Computed tomography coronary angiography (CTCA) for the risk assessment of acute coronary syndrome patients

Steele Butcher
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COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY (CTCA) FOR THE
RISK ASSESSMENT OF ACUTE CORONARY SYNDROME PATIENTS

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MD

A thesis submitted in fulfilment of the requirements for the Master of Philosophy degree¹

School of Medicine
Fremantle Campus
June 2021

¹ Submitted in partial fulfilment of the requirements for the Master of Philosophy degree
Declaration of Authorship:

To the best of the candidate’s knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made. This thesis is the candidate’s own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

Human Ethics:

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018). The proposed research study received human research ethics approval from the Royal Perth Hospital Human Research Ethics Committee (EC00418), Approval Number # REG 15-033
ABSTRACT:

Coronary heart disease is the single most frequent cause of mortality in Western countries. Up to 30% of patients surviving an acute coronary syndrome (ACS) will experience a recurrent event within 5 years. Yet precisely defining which of these patients will go on to experience a recurrent event remains difficult despite the use of contemporary risk scores, such as the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) and GRACE (Global Registry of Acute Coronary Events) scores. Given the important role of computed tomography coronary angiography (CTCA) in defining risk in the low to intermediate risk coronary heart disease cohort, there may be a role for CTCA in better defining risk in higher risk individuals, such as those having suffered ACS. Accurately quantifying total plaque burden and its components (i.e. low attenuation plaque) may provide additional benefit to currently used methods and provide a more accurate measure of risk for these at-risk patients.

This thesis demonstrates that CTCA-derived residual plaque burden and plaque components correlate with risk scores (GRACE and SYNTAX scores) validated as predictors of cardiovascular events and death in individuals following an ACS, providing promising data that suggests CTCA could yet have a role in improving risk stratification in the post-ACS cohort. However, further studies directly comparing CTCA-derived coronary plaque burden with conventional risk stratification models, such as the GRACE and SYNTAX scores, are required to demonstrate any incremental benefit in prognostication for this patient group.
ACKNOWLEDGMENTS:

I would like to thank my wife, Sarah, who has been exceptionally patient and supportive from my first day of enrolment.

I would also like to thank my supervisors, Professor David Playford and Professor Carl Schultz, who provided continuous support throughout my time completing this thesis.

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CHAPTER ONE - INTRODUCTION

Coronary heart disease (CHD) is the most frequent cause of mortality in Western countries\(^1\), accounting for approximately one-fifth of all deaths.\(^2\)-\(^6\) Recently, it has become the single most common cause of death in low, and middle, as well as high income countries.\(^7\) Approximately one-quarter to one-half of all cardiovascular events occur in individuals with established CHD, who account for only 6% of the general population.\(^8\)-\(^10\) Furthermore, 15-30% of patients surviving an acute coronary syndrome (ACS) event will experience a recurrent event within five years, often with a significant mortality rate.\(^8\),\(^11\)

Focus on modifiable risk factors such as smoking, hypertension, low-density lipoprotein (LDL) cholesterol, diabetes and obesity have been important in decreasing cardiovascular events and form the basis of clinical practice guidelines on prevention.\(^12\)-\(^15\) However, control of risk factors alone does not address the significant heterogeneity among individuals who may have future cardiovascular events. In particular, the post-ACS cohort has a heterogeneous risk profile,\(^16\) and accurately defining individual patient risk is necessary to inform on the appropriate medical therapy and/or intervention. Novel methods are required to identify specific markers that characterise an individual at increased risk. Recent focus on coronary plaque quantification and morphology suggest an important role in defining risk and is the subject of this thesis.\(^17\)

Current evaluation of patients with suspected ACS involves the use of biomarkers (i.e. high sensitivity cardiac troponin [hs-cTn]) to identify those at high-risk. Those at high-risk usually undergo invasive coronary angiography (ICA) to confirm or exclude significant coronary luminal stenosis, with subsequent percutaneous coronary intervention (PCI) if deemed appropriate. However, out of those with suspected ACS referred for ICA, 10-28% have only mild coronary artery disease (CAD) or normal coronary arteries, and up to 45% do not
require revascularisation.\textsuperscript{18-21} Furthermore, while ICA provides good assessment of luminal patency, it provides little information regarding the vessel wall. Computed Tomography Coronary Angiography (CTCA), although providing inferior assessment of luminal patency, allows for the quantification of plaque burden and the identification of high-risk plaque (HRP) characteristics in the vessel wall.\textsuperscript{22} The presence of these features may identify patients at a higher risk, allowing for improved risk stratification and prognostication. Indeed, recent research suggests that CTCA may have an important role in the risk stratification of low and intermediate cardiovascular risk patients, due to its ability to identify important features of the vessel wall in addition to luminal patency.\textsuperscript{17, 23-26} Furthermore, CTCA may have a role in clarifying diagnosis in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and could theoretically minimise the need for invasive coronary angiography in certain lower risk ACS patients.

**Pathophysiology of the Acute Coronary Syndrome**

An acute coronary syndrome refers to atheromatous plaque rupture or erosion with associated intraluminal thrombus within the coronary arterial tree, resulting in subsequent myocardial ischaemia and infarction.\textsuperscript{27, 28} Of those with ACS, patients with at least two contiguous leads with ST-segment elevation $\geq 2.5\text{mm}$ in men $< 40$ years, $\geq 2\text{mm}$ in men $\geq 40$ years, or $\geq 1.5\text{mm}$ in women in leads V2–V3 and/or $\geq 1\text{mm}$ in the other leads are defined as having a STEMI (ST-Elevation Myocardial Infarction), while those with not fulfilling these criteria are defined as having NSTEMI (Non ST-Elevation Myocardial Infarction) or Unstable Angina (UA).\textsuperscript{29} NSTEMI is differentiated from UA through the measurement of cardiac troponins greater than the 99\textsuperscript{th} percentile upper reference limit.\textsuperscript{28}

