility studies were performed focusing primarily in patients with low to intermediate burdens of disease. The results were extremely promising, with high degrees of reproducibility noted using automated and semi-automated methods, even when CT scanners used low-radiation dose protocols.[100, 101] The patients recruited to these studies were however highly selected, with excellent heart rates, and minimal calcification. As such, there remained questions about the reproducibility of plaque quantification in an unselected cohort of patients with advanced coronary disease. We will seek to address this question in Chapter 3.

1.6.3 Assessment of temporal changes using plaque quantification

Coronary artery calcium score has previously been used as a surrogate endpoint to assess the clinical benefit of medication, such as statin therapies. Interestingly it was noted that statin therapy led to progression of coronary artery calcification, lending weight to the argument that calcified plaque is stable and unlikely to rupture and cause further events.[104] More recently, exercise has also been linked to progression of calcification in coronary arteries.[105] An important advantage of quantitative plaque analysis is its ability

to perform repeated analysis and track temporal changes in non-calcified plaque, much the same as coronary calcium score does for calcified plaque.

The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography (PARADIGM) trial was a large prospective observational study that evaluated temporal changes in plaque characteristics utilising semi-automated plaque quantification software.[95] Of 1255 patients, 781 were on statin therapy. This trial demonstrated that statins not only resulted in slower rates of progression of non-calcified plaque volume, but also reduced the risk of positive remodelling and high-risk plaque formation. Importantly, they were able to assess quantitatively the impact of statins on the whole coronary tree. Progression of subclinical atherosclerosis was slowed in vessels beyond the proximal segments that are usually assessed by intravascular ultrasound.[95] The authors were also able to describe sex differences in plaque composition (high-risk plaque was more common in men than women) and plaque progression (women had greater progression of calcified plaque and reduced progression of non-calcified plaque).[106]

There have been several studies in recent years which have used quantitative plaque as study endpoints to provide a mechanistic explanation for the effects of novel drugs. The Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridaemia (REDUCE-IT) was a randomised double-blinded placebo-controlled trial that demonstrated a reduction in rates of cardiovascular events and death with icosapent ethyl versus placebo.[107]

However, this beneficial effect appeared to occur independent of demonstrable changes in the concentration of serum lipids. This raised the obvious question of how could such a benefit be observed in the absence of a reduction in lipid-levels? Trialist therefore conducted the Effects of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) trial and measured the effect of icosapent ethyl on coronary atherosclerosis using quantitative plaque analysis. Compared to placebo, it demonstrated a 9% reduction in total plaque volume and 17% reduction in low-attenuation plaque volume in patients taking icosapent ethyl.[108] Quantitative plaque analysis, therefore, provided a possible mechanistic explanation for the effects noted in REDUCE-IT. Assessing the progression of plaque subtypes in such detail can facilitate our understanding of the impact of medications on the atherosclerotic process.

1.6.4 The clinical value of quantitative plaque analysis

Several studies have established the particular importance of low-attenuation plaque. Motoyama *et al* were amongst the first to associate low-attenuation plaque (with an attenuation <30 Hounsfield units) with the thin-cap fibroatheroma seen histologically.[65, 80] In the ICONIC sub-study of the CONFIRM registry, increased cross-sectional plaque burden, fibrofatty plaque volume and necrotic core volume were all associated with increased risk of subsequent acute coronary syndrome in 234 patients with acute coronary syndrome compared to propensity matched control subjects.[85] Interestingly, they found that there were no sex differences in calcified plaque volume, but

women had lower fibrous and fibrofatty plaque volume compared to men.[109] Nadjiri *et al* found that in 1168 patients undergoing CTCA for suspected coronary artery disease, the volume of non-calcified plaque and low-attenuation plaque was higher in patients who experienced MACE during 5 years of follow-up.[94]

A post hoc analysis of the SCOT-HEART trial showed the primacy of low-attenuation plaque burden in the prediction of future fatal or non-fatal myocardial infarction.[97] The total plaque burden, and the burden of all sub-types of plaque, were higher in patients who suffered subsequent myocardial infarction after 4.7 years of follow up. Low-attenuation plaque burden was the strongest predictor of subsequent myocardial infarction (adjusted hazard ratio per doubling 1.60, 95% confidence interval 1.10 to 2.34, p=0.014), over and above cardiovascular risk score, coronary artery calcium score and coronary artery stenoses. Patients with a low-attenuation plaque burden above 4% were at a particularly high risk of subsequent myocardial infarction (hazard ratio 4.65, 95% confidence interval 2.06 to 10.5, p<0.001). Thus, in patients presenting with stable chest pain, quantitative plaque burden provides better prognostic information than classic markers of cardiovascular risk.

1.6.5 Troponin and quantitative plaque analysis

Studies that have measured high-sensitivity cardiac troponin and plaque burden are extremely limited. In 81 patients with stable chest pain, Altintas *et al* showed adverse plaque characteristics were associated with high-sensitivity

cardiac troponin T.[110] However, the study population was small, and troponin is not routinely measured in the stable population. In the acute chest pain population, high-sensitivity cardiac troponins are widely utilised and form the central tenet in the diagnosis of myocardial infarction. Patients presenting with chest pain who have a diagnosis of myocardial infarction excluded, but who have a high-sensitivity cardiac troponin concentration between 5 ng/L and the 99th centile, are 10 times more likely to suffer a cardiovascular event in the following year.[26] The reasons for this are not clearly understood, and they are not routinely offered further investigation or treatment. Some of these patients may have suffered a sub-clinical plaque rupture event and have unstable angina. In Chapter 4, we will explore whether quantitative plaque analysis can provide mechanistic details that explains the higher rate of future cardiovascular events in those with 'intermediate' cardiac troponin concentrations.

1.6.6 Myocardial infarction and CT plaque quantification

CTCA and advanced plaque quantification techniques have been studied in stable populations, such as those with stable angina. However, our understanding of the diagnostic utility of plaque quantification in patients who have presented acutely to the Emergency Department with chest pain, is limited. Early and important observations were made in patients with acute chest pain who were recruited to the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography)[92] and ROMICAT II [93] studies. In post-hoc analyses, they found that patients with acute coronary

syndromes (an umbrella term that encapsulates patients with ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina) had a larger volume of plaque with a low-attenuation density. De Knegt *et al* showed that when compared with asymptomatic patients and patients with non-cardiac chest pain, patients with acute coronary syndromes had a higher total plaque volume and volume of fibrofatty and necrotic core plaque, but a lower volume of densely calcified plaque.[96]

These cohort studies demonstrate that plaque composition differs on quantitative analysis as the clinical profile changes. Those more clinically unstable appear to have a higher burden of plaque. However, there have been no studies assessing the differences in plaque composition between different types of myocardial infarction. Nor are there any data on the ability of plaque quantification to risk stratify patients who present with acute coronary syndromes. In Chapter 5, we will explore whether quantitative plaque analysis can be used to identify differences between type 1 and type 2 myocardial infarction. We will also explore the diagnostic and prognostic value of quantitative plaque analysis in patients presenting acutely to the emergency department in Chapter 6.

1.7 AIMS

The overall aim of this thesis is to explore the ways in which innovative uses of quantitative plaque analysis may provide new clinically relevant information. To do this, we must first determine the reliability of the technique on a cohort of patients with advanced coronary disease by assessing the intraobserver, interobserver and interscan reproducibility of semi-automated quantitative plaque analysis. We will then investigate the relationship between plaque burden and high-sensitivity cardiac troponin I in patients who present acutely with chest pain but without myocardial infarction. We will also explore differences in quantified plaque characteristics between patients with type 1 and type 2 myocardial infarctions and determine whether these differences can be used to differentiate between the two pathologies. Finally, we will determine the diagnostic and prognostic potential of quantitative plaque analysis in patients who present with undifferentiated acute chest pain.

1.8 HYPOTHESES:

The hypotheses of this thesis are:

1. Quantitative plaque analysis has good intraobserver repeatability and interobserver and interscan reproducibility even when there is a high burden of coronary atherosclerosis (Chapter 3).
2. Patients presenting acutely with chest pain in whom myocardial infarction has been excluded, who have a high-risk plasma concentration of high-sensitivity cardiac troponin (≥5 ng/L), have a larger burden of high-risk low-attenuation plaque (Chapter 4).
3. Patients with type 1 myocardial infarction will have higher burdens of plaque on quantitative plaque analysis compared to patients who present with type 2 myocardial infarction. Quantitative plaque analysis may be used to help differentiate between type 1 and 2 myocardial infarction (Chapter 5).
4. In patients who present with acute coronary syndromes, quantitatively assessed plaque burden will correlate with 1-year risk of death or non-fatal myocardial infarction (Chapter 6).

2 CHAPTER 2: Methodology

2.1 OVERVIEW

The study specific designs and methodologies are described in detail in the relevant chapters. The following will provide an overview of the patient populations and the techniques used in these studies. Data for Chapters 3 was produced as pre-specified sub-studies of the Dual antiplatelet therapy to Inhibit coronary Atherosclerosis and MyOcardial injury in patients with Necrotic high-risk coronary plaque Disease (DIAMOND) randomised controlled trial (NCT02110303).[111] Data for Chapter 4 was produced from the Troponin to Risk Stratify Patients for Computed Tomography Coronary Angiography (PRECISE-CTCA) trial (NCT04549805). Data for Chapter 5 were derived from the RAPID assessment of potential ischaemic heart disease with CTCA (RAPID-CTCA) randomised controlled trial (NCT02284191).[112, 113] Data for Chapter 6 were derived from DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction (DEMAND-MI) prospective cohort study (NCT03338504).[114]

2.2 STUDY POPULATION

2.2.1 DIAMOND

The Dual antiplatelet therapy to Inhibit coronary Atherosclerosis and MyOcardial injury in patients with Necrotic high-risk coronary plaque Disease (DIAMOND) study was a double-blind randomised parallel-group placebo-controlled trial conducted at a single centre in Edinburgh. It aimed to investigate whether ticagrelor therapy reduces high-sensitivity troponin I in patient with established coronary disease and high-risk plaque. The primary results of this trial have been published previously.[111] Patients were recruited between 2015 and 2017 and were included if they were ≥40 years of age, on aspirin and with proven multivessel coronary artery disease (defined as at least 2 major epicardial vessels with either >50% stenosis or previous revascularisation). Patients who had recently suffered an acute coronary syndrome within the last year, or who had needed coronary revascularisation within the last 3 months were excluded.

Patients were recruited from the Royal Infirmary of Edinburgh, UK and underwent an electrocardiogram (ECG)-gated ^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET) and coronary CT angiogram at the Clinical Research Imaging Centre. Scans were performed after administration of 50-100 mg of oral metoprolol if the resting heart rate was greater than 65 beats per minute. After this, 250 MBq of ^{18}F-NaF was then administered

intravenously and 60 minutes later patients were imaged with a PET/CT scanner (64-multidetector Biograph mCT, Siemens Medical Systems, Erlangen, Germany). The first 20 patients were scanned again 1 week after the baseline scan and formed the population for our reproducibility study. The full inclusion and exclusion criteria are detailed in Table 2-1.

TABLE 2-1: Inclusion and exclusion criteria for DIAMOND.	
Inclusion Criteria	
1.	Patient aged ≥ 40 years with angiographically proven multivessel coronary artery disease (defined as two major epicardial vessels with either ≥50% stenosis or previous revascularisation).
2.	Proof of informed consent prior to any study specific procedures
3.	Receiving aspirin
Exclusion Criteria	
1.	An acute coronary syndrome within the last 12 months
2.	An indication for dual anti-platelet therapy, such as drug eluting stent
3.	Receiving thienopyridine therapy such as clopidogrel or prasugrel
4.	Coronary revascularisation within the last 3 months
5.	Inability or unwilling to give informed consent
6.	Women who are pregnant, breastfeeding or of childbearing potential
7.	Known hypersensitivity to ticagrelor
8.	Active pathological bleeding or bleeding diathesis
9.	Significant thrombocytopaenia (platelet <100 x 10^9/L)
10.	History of intracranial bleeding
11.	Moderate to severe liver impairment (Child's Grade B or C)
12.	Concomitant need for strong CYP3A4 inhibitor
13.	Major intercurrent illness or life expectancy <1 year
14.	Renal dysfunction (eGFR ≤ 30 mL/min/1.73 m^2)
15.	Contraindication to iodinated contrast agents
16.	Planned coronary revascularisation or major surgery in the next 12 months
17.	Maintenance therapy with simvastatin or lovastatin at doses ≥ 40mg
18.	Receiving oral anticoagulants including warfarin or DOACs

2.2.2 PRECISE-CTCA

The Troponin-Guided Coronary Computed Tomographic Angiography After Exclusion of Myocardial Infarction study was a prospective cohort study of patients who presented to the Emergency Department with suspected acute coronary syndrome and who had a plasma high-sensitivity cardiac troponin I concentration below the 99th centile (NCT04549805).[35] It aimed to evaluate whether high-sensitivity cardiac troponin could be used to select patients for further evaluation with computed tomography coronary angiography, after myocardial infarction had been excluded. The study enrolled 250 patients between 2018 and 2020 in a 2:1 fashion stratified by plasma peak high-sensitivity cardiac troponin concentrations above and below the risk stratification threshold of 5 ng/L respectively. The full inclusion and exclusion criteria are detailed in Table 2-2. The primary outcome was the proportion of participants with obstructive coronary artery disease with secondary endpoints including the proportion of participants with non-obstructive coronary disease and normal coronary arteries.

Patients were recruited from the emergency department at the Royal Infirmary of Edinburgh. All participants underwent CTCA as an outpatient, as soon as possible after their initial hospital attendance. CT scans were performed on 128-detector row scanner (Biograph mCT, Siemens Healthcare) with appropriate administration of rate-limiting medication and

sublingual glyceryl trinitrate. All 250 CT scans were analysed using specialist plaque quantification software.

TABLE 2-2: Inclusion and exclusion criteria for PRECISE-CTCA.	
Inclusion Criteria	
1.	Presentation to hospital with acute chest pain or equivalent symptoms of suspected acute coronary syndrome
2.	Maximum high-sensitivity cardiac troponin-I concentration below the 99th centile (16 ng/L for women and 34 ng/L in men)
Exclusion Criteria	
1.	Diagnosis of myocardial infarction during index presentation.
2.	Clear alternative diagnosis for index presentation.
3.	Recent CT or invasive coronary angiogram (in the last 12 months)
4.	Inability to undergo CT scanning (due to allergy to iodinated contrast media or severe renal failure.
5.	Pregnancy or breast-feeding
6.	Inability to give informed consent
7.	Further investigation for coronary artery disease would not be in the patient's best interest due to limited life expectancy, quality of life or functional

2.2.3 RAPID-CTCA

The Rapid Assessment of Potential Ischaemic Heart Disease with CTCA (RAPID-CTCA) study was an open prospective multicentre parallel-group randomised controlled trial that compared early computed tomography coronary angiography versus standard care in patients who presented with suspected acute coronary syndrome to the emergency department (NCT02284191). The trial protocol and primary results have been published previously.[112, 113] It recruited participants from across the United Kingdom between 2015 and 2019 if they were suspected of having an acute coronary syndrome and had one or more of the following – (a) elevated cardiac troponin, (b) previous history of coronary heart disease, or (c) an abnormal electrocardiogram. The full inclusion and exclusion criteria are detailed in Table 2-3.

Participants who consented and were deemed eligible were randomised on a 1:1 basis to CTCA in addition to standard care, or standard care alone. As the trial was open, the participants and the attending clinicians were not blinded to the results of any intervention. CTCA was delivered using at multidetector CT scanners capable of 64-slice or greater ECG-gated cardiac studies. For our substudy, of the 767 scans conducted, 404 were transferred to Edinburgh for image analysis. These scans were reanalysed on specialist plaque analysis software. The primary endpoint was a composite of all-cause death or recurrent non-fatal type 1 or type 4b myocardial infarction at 1 year. The

endpoint was measured as the time to the first such event and myocardial infarction was defined using the third universal definition of myocardial infarction. Patients were followed up using routine clinical notes and research contact directly with the patient by phone, email, or post. If this was not possible, the patient's general practitioner (GP) was contacted to obtain 12-month follow-up data. All endpoints were adjudicated by blinded independent cardiologists.

TABLE 2-3: Inclusion and exclusion criteria for RAPID-CTCA.	
Inclusion Criteria	
1.	Patient aged ≥ 18 years with symptoms mandating investigation for suspected or confirmed acute coronary syndrome and at least one of the following:
A.	ECG abnormalities consistent with ischaemia
B.	History of ischaemic heart disease
C.	Troponin elevation above the 99th centile of the normal reference range or increase in high-sensitivity troponin meeting ESC criteria for "rule in"
Exclusion Criteria	
1.	Signs, symptoms or investigation supporting high-risk ACS including:
A.	ST elevation MI.
B.	ACS with signs or symptoms of acute heart failure.
C.	ACS with signs or symptoms of circulatory shock.
D.	Crescendo episodes of typical anginal pain.
E.	Marked or dynamic ECG changes e.g., ST depression > 3mm.
F.	Clinical team have scheduled early invasive angiogram on day of trial eligibility assessment.
2.	Patient inability to undergo CT scan
A.	Poor renal function (eGFR <30 mL/min/1.73 m^3)
B.	Contrast allergy
C.	Beta blocker intolerance
D.	Inability to hold breath
E.	Atrial fibrillation (where mean heart rate is anticipated to be ≥75 beats/min)
3.	Patient had invasive angiography or CTCA within the last 2 years revealing obstructive cardiac disease or had invasive angiography or CTCA within the last 5 years and the result was normal.
4.	Previous recruitment to the trial
5.	Known pregnancy or currently breast feeding
6.	Inability to consent
7.	Further investigation for ACS would not be in the patient's interest due to limited life expectancy, quality of life or functional status
8.	Prisoners

2.2.4 DEMAND-MI

The DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction (DEMAND-MI) study was a prospective observational cohort study which aimed to investigate the mechanism of myocardial injury and role of coronary artery disease in patients who had suffered a type 2 myocardial infarction (NCT03338504). The primary results have recently been published.[114]

The study population consisted of hospitalised patients who had suffered an acute myocardial injury (defined as a rise or fall in high-sensitivity cardiac troponin concentration) where the likely mechanism was thought to be myocardial oxygen supply and demand imbalance: for example, secondary to hypotension, hypoxic insult, tachyarrhythmia or anaemia. The full inclusion and exclusion criteria are detailed in Table 2-4. Patients deemed eligible underwent coronary imaging with invasive coronary angiography or CTCA, as well as cardiac magnetic resonance imaging (MRI). Patients were recruited from and underwent imaging at the Royal Infirmary of Edinburgh between 2018 and 2020. Of the 100 participants, 36 patients underwent CTCA and were included in our sub-study. CTCA scans were performed using a 128-slice multidetector row CT scanner (Siemens Biograph, Siemens Healthcare, Erlangen, Germany). The outcome of interest in our sub-study was the final diagnosis of type 2 myocardial infarction as defined by the Fourth Universal Definition.[30]

The diagnosis was made by consensus by an adjudication panel with expertise in cardiology, coronary intervention, and cardiac imaging.

TABLE 2-4: Inclusion and exclusion criteria for DEMAND-MI.	
Inclusion Criteria	
1.	Unscheduled hospital admission with acute myocardial injury (defined by a rise or fall in high-sensitivity cardiac troponin I concentrations)
2.	A suspected aetiology of myocardial oxygen supply and demand imbalance with symptoms or signs of myocardial ischaemia
Exclusion Criteria	
1.	Unable or unwilling to give informed consent
2.	Women who are pregnant, breastfeeding or of child-bearing potential
3.	Probable type 1 myocardial infarction
4.	Poor renal function (eGFR <30 mL/min/1.73 m^3)
5.	Severe hepatic impairment (Child's Grade C)
6.	Frailty with inability to self-transfer (determined using Katz Index)

2.3 ETHICAL CONSIDERATIONS

All studies were approved by both the Research and Development Departments and by Research Ethics Committees. The DIAMOND study was a Clinical Trial of an Investigational Medicinal Product (CTIMP) and was approved by the Medicines and Healthcare products Regulatory Agency (MHRA). All study participants provided informed written consent prior to taking part in any study procedure.

2.4 CARDIAC TROPONIN TESTING

Cardiac troponin testing for Chapter 4 was performed at presentation and repeated 6 or 12 hours after the onset of symptoms at the discretion of the attending clinician. Cardiac troponin was measured in accordance with contemporary national and international guidelines.[29, 115] The ARCHITECT*STAT* high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL, USA) was used which in brief, uses a paramagnetic antibody to bind cardiac troponin I in a sample. The bound troponin I is then extracted from the reaction vessel during a wash phase using a magnetic field. A second detection antibody is then added which is conjugated to acridinium and activated by a trigger agent generating fluorescence. The strength of the signal obtained is proportional to the concentration of cardiac troponin I present in the sample.

For consistency and for the purpose of this analysis, all patients with an undetectable troponin concentration were assigned a value of 1.0 ng/L. The inter-assay coefficient of variation is less than 10% at 4.7 ng/L and the sex-specific 99th centile diagnostic thresholds are 16 ng/L for women and 34 ng/L for men. This assay has a limit of detection of between 1.2 and 1.9 ng/L.[115]

2.5 COMPUTED TOMOGRAPHY

Computed tomography is a widely used imaging modality which is capable of acquiring three dimentional images of the human body by combining a series of X-ray images taken from different angles around the body. In conventional medical X-ray imaging, X-ray beams travel in a straight line through the patient and exit on the opposite side with different intensities based on the attenuation of the beam through tissues of varying densities. Images are generated by measuring the attenuation of X-ray through an area of interest where each pixel is a representation of the mean attenuation. Unlike simple X-ray imaging which utilises a fixed source of X-ray, CT scanners use a motorised source of X-ray which rotates around a circular structure called a gantry. In doing so, thin cross-sectional images can be generated using X-ray, by taking multiple measurements of attenuation throughout a cross section of interest and then reconstructing an image.[116] Detectors rotate parallel to the X-ray source and transmit the attenuation data to a computer. With each rotation of the gantry, the computer uses the attenuation data to construct a 2-dimentional image of the cross-section or slice. Slices are then stacked together by the computer to generate 3-dimentional images of the object of interest.

In 1971, the first patient had their brain imaged using computed tomography in London to widespread scientific and media attention. These early CT systems utilised a single source of X-rays generated as a beam and a single detector that moved laterally to cover the total field of view 1-degree at a time

until the full 180 degrees were scanned. Generating a single axial slice then took up to 4 minutes and the system was geared towards imaging only the brain.[117] It took a number of innovative developments to close the gap from taking 40 minutes to image the brain, to capturing images of a moving coronary artery. For example, the introduction of slip-ring technology, which enabled continuous rotation of the gantry, and the so-called “slice war” of the late 1990s where gradually increasing numbers of detector elements made it possible to capture images of organs in a single rotation of the gantry. The result is that in the 21st century, computed tomography has become an indispensable workhorse in medical practice, with several million CT scans performed annually in the United Kingdom alone.[118]

2.6 CT CALCIUM SCORING

Coronary artery calcium scanning involves a non-contrast cardiac CT scan acquired in the same phase of the cardiac cycle using ECG gating and during breath hold. Coronary calcium is defined as a lesion above 130 Hounsfield units with an area of at least 3 adjacent pixels. Arthur Agatston first developed the calcium score in 1990 using the calcified plaque area and maximal calcium lesion density.[119] Interobserver variability has persistently been low, with Agatston et al demonstrating 80% of scores were identically reproduced and with narrow limits of agreement. Multicenter and multidetector intra and interobserver variability has been tested on more recent scanners and demonstrate excellent agreement particularly for patients with calcium scores less than 1000.[120] As a predictor of the presence of obstructive coronary artery disease on invasive coronary angiography, coronary calcium score has a sensitivity of up to 98% and a negative predictive value of 93%.[121] Calcification is thought to be the healing response to plaque inflammation, similar to that which occurs in granulomatous conditions such as tuberculosis.[122] Whilst the CT calcium score does not directly identify high risk plaque, it provides clinicians with a surrogate marker of underlying plaque burden and is a powerful predictor of future cardiovascular events.[123]

Non-contrast CT images for coronary calcium scoring in our studies were reconstructed in the axial plane after acquisition of scout images and before contrast enhanced coronary angiography. Imaging was performed using a

tube voltage of 120 kV with the tube current automatically selected based on body habitus. Coronary calcium was quantified by trained individuals on dedicated software (Vitrea Advanced, Vital Images, Minnetonka, USA). Coronary artery calcification was defined as an area in the course of a coronary artery with an attenuation threshold ≥ 130 Hounsfield Units (HU) and larger than 1 mm^2. Calcification was quantified as a calcium score (Agatston Units, AU) using the Agatston technique. The area of calcification was measured on each axial slice and multiplied by a weighting factor dependent on the peak attenuation within the region (1 for 130-199 HU, 2 for 200-299 HU, 3 for 300-399 HU, and 4 for ≥400 HU).[119] This was done on a per coronary artery basis and then summed to produce a total coronary artery calcium score for the patient. Coronary stents were excluded from the analysis.

2.7 CT CORONARY ANGIOGRAPHY

Whilst cardiac CT imaging is not a novel concept, with early examples delivered by Godfrey Hounsfield in 1979,[124] images have only been produced with consistent quality since 2004 with the advent of 64-slice multidetector CT scanners. Electrocardiograph (ECG) gated CT has granted the ability to image the heart during specific phases of the cardiac cycle.[125] The diastolic phase can be precisely and prospectively targeted, as this is the phase when the heart is most still and coronary blood flow at its highest. In doing so, the heart can be imaged in several slices over several beats, and then reconstructed as a single structure creating three-dimensional images of cardiac and coronary anatomy with excellent spatial resolution.[66, 78] The use of iodine-based contrast media enhances differences in attenuation between target tissues and the surrounding structures. In our studies, all scans were conducted on a 64-slice (or greater) scanner allowing sufficient morphological data to be captured to conduct detailed assessment with newly developed automated software for plaque quantification.

In our studies, a tube voltage of 100 kVp was used for patients with a BMI <25 kg/m^2 and 120 kVp for those over. Scans were reconstructed using 180-degree rotation, filtered back projection, 512 x 512 matrixmedium smooth reconstruction kernel (B26f) with 0.75-mm slice thickness at 0.5-mm increments.

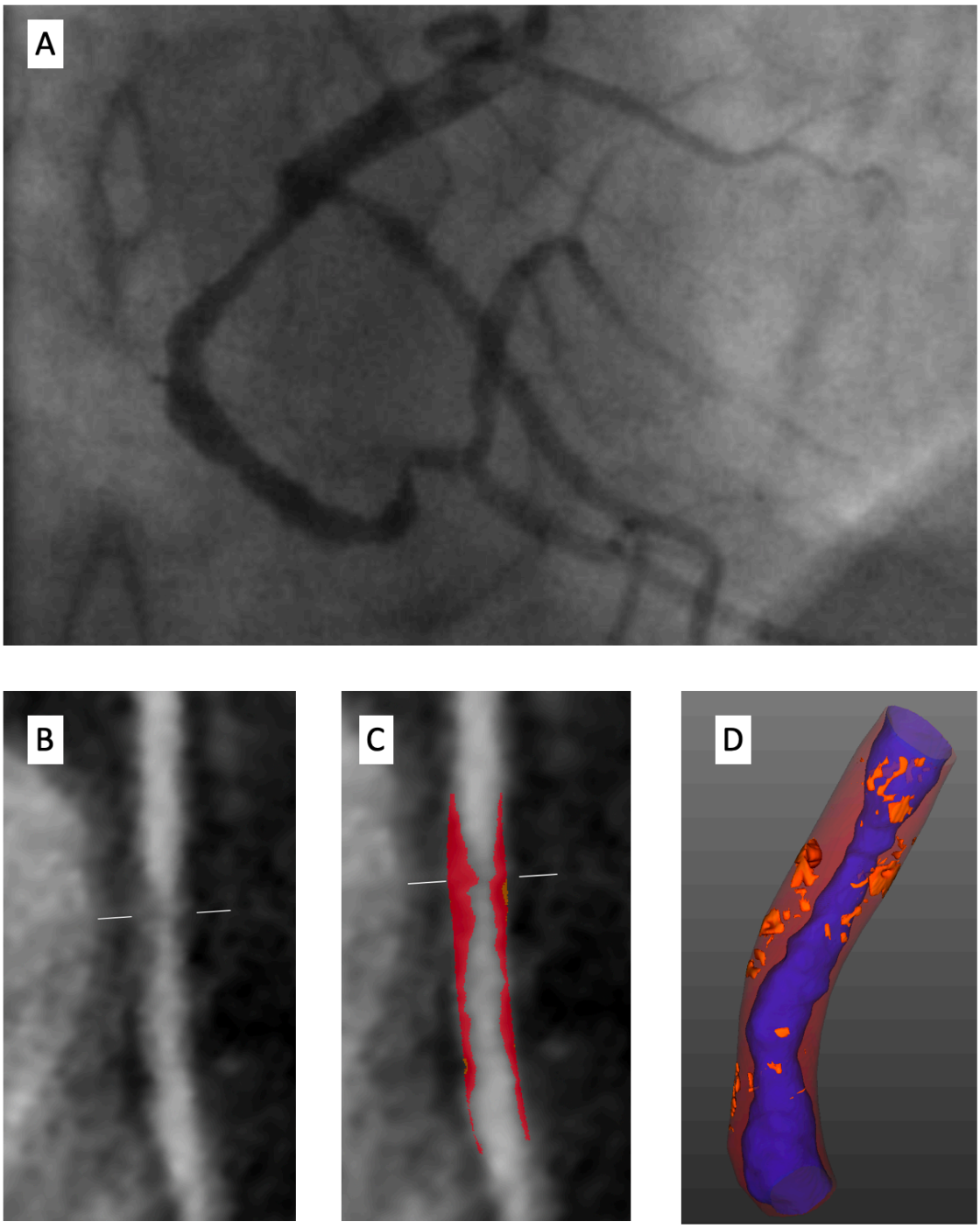

Figure 2-1: Plaque analysis example and invasive coronary angiogram; Images from a 46-year-old male presenting with chest pain and a peak high-sensitivity troponin of 8124 ng/L, diagnosed as a non-ST segment elevation myocardial infarction. (**A**) Invasive angiography demonstrates severe stenosis in the mid right coronary artery. CT curved planar reformation (**B**), quantitative plaque analysis (**C**) and 3D quantitative plaque analysis (**D**) demonstrated a high burden of low attenuation (in orange) and non-calcified plaque. Reproduced from *Williams et al* with permission.[98]

2.7.1 Image acquisition

Several studies have established the optimal conditions under which image quality of CTCA can be improved. In particular, heart rate and heart rate variability are well established factors that can degrade the image quality. When patients have a high heart rate, the time within which images must be acquired is much shorter. This can lead to motion and stitch artefacts, limiting the clinician's ability to interpret the structures. To control for this effect, studies have demonstrated that administering rate limiting medication such as beta-blockers immediately prior to the scan, reduces the heart rate sufficiently to allow prospective imaging during diastole and thereby limiting motion blur.[62, 126] Of equal importance is the use of vasodilatory medication such as sublingual glyceryl trinitrate (GTN) which Williams et al showed also improved the diagnostic quality of images obtained.[126] In our studies, patients were prepared for CTCA using beta blockade to slow the heart rate down to <65 /min (oral or intravenous metoprolol) if there were no contraindications. They were also given sublingual glyceryl trinitrate to vasodilate coronary arteries immediately prior to beginning the scan. Scans were performed during breath-hold, using prospective ECG-gating in the diastolic phase. However, if heart rate control was suboptimal, images were acquired in the systolic phase instead.

The X-ray Tube Voltage (kV) relates to the number of X-rays produced which higher tube voltage relating to an increase in the number of X-rays. An increased kV reduces the attenuation of X-ray signals and affects the amount

of contrast in the resultant image. Increasing the kV therefore allows for clearer imaging of larger patients, however this must be balanced with the risks of increased radiation. Given that between 0.4 and 2% of all cancers are reportedly due to radiation exposure during CT scanning, reducing radiation doses is of paramount importance.[127] Optimising heart rate control and electrocardiographic gating, acquisition of scout images and minimising detector range have all lead to a considerable drop in radiation dose such that studies from 2009 exposed patients to up to 15 mSv of radiation, whereas now, the dose can be below 1 mSv.[128, 129]

In our studies, the scanning protocol included a topogram, coronary artery calcium scan (for Chapter 6), test bolus scan and CTCA. During the test bolus scan, a small dose (20 mL) of contrast agent (Omnipaque or Visipaque, GE Healthcare, New Jersey) was injected via a 20-G cannula. Time delay was set at time to peak contrast in the ascending aorta + 3 seconds. For the CTCA, a larger dose (60±10 mL) of contrast agent was injected followed by a saline flush to improve visualisation of the coronary arteries.

2.7.2 Image analysis

Quantitative CT plaque analysis can be completed using several different software providers which all function slightly differently and use differing terminology. To date, there has been no standardisation of technique and lexicon. However, as its use has grown, there have been areas of agreement that led to an ‘commonly used’ format. Whilst most softwares automatically

detect the boundary between epicardial fat, vessel wall, surface of atherosclerotic plaque and the coronary lumen, these boundaries inevitably require manual adjustment by a trained operator. Even with the most stringent operator delineating these boundaries, there is a risk that the vessel wall may be mistaken for plaque. As such, one accepted form of practice is to exclude visually normal coronary segments from undergoing plaque analysis – to avoid the introduction of noise and bias into the dataset.[98]

Another technical issue is caused by fluctuations in plaque attenuation due to several factors including the concentration of iodine in the coronary artery, scan tube potential and image reconstruction technique. With some softwares, the thresholds used to define calcified and non-calcified plaque, are scan-specific and are adjusted depending on the blood pool attenuation. Calcified plaque typically has a threshold of ≥350 Hounsfield Units, with anything less usually being deemed non-calcified plaque. Non-calcified plaque can be further subdivided into fibrous, fibro-fatty and low-attenuation plaque. Motoyama and colleagues were the first to suggest the currently accepted definition of low-attenuation plaque with a fixed threshold of <30 Hounsfield Units. However there have been some studies that suggest thresholds of up to 60 may perform better.[65, 130, 131] Whilst the optimum threshold remains undetermined, a fixed Hounsfield Unit threshold <30 remains the commonest threshold used for low-attenuation plaque. To this end, validation of techniques is crucial and indeed for this thesis, was performed prior to the completion of other works and forms the basis of Chapter 3.

For our studies, CT datasets were anonymised and exported in a Digital Imaging and Communications in Medicine (DICOM) format. All coronary artery plaque assessments were completed using semi-automated software (Autoplaque, Cedars Sinai Medical Centre, Los Angeles, USA; **Figure 2-1**). Coronary artery centrelines were extracted in a semi-automated fashion by placing a point at the proximal and distal end of each major epicardial coronary artery and any large (>2 mm) tributary branches. A region of interest was placed to define normal blood pool attenuation in the aortic root at the origin of the left main artery. The proximal and distal end of each coronary segment were manually defined using side branches to mark progression consistently according to Society of Cardiac Computed Tomography guidelines.[89, 132] Stented segments and coronary artery bypass graft insertion points were excluded from analysis. This was done for the same reason calcium scores do not include stented segments as the software would misinterpret stent for calcific plaque. Similarly graft insertion points could be misinterpreted as non-calcified plaque. This technique has been extensively validated against intravascular ultrasound.[103]

If image quality was deemed poor in all coronary territories, scans were excluded from plaque analysis. Every segment with visually observed disease was quantitatively assessed for plaque, vessels with no visually observed plaque were not included to avoid the introduction of noise. The vessel lumen, wall and plaque constituents were automatically detected based on

prespecified Hounsfield Unit thresholds, with manual adjustments made where required. Scan specific thresholds Hounsfield Units were used to define non-calcified and calcified plaque constituents, as per established technique.[133] As stated above, low-attenuation plaque was defined by an attenuation of <30 HU as this is the accepted threshold that correlates best with invasive intracoronary imaging.[40] We measured plaque volume in every patient (mm^3) and to adjust for differences in overall vessel volume, plaque burden (%) was also calculated as a percentage of the overall vessel volume included on a per patient level.

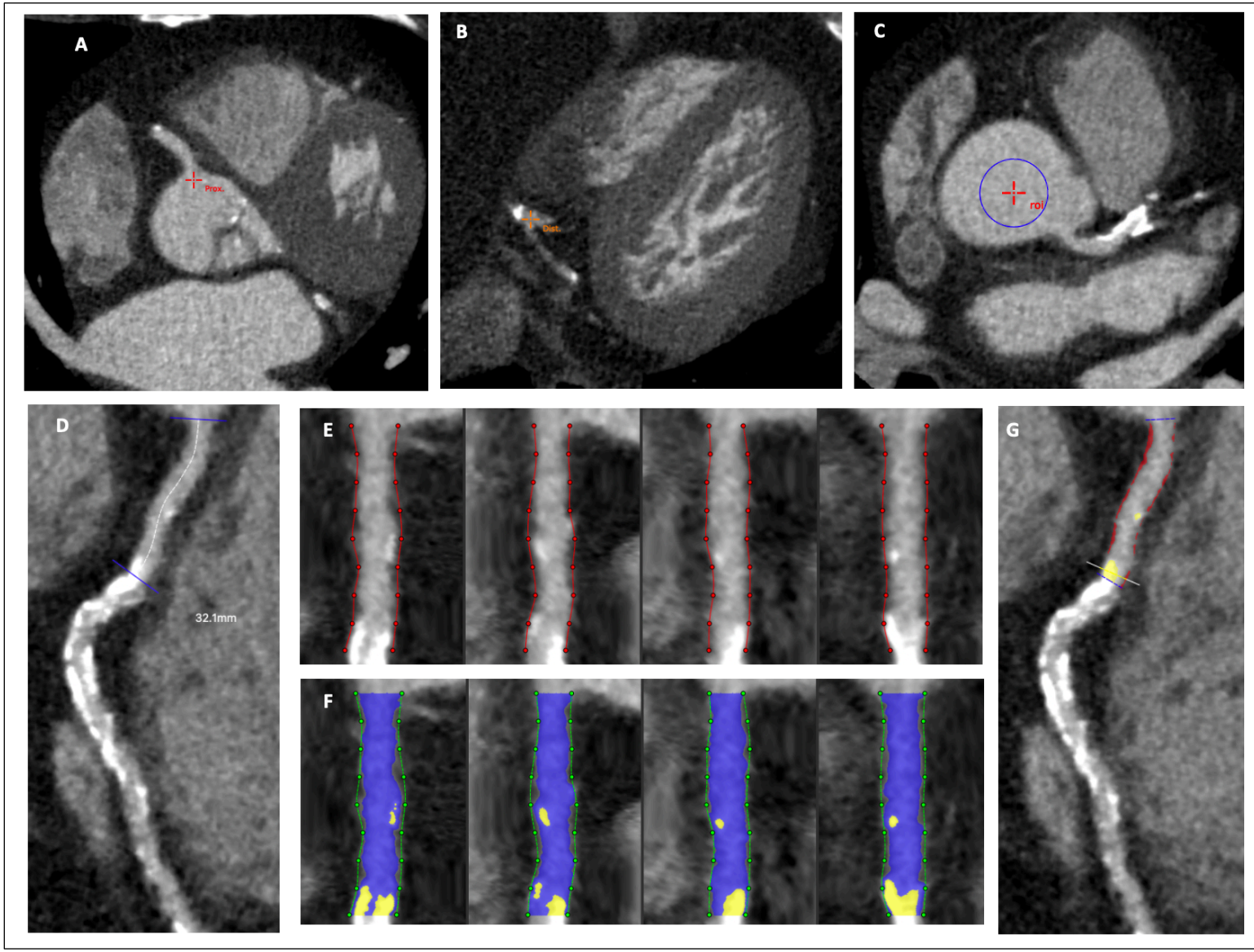

Figure 2-2: Process of conducting plaque analysis

Proximal and distal points of the right coronary artery placed (**A & B**) to extract coronary centreline.

Region of interest placed in aortic root (**C**) to define blood pool.

Proximal segment of right coronary artery manually selected (**D**).

Vessel wall delineated (**E**) and lumen defined (in blue) using scan specific thresholds for non-calcified and calcified plaque (**F**).

Completed analysis of proximal right coronary artery (**G**) demonstrates large burden of non-calcified plaque (in red; 33%) and small burden of calcified plaque (in yellow; 3%).

2.8 STATISTICAL ANALYSIS

Details of specific statistical methodology are described fully in individual results chapters. Continuous variables were presented as median [interquartile range] or mean ± standard deviation if normally distributed. Categorical variables are presented as number (percentage). Normality was tested using Shapiro Wilks test and statistical significance determined using Pearson's Chi-squared test, Wilcoxon rank sum test or Fisher's exact test as appropriate. Logarithmic transformation (Log_2 (1+ 'X')) was used to achieve normality of plaque quantification subtypes.[134] This is commonly done on analyses of coronary calcium score as data on plaque burden have a skewed distribution due in part to the large minority of patients with normal coronary angiograms.[135] Log transformation of the data assists in normalising the distribution and was performed in a consistent manner across all data chapters.

Correlations between continuous variables were assessed using linear regression analysis and Lin's concordance coefficients. We used Lin's concordance coefficients rather than Pearson's correlation coefficient so as to provide a measure of reliability that takes into account covariation and correspondence.[136] Repeatability coefficient was defined as 1.96 x the standard deviation of differences. Coefficients of variation were calculated as the standard deviation of the mean difference between two measurements

divided by the average of the mean values for each pair of results x100. Reproducibility was determined using Bland-Altman analysis and presented along with 95% limits of agreement.

Outcome data were analysed using Cox proportional hazard regression, with hazard ratios and 95% confidence intervals derived from the cox models. Logistic regression analyses (both univariate and multivariate) were performed to determine strength of associations and results presented as odds ratio and 95% confidence intervals. As plaque variables from quantitative plaque analysis are colinearly related, when conducting multivariable analyses, care was taken to create separate models for each plaque subtype.[137]

All statistical analysis was performed on either ***GraphPad Prism*** (Version 8.0, GraphPad Prism, San Diego, California, USA) or ***R*** (R Foundation for Statistical Computing, Vienna, Austria) was used. Statistical significance was defined as a two-tailed p-value of <0.05.

3 CHAPTER 3: Reproducibility of quantitative plaque measurement in advanced coronary artery disease

Published in:

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*Equal contribution as senior author.

3.1 SUMMARY

Background: The ability to characterise and to quantify the extent of coronary artery disease has the potential to improve the prognostic capability of coronary computed tomography angiography. Although reproducible techniques have been described in those with mild coronary disease, this has yet to be assessed in patients with advanced disease.

Methods: Twenty patients with known multivessel disease underwent repeated computed tomography coronary angiography, 2 weeks apart. Coronary artery segments were analysed using semi-automated software by two trained observers to determine intraobserver, interobserver and interscan reproducibility.

Results: Overall, 149 coronary arterial segments were analysed. There was excellent intraobserver and interobserver agreement for all plaque volume measurements (Lin's coefficient 0.95 to 1.0). There were no substantial interscan differences (P>0.05 for all) for total (2063±1246 mm^3, mean of differences -35.6 mm^3), non-calcified (1795±910 mm^3, mean of differences -4.3 mm^3), calcified (298±425 mm^3, mean of differences -31.3 mm^3) and low-attenuation (13±13 mm^3, mean of differences -2.6 mm^3) plaque volumes. Interscan agreement was highest for total and noncalcified plaque volumes. Calcified and low-attenuation plaque (-236.6 to 174 mm^3 and -15.8 to 10.5

mm^3 respectively) had relatively wider 95% limits of agreement reflecting the lower absolute plaque volumes.

Conclusion: In the presence of advanced coronary disease, semi-automated plaque quantification provides excellent reproducibility, particularly for total and non-calcified plaque volumes. This approach has major potential to assess change in disease over time and optimise risk stratification in patients with established coronary artery disease.

3.1 INTRODUCTION

Coronary computed tomography angiography (CCTA) is often the imaging modality of choice for those suspected of having coronary artery disease due to its diagnostic accuracy, prognostic value and ability to guide evidence-based treatments.[47, 138] As technology has evolved, our ability to quantify the extent of coronary artery plaque has improved. Semi-automated software now facilitates the rapid assessment of coronary plaque subtype and burden which is comparable to that achieved with intravascular ultrasound.[139] Recent studies have reported that quantitative evaluation of non-calcified plaque burden, particularly low-attenuation plaque, holds high prognostic value in identifying patients at risk of myocardial infarction.[140] Serial imaging can be performed to monitor the extent and distribution of coronary atheroma such that there is a growing interest in the use of coronary plaque composition as a surrogate endpoint in randomised clinical trials.[141] However, if this metric is to gain more widespread adoption, it is important to validate the precision of measurement on repeated testing.

Robust reproducibility for the quantitative analysis of plaque burden is essential for clinical application. Previous studies have reported excellent reproducibility with quantitative coronary plaque analysis in patients with a low burden of atheroma.[100, 101] However, as coronary artery disease becomes more advanced, extensive vascular calcification can cause blooming artefact and photon starvation which hinders assessment of the coronary lumen.[142, 143]

Moreover, the scan-rescan reproducibility of low-attenuation non-calcified plaque, has not been established. As the residual risk of cardiovascular events is highest in patients with higher burdens of atherosclerosis, we sought to assess whether non-calcified plaque could be precisely quantified in patients with advanced coronary artery disease.

3.2 METHODS

3.2.1 Study Population

The study population was recruited from a randomised controlled trial using CCTA in patients with advanced coronary artery disease [NCT02110303], the results of which have been described previously.[111] In brief, patients were eligible if they were over the age of 40 years and had angiographically proven multivessel coronary artery disease defined as at least 2 major epicardial vessels with either ≥50% luminal stenosis or previous revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery).

3.2.2 CCTA Image Acquisition

The CCTA image acquisition has been described previously.[111] Briefly, patients underwent baseline CCTA (64-multidetector Biograph mCT, Siemens Medical Systems, Erlangen, Germany) after receiving 50 to 100 mg of oral metoprolol to achieve a heart rate of <65 /min and 400 µg of sublingual glyceryl trinitrate. A contrast-enhanced CCTA was performed using prospective electrocardiogram gating, triggering in mid-diastole (60-75% R-R interval) during an expiratory breath-hold (Prospective CareKV, tube voltage of 100 kVp (body-mass index <25 kg/m^2) or 120 kVp (body-mass index ≥25 kg/m^2)). Scans were reconstructed using 180-degree rotation, 512 x 512 matrix and B26f reconstruction kernel with 0.75-mm slice thickness at 0.5-mm increments.

Repeated scans were conducted using the same acquisition protocol within 2 weeks of the baseline scan.

3.2.3 CCTA Image Evaluation

CCTA data sets were anonymised and exported in Digital Imaging and Communications in Medicine (DICOM) format for measurement of coronary plaque. Plaque measurements were performed using semi-automated software (AutoPlaque, Version 2.5, Cedars-Sinai Medical Centre, Los Angeles, USA, **Figure 3-1**) by two trained observers. AutoPlaque has previously been validated against intravascular ultrasound.[139]

Coronary artery centrelines were extracted using a semi-automated method. A region of interest was placed in the proximal aorta to define blood pool attenuation. Where possible, the entire length of each major artery was extracted as well as major tributary branches with visible disease. Coronary artery segments were manually defined by each observer independently, using side-branches to mark progression from proximal to distal segments consistently across both scans according to the Society of Cardiovascular Computed Tomography (SCCT) guidelines.[144] The length of the distal segment was dependent on vessel diameter with a 2-mm minimum threshold for inclusion.[145] Stented segments and graft insertion points were excluded from the final analysis.

Image quality was deemed excellent if every coronary artery was clearly visualised, good if one or more artery had artefact that made analysis suboptimal (requiring multiple or manually generated centrelines), limited if one or more artery could not be analysed, and unanalysable if none of the arteries could be analysed. If a segment or an artery was deemed too poor to analyse in the baseline scan, it was excluded from analysis in the repeat scan, and vice versa. Two blinded observers independently analysed all scans. One observer analysed the baseline scans twice, 3 months apart, in random order to minimise recall bias.

The vessel lumen, wall and plaque constituents were automatically detected with manual adjustments performed where required**.** Scan-specific Hounsfield unit (HU) thresholds were applied to define non-calcified and calcified plaque constituents as described previously.[130, 146] Low-attenuation plaque was defined by a fixed attenuation of <30 HU as this demonstrates the best correlation with intravascular ultrasound.[40] For each patient, plaque volume (mm^3) and burden (normalised to the vessel volume, as a percentage) were calculated for total, non-calcified, calcified and low-attenuation plaque subtypes, as well as diameter stenosis and the maximal remodelling index.

3.2.4 Statistical Analysis

Data are expressed as mean ± standard deviation or mean (95% confidence interval) for continuous variables or median [interquartile range] where not normally distributed. Categorical variables are presented as number

(percentage). Data were analysed by paired two-sided *t*-tests, linear regression analysis and Lin's concordance correlation coefficients. Repeatability coefficient was defined as 1.96 x the standard deviation of the differences. Coefficient of variation was defined as the average of means divided by the standard deviation of mean difference. Reproducibility was determined using Bland-Altman analysis and bias (mean difference) is presented alongside 95% limits of agreement (95% confidence intervals). Statistical analysis was performed using GraphPad Prism (Version 8.0, GraphPad Software, San Diego, California, USA). Two-sided P-value <0.05 was considered statistically significant.

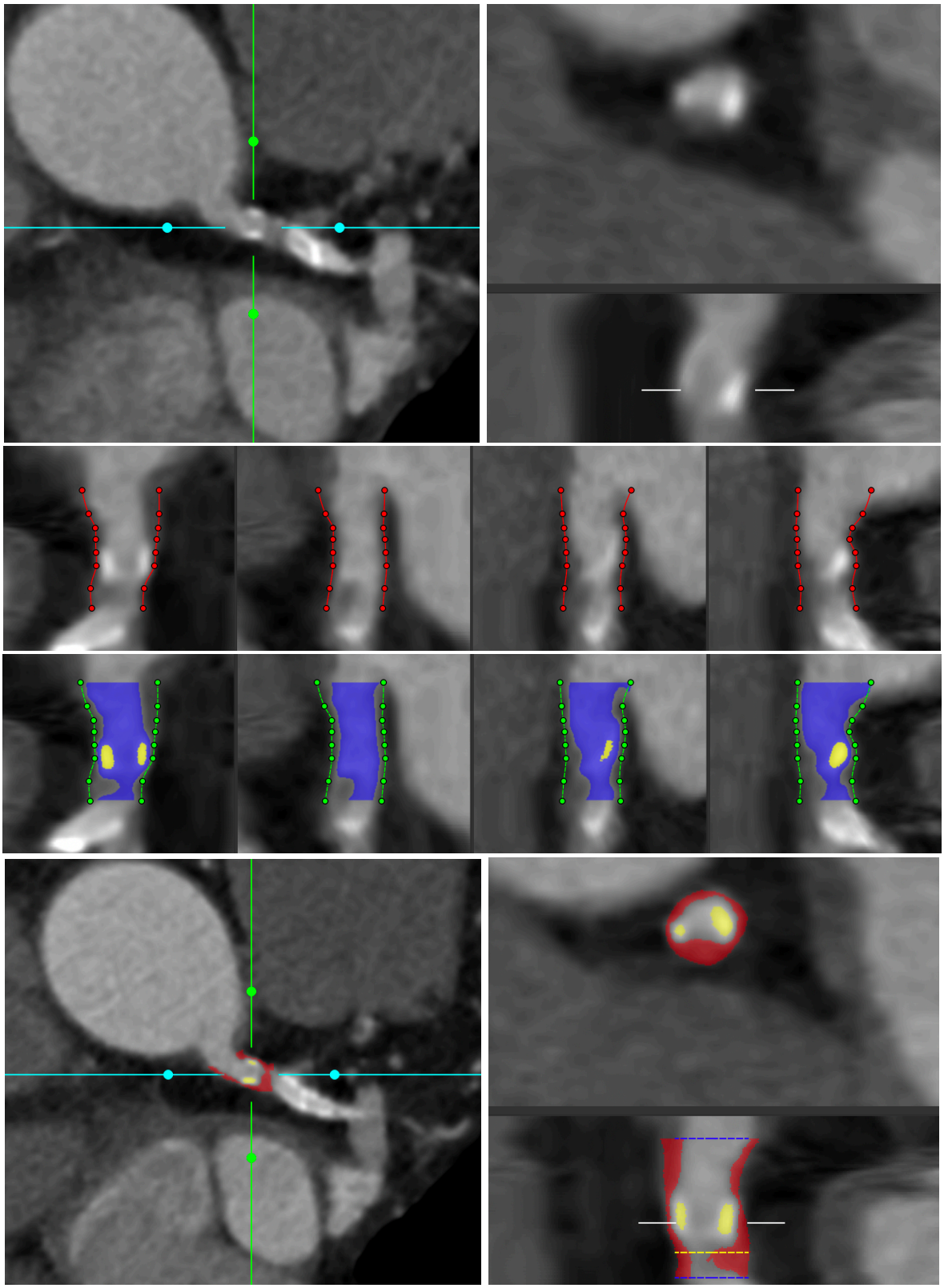

Figure 3-1: Analysis of plaque burden in the left main stem of a 76-year-old male. Vessel wall delineated in red dotted line. Once vessel wall confirmed (green dotted line) and calcified plaque identified (in yellow), vessel lumen delineated in blue. Result of analysis with non-calcified plaque volume of 231.5 mm^3 (highlighted in red) and calcified plaque volume of 12.0 mm^3 (highlighted in yellow)

3.3 RESULTS

Study participants were predominantly male (n=17; 85%) with a mean age of 69±7 years (**Table 3-1**). All but one participant had previously undergone either percutaneous coronary intervention or coronary artery bypass graft surgery. The mean time between CCTA scans was 12±4 days and heart rate at baseline and during interval scanning were comparable (57±8 and 57±10 /min respectively, **Table 3-2**). The median calcium score was 371 [154–1183] Agatston units. Two participants were excluded from the final analysis due to inadequate image quality of one of the paired scans. Branches without visible disease were not analysed, as such, from a total of 177 potential paired segments, 149 (84%) were analysed, the remaining 28 pairs were excluded either due to poor image quality or stent placement.