Understanding of the pathological mechanisms underlying the acute coronary syndrome has advanced significantly over recent decades. Histopathological studies have
demonstrated that the most common cause of ACS is plaque rupture of a thin-capped fibroatheroma (TCFA), in which a disruption of the fibrous cap exposes the underlying necrotic core, resulting in luminal thrombus formation. When the initial thrombotic event causes complete or near-complete occlusion of the epicardial coronary vessel, an occlusive myocardial infarction is said to occur. Occlusive myocardial infarction usually manifests clinically as a STEMI, whereas non-occlusive myocardial infarction is more likely to present clinically as a NSTEMI. Angiographic findings have demonstrated that the culprit lesion for STEMI is typically non-obstructive prior to the thrombotic event. Typically, plaque rupture occurs in lesions demonstrating <50% luminal stenosis usually at the cap margin or shoulder region. TCFAs are most commonly seen in the proximal third of the major coronary arteries, usually at or near a bifurcation, where there is exposure to disturbed flow or lower endothelial shear stress. These segments of the coronary arteries represent the locations where CTCA has the highest image quality and accuracy for the detection of plaque.

Plaque rupture of a TCFA is the most frequent cause of thrombosis and has been shown to account for approximately 79% of fatal myocardial infarctions, with plaque erosion and thrombosis of a calcified nodule thought to account for the remaining events. The TCFA is characterised by a necrotic core, with a fibrous cap <65μm in 95% of lesions, scant smooth muscle cells and abundant macrophages, similar in composition to ruptured plaque. Plaque associated with a TCFA has a mean necrotic core length of 8mm and an area of >1mm² in approximately 80% of cases, dimensions which are greater than the detection threshold of modern CTCA scanners (>1mm). In contrast to plaque rupture, lesions associated with plaque erosion are rich in proteoglycans and smooth muscle cells, typically devoid of a necrotic core. Thrombus formation occurs due to direct contact of blood products with the tunica intima, in an area of the plaque devoid of endothelium. The risk factors for plaque erosion appear to differ significantly from those associated with rupture and remain poorly defined. While the
pathogenesis remains unknown, coronary vasospasm is suspected to play a key role. The least common lesion, the calcified nodule, results in irregularity of the surface of the fibrous cap and lacks endothelial cells, predisposing to thrombus formation, typically in tortuous and calcified arteries of older individuals.

The concept of the vulnerable plaque has previously been used to define a identifiable precursor lesion that is at a high risk for disruption or thrombosis, including TCFA, pathological intimal thickening, thick-capped fibroatheroma and calcified plaque with calcified nodules. However, this model has been challenged, with many authors now insisting that the focus should remain on the atherosclerotic disease burden rather than features of individual plaques. Recent evidence has demonstrated the presence of HRP may have more of a role in identifying patients at risk, rather than specific target lesions at risk.

**Figure 1.1: Features of high-risk vs low risk plaque**

Stable plaque is characterised by a thick, fibrous cap with minimal lipid volume, whereas unstable high-risk plaque has a large volume necrotic core and thin fibrous cap.
Pathophysiological basis of coronary plaque burden as an important predictor of future cardiovascular events

Previously, rather than the direct quantification of coronary plaque burden, the major focus of coronary imaging research was the identification of the ‘vulnerable plaque’, a specific atherosclerotic lesion prone to rupture and characterized by certain high-risk features.\(^47\) It was hoped that the pre-emptive treatment of such lesions, for example with PCI, would reduce cardiovascular events and associated mortality. However, several previous meta-analyses failed to demonstrate a reduction in cardiovascular events or death with lesion-specific intervention in those with stable coronary artery disease when compared to treatment with medical therapy alone.\(^48,49\) These findings were recently confirmed in a major contemporary randomised control trial of over 5000 individuals with stable coronary artery disease.\(^50\) From a pathophysiological perspective, the failure to improve outcomes by intervening on a specific high-risk lesion is perhaps unsurprising, given that many plaque rupture events are subclinical\(^31,51\) and that after 12 months, the majority of high-risk low attenuation plaques become lower risk fibrotic plaque or thick-capped fibroatheroma.\(^52\) However, despite this, numerous studies utilizing a variety of imaging modalities (including CTCA, intravascular ultrasound [IVUS] and optical coherence tomography [OCT]) have demonstrated the independent and incremental prognostic value of the identification of HRP features.\(^45,53-55\) Nonetheless, because these studies did not consider total coronary plaque burden as a potential confounding factor, it is possible that the presence of HRP characteristics simply serve as a surrogate of a more widespread, metabolically active atherosclerotic process.

Contrary to imaging strategies attempting to identify specific vulnerable plaques, the measurement of total coronary plaque burden provides a direct estimation of the diffuse, systemic atherosclerotic disease process. Indeed, the most important predictors of future ACS events are the extent and activity of coronary plaque burden and risk factors for an
inflammatory and prothrombotic environment.\textsuperscript{44, 56, 57} Direct quantification of plaque components, such as higher-risk low attenuation plaque burden, may provide an even closer estimate of a metabolically active, aggressive phenotype of atherosclerosis, of which there is a higher chance of plaque rupture occurring and coinciding with the necessary prothrombotic conditions.\textsuperscript{58} However, precise and accurate prediction of future cardiovascular events remains difficult, as the total burden of atherosclerosis, plaque composition, plaque location, systemic inflammation, neurohormonal dysregulation and thrombogenicity must converge to create a “perfect storm scenario”, where arterial narrowing and subsequent myocardial ischaemia can occur.\textsuperscript{59, 60}

For patients following an ACS event, quantifying the magnitude and activity of coronary plaque burden may be even more important when compared to those without a history of coronary events, as these individuals are more likely to have the pro-thrombotic and inflammatory characteristics necessary for an acute plaque rupture to become clinically significant. Nonetheless, the accurate estimation of total coronary plaque burden and plaque composition remains only one factor, albeit quantifiable and important, in determining whether a future ACS event will occur.