Table 3-1: *Participant Characteristics*	Number of patients (n=20)
Mean age (years)	69 ± 7
Male	17 (85%)
Hypertension	14 (70%)
Hypercholesterolaemia	20 (100%)
Diabetes	2 (10%)
Peripheral vascular disease	1 (5%)
Family history of CHD	12 (60%)
Previous acute coronary syndrome	13 (65%)
Previous percutaneous coronary stenting	13 (65%)
Coronary artery bypass graft	9 (45%)
Mean ± standard deviation or number (%)	

Table 3-2: *Scan characteristics*	Number of patients (n=20)
Time between scans (days)	12 ± 4
Heart rate at baseline scan	57 ± 8
Heart rate at interval scan	57 ± 10
Difference of heart rate	4 ± 3
Median coronary calcium score (Agatston)	371 (154-1183)
Image quality – Excellent	10 (50%)
Image quality – Good	5 (25%)
Image quality – Limited	3 (15%)
Image quality – Unanalysable	2 (10%)
Total patients analysed	18
Total segments analysed	149
Mean ± standard deviation, number (%), or median (interquartile range)	

3.3.1 Intraobserver Repeatability

There were no differences between mean volumes for total, non-calcified and calcified plaque on repeated analysis by the same observer, (p = 0.29, 0.28 and 0.68 respectively, **Table 3-3**). The mean volume of low-attenuation plaque was 13±13 mm^3 on the first analysis and 12±13 mm^3 on the second (mean difference -1.6 mm^3, p=0.02). Correlation was excellent for all plaque volume measurements with Lin's concordance correlation coefficient ranging from 0.97 to 1.0. The coefficients of variation were 2.6%, 3.3%, 4.1% and 21.4% for total, non-calcified, calcified, and low-attenuation plaque volumes. Per patient repeatability coefficient ranged between 5.2 and 114.1 mm^3. Bland Altman

plots highlighting limits of agreement (**Figure 3-2)** demonstrate the excellent intraobserver agreement throughout plaque subtypes.

Table 3-3: *Intraobserver, Interobserver and Scan-Rescan variability of per patient plaque volume measurements.*

Intraobserver Variability	**Observation 1**	**Observation 2**	**LCC (95% CI)**	**Mean difference**	***P* value**	**Bland-Altman 95% LoA (95% CI)**	**CoR**
Total Plaque (mm^3)	2063 ± 1246 [1443-2683]	2077 ± 1260 [1450-2704]	1.0 (1.0 - 1.0)	14.1	0.29	-93 (-155, -58) to +121 (87, 183)	107.0
Non-calcified Plaque (mm^3)	1765 ± 910 [1312-2217]	1780 ± 921 [1322-2238]	1.0 (1.0 - 1.0)	15.4	0.28	-99 (-165, -62) to +129 (93, 196)	114.1
Calcified Plaque (mm^3)	298 ± 425 [87-510]	297 ± 425 [86-508]	1.0 (1.0 - 1.0)	-1.2	0.68	-25 (-39, -17) to +23 (15, 36)	23.7
Low-attenuation Plaque (mm^3)	13 ± 13 [7-20]	12 ± 13 [5-18]	0.97 (0.93 - 0.99)	-1.6	0.02	-7 (-9, -5) to +4 (1, 6)	5.2
Interobserver Variability	**Investigator 1**	**Investigator 2**	**LCC (95% CI)**	**Mean difference**	***P* value**	**Bland-Altman 95% LoA (95% CI)**	**CoR**
Total Plaque (mm^3)	2063 ± 1246 [1443-2683]	1985 ± 1161 [1443-2683]	0.97 (0.93 - 0.99)	-74.2	0.24	-615 (-927, -442) to +459 (286, 770)	537.0
Non-calcified Plaque (mm^3)	1765 ± 910 [1312-2217]	1688 ± 803 [1289-2087]	0.95 (0.88 - 0.98)	-76.5	0.24	-594 (-894, -428) to +441 (275, 742)	517.6
Calcified Plaque (mm^3)	298 ± 425 [87-510]	297 ± 432 [82-512]	1.0 (0.99 - 1.0)	-1.7	0.84	-69 (-97, -41) to 66 (38, 94)	67.5
Low-attenuation Plaque (mm^3)	13 ± 13 [7-20]	14 ± 12 [8-20]	0.90 (0.76 - 0.96)	1.2	0.39	-10 (-14, -5) to +12 (8, 17)	11.0

Scan-Rescan Variability	**Baseline Scan**	**Repeat Scan**	**LCC (95% CI)**	**Mean difference**	***P* value**	**Bland-Altman 95% LoA (95% CI)**	**CoR**
Total Plaque (mm^3)	2063 ± 1246 [1443-2683]	2027 ± 1223 [1419-2635]	0.98 (0.94 - 0.99)	-35.6	0.56	-531 (-735, -328) to 460 (257, 664)	495.7
Non-calcified Plaque (mm^3)	1765 ± 910 [1312-2217]	1760 ± 928 [1299-2221]	0.97 (0.93 - 0.99)	-4.3	0.93	-418 (-587, -248) to +409 (239, 579)	413.4
Calcified Plaque (mm^3)	298 ± 425 [87-510]	267 ±377 [79-455]	0.96 (0.91 – 0.98)	-31.3	0.22	-237 (-321, -152) to +174 (90, 258)	205.2
Low-attenuation Plaque (mm^3)	13 ± 13 [7-20]	10 ±13 [4-17]	0.85 (0.64 – 0.94)	-2.6	0.11	-16 (-21, -10) to +11 (5, 16)	13.1

Mean ± standard deviation [95% confidence interval], LCCC – Lin's concordance correlation coefficient, LoA – Limits of agreement (95% confidence interval), CoR - coefficient of repeatability.

3.3.2 Interobserver Reproducibility

There were no differences between mean volumes for total, non-calcified, calcified and low-attenuation plaque volumes when comparing analysis done by two independent investigators (p = 0.24, 0.24, 0.84 and 0.39 respectively, **Table 3-3**). There was excellent correlation for total, non-calcified and calcified plaque volumes measurements, Lin's coefficient 0.97, 0.95 and 1.0 for total, non-calcified and calcified plaque volumes respectively. Correlation was modest with low-attenuation plaque volumes, Lin's coefficient 0.90. The coefficients of variation were 13.5%, 15.3%,11.6% and 41.0% for total, non-calcified, calcified and low-attenuation plaque volumes. Per patient repeatability coefficients ranged from 11 to 537 mm^3. Bland Altman plots (**Figure 3-3**) highlight excellent agreement particularly for total and non-calcified plaque volumes. Agreement was lower for low-attenuation plaque volume with 95% limits of agreement ranging from -9.9 to +12.2 mm^3.

3.3.3 Interscan Reproducibility and Coronary Characteristics

The mean total plaque volume was similar on the baseline and repeated scan (2063±1246 and 2027±1223 mm^3 respectively, p = 0.56). Similarly, no difference was noted between mean plaque volume for non-calcified, calcified, and low-attenuation plaque volume (**Table 3-3**). Correlations for plaque volumes were excellent for total, non-calcified and calcified plaque volumes (Lin's coefficient 0.98, 0.97 and 0.96 respectively) but lower for low-attenuation plaque (Lin's coefficient 0.85). The 95% limits of agreement were narrow for total plaque volume and non-calcified plaque volume but wider for calcified

plaque (-236.6 to +174 mm^3) and for low-attenuation plaque (-15.8 to +10.5 mm^3) (**Figure 3-4**). The coefficients of variation were 12.4%, 12.0%, 37.0% and 56.8% for total, non-calcified, calcified and low-attenuation plaque volumes respectively. Per patient repeatability coefficients ranged from 13 to 496 mm^3.

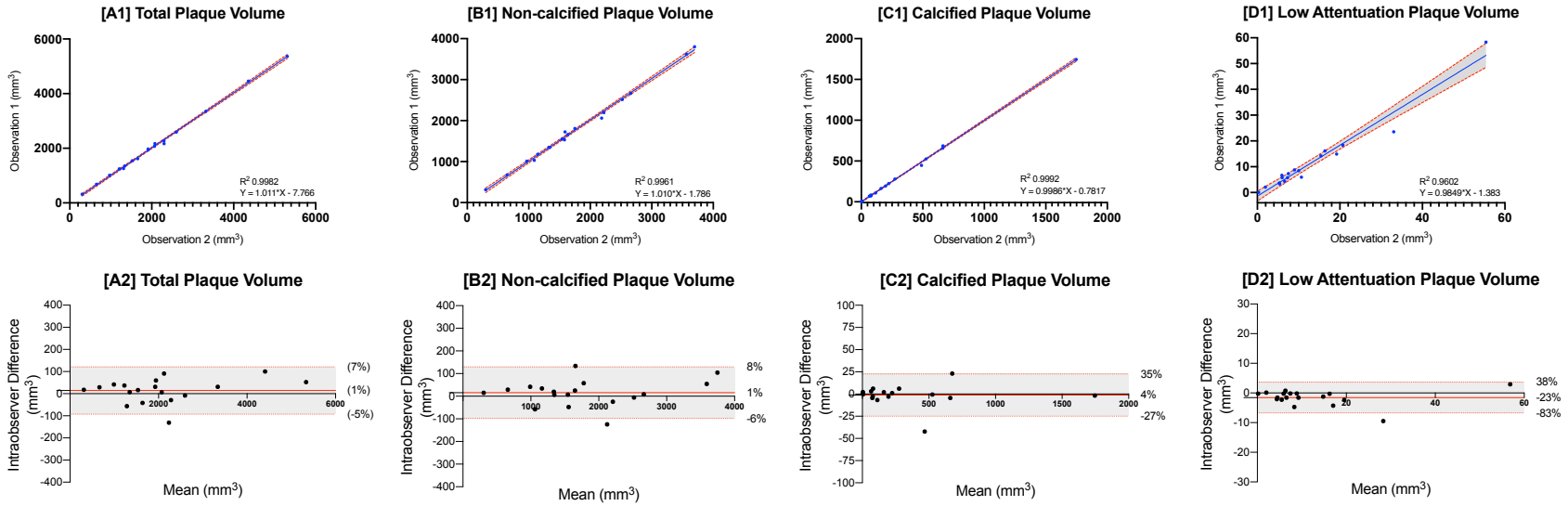

Figure 3-2: Intraobserver variability: Panel [A1-D1] Linear regression analysis for plaque volumes. Panel [A2-D2] Bland-Altman plots demonstrating limits of agreement.

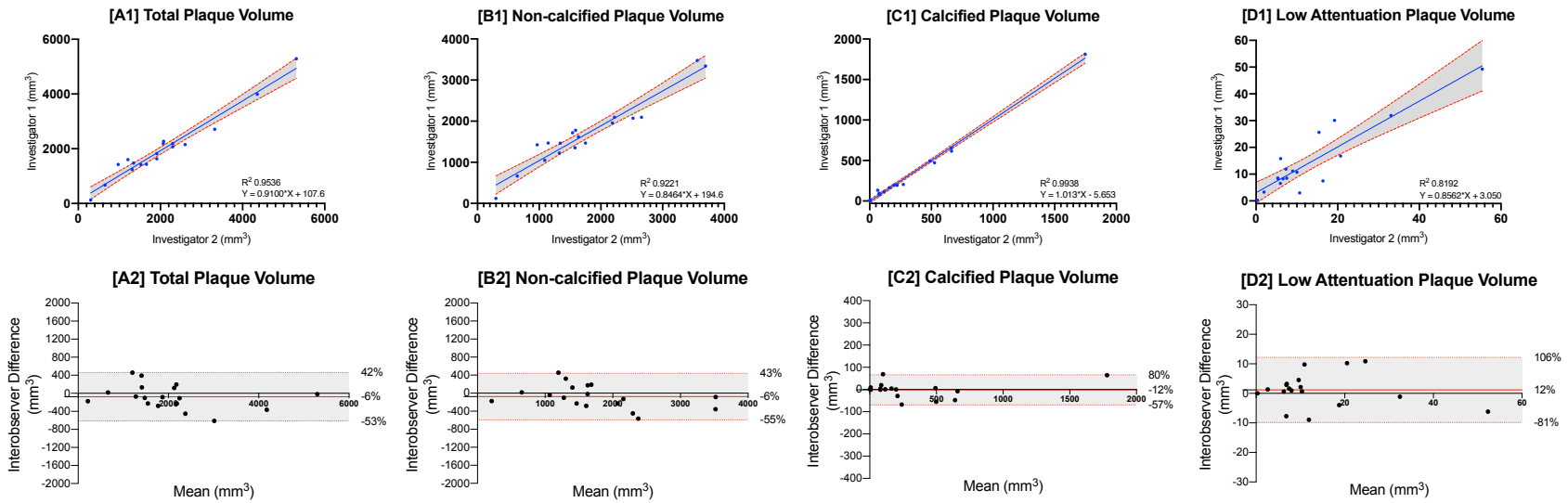

Figure 3-3: Interobserver variability: Panel [A1-D1] Linear regression analysis for plaque volumes. Panel [A2-D2] Bland-Altman plots demonstrating limits of agreement.

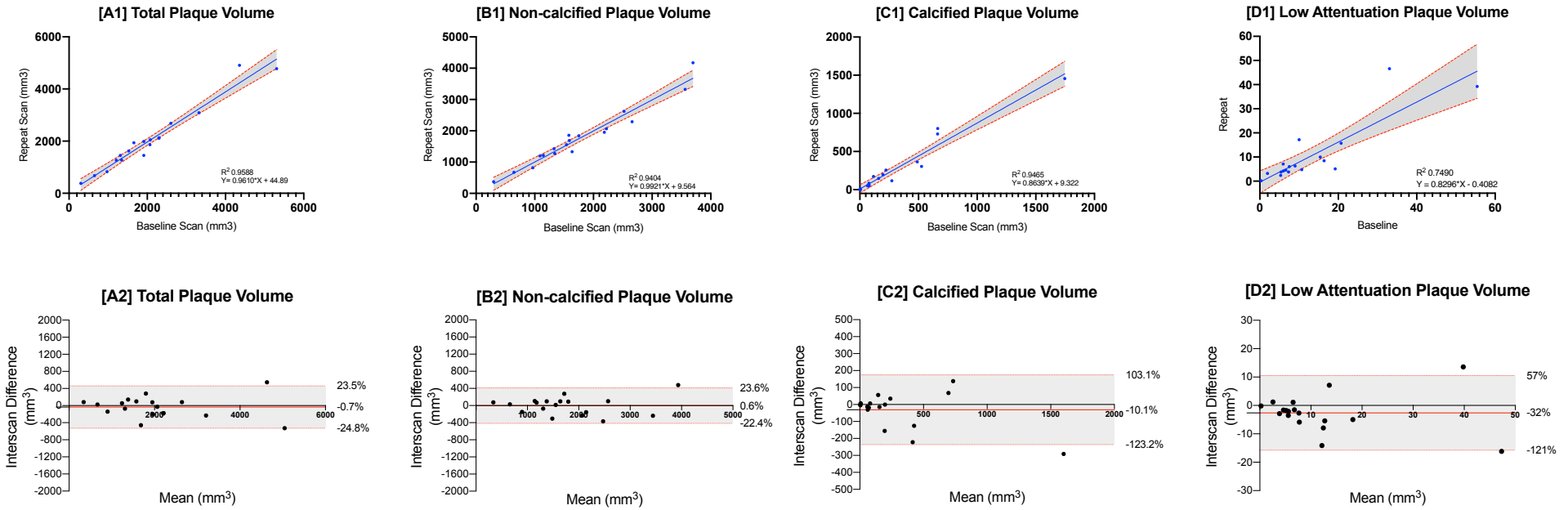

Figure 3-4: Interscan reproducibility: Panel [A1-D1] Linear regression analysis for plaque volumes. Panel [A2-D2] Bland-Altman plots demonstrating limits of agreement.

3.4 DISCUSSION

In this scan-rescan reproducibility study of patients with advanced coronary artery disease, we have demonstrated that coronary plaque volume can be precisely quantified using semi-automated analysis software. Non-calcified plaque has excellent inter- and intraobserver agreement and scan-rescan reproducibility. Low-attenuation plaque and calcified plaque performed less well on repeated testing with narrow absolute but wide relative 95% limits of agreement. Thus, semi-automated plaque volume quantification is a robust and reproducible method that could be used as valuable and precise measure of disease burden and disease progression in patients with advanced coronary disease.

The current standard for the assessment of coronary atherosclerosis using CCTA requires visual assessment of luminal stenosis severity alongside plaque characterisation (calcified, non-calcified or mixed).[144] Whilst these factors are undoubtedly important, recent studies have highlighted the incremental prognostic value of quantifying subtypes of atherosclerotic plaque.[85, 97, 145, 147] Previous iterations of plaque quantification software were time consuming and have limited their widescale applicability.[99] In recent years, the use of a more rapid semi-automated analysis of plaque has expanded and provides a reproducible analytical method, especially when used in patients with a relatively low disease burden.[100, 101] However, as

disease burden increases, the prominence of coronary calcification rises and the overall image quality is often suboptimal. Our study established that despite these factors, semi-automated plaque analysis remained reliable and reproducible, particularly for measuring non-calcified plaque.

In our study cohort, all patients had multivessel disease and 95% had previous coronary revascularisation. Within a two-week window, scans were performed prospectively at the same site using identical reconstruction protocols to ensure consistency. The quality of acquired images was variable, with only 50% being deemed acceptable despite excellent heart rate control at both baseline and interval scans.[148] This is perhaps unsurprising considering the high coronary calcium score, extensive use of coronary revascularisation, and the advanced nature of the coronary artery disease. Reflecting this advanced disease, plaque volumes were at least 5 times larger than in any other previous reproducibility study performed to date. The highest mean total plaque volume reported by Schuhbaeck and colleagues in their study of observer variability was only 399±247 mm^3 compared to our 2063±1246 mm^3.[100]

Previous studies have established that the assessment of stenosis severity on CCTA has excellent agreement between observers.[120] However, the observer variability of visual plaque analysis appears to be poor.[72] Quantitative plaque analysis removes many of the limitations of visual assessment, and has been shown to be reproducible in patients with low and intermediate disease severity. Ovrehus et al showed excellent scan-rescan, interobserver and

intraobserver agreement for the quantitative assessment of non-calcified and calcified plaque volumes.[101] Tzolos et al similarly showed excellent intraobserver and interobserver repeatability for the assessment of non-calcified plaque burden.[149] However, these studies involved patients with less severe coronary artery disease and lower total plaque volumes. Our study adds to this literature by establishing that the observer and scan-rescan agreement for total and non-calcified plaque volume persists in patients with advanced coronary artery disease.

The narrow absolute and wide relative limits of agreements seen with low-attenuation plaque reflect the smaller volumes measured. Consequently, small absolute changes in volumes have a large impact on relative and proportionate changes, translating into relatively large coefficients of variability. Low-attenuation plaque accounted for less than 1% of total plaque volume. In patients who have high use of statin and preventative therapies, this is perhaps not surprising as the phenotypic transformation from low-attenuation to calcified plaque may have already occurred. Moreover, with 65% of patients having had previous percutaneous coronary intervention, much of the 'at-risk' plaque may have already been treated and excluded from our analysis. Our coefficient of variation of 21 to 41% for low-attenuation plaque is lower than previous reports of 30 to 57% in patients with a lower burden of disease.[150] To our knowledge scan-rescan variation for low-attenuation plaque has not previously been reported and as anticipated, was slightly higher than intraobserver and interobserver variability. The presence of low-attenuation

plaque can identify patients at high risk of future cardiovascular events, so whilst its measurement is more variable, this does not detract from its potential clinical utility. However, in this population of people with advanced and well treated disease, measuring progression of low-attenuation plaque may be challenging as small volumes do not allow for precise reproducible quantification. Trialists have begun to use low-attenuation volume as an endpoint to monitor the effect of novel therapies on coronary atherosclerosis.[141] We demonstrate here, that in patients with advanced coronary disease, non-calcified plaque volume is potentially a more reliable metric to use when monitoring disease progression.

Our study has some limitations. The number of patients was relatively small although repeated scanning and radiation exposure does present challenges to conducting such a study in larger numbers of patients. The population was predominantly male, but the results of the plaque reproducibility would be expected to be similar irrespective of gender. We did not compare plaque volumes with a reference standard, such as intravascular ultrasound, although this has been previously reported by others.[102, 139]

3.5 CONCLUSION

In conclusion, we have demonstrated the excellent intraobserver, interobserver and scan-rescan reproducibility of semi-automated plaque volume quantification in patients with advanced coronary artery disease. This validates its use as a novel approach to quantify change in coronary artery disease over time and optimise risk stratification in patients with coronary artery disease.

4 CHAPTER 4: Coronary low-attenuation plaque and high-sensitivity cardiac troponin

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Meah MN, Wereski R, Bularga A, van Beek EJR, , Dweck MR, Mills NL, Newby DE, Dey D*, Williams MC, Lee KK. Coronary low-attenuation plaque and high-sensitivity cardiac tropnin.

4.1 SUMMARY

Background: In patients with acute chest pain who have had myocardial infarction excluded, plasma cardiac troponin concentrations provide important prognostic information with higher values predicting a 3-fold increased risk of future cardiovascular events. We aimed to determine whether quantitative plaque analysis can identify differences in coronary plaque composition between patients with differing high-sensitivity cardiac troponin concentrations.

Methods and Results: In a post-hoc analysis of a single-centre cross-sectional observational study, quantitative plaque analysis was performed on coronary CT angiograms of 242 patients with acute chest pain who had had myocardial infarction excluded. Patients were dichotomised by plasma high-sensitivity cardiac troponin I concentration into low (<5 ng/L, n=81) and high (≥5 ng/L, n=161) risk groups. Patients with high-risk plasma troponin concentrations had larger burdens of total (33 [0-47] *versus* 0 [0-33] %), non-calcified (27 [0-37] *versus* 0 [0-28] %), calcified (2 [0-8] *versus* 0 [0-3] %) and low-attenuation (1 [0-3] *versus* 0 [0-1] %) plaques compared to those with low-risk plasma troponin concentrations (p≤0.001 for all). Logistic regression analysis demonstrated that only low-attenuation plaque burden was independently associated with high-risk plasma troponin concentrations after adjustment for clinically relevant characteristics (adjusted odds ratio per doubling 1.55 [95% CI 1.13-2.20], p<0.009) or the presence of any visible

coronary artery disease (odds ratio per doubling 1.57 [95% CI 1.07-2.37], p=0.026).

Conclusion: In patients with acute chest pain, higher plasma high-sensitivity cardiac troponin concentrations are associated with increased coronary low-attenuation plaque burden. These findings provide mechanistic insight into the underlying cardiovascular risk of these patients.

4.2 INTRODUCTION

Myocardial injury and myocardial infarction can now be detected in a highly sensitive and specific manner by quantifying plasma cardiac troponin concentrations. Indeed, high-sensitivity cardiac troponin assays are now used to both 'rule in' and 'rule out' myocardial infarction in patients who present with acute chest pain to the Emergency Department.[30] However, patients who have plasma cardiac troponin concentrations that fall between these 'rule in' and 'rule out' thresholds are recommended to have further clinical observation before hospital discharge to ensure the absence of myocardial infarction.[151] These latter patients are 3 times more likely to have a major adverse cardiac events at one year compared to those below the 'rule out' threshold.[152] The reasons for this increased risk remain the subject of intense debate.

Computed tomography coronary angiography (CTCA) can non-invasively detect the presence or absence of coronary artery disease with high sensitivity and specificity.[153] Newer quantitative CT-defined plaque characteristics can identify high-risk coronary atherosclerosis which is associated with acute coronary syndromes.[96] In particular, low-attenuation plaque correlates with the lipid-rich necrotic core of high-risk atherosclerotic plaque and is a strong independent predictor of future cardiovascular events.[97] In this post-hoc analysis, we aimed to determine whether plaque composition varies by baseline plasma high-sensitivity cardiac troponin concentration in patients with

acute chest pain who have had myocardial infarction excluded, and whether differences provide mechanistic explanations about their risks and outcomes.

4.3 METHODS

4.3.1 Study population

The study design and population have been described previously.[35] In brief, this was a single-centre prospective cross-sectional cohort study which recruited 250 patients who attended the Emergency Department with suspected acute coronary syndrome. All participants had myocardial infarction excluded with a presentation plasma cardiac troponin concentration below the 99th centile upper reference limit (34 ng/L for men and 16 ng/L for women). Participants were then divided into two groups based on their presentation plasma cardiac troponin concentrations: low-risk (<5 ng/L, below the 'rule out' threshold) or high-risk (≥5 ng/L, for further observation).

4.3.2 CCTA and Quantitative plaque analysis

All recruited participants underwent CCTA using a 128-slice scanner (Biotech mCT, Siements Healthcare). Scans were anonymised and exported in Digital Imaging and Communications in Medicine (DICOM). Quantitative plaque analysis was performed using semi-automated software (Autoplaque version 2.5, Cedars-Sinai Medical Centre, Los Angeles, USA). This method has been validated against intravascular ultrasound and has excellent observer agreement.[79, 103, 154]

A region of interest was placed in the proximal aorta to define blood pool attenuation. Coronary centrelines were then extracted in vessels with visible

coronary artery disease, including side branches ≥2 mm in diameter. Coronary segments were defined manually, using side branches to mark progression from proximal to distal vessel in accordance with the Society of Cardiovascular Computed Tomography guidelines.[132, 144] To avoid introducing noise, stented segments and coronary artery bypass graft insertion points and coronary segments with no visually observed coronary artery disease did not undergo quantitative plaque analysis. Plaque constituents were automatically determined using scan specific Hounsfield unit thresholds. Low-attenuation plaque was defined by a fixed Hounsfield unit threshold of <30 HU as defined previously.[130] If image quality was deemed too poor to complete quantitative plaque analysis, scans were excluded. Scans were analysed by a single trained observer, blinded to the patient results and demographics.

Plaque volume was measured in mm^3 for total plaque burden and all subtypes including non-calcified, calcified, and low-attenuation plaque. To account for differences in vessel volume between patients, plaque burden was calculated by dividing plaque volume by the vessel volume on a per-patient level and multiplying by 100. To determine the relative utility of quantitative plaque analysis, comparisons were made with existing semi-quantitative scores. These include the segment involved score, segment severity score and CT-Leaman score.[155]

4.3.3 Statistical analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range] as appropriate. Statistical significance was assessed using Wilcoxon rank sum, Pearson's Chi-squared or Fisher's exact test as appropriate. Logistic regression analysis was performed in patients to determine the odds ratio with 95% confidence interval of detecting a high-risk plasma high-sensitivity troponin concentration (≥5 ng/L). A multivariable model was created using a priori selection adjusting for age per 10-year increase, sex, smoking history, hypertension, diabetes, estimated glomerular filtration rate and individual plaque subtypes. The model was also used to determine whether traditional markers of coronary artery disease severity, such as the presence of obstructive disease and semi-quantitative coronary CT scores, were independently associated with high-risk plasma high-sensitivity troponin concentrations. For logistic regression analyses, plaque burden was log-transformed ($\log_2$ of 1 plus the plaque variable). Statistical significance was defined as a two-sided *P* value <0.05. All statistical analysis was performed using R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria).

4.4 RESULTS

4.4.1 Study Population

In the 250 study participants, 242 scans were of sufficient quality to undertake plaque analysis. The study population therefore comprised of 242 mostly male (69%) participants with a mean age of 62±12 years. A total of 161 (67%) patients had a high-risk (≥5 ng/L) and 81 had a low-risk (<5 ng/L) plasma cardiac troponin I concentration. Patients with a high-risk plasma troponin concentration were older, more likely to have diabetes mellitus and lower estimated glomerular filtration rates. All other comorbidities were equally distributed between the two groups. Patients with a high-risk plasma troponin concentration were more likely to have visually observed coronary artery disease and higher semi-quantitative CT scores (**Table 4-1**).

4.4.2 Plaque quantification

Overall, participants had a total plaque burden of 27 [0-42] %, which consisted of non-calcified (23 [0-34] %), calcified (1.2 [0-6.1] %) and low-attenuation (0.62 [0-2.5] %) plaque burdens. Patients with low-risk plasma troponin concentrations had lower burdens of total (0 [0-33] *versus* 33 [0-47] %), non-calcified (0 [0-28] *versus* 27 [0-37] %), calcified (0 [0-3] *versus* 2 [0-8] %) and low-attenuation (0 [0-1] *versus* 1 [0-3] %) plaque compared to those with a high-risk plasma troponin concentration (**Table 4-2**). Density plots demonstrated the proportionate differences between low-risk and high-risk

cohorts were most pronounced for the low-attenuation plaque burden (**Figure 4-1**).

Table 4-1: Baseline demographics and characteristics

Characteristic	**Low-risk Troponin** N = 81[1]	**High-risk Troponin** N = 161[1]	**p-value**[2]
Age	57 ± 11	64 ± 12	<0.001
Male sex	51 (63%)	116 (72%)	0.15
Smoking history	46 (57%)	86 (53%)	0.6
Diabetes mellitus	4 (4.9%)	28 (17%)	0.007
Hypertension	29 (36%)	75 (47%)	0.11
Hyperlipidaemia	20 (25%)	31 (19%)	0.6
Family history of coronary artery disease	27 (33%)	62 (39%)	0.4
Previous myocardial infarction	12 (15%)	36 (22%)	0.2
GRACE score	87 ± 25	97 ± 25	0.005
Estimated glomerular filtration rate (mL/min/1.73 m^2)	89 ± 14	82 ± 18	<0.001
Any coronary artery disease	35 (43%)	116 (72%)	<0.001
Obstructive coronary artery disease	16 (20%)	51 (32%)	0.050
Segment Involved Score	0 (0 to 3)	2 (0 to 6)	<0.001
Segment Severity Score	0 (0 to 4)	3 (0 to 9)	<0.001
Computed Tomography Leaman Score	0 (0 to 5)	5 (0 to 10)	<0.001

[1] Median (IQR), Mean ± standard deviation; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
GRACE – Global Registry of Acute Coronary Events

Table 4-2: Quantitative plaque analysis				
Plaque subtype	**Overall** N = 242[1]	**Low-risk Troponin** N = 81[1]	**High-risk Troponin** N = 161[1]	**p-value**[2]
Total Plaque Burden (%)	27 [0 to 42]	0 [0 to 32]	33 [0 to 47]	<0.001
Non-calcified Plaque Burden (%)	23 [0 to 34]	0 [0 to 28]	26 [0 to 37]	<0.001
Calcified Plaque Burden (%)	1.2 [0 to 6.1]	0 [0 to 3.1]	2.0 [0 to 7.5]	<0.001
Low-attenuation Plaque Burden (%)	0.62 [0 to 2.50]	0 [0 to 0.97]	0.92 [0 to 3.16]	<0.001
Total Plaque Volume (mm^3)	146 [0 to 527]	0 [0 to 184]	233 [0 to 653]	<0.001
Non-calcified Plaque Volume (mm^3)	127 [0 to 440]	0 [0 to 167]	201 [0 to 553]	<0.001
Calcified Plaque Volume (mm^3)	7 [0 to 69]	0 [0 to 23]	15 [0 to 101]	<0.001
Low-attenuation Plaque Volume (mm^3)	4 [0 to 29]	0 [0 to 10]	7 [0 to 41]	<0.001

[1] Median [Interquartile Range]
[2] Wilcoxon rank sum test

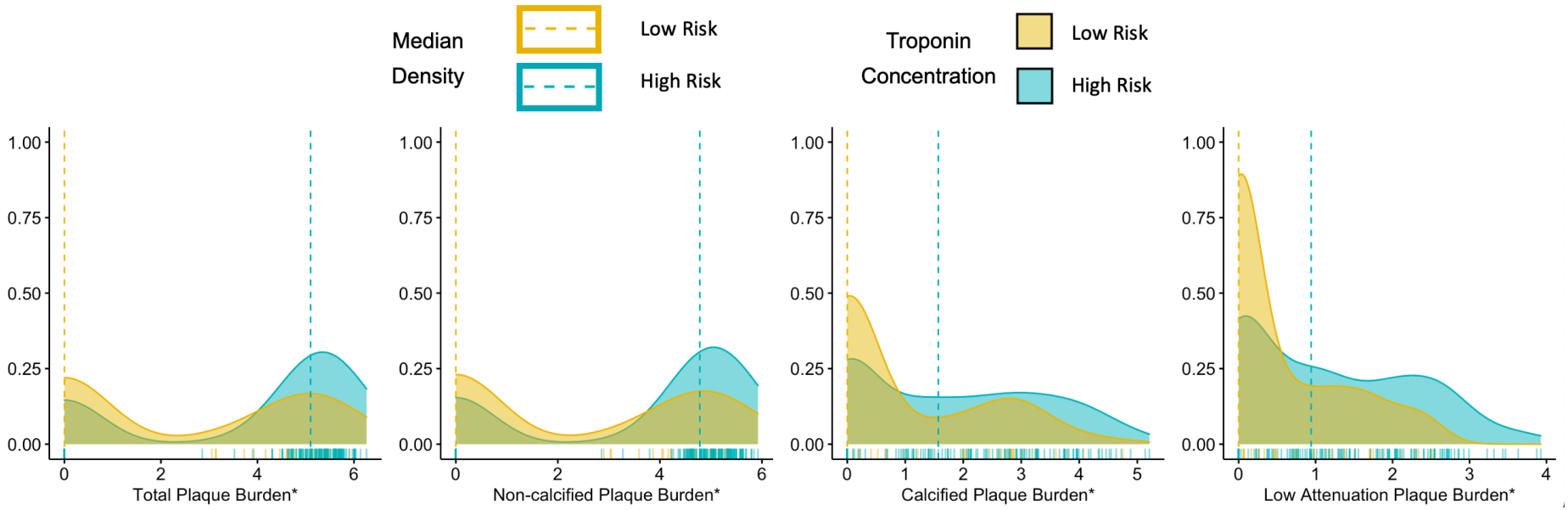

Figure 4-1. Density plot comparing the proportion of patients with low-risk (<5 ng/mL) and high-risk (>5 ng/mL) concentrations of high-sensitivity cardiac troponin for each plaque burden subtype.
Proportionally, low-attenuation plaque burden appears lowest in patients with a high-sensitivity troponin of <5 ng/mL. *Plaque subtype log transformed.

4.4.3 Associations with high-risk plasma troponin concentration

On univariable logistic regression analysis, we found that age (odds ratio 1.65 [95% confidence interval 1.31-2.11], p <0.001) and diabetes mellitus (odds ratio 4.05 [95% confidence interval 1.52-14.1], p=0.011) were associated with high-risk plasma cardiac troponin concentrations. As previously demonstrated, patients were 3 times more likely to have any visual coronary artery disease if they had a high-risk plasma troponin concentration.[35] Higher segment involved score, segment stenosis score and CT-Leaman score were all associated with high-risk plasma troponin concentrations. All plaque burden subtypes were associated with high-risk plasma cardiac troponin concentrations, with low-attenuation plaque burden appearing to have the strongest association (odds ratio per doubling, 1.97 [95% confidence interval 1.45-2.75] p<0.001; **Figure 4-2**).

4.4.4 Multivariable Models

On multivariable logistic regression analysis, the association between the presence of any coronary artery disease and high-risk plasma cardiac troponin concentrations was of borderline statistical significance after adjusting for known clinical risk factors (odds ratio1.95 [95% confidence interval 0.99-3.88], *p*=0.055). This was also the case for all semi-quantitative CT scores. Except for low-attenuation plaque burden (adjusted odds ratio per doubling 1.55 [95% CI 1.13-2.20], p<0.009), none of the other quantitative plaque metrics were associated with high-risk plasma troponin concentrations (**Table 4-3**).

We created a separate multivariable model to look at the relationship between high-risk plasma cardiac troponin concentrations and plaque burden subtypes adjusting for the presence of any coronary artery disease. Again, only low-attenuation plaque burden appeared to be independently associated with high-risk plasma cardiac troponin concentrations (odds ratio per doubling 1.57 [95% CI 1.07-2.37], p=0.026; **Figure 4-3, Table 4-4**).

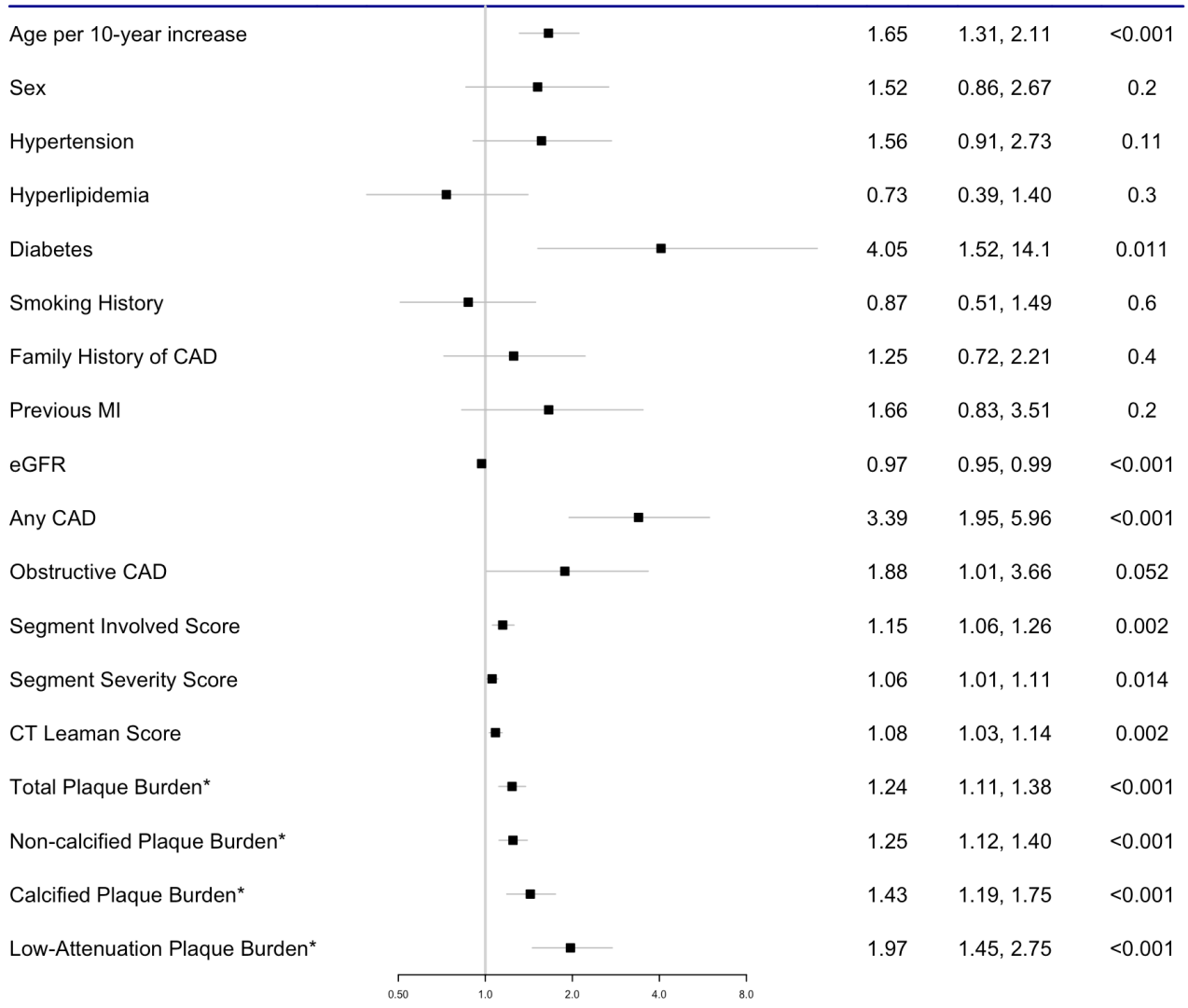

Figure 4-2: Univariable logistic regression analysis to determine the association of clinical and CT characteristics with a plasma troponin concentration of ≥5 ng/L.

OR = Odds Ratio, CI = Confidence Interval,
CAD – Coronary artery disease, MI – myocardial infarction, eGFR- estimated glomerular filtration rate,
CT – Computed tomography ***Log transformed, per doubling of plaque variable**

Table 4-3: Logistic regression analysis comparing association between high-risk plasma troponin concentrations and computed tomography findings adjusted for clinical factors

Characteristic	N	OR[1]	95% CI[1]	p-value
Coronary artery disease	242	1.95	0.99 to 3.88	0.055
Obstructive coronary artery disease	242	0.83	0.38 to 1.82	0.6
Segment involved score	242	1.04	0.94 to 1.16	0.4
Segment severity score	242	1.01	0.96 to 1.06	0.8
CT-Leaman score	242	1.03	0.97 to 1.09	0.4
Total Plaque Burden*	242	1.11	0.97 to 1.26	0.14
Non-calcified Plaque Burden*	242	1.11	0.97 to 1.27	0.14
Calcified Plaque Burden*	242	1.13	0.88 to 1.46	0.3
Low-attenuation Plaque Burden*	242	1.62	1.17 to 2.32	0.005

[1] OR = Odds Ratio, CI = Confidence Interval
*Log transformed- odds ratio per doubling
Multivariable regression adjusted for age per 10-year increase, sex, smoking history, hypertension, diabetes, eGFR and each individual computed tomography (CT) score/plaque subtype.

Table 4-4: Logistic regression analysis comparing association between plasma high-risk plasma troponin concentrations and plaque subtypes adjusted for the presence of any coronary artery disease

Characteristic	N	OR[1]	95% CI[1]	p-value
Total Plaque Burden*	242	1.07	0.89 to 1.29	0.4
Non-calcified Plaque Burden*	242	1.07	0.88 to 1.29	0.5
Calcified Plaque Burden*	242	1.15	0.87 to 1.51	0.3
Low-attenuation Plaque Burden*	242	1.57	1.07 to 2.37	0.026

[1] OR = Odds Ratio, CI = Confidence Interval
*Log transformed- odds ratio per doubling
Multivariable regression adjusted for any visually observed coronary artery disease.

4.5 DISCUSSION

In this post-hoc analysis of patients with acute chest pain in the absence of myocardial infarction, we examined the differences in quantitative plaque characteristics between those with low-risk and high-risk plasma cardiac troponin concentrations. Patients with high-risk plasma cardiac troponin concentrations had a higher burden of coronary plaque, and this was most pronounced for low-attenuation plaque burden. These observations are consistent with the worse prognosis of such patients and suggest that plaque instability may contribute to their underlying cardiovascular risk.

We have previously demonstrated that in patients with acute chest pain but without myocardial infarction, high-risk plasma cardiac troponin concentrations are associated with a 5-fold greater risk of coronary artery disease and a 3-fold greater risk of cardiovascular events at one year.[35, 152] Here, we present data on the burden of plaque subtypes in such patients. We show that there is a large burden of low-attenuation plaque in those with high-risk plasma cardiac troponin concentrations. Low-attenuation plaque is being increasingly recognised as a marker of unstable plaque and a major predictor of risk. Defined as plaque with a Hounsfield unit threshold below 30, it correlates with the lipid-rich necrotic core of high-risk atheroma associated with plaque rupture and acute myocardial infarction.[40, 81] Our findings therefore provide a mechanistic link that may explain why these patients with high-risk cardiac

troponin concentrations are at a substantially increased risk of future cardiovascular events.

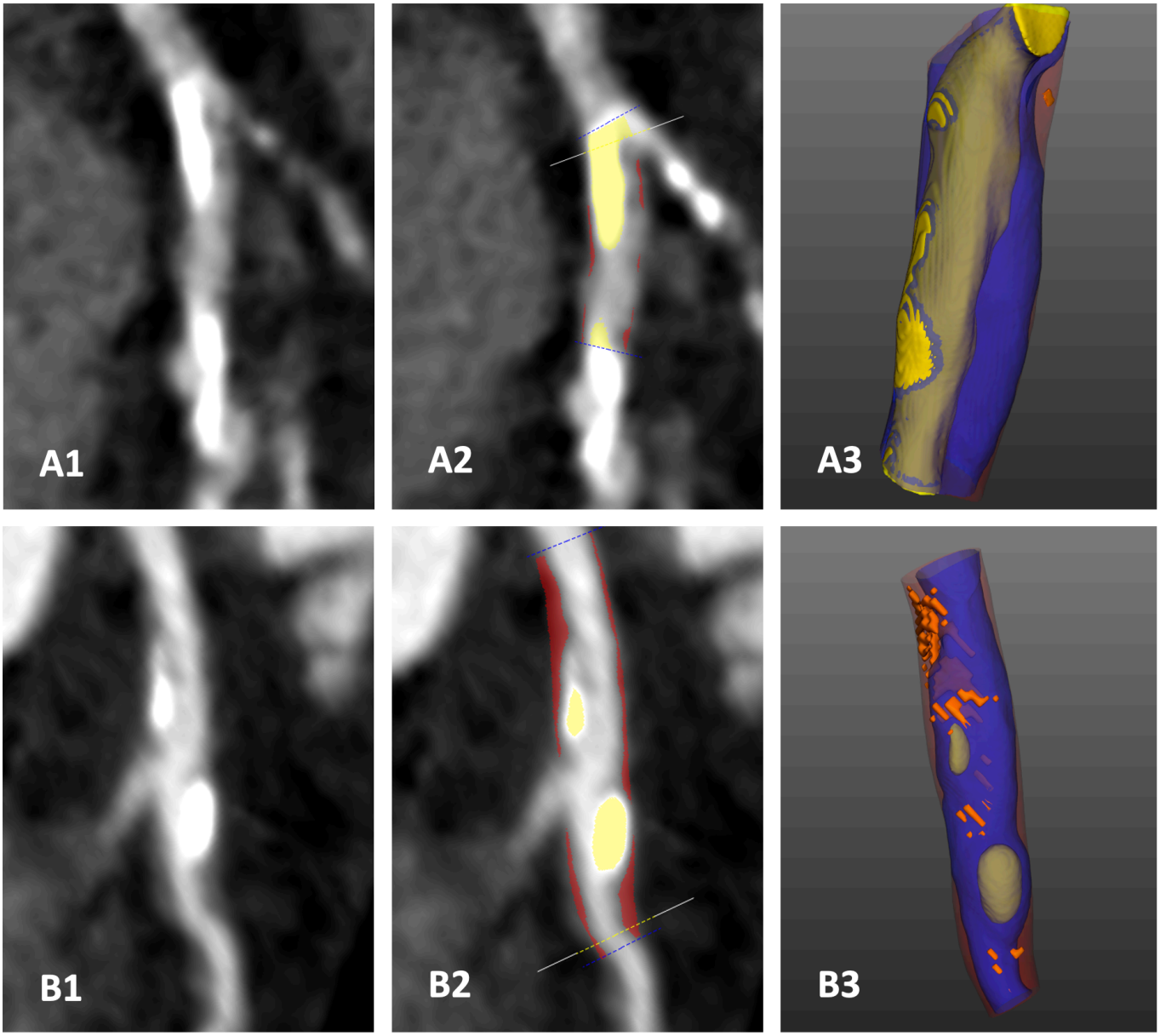

Figure 4-3. Comparative cases of plaque burden in patients with troponin concentration <5 ng/L and >5 ng/L.
A1-A3: 61-year-old male with high sensitivity cardiac troponin concentration <5 ng/L. Plaque analysis of left anterior descending artery demonstrates high burden of total (70%), calcified (35%) and non-calcified (35%) but low burden of low-attenuation plaque (1%).
B1-B3: 63-year-old male with high sensitivity cardiac troponin concentration of 11 ng/L. Plaque analysis of left anterior descending artery demonstrates high burden of total (54%), non-calcified (50%) and low-attenuation plaque (16%) but low burden of calcified plaque (3%).

Blue- lumen, yellow- calcified plaque, red- non-calcified plaque, orange- low-attenuation plaque.

The strength of association between low-attenuation plaque burden and high-risk cardiac troponin concentration was notably greater than that of any other quantitative or semi-quantitative measure. Indeed, even when adjusting for the presence of any coronary artery disease, low-attenuation plaque was the only metric which was associated with high-risk cardiac troponin concentrations. However, low-attenuation plaques do not themselves directly cause the release of cardiac troponin. Why then do we find a high burden of low-attenuation plaque in patients with high-risk troponin concentrations? Cardiac troponin is a continuous variable, and intuitively some individuals may have suffered plaque rupture or erosion, even when troponin concentrations fall below the accepted diagnostic threshold of myocardial infarction.[156] Lowering the threshold for diagnosis of myocardial infarction from the numerically arbitrary 99th centile would identify more patients with myocardial infarction (improved sensitivity), but would increase the risk of over or misdiagnosing myocardial infarction (worse specificity).[157] Indeed, some have suggested a probabilistic approach to the diagnosis of acute myocardial infarction with varying thresholds of cardiac troponin depending on a range of clinical factors.[158] In this setting, plaque quantification and in particular the burden of low-attenuation plaque may help reduce misclassification by revealing patients who are most likely to suffer or have suffered an atherothrombotic plaque rupture event and acute myocardial infarction.

Patients who present with symptoms or evidence of myocardial ischaemia at rest but without a detectable rise or fall in cardiac troponin are often diagnosed

with unstable angina.[159] Despite its declining incidence, unstable angina remains a major cause of hospitalisation[160] and has been associated with improved clinical outcomes in trials of therapeutic interventions for acute coronary syndromes.[161-164] It therefore seems likely that there may have been some patients in our study cohort who had unstable angina, especially in those with high-risk cardiac troponin concentrations. As such, the association with low-attenuation plaque may represent a very useful method of detecting those with underlying plaque instability who have unrecognised unstable angina. These findings may have important sequelae for future clinical practice and assist in the discrimination between those with or without unstable angina, impacting on their subsequent management.

Our study has some limitations which we should acknowledge. First, this was designed as a cross-sectional study, and we do not have outcome data in this cohort. However, we have previously reported the clinical outcomes of such patients and our study population is representative of this prior work. Second, we would also acknowledge the need for further external validation of our findings. Moreover, future studies should focus on whether CT and quantitative plaque analysis can guide treatments to improve outcomes in this patient population. Indeed, this will be addressed in the ongoing Troponin in Acute chest pain to Risk stratify and Guide EffecTive use of Computed Tomography Coronary ANGIOGRAPHY (TARGET-CTCA; NCT03952351) trial, where patients with high-risk cardiac troponin concentrations who have been discharged from hospital are randomised to CTCA or standard of care. Finally,

although the process of plaque analysis is semi-automated, it can still be time consuming, particularly when there is a large burden of disease distributed throughout the coronary tree. Adoption of further automation and machine learning would help facilitate its more widespread clinical use.

4.6 CONCLUSION

In conclusion, we present data that demonstrate the strong association between high-risk plasma high-sensitivity cardiac troponin concentrations and low-attenuation plaque burden. These findings were independent of clinical risk factors and the presence of coronary artery disease. Given that both cardiac troponin and low-attenuation plaque burden are of prognostic value, the use of these metrics may have potential to improve the diagnosis and risk-stratification of patients with acute chest pain without myocardial infarction.

5 CHAPTER 5: Distinguishing type 1 from type 2 myocardial infarction using computed tomography coronary angiography

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Meah MN, Bularga A, Tzolos E, Chapman AR, Daghem M, Hung JD, Chiong J, Taggart C, Wereski R, Gray A, Dweck MR, Roobottom C, Curzen N, Kardos A, Felmeden D, Mills NL, Slomka PJ, Newby DE, Dey D*, Williams MC*. Distinguising type 1 from type 2 myocardial infarction using coronary computed tomography angiography

*Equal contribution as senior author.

5.1 SUMMARY

Background: Distinguishing type 1 from type 2 myocardial infarction remains a major clinical challenge but is essential to direct patient management. We aim to determine whether quantitative plaque characterisation of computed tomography coronary angiography (CTCA) can discriminate between type 1 and type 2 myocardial infarction.

Methods and Results: In two prospective studies, blinded quantitative plaque analysis was performed on CTCA of patients with type 1 myocardial infarction, type 2 myocardial infarction and chest pain without myocardial infarction. Logistic regression analyses were performed to identify predictors of type 1 myocardial infarction. Overall, 155 and 36 patients had type 1 and type 2 myocardial infarction respectively and 136 patients had chest pain without myocardial infarction. Compared with type 2 myocardial infarction, patients with type 1 myocardial infarction had greater total (median 44 [interquartile range 35-50] % *versus* 35 [29-46] %), non-calcified (39 [31-46] % *versus* 34 [29-40] %) and low-attenuation (4.15 [1.88-5.79] % *versus* 1.64 [0.89-2.28] %) plaque burdens ($p<0.05$ for all). Patients with type 2 myocardial infarction had a similar burden of low-attenuation plaque to those patients with chest pain without myocardial infarction ($p=0.4$). Low-attenuation plaque was an independent predictor of type 1 myocardial infarction (adjusted OR 3.44, [95% CI 1.84-6.96]; $p<0.001$) and had better discrimination than non-calcified plaque

burden and maximal area of coronary stenosis (c-statistic 0.75 [0.67-0.83] *versus* 0.62 [0.53-0.71] and 0.61 [0.51-0.70] respectively; $P \leq 0.001$ for both).

Conclusion: Patients with type 1 myocardial infarction have an increased burden of coronary low-attenuation plaque that may help distinguish them from patients with type 2 myocardial infarction.

5.2 Introduction

According to the Fourth Universal Definition, myocardial infarction is diagnosed when a patient has evidence of acute myocardial injury in the setting of myocardial ischaemia.[30] Type 1 myocardial infarction is caused by atherosclerotic plaque disruption, coronary thrombosis, and vessel occlusion. In contrast, type 2 myocardial infarction occurs when there is myocardial oxygen supply and demand mismatch induced by numerous pathophysiological precipitants.[165] Differentiating between type 1 and type 2 myocardial infarction is a common clinical conundrum that can be difficult to resolve,[34] particularly as both can occur in the presence or absence of obstructive coronary artery disease.[38] This is important because treatment strategies vary substantially and the correct diagnosis can have major implications for patient outcomes.[166] For example, in type 1 myocardial infarction, dual antiplatelet therapy plays an important role in the treatment and prevention of recurrent coronary atherothrombotic events whereas in type 2 myocardial infarction, dual antiplatelet therapy may be harmful, especially when occult bleeding and anaemia are contributing factors. Thus, a non-invasive test which can distinguish between type 1 and type 2 myocardial infarction would be of major clinical benefit.

Computed tomography (CT) coronary angiography can non-invasively assess both the severity of coronary artery stenosis and the characteristics of coronary atherosclerotic plaque. The necrotic core of high-risk atherosclerotic plaque is

thought to be the pathological precursor to type 1 myocardial infarction and, with the advent of quantitative CT plaque analysis, the presence and extent of low-attenuation plaque features can now be quantified.[101, 167, 168] CT-defined high-risk low-attenuation plaque can be used to risk stratify patients with coronary artery disease and is one of the strongest predictors of future myocardial infarction.[85] Whilst this prognostic value in patients with stable coronary artery disease has been established, the diagnostic potential of quantitative plaque analysis in patients with acute chest pain is less clear. Identification and quantification of high-risk low-attenuation plaque on CT prior to revascularisation may provide a novel diagnostic approach that could help distinguish between type 1 and type 2 myocardial infarction.

In this study, we aimed to describe the differences in CT-defined coronary atherosclerosis in patients with acute chest pain, and to determine whether quantitative CT angiographic measures of plaque composition and burden can differentiate between type 1 and type 2 myocardial infarction.