**Basic Principles of CT Imaging**

CT scanners utilize an x-ray tube and detectors mounted on opposing sides of a gantry that continuously rotate around a patient, with images acquired as the patient moves through the gantry.\textsuperscript{61} The transmitted intensity of the x-ray beam decreases exponentially as it traverses the patient, with this decrease varying based on the penetrating characteristics of the x-ray beam and physical characteristics of the specific tissue.\textsuperscript{62} The data acquisition system converts the raw data from the CT scan detector to produce images composed of voxels of varying shades of grey, based on the mean attenuation of the tissue within a given voxel.\textsuperscript{61} Attenuation is the
reduction of the intensity of an x-ray beam as it traverses matter. This reduction may be caused by either absorption or deflection and can be quantified by the linear attenuation coefficient, the fractional change in x-ray intensity per thickness of the attenuating material. Attenuation on CT imaging is quantified by Hounsfield Units (HU), which are defined as linear transformations of measured attenuation coefficients of a material with reference to water. White areas typically represent regions of high attenuation (high HU values), while darker areas represent regions of lower attenuation (lower HU values). Modern multiple-row detector CT (MDCT) enables the acquisition of three-dimensional cardiac images with high spatial and temporal resolution, with an array of x-ray detectors that encompass a greater area, while collecting data from multiple slices for each rotation of the scanner.

**Coronary artery stenosis**

Coronary artery stenosis is a reduction in arterial luminal diameter typically occurring as a result of the progression of coronary atherosclerosis. It may occur secondary to continual plaque growth of a positively remodelled vessel segment, or due to shrinkage of a particular vessel segment. The earliest progressive atherosclerotic lesion is that of pathological intimal thickening, characterised by layers of smooth muscle cells in a proteoglycan-collagen matrix with an underlying lipid pool and a variable number of macrophages on the luminal aspect of the plaque. Plasma lipoproteins, especially LDL, aggregate and bind to proteoglycans located within the extracellular matrix of the lipid pool. Pathological intimal thickening may eventually progress to fibroatheroma, characterised by the presence of an acellular necrotic core composed of cellular debris devoid of extracellular matrix and apoptotic macrophages. This necrotic core is typically covered by a thick fibrous cap composed of smooth muscle cells within a proteoglycan-collagen extracellular matrix. The fibrous cap is critical in determining the stability and integrity of the fibroatheroma, and with the progression of disease may thin
forming a TCFA.\textsuperscript{65} Frequently, the initial accumulation of atherosclerotic plaque manifests as an increase in vessel size without a reduction in luminal diameter, known as positive remodelling.\textsuperscript{66} This compensatory enlargement may delay luminal stenosis until plaque burden is >40\%\textsuperscript{66} and is associated with increasing lipid content, macrophage infiltration and plaque vulnerability.\textsuperscript{57} In contrast, negative remodelling, defined as a reduction in vessel size, is associated with fibrous tissue and few inflammatory cells. It is seen more commonly in chronic total occlusions and in lesions associated with plaque erosion.\textsuperscript{67}

Many published studies have demonstrated the excellent negative predictive value (typically greater than 99\%) of CTCA in symptomatic patients.\textsuperscript{24, 68-73} The utilisation of newer CT technology, such as 320-segment, 256 slice and dual-source CT scanners, has confirmed the high negative predictive value of CTCA for ruling out anatomically significant coronary artery disease.\textsuperscript{74-76} A meta-analysis of 54 studies\textsuperscript{77} demonstrated an increase in the sensitivity for the detection of >50\% obstructive stenosis with 64-slice CT scanners compared with a 16-slice CT scanners (93\% vs 83\%). Significant reductions in motion\textsuperscript{78} and calcium artefacts have played important roles in this improvement. In a systematic review of 22 studies examining the accuracy of dual-source CT for detection of arterial stenosis in difficult to image patient groups, Westwood et al.\textsuperscript{79} reported a pooled, per-patient estimate of sensitivity of 97.7\% and 97.7\% and specificity of 81.7\% and 86.3\%, for patients with arrhythmias and high heart rates respectively.

Several studies have suggested that significant coronary artery stenosis predicts worse cardiovascular outcomes.\textsuperscript{24, 80} For example, in a retrospective analysis of a large, multicentre observational study of 15,187 patients without prior known CAD who were referred by a physician for CTCA, those with obstructive CAD (>50\% stenosis) were more likely to experience major adverse cardiovascular events (MACE) when compared with patients with a normal CTCA at a mean of 2.4 (±1.2) years follow-up (HR: 11.21, \textit{p}<0.001).\textsuperscript{81} Similar findings
were seen in two single-centre consecutive cohort studies: In a study of 1,127 patients, Min et al.\textsuperscript{82} demonstrated that moderate (>50%) or severe (>70%) coronary stenosis (per segment) on CTCA predicted increased all-cause mortality (risk-adjusted HR: 1.05 (95% CI: 1.02–1.09), p<0.01) at a mean follow-up of 15.3 (3.9) months. In a study of 1,304 patients investigated for suspected CAD,\textsuperscript{83} cumulative event-free survival was 54% for hard events and 31% for all events in patients with obstructive CAD (>50% stenosis) on CTCA at a mean of 52 (± 22) months of follow-up.

A meta-analysis\textsuperscript{84} of 33 studies comparing CTCA with IVUS, including a total of 946 patients, demonstrated that the percent area stenosis of coronary arteries was comparable between CT and IVUS (weighted mean difference -1.8%, 95% CI -4.10 to 0.49, p<0.12). However, multiple studies\textsuperscript{85-88} have demonstrated that while CTCA correlates well with quantitative ICA and IVUS in terms of percent maximal diameter stenosis, it does so with a relatively large standard deviation, typically to within 25% of the mean percent maximal diameter stenosis of ICA (with a 95% CI) at best. CTCA has a tendency to overestimate the degree of stenosis, at least in part because of partial volume effects that lead to the amplification of the size of high attenuation components such as calcified plaque.\textsuperscript{78, 84} Extensive calcification frequently leads to overestimation or paradoxical underestimation of coronary artery stenosis severity.\textsuperscript{89} Furthermore, the limited spatial resolution of CTCA compared to ICA remains a significant limitation when comparing these imaging modalities.\textsuperscript{90} Therefore, CTCA is typically utilised for ruling out coronary artery disease rather than accurately determining the degree of coronary stenosis and the need for intervention.

**Coronary plaque burden**

Total burden of atherosclerosis is a major determinant of cardiovascular disease (CVD) risk and can be assessed by coronary CT, providing incremental prognostication over and above
calcium quantification and the non-invasive identification of luminal narrowing. In an ex-vivo heart model, Knollman et al. demonstrated a significant correlation between the total plaque area measured by CTCA and findings on histology. Small studies have demonstrated that segmental plaque burden on CTCA is highly correlated with plaque burden identified by IVUS. It has been estimated that CTCA detects approximately two times the number of atherosclerotic lesions as ICA. The risk of future coronary events increases with the extent of atherosclerotic disease burden, presumably because there is an increased chance of an individual plaque rupturing, resulting in a thrombotic event. Alternatively, a greater plaque burden may be indicative of a more rapidly progressive, virulent atherosclerotic process.

Figure 3 and Table 1 below demonstrate the numerous studies that have consistently reported an association between increasing plaque burden and mortality/MACE in patients investigated for suspected CAD. This association is seen despite the heterogeneity in defining and quantifying plaque burden within the literature. Plaque burden is most often calculated by the following equation: \( \text{Plaque burden} = \frac{(\text{Vessel Area} - \text{Lumen Area})}{\text{Vessel area}} \times 100 \). However, many different scoring systems for the quantification of plaque burden have been described. For example, Min et al. described the segment involvement score (SIS) and segment stenosis score (SSS) to objectively quantify plaque burden, demonstrating an increase in risk-adjusted all-cause mortality with increasing scores. Other studies using the SIS and SSS reported similar associations. However, there are important limitations of these scoring systems which must be considered, including a failure to account for the anatomical distribution of atherosclerosis and the assumption that all plaque burden is additive, regardless of lesion location. For example, results from the CONFIRM (CORonary CT Angiography Evaluation For Clinical Outcomes: An InterNational Multicenter Registry) registry demonstrate these limitations, where it was shown that proximal segmental involvement has a larger influence on clinical outcomes than distal segmental involvement. Other described scoring systems include
the three-vessel score,\textsuperscript{82, 83} the Duke CAD index,\textsuperscript{82, 86} the CT SYNTAX score\textsuperscript{100, 101} and the CTA-adapted Leaman score.\textsuperscript{102-104} Thus far, no single scoring method has been proven as superior with few studies comparing these scores directly.

Two previous studies have examined the relationship between plaque burden or volume and prognosis in patients following an ACS event. In a study of 312 consecutive patients presenting with NSTEMI who underwent CTCA prior to ICA, over a median follow-up of 16 months, it was demonstrated that total non-calcified plaque volume (defined as any plaque <130 HU) in nonobstructive lesions was independently associated with cardiac events (HR=1.18 \textasciitilde 100mm\textsuperscript{3} plaque volume increase, 95% CI=1.06-1.31, p=0.01).\textsuperscript{105} Further characterisation of plaque composition (i.e. LAP) was not reported. In another study of 169 patients with NSTEMI, residual plaque burden index (defined as total plaque volume divided by vessel length, excluding stented coronary segments) was significantly associated with MACE at a median follow-up of 4.8 years (HR=1.22, 95% CI = 1.01-1.48, p=0.04). However, no characterisation of plaque composition was reported. Increasing plaque burden on CTCA has also been demonstrated to improve the prediction of future cardiovascular events and mortality beyond that of stenosis severity and clinical risk scores in the low-to-intermediate cardiovascular risk population.\textsuperscript{73, 106, 107} In low CV risk populations, extensive non-obstructive CAD on CTCA identifies patients with CVD event rates similar to those with obstructive single vessel disease.\textsuperscript{106, 108} The presence of any non-obstructive CAD predicts CVD event rates 2 to 4.5 fold higher than those without identifiable CAD.\textsuperscript{106, 109, 110} Furthermore, several studies have demonstrated that the quantification of plaque burden composition, specifically the quantification of LAP burden, provides the most robust prognostication of the low to intermediate CVD risk population.\textsuperscript{58, 111} Further studies are required to determine the value of the quantification of plaque burden composition in the post-ACS cohort.
In the future, the automation of the quantification of plaque burden will likely improve the reproducibility, accuracy and efficiency of CTCA imaging analysis.\textsuperscript{42} A prospective study\textsuperscript{112} of 1650 patients demonstrated that semi-automated plaque quantification (reporting volumetric and geometric plaque properties) provides incremental prognostic value over Framingham Risk Score (FRS) and conventional CTCA reading (area under the ROC curve (AUC) of 0.79 vs 0.64, p <0.05). Other studies using alternative or the same software for quantification also reported that plaque volume assessment predicts future clinical outcomes in patients with stable coronary artery disease, beyond that of conventional coronary CTA analysis.\textsuperscript{111, 113}

**Figure 1.3: Hazard ratios for all-cause mortality and MACE according to different plaque burden scoring parameters**

Numerous studies have demonstrated the prognostic utility of plaque burden quantification for the prediction of cardiovascular events and mortality in the stable coronary artery disease population.