5.3 Methods

5.3.1 Study Population

Participants included in this study had been recruited into two prospective clinical studies evaluating the role of CT coronary angiography in the diagnosis of acute coronary syndromes and type 2 myocardial infarction. A detailed description of the inclusion and exclusion criteria can be found in the Supplementary Appendix. The studies were approved by research ethics committees, and written informed consent was received from all participants.

The RAPID-CTCA (Rapid Assessment of Potential Ischaemic heart Disease with Computed Tomography Coronary Angiography) study was a multicentre open prospective parallel group randomised controlled trial that recruited 1,748 patients presenting to the Emergency Department with suspected or provisionally diagnosed acute coronary syndrome in 37 centres across the United Kingdom (NCT02284191). Patients were required to have symptoms consistent with cardiac ischaemia, together with at least one of the following: an abnormal 12-lead electrocardiogram (ECG), history of prior ischaemic heart disease, or an elevated plasma cardiac troponin concentration.[169] Of the 887 patients who were randomised to CT coronary angiography, 767 completed CCTA. In total, 422 scans were available and consecutively analysed comprising of all scans from the top five recruitment centres and a quality assurance cohort of 121 scans obtained from all participating sites. In RAPID-CTCA, the clinical diagnosis was not independently adjudicated but assigned

by the attending clinician. To avoid potential diagnostic misclassification, patients with myocardial injury of uncertain aetiology or unstable angina were *a priori* excluded, and only those with either type 1 myocardial infarction or chest pain without myocardial infarction were included.

The DEMAND-MI (DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction) study was a prospective single-centre observational cohort of 100 patients with a clinical diagnosis of type 2 myocardial infarction that aimed to determine the mechanism of myocardial injury and role of coronary artery disease (NCT03338504).[170] DEMAND-MI enrolled patients with evidence of acute myocardial injury (defined as a rise and or fall in cardiac troponin concentration), clinical symptoms of myocardial ischaemia or signs of myocardial ischaemia on the 12-lead electrocardiogram, and objective evidence of myocardial oxygen supply or demand imbalance, consistent with a clinical diagnosis of type 2 myocardial infarction. All patients underwent extensive imaging to confirm the diagnosis of type 2 myocardial infarction including systematic coronary and structural imaging with invasive or CT coronary angiography and cardiac magnetic resonance imaging or echocardiography. The final diagnosis was adjudicated by consensus of an expert panel. Every patient who underwent CT coronary angiography was included in the current analysis.

5.3.2 CT Angiography and Quantitative Plaque Analysis

CT imaging was performed on ≥64-multidetector row CT according to the study protocol (NCT03338504, NCT02284191).[112] Reconstructions of contrast-enhanced images were performed on the best phase in mid-diastole or end-systole based on established techniques.[171] CT angiography datasets were anonymised and exported in a Digital Imaging and COmmunications in Medicine (DICOM) format to allow quantitative measurement of plaque subtypes. Plaque analysis was performed using semi-automated software (Autoplaque version 2.5, Cedars-Sinai Medical Centre, Los Angeles, USA) by a trained observer blinded to study of origin and diagnosis. This method has excellent observer agreement, even in patients with advanced coronary disease, and has been validated against intravascular ultrasound.[103, 167, 172]

Coronary artery centrelines were extracted in a semi-automated fashion for each major artery and any tributary of >2 mm in diameter with visually observed disease. A region of interest was placed in the aorta to define blood pool attenuation. Coronary artery segments were defined manually according to the Society of Cardiovascular Computed Tomography guidance, using side-branches to mark progression from proximal to mid and distal segments.[132, 144] Segments with visible disease were manually identified, and vessel wall and plaque constituents were automatically determined using scan-specific thresholds with manual adjustments made as required. Area stenosis was calculated automatically and refers to the maximal area of stenosis on a per-patient level. Stented segments, and graft insertion points were excluded from

analysis in line with previously described methodology.[167] Where image quality was too poor to complete quantitative plaque analysis, scans were excluded.

Plaque volume was measured (in mm^3) for total, non-calcified, calcified, and low-attenuation plaque subtypes (defined by an attenuation of <30 Hounsfield Units). To normalise for differences in vessel volume, plaque burden was calculated by dividing plaque volume by the vessel volume of the segments assessed and multiplying by 100.

5.3.3 Statistical Analysis

Categorical variables are presented as number and percentage. Continuous variables are presented as median [interquartile interval] or mean ± standard deviation, when normally distributed. Statistical significance was assessed using Wilcoxon rank sum test, Pearson's Chi-squared test and Fisher's exact test as appropriate. Logistic regression analysis was performed in patients with either a diagnosis of type 1 or type 2 myocardial infarction, to determine the odds ratios with [95% confidence intervals] of type 1 myocardial infarction. Multivariable regression models were constructed using a priori selection, adjusting for age, sex, history of smoking, hypertension, hyperlipidaemia, the maximal area stenosis, and individual plaque subtype burdens. Plaque burdens for each subtype were log-transformed for this analysis (log_2 of 1 plus the plaque variable). Receiver operator characteristic curves were created to discriminate patients with type 1 myocardial infarction from patients with adjudicated type 2 myocardial infarction ('*pROC*' package version 1.17.0 in

R).[173] Differences between curves were compared by DeLong's test and the optimal threshold determined using Youden's J statistic.[173, 174] Statistical significance was defined as a two-sided *P* value <0.05. All statistical analysis was performed using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

5.4 Results

5.4.1 Study Populations

In total, 460 CT scans were assessed, of which 20 were excluded due to poor image quality, 113 due to a diagnosis of myocardial injury of uncertain aetiology and 38 due to a diagnosis of unstable angina (**Figure 5-1**). The final study population comprised of 327 participants: 155 patients had type 1 myocardial infarction, 36 had type 2 myocardial infarction, and 136 had chest pain without infarction (**Table 5-1**). The subgroup of participants from the RAPID-CTCA trial were representative of the overall trial population (**Table 5-2**).

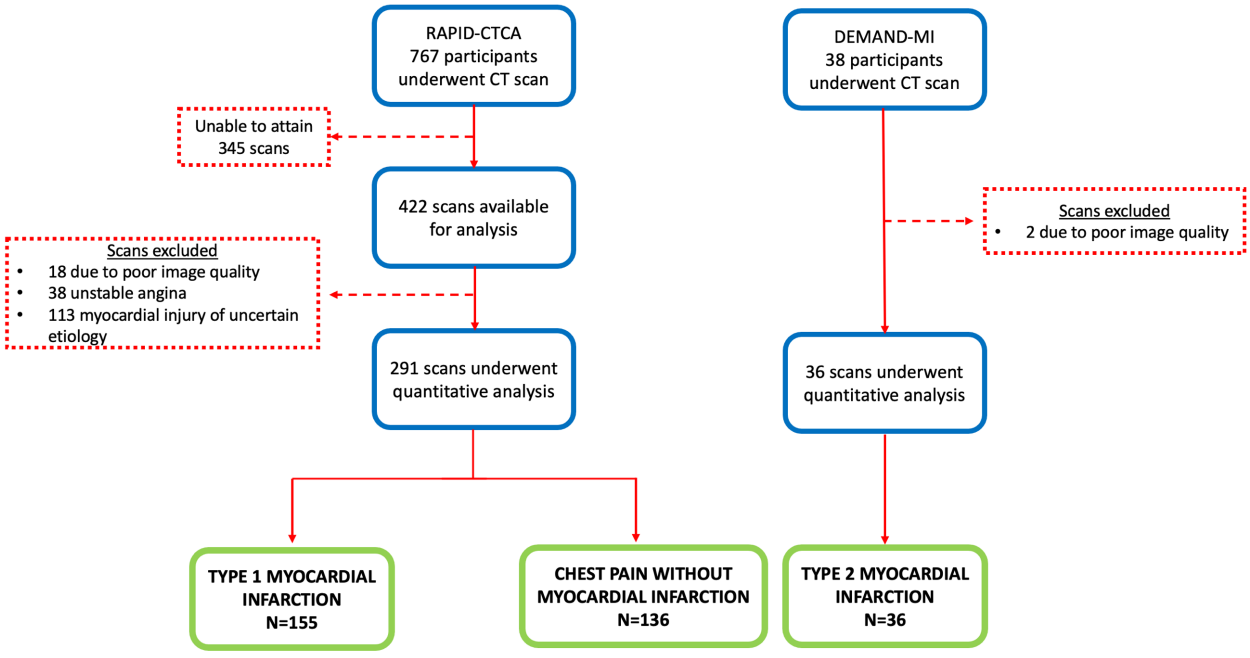

Figure 5-1- Sub-study diagram showing the screening and final study population.
CT- Computed tomography

Table 5-1: Baseline characteristics						
Characteristic	**Type 1 MI** N = 155	**Type 2 MI** N = 36	**Acute chest pain Without MI** N = 136	**p-value*** *Type 1 MI vs Type 2 MI*	**p-value*** *Type 1 MI vs Non-MI*	**p-value*** *Type 2 MI vs Non-MI*
Age	64 ± 12	67 ± 12	62 ± 12	0.075	0.3	0.008
Sex						
Women	41 (26%)	17 (47%)	58 (43%)	**0.015**	0.004	0.6
Men	114 (74%)	19 (53%)	78 (57%)			
Smoking Habit						
Ex-smoker	74 (48%)	11 (31%)	51 (38%)	**0.001**	0.013	0.2
Non-smoker	46 (30%)	22 (61%)	63 (46%)			
Smoker	35 (23%)	3 (8%)	22 (16%)			
Family history of CAD	53 (34%)	8 (25%)	48 (35%)	0.3	0.8	0.3
Hypertension	73 (47%)	16 (44%)	60 (44%)	0.8	0.6	>0.9
Hyperlipidaemia	67 (43%)	6 (17%)	57 (42%)	**0.003**	0.8	**0.005**
Diabetes	17 (11%)	5 (14%)	22 (16%)	0.6	0.2	0.7
Previous MI	19 (12%)	6 (17%)	42 (31%)	0.6	**<0.001**	0.091

Previous PCI	14 (9.0%)	4 (11%)	29 (21%)	0.8	**0.003**	0.2
Previous CABG	10 (6.5%)	4 (11%)	8 (5.9%)	0.3	0.8	0.3
Previous CVD	4 (2.6%)	1 (2.8%)	7 (5.1%)	>0.9	0.3	>0.9
Haemoglobin (g/L)	145 [134 to 154]	132 [112 to 150]	142 [131 to 151]	**0.008**	0.14	0.051
White cell count (10^9/L)	8.1 [7.2 to 10.4]	10.3 [8.3 to 11.9]	7.6 [6.4 to 9.2]	**0.007**	**0.004**	**<0.001**
Creatine (μmol/L)	82 [69 to 93]	74 [66 to 102]	78 [67 to 86]	0.4	**0.030**	>0.9
Peak high sensitivity troponin (ng/L)	156 [60 to 839]	277 [75 to 1026]	5 [3 to 9]	0.4	**<0.001**	**<0.001**
Chest pain on admission	144 (93%)	27 (75%)	122 (90%)	**0.004**	0.3	**0.029**
Ischaemic ECG on admission	98 (63%)	19 (53%)	96 (71%)	0.2	0.2	**0.044**

Mean ± standard deviation; Median [interquartile interval]; Number (%)
*Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
MI – myocardial infarction, CAD – coronary artery disease, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting, CVD – cerebrovascular disease, ECG – electrocardiogram.

Table 5-2: Overall and subgroup populations of the RAPID-CTCA trial

Characteristic	**RAPID CTCA trial population** N = 767[1]	**RAPID CTCA trial sub-study cohort** N = 404[1]	**p-value**[2]
Age (years)	61 [53 to 71]	63 [54 to 73]	0.2
Male	482 (63%)	259 (64%)	0.8
Diabetes	127 (17%)	57 (14%)	0.2
Hypertension	346 (45%)	180 (45%)	0.9
Hyperlipidaemia	308 (40%)	165 (41%)	0.8
Any smoking history	454 (61%)	79 (60%)	0.8
Previous myocardial infarction	159 (21%)	91 (23%)	0.5
Previous coronary stenting	99 (13%)	58 (14%)	0.8
Previous coronary artery bypass grafting	48 (6.3%)	24 (5.9%)	0.8
RAPID CT scan interpretation			
Normal	178 (23%)	95 (24%)	0.8
Nonobstructive	222 (29%)	122 (30%)	
Obstructive	359 (47%)	187 (46%)	
GRACE Score	112 [90 to 137]	110 [88 to 137]	0.6

[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test
GRACE- Global Registry of Acute Coronary Events, CT- computed tomography

5.4.3 Clinical Characteristics of the Study Populations

Patients with type 1 myocardial infarction were less likely to be female or to have undergone coronary artery bypass grafting and more likely to have a history of smoking or hyperlipidaemia. All other risk factors for myocardial infarction were similar between cohorts (**Table 5-1**). Compared to type 2 myocardial infarction, patients with type 1 myocardial infarction had higher haemoglobin concentrations and lower white cell counts, but similar maximal high-sensitivity cardiac troponin concentrations. More patients with type 1 myocardial infarction presented with chest pain (93% *versus* 75%, *P*=0.004), but similar proportions had abnormal electrocardiograms at presentation (63% *versus* 53%, *P*=0.2). The three commonest mechanisms of supply-demand imbalance in patients with type 2 myocardial infarction were tachyarrhythmia (50%), anaemia (14%), and hypoxia (11%; **Table 5-3**).

In general, patients with chest pain without myocardial infarction had a similar profile to those with myocardial infarction (**Table 5-1**). The three commonest discharge diagnoses in those presenting with chest pain in the absence of myocardial infarction included chest pain of uncertain aetiology (58%), gastrointestinal causes (10%), and musculoskeletal pain (10%; **Table 5-3**).

Table 5-3: Aetiology of clinical presentation

Type 2 myocardial infarction N = 36		**Acute chest pain without myocardial infarction N = 291**	
Mechanism of Injury	**Frequency**	**Discharge Diagnosis**	**Frequency**
Tachyarrhythmia	18 (50%)	Chest pain unclear aetiology	58 (20%)
Anaemia	6 (17%)	Gastrointestinal symptoms	21 (7%)
Hypoxic injury	5 (14%)	Musculoskeletal symptoms	20 (7%)
Hypertensive injury	4 (11%)	Stable angina	20 (7%)
Hypotensive injury	2 (6%)	Pericarditis	1 (0.3%)
Bradyarrhythmia	1 (3%)	Pulmonary embolism	2 (1%)
		Aortic dissection	1 (0.3%)
		Pneumonia/LRTI	4 (1%)
		Anxiety	3 (1%)
		Arrhythmia	1 (0.3%)
		Heart Failure	2 (0.6%)
		Hypertensive injury	1 (0.3%)

Table 5-4: Comparison of CT analysis

Characteristic	**Type 1 MI** N = 155	**Type 2 MI** N = 36	**Acute chest pain Without MI** N = 136	**p-value*** *Type 1 MI vs Type 2 MI*	**p-value*** *Type 1 MI vs Non-MI*	**p-value*** *Type 2 MI vs Non-MI*
Presentation to scan (days)	1 [0 to 1]	16 [7 to 23]	1 [0 to 1]	**<0.001**	0.5	**<0.001**
Normal coronary arteries	8 (5.2%)	4 (11%)	39 (29%)	0.2	**<0.001**	**0.030**
Non-obstructive disease	68 (44%)	15 (42%)	76 (56%)	0.8	**0.041**	0.13
Obstructive disease	79 (51%)	17 (47%)	21 (15%)	0.7	**<0.001**	**<0.001**
Left main stem disease	27 (17%)	1 (2.8%)	16 (12%)	**0.025**	0.2	0.13
Single vessel disease	22 (14%)	3 (8.3%)	25 (18%)	0.4	0.3	0.15
Two-vessel disease	50 (32%)	7 (19%)	24 (18%)	0.13	**0.004**	0.8

Triple vessel disease	73 (47%)	22 (61%)	47 (35%)	0.13	**0.030**	**0.004**
Maximum area stenosis (%)	76 [60 to 100]	67 [50 to 79]	50 [33 to 70]	**0.04**	**<0.001**	**0.001**
Remodelling index	1.43 [1.25 to 1.65]	1.33 [1.21 to 1.57]	1.30 [1.11 to 1.49]	0.2	**<0.001**	0.2

Median [interquartile interval]; Number (%)
*Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

5.4.4 CT Coronary Angiography

CT coronary angiograms were performed within a median interval of 1 [0 to 1] day in patients with type 1 myocardial infarction and those with chest pain in the absence of myocardial infarction, and within 16 [7 to 23] days after presentation in patients with type 2 myocardial infarction. Patients with type 1 myocardial infarction had similar proportions of normal, non-obstructive and obstructive coronary artery disease compared to patients with type 2 myocardial infarction (**Table 5-4**), but there was more disease in the left main stem of those with type 1 myocardial infarction (p=0.025). Compared to participants without myocardial infarction, patients with type 1 myocardial infarction were more likely to have obstructive (P<0.001), two or three vessel coronary disease (P≤0.03 for both). This was similarly the case when participants without myocardial infarction were compared to patients with type 2 myocardial infarction, who were more likely to have obstructive and triple vessel coronary disease (p≤0.004 for both).

5.4.5 Plaque Characteristics

Compared to those with type 2 myocardial infarction, patients with type 1 myocardial infarction had greater maximal area stenosis and total, non-calcified and low-attenuation plaque, but there was no difference in calcified plaque burden (**Figures 5-2; Table 5-5**). Respective plaque volume measurements demonstrated similar relationships (**Table 5-5**). Patients with chest pain without myocardial infarction had lower maximal area stenosis and coronary plaque burdens compared to those with type 1 or type 2 myocardial

infarction although the burdens of calcified and low-attenuation plaque were similar to those with type 2 myocardial infarction (**Table 5-4, 5-5 & Figure 5-2**).

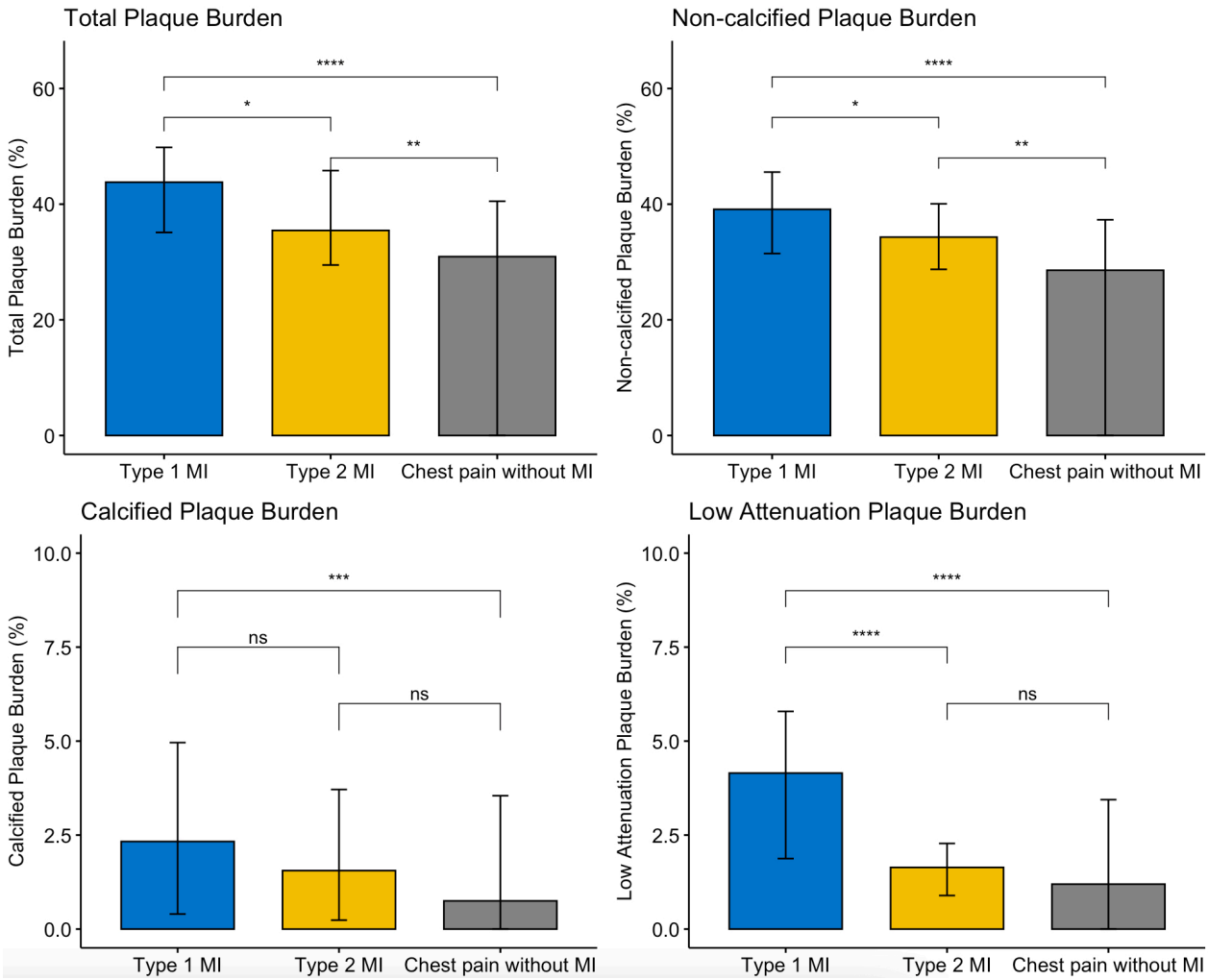

Figure 5-2: Comparison of plaque burden subtypes in patients with type 1 myocardial infarction, type 2 myocardial infarction and acute chest pain without myocardial infarction.

Histograms (median ± interquartile interval) comparing burden of plaque subtypes demonstrate that patients with type 1 myocardial infarction have higher burdens of total, non-calcified and low-attenuation plaque burden. MI – myocardial infarction, ns- not significant, *p < 0.05, ** p<0.01, *** p < 0.001, **** p < 0.0001.

Table 5-5: Comparison of plaque burden and plaque burden

Characteristic	**Type 1 MI** N = 155	**Type 2 MI** N = 36	**Acute chest pain Without MI** N = 136	**p-value*** *Type 1 MI vs Type 2 MI*	**p-value*** *Type 1 MI vs Non-MI*	**p-value*** *Type 2 MI vs Non-MI*
Total plaque burden (%)	44 [35 to 50]	35 [29 to 46]	31 [0 to 41]	**0.024**	**<0.001**	**0.006**
Non-calcified plaque burden (%)	39 [31 to 46]	34 [29 to 40]	29 [0 to 37]	**0.023**	**<0.001**	**0.003**
Calcified plaque burden (%)	2.3 [0.4 to 5.0]	1.6 [0.2 to 3.7]	0.8 [0 to 3.5]	0.3	**<0.001**	0.092
Low attenuation plaque burden (%)	4.15 [1.88 to 5.79]	1.64 [0.89 to 2.28]	1.19 [0 to 3.44]	**<0.001**	**<0.001**	0.4
Total plaque volume (mm^3)	688 [285 to 1216]	827 [490 to 1159]	224 [0 to 717]	0.4		
Non-calcified plaque volume (mm^3)	606 [258 to 1104]	718 [479 to 1016]	215 [0 to 631]	0.3		
Calcified plaque volume (mm^3)	35 [6 to 119]	26 [4 to 92]	6 [0 to 50]	0.8		
Low attenuation plaque volume (mm^3)	56 [18 to 131]	32 [16 to 56]	11 [0 to 49]	0.014		

Median [interquartile interval]; Number (%), *Wilcoxon rank sum test
MI- myocardial infarction

5.4.6 Predictors of Type 1 Myocardial Infarction

On univariable logistic regression analysis of all patients with myocardial infarction (type 1 or type 2), male sex and hyperlipidaemia were associated with an increased likelihood of type 1 myocardial infarction (*P*<0.02 for all, **Table 5-6**). On univariable analysis of imaging assessments, only low-attenuation plaque burden was associated with an increased likelihood of type 1 myocardial infarction (odds ratio (OR) 2.34 [95% confidence interval (CI) 1.58-3.55] *P*<0.001; **Table 5-6**). On multivariable analysis, low-attenuation plaque burden remained an independent predictor of type 1 myocardial infarction (adjusted OR 3.44 [95% CI 1.84-6.95], *P*<0.001, **Table 5-6**). Receiver operator characteristic curves illustrate the discrimination of area stenosis, non-calcified plaque burden and low-attenuation plaque burden for type 1 myocardial infarction (**Figure 5-3**). Non-calcified plaque had a c-statistic of 0.62 [95% CI 0.53-0.71] and maximal area stenosis of 0.61 [95% CI 0.51-0.70]. Low-attenuation plaque burden performed better than both, with a c-statistic of 0.75 [95% CI 0.67-0.83; *P*≤0.001 for both]. Youden's J statistic suggested the optimal threshold was a low-attenuation plaque burden of 2.34% which identified 75% of patients as more likely to have type 1 myocardial infarction with a sensitivity of 72% [95% CI 65-79%] and specificity of 78% [95% CI 64-89%] though specificity increased with higher thresholds (**Table 5-7**).