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadji et al, 2016</td>
<td>4.7 (3.1-7.0)</td>
</tr>
<tr>
<td>Deselve et al, 2018</td>
<td>6.4 (3.2-12.8)</td>
</tr>
<tr>
<td>Gitsioudis et al, 2015</td>
<td>4.78 (2.27-10.04)</td>
</tr>
<tr>
<td>Chow et al, 2011</td>
<td>1.58 (1.42-1.76)</td>
</tr>
<tr>
<td>Hadamitzky et al, 2013</td>
<td>1.77 (1.30-2.42)</td>
</tr>
<tr>
<td>Chow et al, 2010</td>
<td>1.17 (1.06-1.29)</td>
</tr>
<tr>
<td>Lin et al, 2011</td>
<td>4.75 (2.10-10.75)</td>
</tr>
<tr>
<td>Ostrom et al, 2008</td>
<td>1.74 (1.49-2.05)</td>
</tr>
<tr>
<td>Mushtaq et al, 2015</td>
<td>3.09 (2.00-4.75)</td>
</tr>
<tr>
<td>Dougoud et al, 2014</td>
<td>1.18 (1.06-1.31)</td>
</tr>
<tr>
<td>Bittencourt et al, 2014</td>
<td>3.10 (1.50-6.40)</td>
</tr>
<tr>
<td>Hadamitzky et al, 2013</td>
<td>1.22 (1.03-1.44)</td>
</tr>
<tr>
<td>Andreini et al, 2012</td>
<td>1.38 (1.31-1.47)</td>
</tr>
<tr>
<td>Min et al, 2007</td>
<td>1.16 (1.05-1.28)</td>
</tr>
</tbody>
</table>

CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular events
Table 1.1: Hazard ratios for mortality and MACE according to different plaque burden scoring parameters

<table>
<thead>
<tr>
<th>First author, Year published</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Plaque Burden Scoring Parameter</th>
<th>Clinical Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min et al(^{82}), 2007</td>
<td>Retrospective</td>
<td>1127</td>
<td>SIS (per segment involved)</td>
<td>All-cause mortality</td>
<td>1.16</td>
<td>1.05 – 1.28</td>
</tr>
<tr>
<td>Andreini et al(^{83}), 2012</td>
<td>Prospective</td>
<td>1234</td>
<td>SIS&gt;5</td>
<td>Hard Cardiac Events (cardiac death and nonfatal ACS)</td>
<td>1.38</td>
<td>1.31 – 1.47</td>
</tr>
<tr>
<td>Hadamitzky et al(^{80}), 2013</td>
<td>Retrospective</td>
<td>17793</td>
<td>SIS (Number of segments with any plaque or stenosis)</td>
<td>All-cause mortality</td>
<td>1.22</td>
<td>1.03 – 1.44</td>
</tr>
<tr>
<td>Bittencourt et al(^{106}), 2014</td>
<td>Retrospective</td>
<td>3242</td>
<td>Extensive (SIS&gt;4) nonobstructive CAD</td>
<td>Cardiovascular death or MI</td>
<td>3.1</td>
<td>1.5 – 6.4</td>
</tr>
<tr>
<td>Dougoud et al(^{79}), 2014</td>
<td>Retrospective</td>
<td>218</td>
<td>SIS (per segment involved)</td>
<td>MACE (death, MI, revascularization)</td>
<td>1.18</td>
<td>1.06 – 1.31</td>
</tr>
<tr>
<td>Mushtaq et al(^{103}), 2015</td>
<td>Prospective</td>
<td>1196</td>
<td>SIS&gt;5</td>
<td>Hard cardiac events</td>
<td>3.09</td>
<td>2.00 – 4.75</td>
</tr>
<tr>
<td>Ostrom et al(^{114}), 2008</td>
<td>Retrospective</td>
<td>2538</td>
<td>Nonobstructive CAD in 3 epicardial vessels</td>
<td>All-cause mortality</td>
<td>1.74</td>
<td>1.49 – 2.05</td>
</tr>
<tr>
<td>Lin et al(^{107}), 2011</td>
<td>Prospective</td>
<td>2583</td>
<td>Nonobstructive CAD in 3 epicardial vessels</td>
<td>All-cause mortality</td>
<td>4.75</td>
<td>2.1 – 10.75</td>
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<tr>
<td>Chow et al(^{173}), 2010</td>
<td>Prospective</td>
<td>2076</td>
<td>Total plaque score</td>
<td>All-cause mortality and non-fatal MI</td>
<td>1.17</td>
<td>1.06 – 1.29</td>
</tr>
<tr>
<td>Hadamitzky et al(^{124}), 2013</td>
<td>Prospective</td>
<td>1584</td>
<td>Total plaque score</td>
<td>Death and non-fatal MI</td>
<td>1.77</td>
<td>1.3 – 2.42</td>
</tr>
<tr>
<td>Chow et al(^{102}), 2011</td>
<td>Retrospective</td>
<td>13966</td>
<td>CAD Severity</td>
<td>All-cause mortality</td>
<td>1.58</td>
<td>1.42 – 1.76</td>
</tr>
<tr>
<td>Gitsiouidis et al(^{145}), 2015</td>
<td>Prospective</td>
<td>521</td>
<td>Plaque volume tertiles</td>
<td>Cardiac events</td>
<td>4.78</td>
<td>2.27 – 10.04</td>
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</table>
High risk plaque (HRP) characteristics on CTCA

Coronary CTA allows for the identification of several features of HRP, the quantification of overall plaque burden and the non-invasive assessment of the degree of luminal narrowing. Clinical and pathophysiological studies have identified the features of plaque composition and morphology that are associated with plaque vulnerability and likelihood of future rupture. When compared using invasive fractional flow reserve (FFR), HRP features and plaque volume appear to influence the haemodynamic significance of a coronary stenosis almost to the same extent as the anatomical degree of luminal narrowing. The close relationship between HRP characteristics and invasive FFR has been demonstrated in several recent studies, with the incorporation of physiological stenosis severity and HRP features providing better prognostic stratification of patients than with the use of either individual component alone. Many studies investigating HRP characteristics on CTCA have demonstrated an independent and incremental improvement in prognostication for the low-intermediate cardiovascular risk cohort. However, as discussed in more detail later, these studies share the collective limitation that they do not adjust for total atherosclerotic plaque burden as a confounding factor.