Table 5-6: Univariable and multivariable models for type 1 myocardial infarction compared to type 2 myocardial infarction

Characteristic	Univariable regression				Multivariable regression		
	N	OR[1]	95% CI[1]	p	OR[1]	95% CI[1]	p
Age	191	0.97	0.94, 1.00	0.10			
Male	191	2.49	1.17, 5.26	**0.017**			
Hypertension	191	1.11	0.54, 2.33	0.8			
Hyperlipidaemia	191	3.81	1.59, 10.6	**0.005**			
Diabetes	191	0.76	0.28, 2.46	0.6			
Smoking	191	3.21	1.07, 13.9	0.065			
Family history of CAD	187	1.56	0.68, 3.92	0.3			
Previous MI	191	0.70	0.27, 2.05	0.5			
Previous PCI	191	0.79	0.26, 2.94	0.7			
Previous CVA	191	0.93	0.13, 18.4	>0.9			
Normal CT	191	0.44	0.13, 1.71	0.2			
Non-obstructive disease	191	1.09	0.53, 2.31	0.8			
Obstructive disease	191	1.16	0.56, 2.42	0.7			
Left main stem disease	191	7.38	1.49, 134	0.054			
Single vessel disease	191	1.82	0.58, 8.01	0.4			
Two vessel disease	191	1.97	0.85, 5.17	0.14			
Triple vessel disease	191	0.57	0.27, 1.18	0.13			
Remodelling Index	191	1.56	0.58, 5.11	0.4			

***Maximum Area Stenosis**	191	1.43	0.77, 2.55	0.2			
***Total plaque burden**	191	0.94	0.64, 1.24	0.7	0.66	0.35 to 1.07	0.13
***Non-calcified plaque burden**	191	0.91	0.60, 1.22	0.6	0.64	0.34 to 1.04	0.1
***Calcified plaque burden**	191	1.18	0.88, 1.59	0.3	1.14	0.79 to 1.67	0.5
***Low attenuation plaque burden**	191	2.34	1.58, 3.55	**<0.001**	3.44	1.84 to 6.95	**<0.001**

[1] OR = Odds Ratio, CI = Confidence Interval, *Log transformed
Multivariable regression adjusted for age, sex, smoking, hypertension, hyperlipidaemia, area stenosis

MI – myocardial infarction, CAD – coronary artery disease, PCI – percutaneous coronary intervention, CVA – cerebrovascular accident

Table 5-7: Sensitivity and specificity of various low-attenuation plaque burden thresholds at identifying type 1 myocardial infarction

Low-attenuation plaque burden threshold %	Sensitivity % [95% CI]	Specificity % [95% CI]
0.69	89 [84-97]	19 [8-33]
1.08	85 [79-90]	31 [19-50]
1.60	77 [70-83]	50 [33-67]
2.00	74 [67-81]	64 [47-78]
2.34*	72 [65-79]	78 [64-89]
2.85	64 [57-72]	81 [67-92]
3.10	61 [53-68]	89 [78-97]
3.83	54 [46-61]	94 [86-100]
6.18	22 [15-28]	97 [92-100]

*Optimal low-attenuation plaque threshold according to Youden's J statistic.
CI – confidence interval

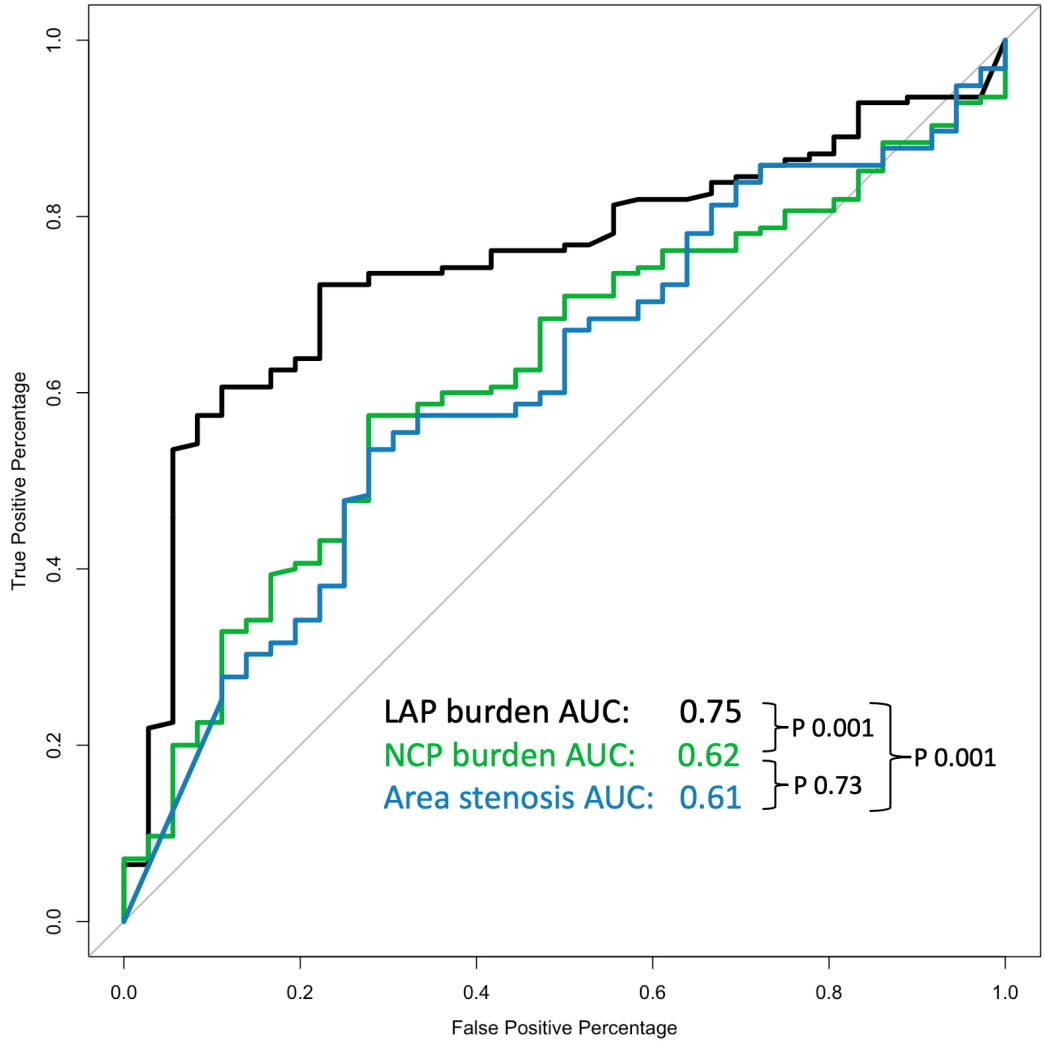

Figure 5-3: Predictors of type 1 myocardial infarction
Receiver operator characteristics comparing ability of low-attenuation plaque (LAP; black) burden, non-calcified plaque (NCP; green) burden and maximal area stenosis (blue) to discriminate between type 1 and type 2 myocardial infarction.

5.5 DISCUSSION

In this secondary analysis of two prospective clinical studies of patients with acute chest pain, we demonstrate that quantitative coronary artery plaque characteristics differ between patients with type 1 and type 2 myocardial infarction. In particular, low-attenuation plaque burden distinguished between these two distinct pathologies independent of maximal area stenosis and standard clinical characteristics. These findings suggest that quantitative CT plaque analysis holds major promise in discriminating between type 1 and type 2 myocardial infarction, potentially informing the clinical management of patients with myocardial infarction of uncertain aetiology.

Type 1 myocardial infarction is defined by acute atherosclerotic plaque rupture or erosion leading to coronary thrombosis and luminal obstruction.[30, 175] The lipid-rich necrotic core is central to the pathogenesis of type 1 myocardial infarction and correlates closely to CT-defined low-attenuation plaque.[103, 130, 168, 176] For the first time, our study demonstrates a higher burden of low-attenuation plaque on quantitative CT in patients suffering type 1 myocardial infarction compared to type 2 myocardial infarction or chest pain without infarction. These findings are logical and intuitive because low-attenuation lipid-rich necrotic plaque is the primary driver for type 1 myocardial infarction and our cohort is unique in that CT scans were completed prior to invasive angiography and revascularisation.

With the widespread adoption of high-sensitivity cardiac troponin testing, the diagnosis of myocardial injury and infarction has increased,[177] and up to 20% of patients with an elevated cardiac troponin concentration are now diagnosed with type 2 myocardial infarction.[34, 178, 179] However, plasma cardiac biomarkers have a limited ability to discriminate between type 1 and type 2 myocardial infarction.[180] This is due in part to the complex nature of type 2 myocardial infarction which often occurs in a heterogeneous group of patients with multiple co-morbidities and can have an unclear aetiology or pathophysiology.[41, 181, 182] Infarction may occur due to unmet myocardial oxygen demand (tachyarrhythmia, hypertrophy) or a reduction in myocardial oxygen supply (anaemia, hypotension, hypoxia).[165, 183] Whilst this often happens in the presence of obstructive coronary artery disease, it may also occur when myocardial demand outstrips supply even in the absence of flow limitation or obstruction. This begs the question when a patient with obstructive coronary artery disease has a myocardial infarction, how do we know if it is due to plaque rupture or a supply and demand mismatch? In our study, the presence of obstructive coronary artery disease was not sufficient to distinguish between type 1 and type 2 myocardial infarction. However, many patients with type 2 myocardial infarction had substantial coronary artery disease but a reduced burden of low-attenuation plaque. This raises the possibility that CT coronary angiography with quantitative plaque characterisation may help in the evaluation of patients with myocardial infarction of uncertain aetiology. In those with reduced low-attenuation plaque,

clinicians may be reassured that plaque disruption and type 1 myocardial infarction is unlikely.

Irrespective of the presence of non-obstructive or obstructive coronary artery disease, it can be challenging to confirm whether or where acute plaque rupture or erosion has occurred. The culprit lesion is often mis-ascribed on invasive angiography with discordance between the treated lesion and the territory of infarction in up to a half of cases.[184] Whilst invasive adjunctive coronary imaging, such as optical coherence tomography or intravascular ultrasound, can assist in diagnosing acute plaque disruption, the cost, necessary expertise and inability to cross or to image the majority of lesions with severe disease are barriers to widespread adoption in routine clinical practice.[41] In contrast, CT angiography can provide a global assessment of coronary atherosclerotic plaque that includes the vessel wall and plaque, can assess critically stenosed lesions, and is not merely limited to assessing the luminal stenosis. The identification of high-risk low attenuation plaque may also provide an opportunity to intensify the application of more advanced preventative therapies to reduce recurrent events.

Our study reported on a third group of patients who presented with chest pain but without evidence of myocardial injury or infarction. Acute chest pain is one of the commonest reasons for individuals to present to the Emergency Department, and patients with a prior history of coronary heart disease are more likely to attend.[185] It has previously been reported that patients

presenting with acute chest pain without myocardial infarction have a higher burden of plaque compared to asymptomatic individuals.[96] Moreover, because of the inclusion criteria, our study population was enriched for patients with a prior history of coronary heart disease. Despite this enhanced prevalence of coronary artery disease, patients without myocardial infarction had a low burden of low-attenuation plaque equivalent to those suffering type 2 myocardial infarction. This reinforces the study conclusion that coronary artery disease in type 2 myocardial infarction is predominantly stable and myocardial infarction has occurred due to a supply and demand imbalance. It also lends weight to the argument that a high burden of low-attenuation plaque is more specific to those with type 1 myocardial infarction.

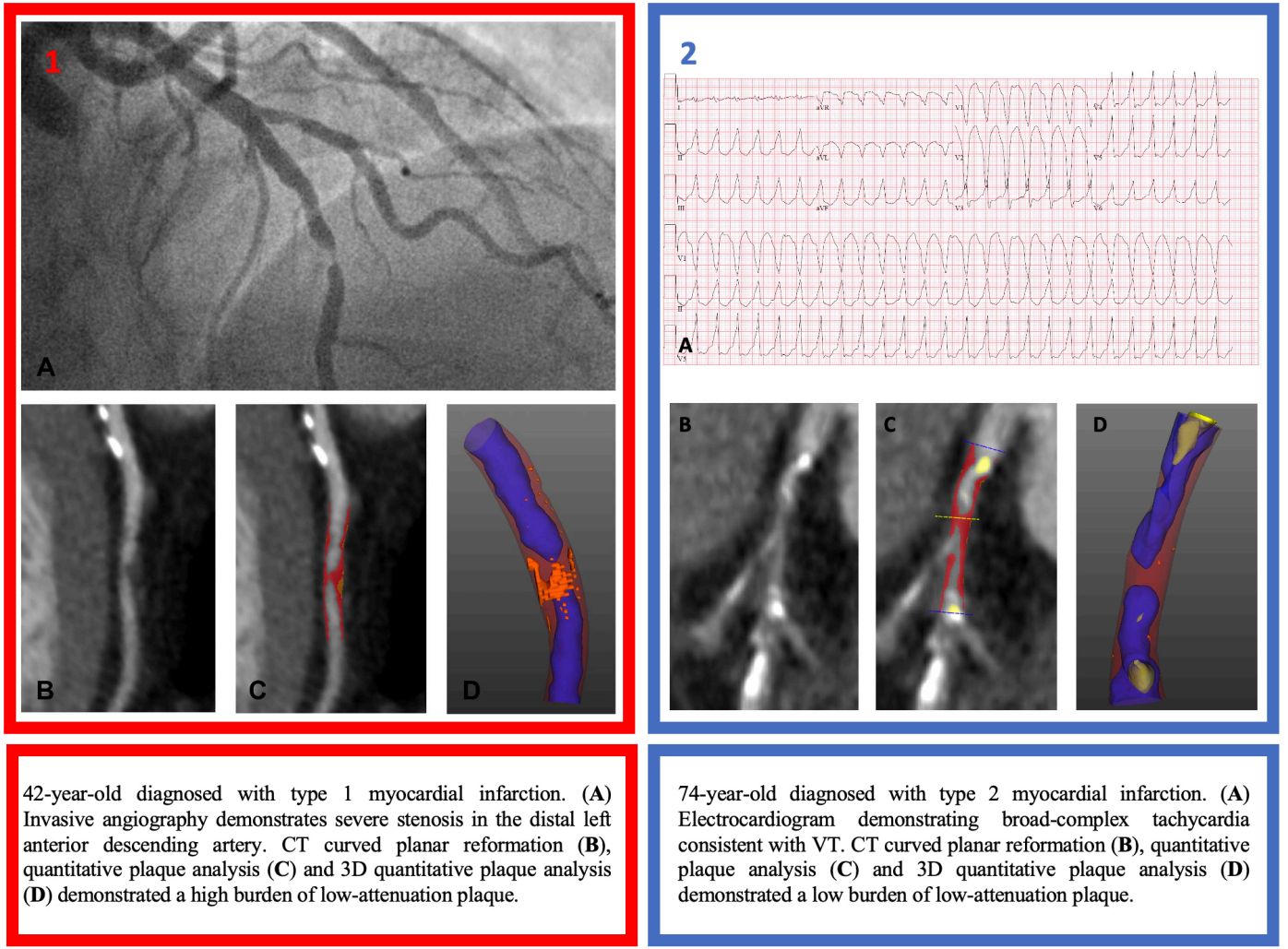

Figure 5-4: Graphical representation of CT plaque analysis demonstrating differences between type 1 and type 2 myocardial infarction.

CT images from a patient with type 1 (Panel 1- RED) and a patient with type 2 (Panel 2- BLUE) myocardial infarction showing curved planar reformation, superimposed quantitative plaque analysis and 3D plaque analysis. Both have obstructive coronary artery disease detected by coronary CT angiography. Quantitative plaque analysis demonstrates clear differences with a higher burden of low-attenuation plaque in patients presenting with type 1 myocardial infarction than those with type 2.

Colour shading – Red represents non-calcified plaque, yellow is calcified plaque, orange is low-attenuation plaque and blue represents lumen.

Our study has several limitations which we should acknowledge. First, our study population was pooled from two different studies with differing study designs. However, patients were consecutively recruited, and image analysis was performed in a single core laboratory blinded to the trial of origin and clinical diagnosis to limit any ascertainment bias. Image acquisition protocols were also identical as both trials were designed and led by the same investigators. We confirmed that our cohort of patients with type 1 myocardial infarction was representative of the overall trial population and every patient who suffered a type 2 myocardial infarction and underwent CT was included. This has minimised any case selection bias. Moreover, because the diagnosis of type 2 myocardial infarction can be heterogeneous, its categorisation was carefully and independently adjudicated by an expert panel following systematic and comprehensive cardiac imaging including echocardiography and cardiac magnetic resonance imaging. Although a semi-automated process, quantification of plaque subtype can take up to 20 min per scan and this may limit uptake of this approach into the clinic. Further automation and machine learning algorithms could improve the rapidity and practical application of plaque quantification.[186] Prospective studies are now needed to validate this technique further, and external confirmation of our promising initial findings is required.

5.6 CONCLUSION

In conclusion, quantitative CT coronary angiography identified important differences between the plaque characteristics of patients with type 1 and type 2 myocardial infarction. Future studies should investigate whether these differences could be used to differentiate between these distinct pathologies in clinical practice.

6 CHAPTER 6: Plaque burden and one-year outcomes in patients with acute chest pain

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Meah MN, Tzolos E, Wang KL, Bularga A, Dweck MR, Curzen N, Kardos A, Keating L, Storey RF, Mills NL, Slomka PJ, Dey D, Newby DE, Gray A, Williams MC*, Roobottom C*. Plaque burden and one-year outcomes in patients with acute chest pain; Results from the multicenter Rapid Assessment of Potential Ischaemic hearet Disease with CT coronary Angiography Trial.

*Equal contribution as senior author.

6.1 SUMMARY

Background: In patients with stable chest pain, computed tomography (CT) plaque burden is an independent predictor of future coronary events. We aim to determine whether quantitative plaque analysis can predict subsequent death or myocardial infarction in patients presenting with acute chest pain.

Methods and Results: In a post-hoc analysis of a multicentre trial of early coronary CT angiography, we performed quantitative plaque analysis to assess the association between primary endpoint of 1-year all-cause death or myocardial infarction and the GRACE score, presence of obstructive coronary disease and plaque burden in patients with suspected acute coronary syndrome. The sub-study population comprised of 404 patients of whom 198 (48%) were diagnosed with acute coronary syndrome at index presentation and 25 (6.2%) went on to have a primary event. Events were associated with a higher GRACE score (134±44 versus 113±35; p=0.012), larger burdens of total (46[43-50] % versus 36 [21-46]%; p<0.001), non-calcified (41 [37-47]% versus 33 [20-41]%; p<0.001) and low-attenuation plaque (4.22 [3.3-5.68] % versus 2.14 [0.5-4.88] %; p<0.001), but not obstructive coronary disease (p=0.065). The primary endpoint was associated with high burdens of total (hazard ratio 25.4, 95% confidence interval 3.44-188.0, p=0.002), non-calcified (hazard ratio 26.4, 95% confidence interval 3.58-196.0, p=0.001) and low-attenuation (hazard ratio 7.80, 95% confidence interval 2.33-26.0, p<0.001) plaque but not calcific plaque (hazard ratio 1.76, 95% confidence interval 0.78-

3.99, p=0.20). In multivariable analysis, total, non-calcified and low-attenuation plaque burdens were the strongest predictors of the primary endpoint, independent of the GRACE score or the presence of obstructive coronary artery disease (p≤0.002 for all).

Conclusion: In patients with acute chest pain, total, non-calcified and low-attenuation plaque burdens predict one-year all-cause death or subsequent myocardial infarction. Measures of non-calcific plaque burden outperform traditional estimates of future risk including the GRACE score and the presence of obstructive coronary artery disease.

6.2 INTRODUCTION

Myocardial infarction remains the leading cause of death in the Western world, with estimates suggesting 1 in 7 deaths are attributed to coronary heart disease in the United States alone.[187, 188] Although rates of survival and recurrent myocardial infarction have improved, there remains a substantial burden of subsequent or recurrent events.[189] When patients present with acute chest pain or myocardial infarction, guidelines suggest the use of stratification tools, such as the Global Registry of Acute Coronary Events (GRACE) risk score, to estimate the risk of downstream adverse cardiovascular events.[29, 190, 191] This score has been extensively validated for in-hospital and 6-month outcomes.[192, 193]

Coronary computed tomography (CT) angiography has the potential to provide more precise risk stratification based upon direct coronary plaque assessments including the total plaque burden as well as the identification and quantification of higher risk plaque types, such as non-calcified plaque and low-attenuation plaque (a marker of necrotic core).[90, 194] While traditionally the presence of obstructive coronary artery disease was seen as the primary determinant of risk in patients with stable chest pain, we recently demonstrated that low-attenuation plaque burden was the strongest predictor of future fatal or non-fatal myocardial infarction, outperforming both cardiovascular risk scores and coronary artery stenosis in this group.[97] It remains to be

established whether similar assessments have prognostic utility in patients with undifferentiated acute chest pain.

In a post hoc secondary analysis of a multicentre randomised controlled trial of early coronary CT angiography in patients presenting with suspected acute coronary syndrome, we assessed whether quantification and characterisation of plaque burden is associated with the primary endpoint of subsequent one-year non-fatal myocardial infarction or all-cause death and compare this relationship with the GRACE score and the presence of obstructive coronary artery disease.

6.3 METHODS

6.3.1 Study Population

Patients were participants of the Rapid Assessment of Potential Ischaemic heart Disease with Coronary Computed Tomography Angiography (RAPID-CTCA) trial. This was a multicentre open prospective parallel-group randomised controlled trial that recruited 1748 patients who presented to the Emergency Department with suspected acute coronary syndrome across 37 sites in the United Kingdom **(**NCT02284191).[112] The primary findings of the trial have been reported previously.[113] Patients had symptoms of suspected acute coronary syndrome together with: a prior history of ischaemic heart disease, an abnormal 12-lead electrocardiogram (ECG) or an elevated plasma cardiac troponin concentration. They were randomised to early coronary CT angiography plus standard of care or standard of care alone. Of the 887 randomised to coronary CT angiography, 767 completed their scan. In this sub-study, a total of 422 unselected consecutive scans were available from a quality assurance cohort from all participating centres, collected as part of an internal audit to ensure consistency of scan reporting (n=121), and every participant from the top five recruiting centres (Southampton [n=79], Plymouth [n=71], Edinburgh [n=61], Milton Keynes [n=49] and Reading [n=41]). We were unable to obtain the remaining 345 scans from the other 32 centres due to logistic, contractual and resource restrictions. The study was approved by local ethics committees, and written informed consent was received from all participants in line with the Declaration of Helsinki.

6.3.2 Coronary CT Angiography

All scans were performed on ≥64-slice multidetector row CT scanners as per the study protocol (NCT02284191).[112] The use of intravenous or oral beta-blockade for those with a heart rate >60 /min and sublingual glyceryl trinitrate was encouraged, where possible. Contrast-enhanced electrocardiogram (ECG) gated coronary CT angiography was performed in mid-diastole or end systole as per established techniques.[171]

6.3.3 Image Analysis

Coronary CT datasets were anonymised and exported in DICOM (Digital Imaging and Communications in Medicine) format to allow quantitative analysis of coronary plaque. Segments were defined manually as per Society of Cardiovascular Computed Tomography guidelines, using side branches to mark progression from proximal to distal segments.[132] Semi-quantitative scores were calculated including the segment involvement score (defined as the sum of the number of segments involved) and the segment stenosis score where each segment was given a score based on severity in a previously established technique.[195]

Plaque analysis was performed using semi-automated software (Autoplaque version 2.5, Cedars-Sinai Medical Centre, Los Angeles, USA) by a trained observer at a core laboratory, blinded to patient outcomes. This technique has been validated against intravascular ultrasound, is comparable across

differences in tube voltages or reconstruction algorithms and has excellent inter-scan reproducibility and observer agreements.[40, 79, 103, 130, 154]

Coronary centrelines were extracted using a semi-automated process. Stented segments and graft insertion points were excluded from analysis. Only coronary segments with visible disease were manually identified and analysed, including large (≥2 mm in diameter) branches. Segments with no disease did not undergo quantitative plaque analysis. Plaque constituents were automatically determined using scan-specific Hounsfield unit (HU) thresholds with manual adjustments when required (**Figure 1**). Low-attenuation plaque as a marker of necrotic core was defined by a fixed threshold of <30 HU.[130] Area stenosis was computed automatically and was defined as the maximal area of stenosis on a per-patient level. Plaque volume was measured in mm^3 for total, non-calcified, calcified, and low-attenuation plaque subtypes. To account for differences in patient size and coronary vessel volume, plaque burden was calculated by dividing the plaque volume by the vessel volume of the diseased segments analysed and multiplying by 100.[196]

6.3.4 Clinical outcomes and definitions

The primary endpoint of the RAPID-CTCA trial was a composite of all-cause death or subsequent non-fatal type 1 or 4b myocardial infarction at one year, measured as the time to the first event.[112] Index admission in-hospital events were excluded. Myocardial infarction was defined by the Third Universal

Definition and was adjudicated by two independent cardiologists blinded to the trial intervention.[151] Index revascularisation refers to those who underwent coronary revascularisation either by percutaneous coronary intervention or coronary artery bypass grafting during the index hospitalisation. Severity of disease was defined by the core laboratory as per Society of Cardiovascular Computed Tomography guidelines. Obstructive disease was defined as stenosis ≥70%, non-obstructive disease as stenoses between 10-69% and normal as ≤10%.[144]

6.3.5 Statistical analysis

Quantitative variables are presented as median [interquartile range] or mean ± standard deviation when normally distributed. Statistical significance was assessed using Pearson's Chi-squared test, Wilcoxon rank sum test and Fisher's exact test as appropriate. Outcome data were analysed using Cox proportional hazard regression and presented graphically with cumulative incidence plots for a high Global Registry of Acute Coronary Events (GRACE) score (>140) and presence of obstructive coronary artery disease. Cumulative incidence plots were also created for plaque burdens using the median plaque burden as the threshold for each of the total, non-calcified, calcified and low-attenuation plaque burden. Hazard ratios and 95% confidence intervals were calculated from the Cox model. Logistic regression was performed for individual patient characteristics.

Multivariable models were also constructed in a sensitivity analysis using *a priori* selection and adjusted for factors known to predict subsequent risk including GRACE score (which includes age, hemodynamic variables at presentation, creatinine, the presence of ST changes on ECG and elevated cardiac biomarkers) and presence of obstructive coronary artery disease. Total and subtypes of plaque burden were included in this model separately to avoid introducing collinearity into the model. Plaque burdens were log transformed for univariable and multivariable analysis (log_2 of 1 plus the plaque variable) to normalise the distribution of data and give hazard ratios per doubling of plaque variable. Statistically significance was defined as 2-sided P value <0.05. All statistical analysis was performed using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

6.4 RESULTS

6.4.1 Study population

Of the 422 scans available, 18 (4.3%) were excluded due to inadequate image quality. The study population (n=404) was representative of the overall trial population (**Table 6-1**) and comprised of middle-aged patients with a slight male preponderance and intermediate GRACE score (**Table 6-2**). Coronary CT angiograms were performed at a median of 4.2 hours from trial randomisation. At index hospitalisation, the three commonest discharge diagnoses were non-ST segment elevation myocardial infarction (38%), chest pain of uncertain aetiology (23%) and unstable angina (10%) (**Table 6-3**).

6.4.2 Coronary CT Angiography

Normal coronary arteries were identified in 71 patients (18%), non-obstructive coronary artery disease in 206 patients (51%), and obstructive coronary artery disease in 127 (31%). Coronary artery disease in 3 or more vessels was found in 155 patients (38%) and left main stem disease seen in 61 (15%). Across the entire population, the median total plaque burden was 37 [23-46] %, the median non-calcified plaque burden was 34 [21-41] %, the median calcified plaque burden was 1.31 [0-4.51] % and the median low-attenuation plaque burden was 2.48 [0.6-4.97] %.