Five major features of high-risk plaque can be identified on CTCA including: positive remodelling index (PRI), low attenuation plaque (LAP), the napkin-ring sign (NRS), spotty

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>n</th>
<th>Feature</th>
<th>Mortality Endpoint</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deseive et al</td>
<td>Prospective</td>
<td>1577</td>
<td>High plaque volume</td>
<td>All-cause mortality and MI</td>
<td>6.4</td>
<td>3.2 – 12.8</td>
</tr>
<tr>
<td>Nadjiri et al</td>
<td>Prospective</td>
<td>1168</td>
<td>SSS</td>
<td>MACE</td>
<td>4.7</td>
<td>3.1 – 7.0</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease, MACE = major adverse cardiovascular events, MI = myocardial infarction, SIS = segment involvement score, SSS = segment stenosis score.
calcification and the degree of luminal impingement (MLA) or the percentage area of stenosis. CTCA plaque types are usually subdivided as either non-calcified (no calcium density), calcified (the entire plaque appears as calcium density) or partially calcified by SCCT (Society of Cardiovascular Computed Tomography) criteria, with excellent inter- and intraobserver agreement.\textsuperscript{84, 123-125}

**Minimal luminal area (MLA) and percentage area stenosis**

The MLA on CTCA is defined as the narrowest lumen area in a given segment\textsuperscript{126}, while percentage area stenosis (%AS) at the level of the MLA is defined by \[1-(\text{MLA/corresponding reference lumen area}) \times 100\].\textsuperscript{98} MLA (Specificity [Sp] 68%; 95% CI, 57%–77%; \(p=0.001\)) and %AS (76%; 95% CI, 65%–84%; \(p<0.001\)) both are more specific for detection of functionally significant lesions when compared to visual analysis alone (42%; 95% confidence interval [CI], 31%–54%) when using invasive FFR as the reference standard.\textsuperscript{98}

**Positive remodelling index (PRI)**

The arterial remodelling index (RI) has been defined as the ratio between the outer vessel cross-sectional area at the site of maximal luminal narrowing and the mean vessel area of the proximal and distal reference sites.\textsuperscript{127, 128} A PRI is often defined as a RI \( \geq 1.10.\textsuperscript{129-131}\) Arterial remodelling may be expansive, constrictive, or a combination of the two processes. A positive remodelling index identifies expansive remodelling, the type most frequently observed during the development of fibroatheromas.\textsuperscript{31} In histo-pathological studies, the extent of expansive remodelling is correlated with lipid core size, plaque inflammation, calcification and medial atrophy, and is negatively associated with fibrotic regions.\textsuperscript{67, 132} CTCA measurement of positive remodelling is moderately correlated with that of IVUS and intravascular ultrasound virtual histology (IVUS-VH),\textsuperscript{133-135} typically overestimating both PRI and vessel area.\textsuperscript{135} Nonetheless, numerous studies\textsuperscript{127, 136, 137} have reported that the RI and plaque area of ACS lesions (or plaque rupture groups) are larger than those of non-ACS lesions (non-plaque rupture
groups) as measured on CTCA, indicating the potential utility of PRI in detecting patients of higher risk. Indeed, in a prospective study of 1059 patients undergoing CTCA for suspected or known coronary artery disease, Motoyama et al.\textsuperscript{130} demonstrated that the presence of PRI and/or LAP on CTCA independently predicted future ACS events (HR 22.8; 95% CI, 6.9-75.2; p<0.001).

**Low attenuation plaque (LAP)**

LAP has been defined as a focal, non-calcified plaque with a low-attenuation threshold of <30 HU, with 30-150 HU described as intermediate-attenuation plaque.\textsuperscript{130, 131, 138, 139} To define the minimum CT density in a non-calcified plaque, typically 5 regions of interest (areas of 1mm\(^2\)) are evaluated for each lesion, with the mean value defined as the plaque density.\textsuperscript{117, 131, 140} Low attenuation plaque is correlated directly with the presence of TCFA, although there is significant overlap between the HU of the lipid-rich and fibrous plaque groups. Increased LAP volume contributes to positive remodelling, fibrous cap attenuation and impaired vasodilation, features predisposing to ischaemia and plaque rupture.\textsuperscript{141} For example, Kashiwagi et al.\textsuperscript{128} evaluated culprit lesions in 105 patients with ACS and stable angina pectoris (SAP) with CTCA and OCT. Patients were divided into a TCFA and a non-TCFA group according to OCT findings, demonstrating that the attenuation value of the culprit plaque in the TCFA group was significantly lower than the non-TCFA group (35.1± 32.3 HU vs 62.0± 33.6 HU, p<0.001). Motoyama et al.\textsuperscript{139} demonstrated that a proposed cut-off of 30 HU had a sensitivity of 91% and specificity of 100% for the detection of plaques that matched to low attenuation areas as detected by IVUS of the corresponding coronary segment.\textsuperscript{139, 142} In a retrospective study of 60 patients with unstable angina, Madder et al.\textsuperscript{143} demonstrated that CTCA defined high-risk plaque (with ulceration or intraplaque contrast penetration) contained more LAP when compared to non-disrupted lesions (99 ± 161mm\(^3\) vs 19 ± 18mm\(^3\), p<0.0001). Although utilising a novel comparator that is yet to be validated, this study emphasises the important
association of low-density plaque with unstable coronary lesions. As with PRI, LAP on CTCA is present more often in patients with ACS compared to those with SAP.  

Napkin-ring sign (NRS)

The NRS was originally described by Tanaka et al. and is typically defined by the following criteria:

1. The presence of a ring of higher attenuation around a specific coronary artery plaque, and
2. The attenuation of the ring being higher than those of the adjacent plaque and no greater than 130 HU (to differentiate from calcium depositions).

There are several theories regarding the pathogenesis of the napkin-ring sign. These include intraplaque vasa vasorum contrast enhancement, thrombus with peripheral contrast enhancement, intraplaque haemorrhage or plaque micro-calcifications. All of these proposed mechanisms are strongly associated with high-risk plaque. Furthermore, several studies have demonstrated that vasa vasorum density correlates with plaque progression. This suggests that the NRS may be a potential surrogate marker of future plaque vulnerability.