Table 6-1: Comparison of total and sub-study populations of participants undergoing CT coronary angiography as part of the RAPID-CTCA trial

Characteristic	**Total RAPID-CTCA cohort** N = 767[1]	**RAPID-CTCA sub-study cohort** N = 404[1]	**p-value**[2]
Age (years)	61 [53 to 71]	63 [54 to 73]	0.2
Male	482 (63%)	259 (64%)	0.8
Diabetes	127 (17%)	57 (14%)	0.2
Hypertension	346 (45%)	180 (45%)	0.9
Hyperlipidaemia	308 (40%)	165 (41%)	0.8
Any smoking history	454 (61%)	79 (60%)	0.8
Previous myocardial infarction	159 (21%)	91 (23%)	0.5
Previous coronary stenting	99 (13%)	58 (14%)	0.8
Previous coronary artery bypass grafting	48 (6.3%)	24 (5.9%)	0.8
Computed tomography coronary angiogram findings			
Normal	178 (23%)	95 (24%)	0.8
Nonobstructive	222 (29%)	122 (30%)	
Obstructive	359 (47%)	187 (46%)	
GRACE Score	112 [90 to 137]	110 [88 to 137]	0.6

[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test
GRACE- Global Registry of Acute Coronary Events

Table 6-2: Baseline Characteristics	
Characteristic	**Overall** n = 404
Age (years)	63±12
Male	259 (64%)
Body-mass index (kg/m^2)	28.9 [25.3 to 31.7]
Current or ex-smoking habit	242 (60%)
Diabetes mellitus	57 (14%)
Hypertension	180 (45%)
Hyperlipidaemia	165 (41%)
Family history of coronary artery disease	136 (34%)
Previous myocardial infarction	91 (23%)
Previous coronary artery bypass grafting	24 (5.9%)
Previous percutaneous coronary intervention	58 (14%)
Cerebrovascular disease	17 (4.2%)
GRACE Score	114±36
Coronary computed tomography angiography	
Normal	71 (18%)
Non-obstructive coronary artery disease	206 (51%)
Obstructive coronary artery disease	127 (31%)
Coronary disease in 1 vessel only	64 (16%)
Coronary disease in 2 vessels	114 (28%)
Coronary disease in ≥3 vessels	155 (38%)
Left main stem disease	61 (15%)

Medication	
Aspirin pre-admission	95 (24%)
Statin pre-admission	117 (29%)
Statin therapy initiated (post CCTA)	175 (43%)
Dual-antiplatelet therapy initiated (post CCTA)	141 (35%)

Median [Interquartile range], Mean ± standard deviation, Number (%)

GRACE- Global Registry of Acute Coronary Events, CCTA- coronary computed tomography angiography

Table 6-3: Discharge Diagnosis

Diagnosis	Total N = 404[1]	Normal N = 71[1]	Non-obstructive N = 206[1]	Obstructive N = 127[1]
Non-ST-segment elevation myocardial infarction	155 (39%)	8 (11%)	68 (34%)	79 (62%)
Chest pain uncertain cause	94 (23%)	30 (42%)	56 (27%)	7 (5.5%)
Unstable Angina	38 (9.4%)	2 (2.8%)	20 (9.7%)	17 (13%)
Stable Angina	31 (7.7%)	2 (2.8%)	19 (9.2%)	10 (7.9%)
Musculoskeletal chest pain	21 (5.2%)	6 (8.5%)	12 (5.8%)	3 (2.4%)
Gastro-intestinal cause	18 (4.5%)	5 (7.0%)	10 (4.9%)	3 (2.4%)
Arrhythmia	11 (2.7%)	4 (5.6%)	6 (2.9%)	1 (0.8%)
Myocarditis	7 (1.7%)	4 (5.6%)	2 (1.0%)	1 (0.8%)
Pericarditis	4 (1.0%)	0 (0%)	3 (1.5%)	1 (0.8%)
Esophagitis	4 (1.0%)	2 (2.8%)	1 (0.5%)	1 (0.8%)
Anxiety	3 (0.7%)	2 (2.8%)	1 (0.5%)	0 (0%)
Heart Failure	3 (0.7%)	1 (1.4%)	1 (0.5%)	1 (0.8%)
Lower respiratory tract infection	3 (0.7%)	1 (1.4%)	1 (0.5%)	1 (0.8%)
Pulmonary embolism	3 (0.7%)	0 (0%)	3 (1.5%)	0 (0%)
Cardiomyopathy	2 (0.5%)	0 (0%)	2 (1.0%)	0 (0%)
Other	2 (0.5%)	2 (2.8%)	0 (0%)	0 (0%)
Pneumonia	2 (0.5%)	1 (1.4%)	0 (0%)	1 (0.8%)
Acute aortic syndrome	1 (0.2%)	0 (0%)	1 (0.5%)	0 (0%)
Aortic dissection	1 (0.2%)	0 (0%)	0 (0%)	1 (0.8%)
Hypertensive heart disease	1 (0.2%)	1 (1.4%)	0 (0%)	0 (0%)

Patients with a lower GRACE score had a lower burden of total, non-calcified, calcified, and low-attenuation plaque (**Table 6-4**). Patients with non-obstructive coronary artery disease had a lower burden of total, non-calcified and low-attenuation plaque but similar calcified plaque burden compared to those with obstructive coronary artery disease (**Table 6-4**). Patients who underwent coronary revascularisation during their index hospitalisation had higher burdens of all plaque variables (**Table 6-4**).

6.4.3 Primary Events

In total, there were 25 primary endpoint events (**Table 6-5**). Patients who had a subsequent event were of a similar demographic and had equivalent distribution of co-morbidities except for hypertension, which occurred more frequently when compared to those who did not (**Table 6-6**). In those who had a primary event, the GRACE score was higher, but the presence of obstructive coronary artery disease, and higher semi-quantitative measures of plaque burden (segment involvement score and segment stenosis score) were of borderline statistical significance. In patients who did and did not experience a primary event, the total plaque burden was 46 [95% interquartile range 43-50] % versus 36 [95% interquartile range 21-46] % and the non-calcified plaque burden was 41 [95% interquartile range 37-47] % versus 33 [95% interquartile range 20-41] % ($p<0.001$ for both). Low-attenuation plaque burden was nearly double in patients who had an event compared to those who did not (4.22 [95% interquartile range 3.30-5.68] % versus 2.14 [95% interquartile range 0.50-

4.88] % **Table 6-6; Figure 6-1**). Plaque volume measurements were also distributed similarly.

Table 6-4: Plaque burden in patients stratified by GRACE score, obstructive coronary artery disease and index coronary revascularisation

Variable	Plaque burden subtypes			
	Total plaque burden (%)	**Non-calcified plaque burden (%)**	**Calcified plaque burden (%)**	**Low-attenuation plaque burden (%)**
All patients (n=404)	37 [23 to 46]	34 [21 to 41]	1.31 [0 to 4.51]	2.48 [0.60 to 4.97]
GRACE score				
<140 (n=311)	36 [19 to 45]	33 [17 to 41]	1.00 [0.00 to 3.89]	2.20 [0.43 to 4.78]
≥140 (n=93)	41 [31 to 49]	37 [26 to 43]	3.04 [0.71 to 6.71]	3.14 [1.16 to 5.52]
***P* value**	<0.001	0.004	<0.001	0.015
Coronary Computed Tomography Angiography				
Non-obstructive* (n=206)	36 [29 to 43)	32 [25 to 38]	1.90 [0.60 to 4.91]	1.94 (1.02, 3.74)
Obstructive (n=127)	48 [42 to 52]	42 [38 to 48]	2.81 [0.81 to 5.32]	5.08 [3.44 to 6.60]
***P* value**	<0.001	<0.001	0.14	<0.001
Index Coronary Revascularisation				
No coronary revascularisation (n=259)	31 [0 to 41]	29 [0 to 37]	1.00 [0.00 to 4.10]	1.37 [0.00 to 3.38]
Coronary revascularisation (n=145)	45 [37 to 50]	40 [35 to 46]	2.32 [0.41 to 4.82]	4.49 [2.73 to 6.23]
***P* value**	<0.001	<0.001	<0.001	<0.001

Median [interquartile range]; Wilcoxon rank sum test; Pearson's Chi-squared test
*Non-obstructive does not include scans reported as “Normal”.
GRACE, Global Registry of Acute Coronary Events

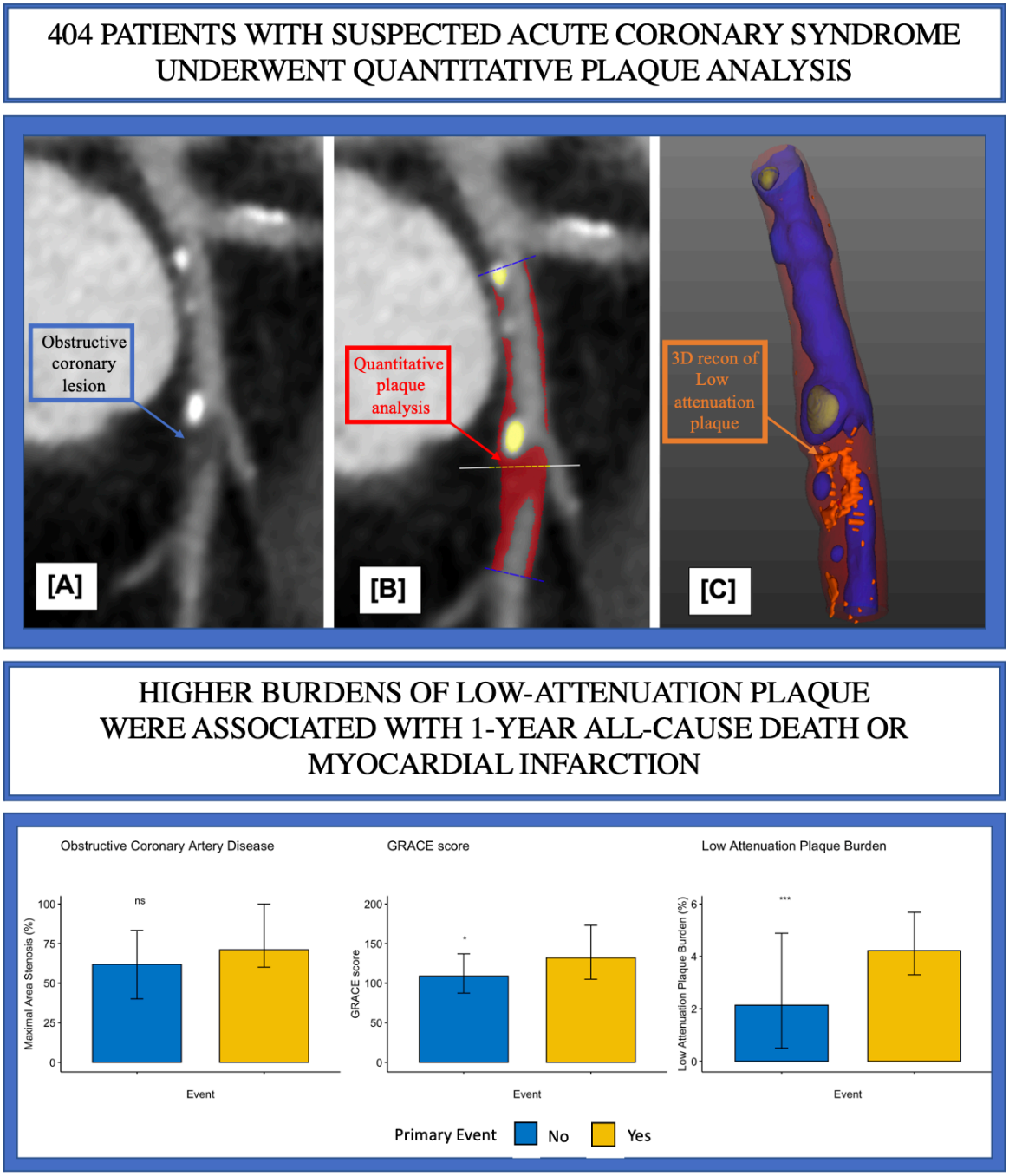

Figure 6-1: Graphic Summary. Case example high burden of low attenuation plaque on coronary CT angiography quantitative plaque analysis. Diseased proximal and occluded mid segment of left anterior descending artery. **[A]** CT curved planer reformation, **[B]** quantitative plaque analysis and **[C]** 3D quantitative plaque analysis demonstrating a high burden of low attenuation (orange) and non-calcified plaque (red) with small amounts of calcification (yellow). Performed using Autoplaque (Cedars Sinai Medical Centre, LA). Clinical events were not associated with presence of obstructive coronary artery disease, had a modest association with the GRACE score and a strong association with low-attenuation plaque burden. ns- not significant, * $p<0.05$, *** $p<0.001$.

Table 6-5: Clinical Events				
	Overall N = 404[1]	**Normal CT** N = 71[1]	**Non-obstructive disease** N = 206[1]	**Obstructive disease** N = 127[1]
Primary outcome	25 (6.2%)	0 (0%)	13 (6.3%)	12 (9.4%)
Death	9 (2.2%)	0 (0%)	4 (1.9%)	5 (3.9%)
Cardiovascular Death	6 (1.5%)	0 (0%)	3 (1.5%)	3 (2.4%)
Non-cardiovascular Death	3 (0.7%)	0 (0%)	1 (0.5%)	2 (1.6%)
Adjudicated MI type 1 & 4b	18 (4.5%)	0 (0%)	9 (4.4%)	9 (7.1%)
Adjudicated MI type 1	18 (4.5%)	0 (0%)	9 (4.4%)	9 (7.1%)
Index Revascularisation	145 (36%)	4 (5.6%)	57 (28%)	84 (66%)
Representation with suspected ACS	67 (17%)	6 (8.5%)	33 (16%)	28 (22%)

[1] n (%)
MI- Myocardial infarction, ACS- Acute coronary syndrome, CT- computed tomography

Table 6-6: Variables by Primary Endpoint			
Variable	**Primary Endpoint**		
	No Event N = 379	**Event** N = 25	**p-value**
Age (years)	62±12	68±15	0.12
Male	242 (64%)	17 (68%)	0.7
Body-mass index (kg/m^2)	27.9 [25.3 to 31.7]	29.7 [23.8 to 31.4]	>0.9
Current or ex-smoking habit	225 (59%)	17 (68%)	0.2
Diabetes mellitus	55 (15%)	2 (8.0%)	0.6
Hypertension	164 (43%)	16 (64%)	0.043
Hyperlipidaemia	154 (41%)	11 (44%)	0.7
Family history of coronary artery disease	130 (34%)	6 (24%)	0.3
Previous myocardial infarction	86 (23%)	5 (20%)	0.8
Previous coronary artery bypass grafting	23 (6.1%)	1 (4.0%)	>0.9
Previous percutaneous coronary intervention	57 (15%)	1 (4.0%)	0.2
Cerebrovascular disease	14 (3.7%)	3 (12%)	0.080
GRACE score	113 ± 35	134 ± 44	0.012
Index coronary revascularisation	134 (35%)	11 (44%)	0.4
Coronary computed tomography angiography variables			
Obstructive coronary artery disease	115 (30%)	12 (48%)	0.065
Left main stem disease	58 (15%)	3 (12%)	>0.9
Segment involvement score (SIS)	3 [1 to 5]	5 [2 to 6]	0.057
Segment stenosis score (SSS)	5 [2 to 9]	7 [4 to 10]	0.065
Plaque subtype			
Total plaque burden	36 [21 to 46]	46 [43 to 50]	<0.001

Non-calcified plaque burden	33 [20 to 41]	41 [37 to 47]	<0.001
Calcified plaque burden	1.22 [0.00 to 4.41]	2.70 [0.81 to 7.30]	0.057
Low-attenuation plaque burden	2.14 [0.50 to 4.88]	4.22 [3.30 to 5.68]	<0.001
Total plaque volume	413 (112, 910)	874 (453, 1,299)	0.005
Non-calcified plaque volume	379 (103, 796)	707 (450, 1,228)	0.006
Calcified plaque volume	15 (0, 74)	49 (4, 180)	0.043
Low-attenuation plaque volume	27 (4, 83)	63 (38, 113)	0.002

Median [interquartile range]; mean ± standard deviation; n (%), Wilcoxon rank sum test; Pearson's Chi-squared test
GRACE, Global Registry of Acute Coronary Events

A GRACE score of >140 was associated with the primary event (hazard ratio 3.8 [95% confidence interval 1.45-6.98], p=0.004; **Figure 6-2 [A]**). However, the presence of obstructive coronary artery disease (hazard ratio 2.07 [95% confidence interval 0.94-4.53], p=0.065; **Figure 6-2 [B]**) was not associated with the primary event. Comparing patients with plaque burdens above or below the median, the primary endpoint was substantially more frequent in patients with higher plaque burdens of all sub-types except calcified plaque (**Figure 6-3**).

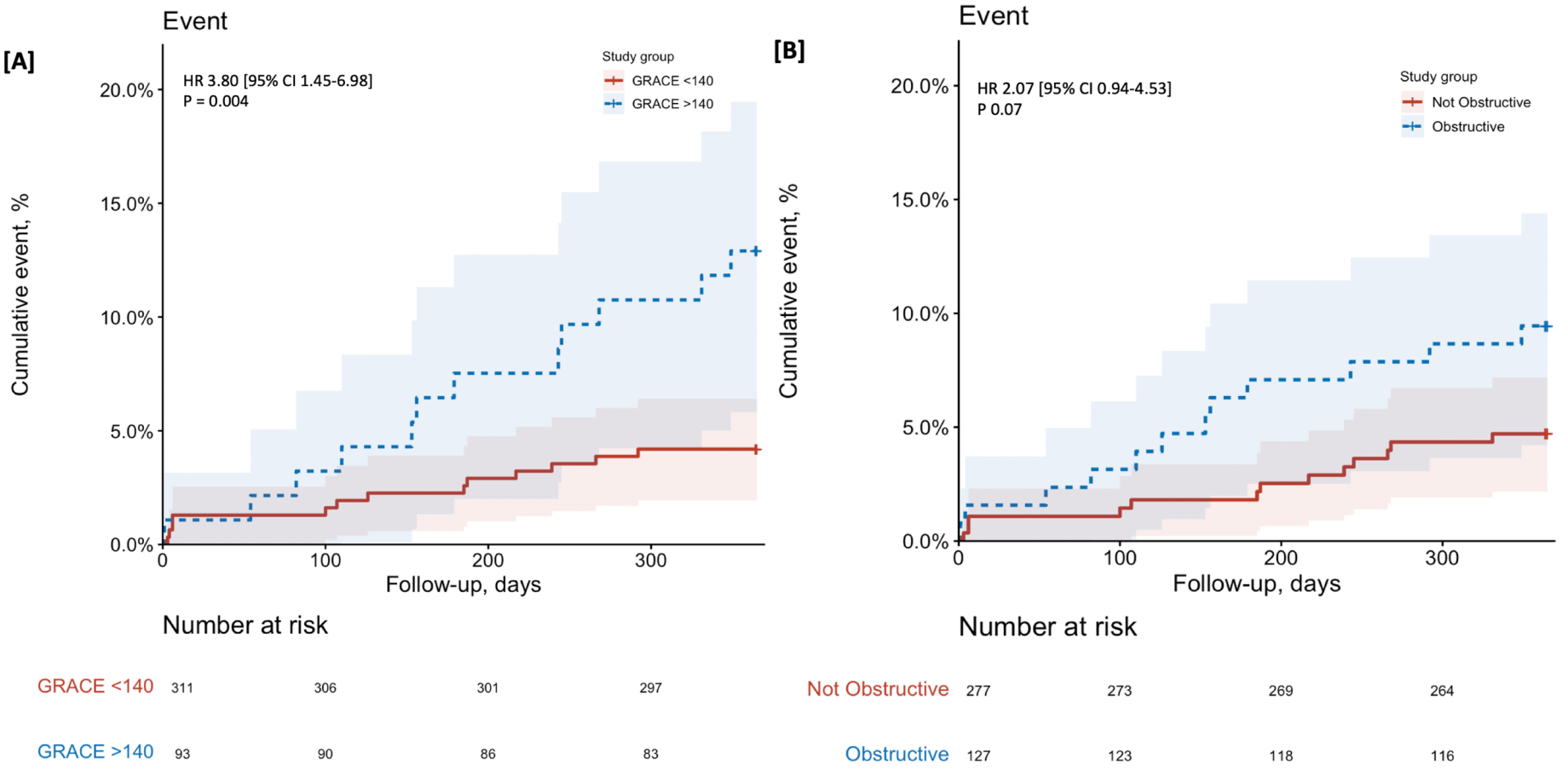

Figure 6-2: GRACE score, presence of obstructive disease and primary endpoint. **[A]** Cumulative incidence of death or recurrent non-fatal myocardial infarction in patient with a low (≤140) and high (140) GRACE score. **[B]** Cumulative incidence of death or recurrent non-fatal myocardial infarction in patient with and those without obstructive disease on coronary CT angiography. HR – Hazard ratio.

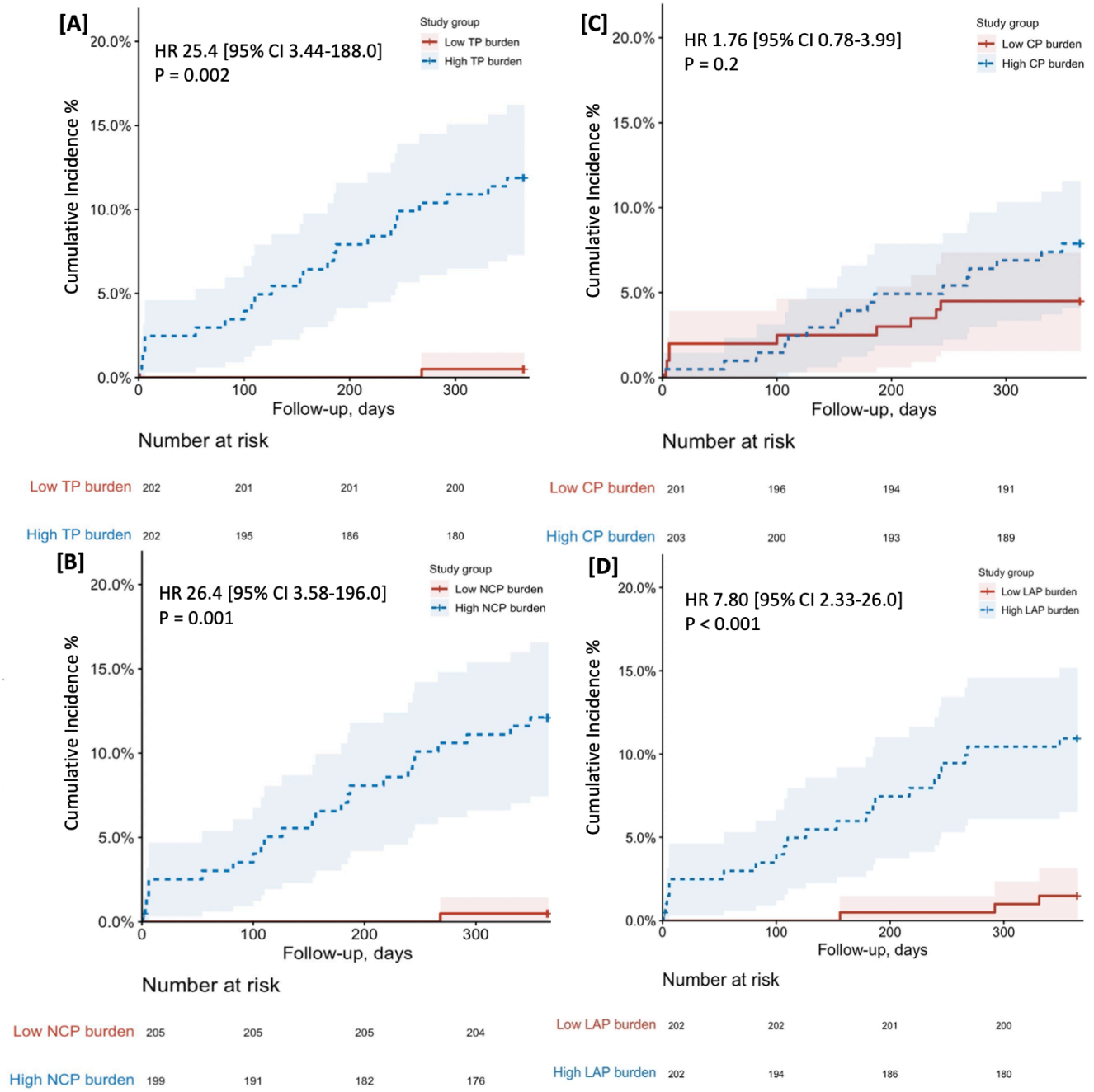

Figure 6-3: Plaque burden and the primary endpoint. Cumulative incidence of the primary endpoint in patient with plaque burden above and below the threshold of median plaque burden in **[A]** total (37%), **[B]** non-calcified (34%), **[C]** calcified (1.3%) and **[D]** low attenuation (2.5%) plaque. CP – Calcified plaque, LAP – low attenuation plaque, HR – Hazard ratio, NCP – Non-calcified plaque, TP – Total plaque.

In univariable analysis, age and hypertension were associated with an increased risk of the primary endpoint. The GRACE score (which includes age, hemodynamic measures, ST changes on ECG as well as elevated cardiac biomarkers) and total, non-calcified and low-attenuation plaque burden were all associated with an increased risk of the primary endpoint (**Table 6-7**). In a sensitivity analysis, total, non-calcified and low-attenuation plaque burden had independent prognostic value in multivariable models adjusting for GRACE score >140 and the presence of obstructive coronary artery disease (**Table 6-8**). The association did not change when male sex and revascularisation at index presentation were included in the model (**Tables 6-9**). Semi-quantitative measures including the segment involvement score and segment stenosis score were not associated with the primary endpoint.

Table 6-7: Univariable analysis

Variable	Odds Ratio	95% Confidence Interval	p-value
Age per 10-year increase	1.45	1.03 to 2.08	0.037
Male	1.20	0.52 to 3.02	0.7
Hypertension	2.33	1.02 to 5.63	0.049
Hyperlipidaemia	1.15	0.50 to 2.59	0.7
Diabetes Mellitus	0.51	0.08 to 1.80	0.4
Smoking	1.32	0.47 to 3.26	0.6
Family history of coronary artery disease	0.60	0.22 to 1.47	0.3
Previous myocardial infarction	0.85	0.28 to 2.18	0.8
Previous coronary artery bypass grafting	0.24	0.01 to 1.15	0.2
Previous percutaneous coronary intervention	0.64	0.04 to 3.28	0.7
Cerebrovascular disease	3.56	0.78 to 11.9	0.059
Obstructive coronary artery disease	2.12	0.93 to 4.81	0.071
Index coronary revascularisation	1.44	0.62 to 3.25	0.4
Discharge diagnosis of ACS	2.01	0.88 to 4.85	0.10
GRACE score ≥ 140	3.40	1.47 to 7.77	0.004
Segment involved score	1.12	0.98 to 1.29	0.10
Segment severity score	1.06	0.98 to 1.14	0.13
SIS score 1-2 (Mild)	1.55	0.58, 3.70	0.3
SIS score 3-4 (Moderate)	0.58	0.17, 1.56	0.3
SIS score 5-7 (Extensive)	2.08	0.88, 4.74	0.09

SIS score ≥8 (Very Extensive)	1.61	0.45, 4.50	0.4
*Total plaque volume	1.35	1.10, 1.82	0.017
*Non-calcified plaque volume	1.36	1.11, 1.86	0.017
*Calcified plaque volume	1.16	1.00, 1.35	0.049
*Low-attenuation plaque volume	1.40	1.15, 1.80	0.003
*Total plaque burden	9.34	2.50 to 43.4	0.002
*Non-calcified plaque burden	8.56	2.37 to 38.5	0.003
*Calcified plaque burden	1.33	0.98 to 1.79	0.063
*Low-attenuation plaque burden	2.19	1.43 to 3.58	<0.001
[1] OR = Odds Ratio, CI = Confidence Interval, ACS = acute coronary syndrome			

Table 6-8: Multivariable analysis for the primary endpoint

Characteristic	**Multivariable HR[1]**	**95% CI[1]**	**p-value**
Segment involvement score	1.04	0.89 to 1.21	0.6
Segment stenosis score	1.01	0.92 to 1.11	0.8
*Total plaque burden	8.70	2.30 to 33.0	0.001
*Non-calcified plaque burden	10.7	2.44 to 47.3	0.002
*Calcified plaque burden	1.18	0.87 to 1.60	0.3
*Low-attenuation plaque burden	2.13	1.31 to 3.47	0.002

HR = Hazard ratio, CI = Confidence interval
*LOG transformed (Log base 2, HR per doubling of variable)
Multivariable models including individual variables adjusted for GRACE score >140 and presence of obstructive coronary artery disease.
GRACE (Global Registry of Acute Coronary Events score includes age, heart rate, blood pressure, creatinine, ST changes on ECG and elevated cardiac enzymes).

Table 6-9: Example Multivariable Models				
	Variable	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Model 1	Male	0.67	0.28 to 1.60	0.4
	Grace score ≥ 140	2.38	1.07 to 5.30	0.033
	Obstructive coronary disease	0.77	0.32 to 1.85	0.6
	Index revascularisation	0.79	0.34 to 1.80	0.6
	*Total plaque burden	10.1	2.63 to 38.9	<0.001
Model 2	Male	0.79	0.33 to 1.87	0.6
	Grace score ≥ 140	2.53	1.14 to 5.61	0.022
	Obstructive coronary disease	0.67	0.27 to 1.68	0.4
	Index revascularisation	0.70	0.30 to 1.64	0.4
	*Non-calcified plaque burden	12.5	2.75 to 57.0	0.001
Model 3	Male	0.92	0.37 to 2.28	0.9
	Grace score ≥ 140	2.71	1.21 to 6.09	0.016
	Obstructive coronary disease	1.63	0.67 to 3.96	0.3
	Index revascularisation	1.08	0.46 to 2.54	0.9
	*Calcified plaque burden	1.18	0.87 to 1.62	0.3
Model 4	Male	0.75	0.31 to 1.81	0.5
	Grace score ≥ 140	2.66	1.20 to 5.92	0.016
	Obstructive coronary disease	0.85	0.34 to 2.17	0.7
	Index revascularisation	0.77	0.33 to 1.82	0.6
	*Low-attenuation plaque burden	2.28	1.38 to 3.78	0.001

*LOG transformed (Log base 2, HR per doubling of variable)
GRACE (Global Registry of Acute Coronary Events) score includes: Age, heart rate, blood pressure, creatinine, ST changes on ECG and elevated cardiac enzymes).

6.5 DISCUSSION

In patients with acute chest pain, we have demonstrated that plaque burden identifies patients at risk of death or subsequent non-fatal myocardial infarction. These associations are stronger than for traditional predictors of future cardiovascular events, such as GRACE score or the presence of obstructive coronary artery disease. Our findings indicate that quantitative CT plaque analysis may be better able to predict one-year risk beyond the index hospitalisation and thereby guide clinical management.

The GRACE score was developed from an international registry and has been well validated across multiple cohorts of patients with acute coronary syndrome across the world.[197],[198] It is an integral component of many major guidelines for risk stratification of patients with acute coronary syndrome.[29, 190, 191] In our study, a higher GRACE score was associated with larger plaque burdens which may, in part, explain its prognostic value. However, we observed that 13 of the 25 primary endpoints occurred in patients with a GRACE score less than the accepted 'high-risk' threshold of 140.[29] Indeed, total, non-calcified and low-attenuation plaque burden were more precise predictors of future events compared to the GRACE score.

Identifying obstructive disease on coronary CT angiography has been associated with long-term risk of death or subsequent myocardial infarction and is often used to direct clinical management.[71, 199] In our cohort, those with

obstructive disease unsurprisingly had a higher burden of total, non-calcified and low-attenuation plaque. However, unlike plaque burden, the presence of obstructive disease, segment involvement score and the segment stenosis score failed to predict the primary endpoint. There are two potential and independent reasons for these findings. First, the coronary CT angiogram was performed at the initial presentation and before coronary revascularisation decisions were made. Consequently, many patients with obstructive disease will have gone on to have coronary revascularisation, potentially modifying the subsequent risk of events.[200] Second, and perhaps more importantly, the majority of recurrent events occurred in patients with non-obstructive coronary disease, which is consistent with previous findings.[73] Thus, given current management and treatment strategies for patients with acute chest pain, the relatively poor performance of obstructive disease and coronary revascularisation is not unexpected and underlines the importance of more relevant measures for subsequent downstream risk stratification, such as the burden of atherosclerotic coronary artery disease.

Several previous studies have assessed plaque burden in patients presenting with acute chest pain.[201] In the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) I and II trials, quantitative plaque analysis was performed on 368 and 260 patients suspected of having acute coronary syndrome respectively.[92, 93] These studies demonstrated that patients presenting with acute coronary syndromes had a high prevalence of low-attenuation plaque, particularly in lesions with the most severe stenosis. More

recently, de Knegt and colleagues performed quantitative plaque analysis in patients from three studies presenting with different symptoms.[96] In these unmatched cohorts, plaque volumes progressively increased in the three separate populations of patients from an asymptomatic screening cohort, patients with acute chest pain without acute coronary syndrome, and patients with acute coronary syndrome. In contrast, we have assessed plaque burden across a range of presentations in a single cohort, and for the first time provide information on the downstream prognostic implications of quantitative plaque analysis.

The long-term prognostic value of plaque quantification has been previously established in patients with stable coronary artery disease. Nadjiri and colleagues first demonstrated the incremental prognostic value of low-attenuation plaque over the cardiovascular risk score and coronary artery calcium score.[94] Subsequently, we demonstrated that low-attenuation plaque burden was superior to risk scores, coronary artery calcium and the severity of coronary artery stenosis for predicting the risk of future myocardial infarction.[97] Our current findings indicate that in patients with acute chest pain, total, non-calcified and low-attenuation plaque burden also predict risk of death or future myocardial infarction. The hazard ratio for the primary endpoint for total and non-calcified plaque burden were higher than that of low-attenuation plaque burden, but the 95% confidence intervals were much wider. This likely reflects the relative imprecision in the measurements of total and non-calcified plaque burden over low-attenuation plaque burden. Moreover, the proportional

differences in plaque burden between patients with and without the primary endpoint is striking. Patients who went on to have subsequent events had nearly double the burden of low-attenuation plaque compared to those who did not. These observations suggest that consistent with our previous findings, low-attenuation plaque is a particularly important predictor of future events. It also confirms prior observational data that calcified plaque represents a quiescent and stable form of coronary atherosclerosis which does not predict one-year events in this population of patients.[81, 202]

We should acknowledge several limitations of our study. Although plaque analysis is semi-automated, it can be time consuming particularly when there is a high burden of coronary disease, taking up to 30 min in the most severe cases. Adoption of further automation and machine learning would help facilitate more widespread clinical use. Whilst we did not have access to all trial scans, we included over half the study population which was representative of the overall trial population (**Table 1**) and incorporated scans from every centre that recruited to the trial as well as every scan from the top 5 recruiting centres. Moreover, we were able to centralise the image analysis in a single core laboratory which was performed blind to the clinical diagnosis and trial outcome data. Importantly, our primary endpoint was adjudicated by an independent endpoint adjudication committee. We also acknowledge the modest number of clinical events which limits our ability to adjust for other confounding factors, suggesting further prospective validation of our findings is warranted. Finally, our findings were present despite the initiation of new

treatments, including pharmacotherapies and coronary revascularisation. This will have impacted on the frequency of subsequent clinical events. However, we would suggest that such interventions are likely to have made our findings conservative and enhance their clinical applicability for on-treatment risk prediction.

6.6 CONCLUSION

In conclusion, this analysis represents the largest single cohort of patients who had quantitative plaque analysis after early coronary CT angiography for suspected acute coronary syndrome.[203] We present the first report on the prognostic value of plaque quantification in those who present acutely with undifferentiated chest pain. Our findings establish that quantitatively assessed measures of plaque burden predicts future myocardial infarction or death independent of both the GRACE score or the presence of obstructive coronary disease in patients with and without acute coronary syndromes.

7 CHAPTER 7: Conclusions and Future Directions

Includes extracts and adaptations from:

Meah, MN *et al*. Clinical relevance of coronary computed tomography angiography beyond coronary artery stenosis. ROFO. 2021;193(10):1162-1170

7.1 SUMMARY OF FINDINGS

Despite technological advances in the field of computed tomography coronary angiography, the mainstay of routine clinical practice continues to focus on invasive coronary angiography and so-called 'lumenography'. Plaque quantification and characterisation represents a significant advance in our ability to gain additional clinically relevant information. Quantification of plaque subtypes has improved the assessment of coronary plaque on CT. Quantitatively assessed low-attenuation plaque in patients with stable symptoms, has demonstrated superiority over stenosis severity and coronary calcium score in predicting subsequent myocardial infarction. However, its utility in patients who present acutely to the hospital with chest pain is less well delineated.

The principal aim of this thesis was to find innovative uses for plaque quantification in patients who present to the hospital with suspected acute coronary syndromes.

7.1.1 Can we quantify plaque in patients with advanced coronary disease?

The repeatability and reproducibility of semi-automated plaque quantification has previously been shown to be good in patients with minor coronary disease.[172] However, as disease burden increases, particularly as calcified

plaque burden rises, its reliability was unclear. In our scan-rescan study of patients with advanced coronary artery disease, we demonstrated that plaque volume could be quantified precisely using semi-automated analysis software. Intraobserver, interobserver and interscan agreement was excellent, suggesting that this technique remains a robust and reproducible method to measure both disease burden and composition even in patients with advanced coronary disease. This validates the use of quantitative plaque analysis in patient cohorts likely to have a higher burden of coronary disease such as those presenting to the Emergency Department with acute chest pain.

7.1.2 High-sensitivity cardiac troponin and quantitative plaque analysis.

In patients who present to hospital with chest pain and have had myocardial infarction excluded, high-sensitivity cardiac troponin I concentrations above the risk stratification threshold of 5 ng/L have a greater risk of future adverse cardiovascular events. The reasons for this are unclear and previous studies established that even patients with a troponin <5 ng/L could have coronary disease. We demonstrated marked differences in the burden and composition of plaque between patients with a high-sensitivity troponin concentration above or below 5 ng/L. Most striking was the independent association between low-attenuation plaque burden and high-sensitivity cardiac troponin I. Quantitative plaque analysis in this setting provided mechanistic insights into the worse prognosis of patients with troponin concentrations above 5 ng/L. These observations could help to risk stratify patients with acute chest pain but without myocardial infarction.

7.1.3 Plaque composition in patients with type 1 and type 2 myocardial infarction

Distinguishing type 1 from type 2 myocardial infarction remains a major clinical challenge that is essential to direct patient management. To determine the differences in plaque composition in patients with these two distinct pathologies, we recruited patients from two prospective clinical studies who were admitted to hospital with acute chest pain. We demonstrated marked differences in coronary plaque burden between patients with type 1 and type 2 myocardial infarction. Low-attenuation plaque burden provided strong discrimination, independent of the severity of coronary stenosis or clinical characteristics. Quantitative plaque analysis could therefore help differentiate between type 1 and type 2 myocardial infarction, potentially informing the management of patients with myocardial infarction of uncertain aetiology.

7.1.4 Prognostic value of plaque quantification in patients with acute chest pain

Despite advances in clinical management, there remains a considerable burden of subsequent cardiovascular events in patients presenting with acute chest pain. We determined the prognostic value of coronary plaque burden in this patient population, for the primary endpoint of one-year death or subsequent type 1 or 4b myocardial infarction. We demonstrated that total, non-calcified and low-attenuation plaque burdens are major predictors of one-year all-cause death or subsequent non-fatal myocardial infarction. In

particular, low-attenuation plaque burden outperformed traditional measures of future risk including the GRACE score and the presence of obstructive coronary artery disease. In patients who presented acutely with chest pain, with and without myocardial infarction, quantifying the burden of plaque incrementally improves the risk stratification of this already high-risk population and could therefore assist in the administration of aggressive preventative therapies.

The burden of low-attenuation plaque has significant value in understanding the diagnosis and prognosis of patients who attend hospital with acute chest pain. Taken together, these studies lay the foundation for important future trials and help shift the focus from the status quo of determining severity of stenosis in the diagnosis, risk stratification and management of patients with coronary artery disease.

7.2 FUTURE DIRECTIONS

7.2.1 Radiomics & machine learning in plaque analysis

Fundamentally radiological images are large 3-dimensional vaults of data, with each voxel representing unique tissue dependent measurements. As we image structures in higher resolution, these datasets have grown exponentially in size, providing us with ever increasing quantities of information. Radiomics aims to extract further information from these datasets by using mathematical techniques to extract higher dimension data such as spatial interrelationships and textural information. Machine learning, a branch of artificial intelligence, can be used to mine these datasets to identify radiomic patterns associated with increased risk of cardiac events. Kolossvary *et al* showed that radiomic features can identify high-risk plaques with diagnostic accuracy similar to that of IVUS and 18F-sodium fluoride PET and better than with visual assessment alone.[204]

There are numerous applications of both supervised and unsupervised machine learning in CCTA, including the identification and quantification of atherosclerotic plaque. The identification of calcified plaque on CT using deep learning has been widely studied, particularly on non-contrast images, but the automatic identification of non-calcified and high-risk plaque subtypes is more challenging.[205] Recently a deep learning algorithm that identified CCTA without calcification has been proposed as a method to help prioritise work lists.[206] Further advancements in machine learning to automate plaque analysis aim

to reduce the time to perform this analysis and increase its application in clinical practice. Indeed, a recent deep learning system provided rapid quantitative measurements of plaque volume and stenosis severity from CCTA that shared excellent agreement with both expert readers and intravascular ultrasound.[207] This system was externally validated against the DIAMOND plaque analysis conducted as part of this body of works. This work is crucial as a key limitation of plaque analysis is its time-consuming nature. Machine learning may be able to automate this process, thereby making widespread use in clinical practice more viable.

7.2.2 Other applications for radiomics & machine learning

Machine learning techniques can also be used to analyse the complex interactions between multiple parameters in large datasets. For example, when machine learning was used to combined clinical and CCTA data from the CONFIRM registry, it performed better than clinical risk scores (Framingham) and CCTA severity scores (SIS and SSS) at predicting all-cause mortality.[208] Machine learning has been used to integrate quantitative CCTA plaque metrics including plaque measurements, diameter stenosis, and contrast density difference data (maximal difference in luminal attenuation per unit area), and is better at predicting ischaemia by fractional flow reserve than any other individual measure.[133] In another example, a machine learning model combined clinical data with quantitative plaque analysis measures and ^{18}F-sodium fluoride PET uptake with the result being a substantial

improvement in the ability to predict the primary outcome of fatal or non-fatal myocardial infarction.[209]

Thus, the potential applications of machine learning include precision diagnostics, automated risk stratification and reduced healthcare costs by saving clinicians' valuable time. At present, the clinical applications are limited, but machine learning is an exciting avenue for future research and is likely to become an integral part of clinical practice over the coming decades.

7.2.3 Diagnostic utility of plaque quantification for 'those in the middle'

Contemporary medical practice uses clinical symptoms and high-sensitivity cardiac biomarkers to divide patients with coronary artery disease into stable and unstable populations. However, there remains a major overlap between these diagnoses due to the inherent limitations of internationally accepted diagnostic algorithms which have focused on accelerating the management of patients who present acutely with chest pain. Primarily this has been achieved by using pathways which centre around 'rule-in' and 'rule-out' high-sensitivity cardiac troponin thresholds. However, there remains considerable uncertainty on what should be done for those 'in the middle' between these two thresholds who are often assigned to the observation zone of cardiac troponin concentration.[29] For the most part, once myocardial infarction is ruled out, most patients are discharged from hospital without further investigation or treatment, even though a substantial proportion may subsequently suffer myocardial infarction. By ignoring those in this observation zone, we are not using high-

sensitivity cardiac troponin to its full potential.[25-27, 32] These intermediate patients represent one in three of all patients without myocardial infarction and are up to ten times more likely to have a major cardiac event at 1 year compared to those with a low cardiac troponin concentration.[25]

Very few studies have examined the role of CT coronary angiography in the present era of high-sensitivity cardiac troponins. Ferencik *et al* demonstrated that the use of plaque characterisation reduced the number of patients classified to the intermediate risk category by almost half when compared to traditional CT assessment based on luminal stenosis.[91] However, the findings of this study are limited by its observational design. To this end, the TARGET-CTCA trial (NCT03952351) aims to recruit patients from Emergency Departments in whom myocardial infarction has been excluded, but who have a high-sensitivity cardiac troponin I concentration above 5 ng/L and prospectively randomise them to CT coronary angiography or standard of care alone. Patients in the CT arm with coronary disease would receive advice to commence preventative therapies and those with obstructive coronary disease would receive routine outpatient review by a Cardiologist. The question this study seeks to answer is: can the use of high-sensitivity troponin testing guide computed tomography coronary angiography and thereby improve our ability to diagnose patients in the unstable spectrum of coronary artery disease who would otherwise have been labelled as “not myocardial infarction”? Crucially there is a plan to validate our findings from the PRECISE-CTCA study on the diagnostic value of plaque burden in this patient cohort.

There are also two additional studies, the Coronary CT Angiography for Improved Assessment of Suspected Acute Coronary Syndrome With Inconclusive Diagnostic Work-up (COURSE; ClinicalTrials.gov identifier, NCT03129659) and the Prospective RandOmised Trial of Emergency Cardiac CT (PROTECCT; ClinicalTrials.gov identifier, NCT03583320) which together will determine whether CTCA can help clarify the diagnosis in patients with a 'non-diagnostic' cardiac troponin concentration. COURSE aims to determine the accuracy with which coronary CT angiography can identify non-ST segment elevation myocardial infarction. While it currently is focusing on the presence of obstructive coronary disease to test its hypothesis, there are plans to assess plaque characterisation. PROTECCT will seek to understand the impact of coronary CT angiography on the speed of clinical decision making by randomising patients who attend the Emergency Department with chest pain with an intermediate troponin concentration to a standard care and CT angiography or standard care alone. It will take the novel approach of consenting patients in the control arm to also undergo coronary CT angiography however the result of CT will not form a part of their in-patient clinical management, with the clinical team being blinded to the findings. In doing so, a true like-for-like comparison can be made in terms of length of hospital stay, down-stream management, health economics and rates of relevant clinical outcomes.

7.2.4 Other diagnostic uses for plaque quantification

Low-attenuation plaque has clear potential to identify patients at high risk of future cardiac events both in the acute and stable populations. In the stable angina population, low-attenuation plaque may identify those with high-risk disease that warrant more intensive or urgent treatment. In acute patients who have had myocardial infarction excluded by use of high-sensitivity cardiac biomarkers, low-attenuation plaque may help identify a high-risk subgroup. The presentations of coronary artery disease, though divided into acute (myocardial infarctions) and chronic (stable angina) are less dichotomous and better presented as a spectrum of severity. Historically a group in the middle labelled as “unstable angina” would capture this cohort but high-sensitivity cardiac biomarkers have led to the diagnosis being infrequently and inconsistently applied. However, his cohort were often included in landmark trials that demonstrated the prognostic benefit on treatments such as dual-antiplatelet therapy. Prospective randomised trials should seek to determine whether plaque quantification could be used to assist in the diagnosis and perhaps even the re-defining of ‘unstable angina’ and determine whether intensive medical therapy is appropriate in this patient population.

The era of high-sensitivity cardiac biomarkers has led to a reduction in the diagnostic specificity for type 1 myocardial infarction. This ‘noise’ often takes the form of myocardial injury and type 2 myocardial infarction. The RAPID-CTCA trial demonstrated the frequency with which coronary artery disease is detected, even in patients who have not had type 1 myocardial infarction. In

addition to 'ruling-in' patients who warrant intensive medical therapies, another implication of plaque imaging is the potential to categorise the pathophysiological mechanisms that have led to a rise in cardiac troponin. Plaque characterisation could assist in reducing the noise created by high-sensitivity cardiac biomarkers because if there is no low-attenuation plaque, type 1 myocardial infarction is less likely to have occurred. At present, we use scores such as the GRACE or TIMI score to determine the risk of adverse cardiac events and guide the application of invasive angiography with a view to revascularisation. However, these scores are imperfect, subject to clinician error and specific to circumstances (for example GRACE score is specific to suspected acute coronary syndromes). Moreover, they become significantly less useful in patients who are known to have coronary artery disease.[39] By contrast, low-attenuation plaque has now demonstrated an association with future events, regardless of presentation and presence of coronary artery disease.

Our studies demonstrate that patients at risk of, or suffering from, type 1 myocardial infarction have unique plaque characteristics that may be of use in reducing the misclassification and misdiagnosis of patients. We have shown how this could potentially be used to differentiate between type 1 and type 2 myocardial infarction. It may be helpful in other clinical conundrums, such as that of myocardial infarction in the absence of obstructive coronary disease (MINOCA). International guidelines often recommend invasive coronary imaging such as IVUS to determine whether plaque disruption has

occurred.[210, 211] There may be multiple situations where assessment with quantitative plaque analysis and determining the presence and burden of low-attenuation plaque could clarify a diagnosis and help clinicians consider medical or interventional therapies.

7.2.5 The future for CT in risk-stratification

While this body of work establishes strong associations between low-attenuation plaque and myocardial infarction, these findings require external validation and prospective assessment. There are other techniques that may also be of use in risk stratification of patients. For example, there has been renewed interest in the value of perivascular inflammation which may play a crucial role in the early phase of coronary atherosclerosis and plaque rupture.[212] Tzolos *et al* demonstrated the complementary and predictive value of pericoronary adipose tissue attenuation and low-attenuation plaque defined on CT coronary angiography in patients with stable angina.[213] CT based radiomic profiling of coronary artery perivascular fat has led to the creation of a novel imaging biomarker termed 'fat radiomic profile' utilising machine learning algorithms which has potential to predict those at risk of myocardial infarction over and above current approaches.[214]

Computed Tomography Fractional Flow Reserve (CT-FFR) is another technique that may be of benefit. It uses computational fluid dynamics and models physiological conditions of hyperaemia to produce an estimate of the invasive FFR. The diagnostic accuracy of these calculations has been

confirmed in several studies where CT-FFR results were compared directly to invasive FFR. [215, 216] Correlation between both were good, and the diagnostic accuracy of CT-FFR appeared to be better than with CCTA alone for the identification of haemodynamically significant lesions. However, the FORECAST trial (Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain)[217] demonstrated that a strategy of CT coronary angiography with selective CT-FFR in patients with stable angina did not differ significantly from standard care pathways in cost or clinical outcomes suggesting it has a very limited role in routine clinical practice.[217]

Whilst the use of such derived measures of ischaemia appears limited in stable chest pain cohorts, there is potential for it to be a useful metric in patients who suffer myocardial infarction due to a supply-demand mismatch: type 2 myocardial infarction. The DEFINing the PrEvalence and Characteristics of Coronary Artery Disease Among Patients with TYPE 2 Myocardial Infarction Using CT-FFR (DEFINE TYPE 2 MI; NCT04864119) study will use advanced CTCA techniques including plaque quantification and CT-FFR, to assess the plaque characteristics and haemodynamic significance of coronary disease in patients with type 2 myocardial infarction. The advantages of CT-FFR over other non-invasive tests lies in its ability to provide anatomical and functional information, without the requirement to perform additional imaging or radiation exposure. However, at present its use remains limited due to the need for careful selection on the basis that image quality can greatly affect the reliability

of results.[218] The data from DEFINE TYPE 2 MI has potential to improve our understanding of type 2 myocardial infarction and indeed may highlight missed treatment opportunities.

7.2.6 Implications on disease progression and treatment decisions

Another interesting way in which plaque quantification is being used, is to document the natural progression of coronary artery disease. We still have very limited understanding of the process of atherosclerosis in coronary arteries and the use of non-invasive plaque quantification opens avenues of exploration and innovation in the field of medical and interventional therapeutics. For example, a recent international registry of consecutive patients that underwent serial imaging of demonstrated marked variation in not just the progression of plaque but in the development of new high-risk plaque features. The left anterior descending artery suffered the greatest progression in plaque build-up and was associated with 2.45 times greater risk of progression to obstructive coronary disease and the highest rates for formation of high-risk plaque.[219] In another study of patients who underwent coronary artery bypass grafting plaque quantification demonstrated that native vessels that had been bypassed had increased disease activity and accelerated disease progression compared to non-bypassed coronary arteries independent of baseline atherosclerotic plaque burden.[220]

In addition to studying the natural progression of coronary artery disease in a variety of settings, trialists have started to conduct studies using plaque burden as an endpoint of interest. Newer drugs are tested and the patient response to

treatment monitored using follow-up CT coronary angiography. This has already been done in published trials,[108] and is ongoing in trials such as the PASSIvation of Vulnerable plaque with AZD5718 in AcuTe coronary syndromE (PASSIVATE; NCT04601467) trial which aims to determine if a novel inhibitor of leukotriene production could attenuate the progression of non-calcified plaque in patients who have suffered a myocardial infarction.

Quantitative plaque analysis is also being utilised to help clinicians understand atherosclerosis through its novel association with Lipoprotein(a) (Lp(a)). Lp(a) is a plasma lipoprotein made up of low-density lipoprotein particles which are covalently bonded to apolipoprotein(a). It is more atherogenic than low-density lipoprotein because of its ability to not only promote vascular inflammation but also inhibit fibrinolysis by blocking plasminogen.[221, 222] The large UK Biobank study found that Lp(a) was independently associated with incidence of atherosclerotic cardiovascular disease during a mean follow-up of over 11 years (hazard ratio per 120 nmol/L increase, 1.26 [95% confidence interval 1.23 to 1.28).[223] The evidence built up is such that guidelines have started to recommend measuring Lp(a) in specific at risk groups.[224] Using serial quantitative plaque analysis, we recently described an association between increasing Lp(a) and the progression of low-attenuation plaque burden.[225] This interesting observation provides a mechanistic explanation for the association between Lp(a) and myocardial infarction and provides support for Lp(a) as a target for the treatment of atherosclerosis. Indeed there have already been studies on existing treatments and their effects on Lp(a) such as statins and

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[226] There is even some suggestion from studies using invasive quantitative angiography, that more intensive treatments such as Lp(a) apheresis can lead to disease regression reducing the atherosclerotic burden in carotid and coronary arteries.[227]

7.3 CLINICAL PERSPECTIVE

In this thesis, we have shown that quantitative plaque analysis is a robust and reliable tool that can be appropriately used in patients with a high burden of coronary artery disease. We have shown that it can be used to clarify the diagnosis when clinicians are uncertain if a patient has had a myocardial infarction due to plaque rupture. We have also used it to provide a mechanistic explanation for the differing outcomes in patients with a troponin above the risk stratification threshold. Perhaps most crucially, we have established a strong association with future risk of cardiovascular events in those patients who are in the throes of having a myocardial infarction.

The technological advances both in how we acquire and how we interpret CT coronary angiography images have undergone rapid and sustained innovation particularly in the last decade. However, there is a considerable lag in its translation into routine clinical practice, which remains largely based on lumenography. Whilst severity of stenosis is one important variable, this body of works highlights the critical importance of quantifying and classifying coronary artery plaque to improve the diagnostic and prognostic potential of CT coronary angiography. Completing this thesis has left me pondering on some important topics. We focus on medical therapy in the management of patients with coronary artery disease, because to a certain extent, invasive therapies, such as percutaneous coronary intervention, have limited or no prognostic benefit. In the stable angina populations, treatment of severe

stenoses and associated ischaemia with percutaneous coronary intervention has no major impact on the long-term outcomes. Moreover, we have known for many years that most myocardial infarctions occur in coronary arteries with non-obstructive disease that are not likely to cause symptoms of ischaemia and angina. I find myself reflecting whether consideration of plaque characteristics could change this paradigm and assist in improving the way in which we select who should undergo invasive coronary interventions. Currently guidelines suggest coronary intervention in patients who have refractory symptoms despite optimal medical management. However, in the presence of obstructive coronary disease, should burden of low-attenuation plaque determine who receives revascularisation? Should a non-obstructive lesion with a large burden of low-attenuation plaque be revascularized? These scenarios require proper randomized controlled trials and warrant investigation as the observational data suggests a possibility of prognostic benefit.

Plaque quantification has the potential to clarify diagnoses, more accurately risk stratify, direct medical therapies, and even monitor the down-stream effect of treatments. The recent and ongoing studies described above will help clinicians and patients gain as much value as possible from their CT coronary angiograms. The potential application to clinical practice is great although limited by its time-consuming nature. However, with the help of artificial intelligence, the future is bright for plaque analysis.

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