Several small prospective studies and case reports utilising a variety of comparators, including IVUS, OCT and histopathological analysis, have suggested that the NRS represents a CTCA specific feature of a TCFA. For example, in a prospective study of 108 patients with coronary artery disease, Kashiwagi et al. demonstrated that the NRS in the OCT-defined TCFA group was eleven times more frequent than in the non-TCFA group (44% vs. 4%, p<0.0001). However, while this sign has been shown to be highly specific for the prediction of TCFA, this is at the cost of lower sensitivity, with one study demonstrating a specificity of 96% and a sensitivity of 44%. Otsuka et al. prospectively examined 894 patients who were being investigated for stable chest pain over a mean follow-up of 2.3 years, demonstrating that the napkin-ring sign was of significant prognostic importance for future ACS events, independent of other high-risk CTCA plaque features, including PR and LAP
(HR: 5.55, 95% CI 2.10–14.70, p<0.001). Similarly, in a prospective cohort study of 1469 patients who presented with either atypical chest pain, stable angina or were asymptomatic with a high risk of CHD, Feuchtner et al.\textsuperscript{151} demonstrated that the CTCA findings that were the strongest predictors of MACE were LAP <60 HU and the NRS.

\textit{Spotty calcification}

Spotty calcification on CTCA is defined as a small, highly attenuated (>130 HU) plaque component that is surrounded by non-calcified plaque tissue,\textsuperscript{42} typically described as <3mm in size on curved multiplanar reformation (MPR) images.\textsuperscript{129, 139, 152} Spotty calcifications on CTCA have been further characterised as small (<1mm), intermediate (1-3mm) or large (>3mm), with small spotty calcifications showing the strongest association with vulnerable plaque features on IVUS-VH.\textsuperscript{153} Motoyama et al.\textsuperscript{139} reported that spotty calcification was significantly more frequent in the culprit lesions of patients with ACS when compared to the target lesions of those with SAP (63% vs 21%, p<0.0005). In one study of 57 patients, Ozaki et al.\textsuperscript{129} demonstrated that spotty calcification was more frequent in patients with ACS with ruptured fibrous cap lesions compared to those with intact fibrous cap lesions (20% vs 80%, p=0.001) and when compared to those with SAP (80% vs 23%, p=0.001). Similar findings are reported by several other studies.\textsuperscript{117, 144, 154}

\textbf{Current methods of risk stratification following an ACS}

The risk stratification of the ACS patient may be performed in two distinct stages. The first stage involves the estimation of the risk of a patient with suspected ACS, a situation where the diagnosis is yet to be confirmed. This is accomplished through the evaluation of history, physical examination, clinical risk scores (i.e. HEART\textsuperscript{155} and TIMI\textsuperscript{156} scores) and relevant biomarkers (i.e. high-sensitivity cardiac troponin [hs-cTn]). Further risk stratification of high-risk patients with suspected ACS is usually through evaluation by ICA.
The second stage involves evaluating the risk of recurrent ACS event in a patient with confirmed ACS. Current risk stratification models for the post-ACS patient group typically utilise the Gensini\textsuperscript{157}, SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery)\textsuperscript{158} or GRACE (Global Registry of Acute Coronary Events)\textsuperscript{159} scores, although these are infrequently used for this purpose in clinical practice.

**Biomarkers**

According to the Fourth Universal Definition of Myocardial Infarction\textsuperscript{28} an acute myocardial infarction is defined by elevated cardiac troponin values (cTn) with at least one value above the 99th percentile URL, with a rise and/or fall of cTn values, in the presence of particular clinical, ECG or imaging findings. The presence of elevated cTn in patients with ACS differentiates myocardial infarction from unstable angina. Beyond presence or absence, as included in the GRACE score, higher levels of cardiac troponin have been correlated with a larger infarct size and as might be anticipated, also a greater mortality risk.\textsuperscript{160, 161} The measurement of several different biomarkers (hs-cTn, CRP, BNP, NT-proBNP, HbA1c, Lipoprotein(a) [Lp(a)] etc.) has been shown to provide additional prognostic information beyond traditional risk predictors in the post-ACS population.\textsuperscript{162-166} For example, in a study\textsuperscript{167} of 6,809 patients, increasing quartiles of NT-proBNP measured soon after admission were associated with increasing mortality rates of 1.8%, 3.9%, 7.7%, and 19.2% at 1-year of follow-up. Recently cysteine-rich angiogenic inducer 61 (Cyr61), a novel biomarker of plaque stability during acute coronary occlusion, independently improved risk stratification beyond the GRACE score alone at 1 year (c= 0.77 to c=0.80, p< 0.001).\textsuperscript{168} Likewise, a recent study by Wildera et al.\textsuperscript{169} demonstrated incremental predictive value with the use of hs-cTn (c=0.763; 95% CI: 0.710 to 0.816) and BNP (c=0.773; 95% CI: 0.717 to 0.82) when compared to the GRACE score alone (c=0.749; 95% CI: 0.696–0.801, all p<0.001). While the role of cTn in
the post-ACS cohort is clear, the prognostic value of these other biomarkers remains to be determined.

**Clinical risk scores**

While there are several clinical risk scores used for the prediction of short and long-term risk in post-ACS patients (i.e. the TIMI score), the most widely used and recommended by guidelines is the GRACE score, which will be the main focus of our discussion. The GRACE score is calculated based on patient age, Killip Class, systolic blood pressure, the presence of ST segment deviation, cardiac arrest during presentation, serum creatinine concentration, elevated serum cardiac markers (e.g. troponin) and heart rate. Multiple studies have validated this scoring system in the post-ACS population.\textsuperscript{16, 170} A meta-analysis\textsuperscript{171} of 216,552 patients from 40 derivation studies and 31,625 patients from 42 validation studies demonstrated a c-statistic of 0.82 (95% CI: 0.80-0.89) and 0.84 (95% CI: 0.82-0.87) at short and long term follow-up of post-ACS patients, respectively. The GRACE score 2.0 is an updated and refined score based on the outcomes of the GRACE registry, comprising 32,037 patients across 14 countries. This score has been validated in a French registry\textsuperscript{172} of 3059 patients, providing in-hospital, 6-month, 1-year and 3-year mortality. This study demonstrated a c-statistic of 0.82 for death at 1 and 3 years, with slightly lower discrimination for death or myocardial infarction (c=0.78). While being cheap, relatively easy to use and providing moderate to good prediction of prognosis post-ACS, the GRACE and GRACE score 2.0 do not account for the individualised burden of anatomical coronary disease, including high-risk plaque features and several other factors.

**Angiographic complexity**

The majority of ACS patients who are not low risk may undergo catheter-based coronary angiography and revascularisation of culprit lesions to reduce the risk of future cardiovascular events. Diagnostic angiography enables assessment of the angiographic complexity of
coronary disease, an important predictor of future and recurrent events. Various approaches have been used, most commonly the Gensini score, while the SYNTAX score has been recently validated with outcome data and is currently recommended to facilitate risk assessment in international guidelines. Neither were specifically developed for ACS populations.

The most widely utilised score to quantify angiographic coronary artery disease is the Gensini score. Developed by Gensini in 1983, the Gensini score evaluates the severity of individual coronary lesions while considering the cumulative effects of multiple obstructions and the functional significance of their location within the coronary tree. The Gensini score correlates well with average percent plaque burden (%) \( r=0.76, p<0.0001 \) and moderately with average plaque area \( \text{mm}^2 \) \( r=0.58, p<0.0001 \) as measured by intravascular ultrasound (IVUS).

The SYNTAX score is a lesion-based scoring system, calculated based on the interpretation of the images obtained during ICA, allowing for the objective quantification of the complexity of coronary artery disease. The SYNTAX score has been shown to be a strong predictor of outcome in single vessel, multi-vessel and left main CAD treated by PCI and in left main CAD treated with CABG, but not in the minority of ACS patients who undergo CABG. One study demonstrated a c-statistic for the SYNTAX score of 0.62 (95% CI: 0.52-0.73, \( p=0.03 \)) and 0.59 (95% CI: 0.53-0.65, \( p=0.002 \)) for the prediction of 5-year mortality and 5-year major adverse cardiovascular events (MACE), respectively. Typically, the SYNTAX score is used to guide the optimal selection of revascularisation therapy (either CABG or PCI) in patients with CAD. The recently developed SYNTAX II score, augmented by clinical variables (including age, serum creatinine and left ventricular ejection fraction [LVEF]) has also been externally validated, providing another system to guide the decision between revascularisation with PCI versus CABG. While both Gensini and SYNTAX
scores appropriately give higher weighting to more proximal plaque, they are indirect measures of plaque burden, with neither directly measuring plaque burden, plaque composition, nor evaluating high-risk plaque features identifiable only within the vessel wall

Impact of CTCA on clinical decision-making and outcomes

There are currently no trials that have evaluated the utility of CTCA in altering clinical decision making and improving outcomes for the post-ACS patient group. However, there are several trials that have examined the effect of CTCA on management and subsequent clinical outcomes in the low to intermediate risk population. The landmark SCOT-HEART trial randomised 4,146 low to intermediate cardiovascular risk outpatients with suspected angina from 12 cardiology chest pain clinics across Scotland, to receive either standard care or standard care and assessment with CTCA. The primary endpoint of the study was the proportion of patients diagnosed with angina pectoris secondary to coronary heart disease at 6 weeks. At 6 weeks, CTCA reclassified the diagnosis of CAD in 27% of patients and the diagnosis of angina secondary to CAD in 23%, changing the future utilisation of investigations (15% vs 1%, p<0.0001) and treatment (23% vs 5%, p<0.0001) significantly. CTCA was associated with a 20% increase in the utilisation of ICA at 6 weeks, although the proportion of revascularisation was similar (11.2 vs 9.7%; p=0.0611). After 1.7 years of follow-up, the utilisation of CTCA was associated with a substantial reduction in fatal and nonfatal myocardial infarction (HR=0.62, 95% CI 0.38-1.01; p=0.0527), although this was not statistically significant and event rates were low in both arms. Post-hoc analysis of the SCOT-HEART data from the median time for preventative therapy initiation (50 days) demonstrated that the use of CTCA led to more appropriate utilisation of ICA and preventative medical therapy, manifesting as a halving of the rate of fatal and non-myocardial infarction compared to management with standard care alone (HR: 0.50, 95% CI 0.28-0.88, p=0.020). This post-hoc analysis would later be confirmed in the 5-year follow-up study, where the CTCA group had a significant
reduction in death from coronary heart disease or nonfatal myocardial infarction compared to the standard of care group (2.3% vs. 3.9%; HR=0.59, 95% CI 0.41-0.84; p=0.004). Furthermore, overall rates of coronary revascularisation (HR 1.07, 95% CI 0.91-1.27) and ICA (HR 1.00, 95% CI 0.88-1.13) were similar between groups at 5 years.

The PROMISE trial\textsuperscript{191} randomised 10,003 participants from 192 centres across the USA and Canada to diagnostic testing with either CTCA or functional stress testing, with a primary endpoint of death, nonfatal MI, hospitalization for unstable angina and major CV procedural complications (anaphylaxis, stroke, major bleeding, and renal failure). In contrast to the SCOT-HEART trial, at 25 months of follow-up, there was no statistically significant difference in the rate of the primary endpoint between groups, with 3.3% (164/4996) of patients in the CTA group and 3.0% (151/5007) of patients in the functional-testing group experiencing an event (adjusted HR: 1.04; 95% CI 0.83-1.29; p=0.75), although some authors have criticised this trial for being underpowered.\textsuperscript{192, 193} Furthermore, there was a significant increase in the rate of coronary revascularisation in patients randomised to receive CTCA compared to the functional stress testing group (6.2% vs 3.2%; p>0.001). Several other smaller trials have recently examined the effect of CTCA on clinical outcomes, demonstrating a reduction in the number of hospital admissions and investigations,\textsuperscript{194} with equivocal results pertaining to cardiovascular event rates and mortality.\textsuperscript{195, 196} Overall, there is certainly promise that the utilisation of CTCA may directly improve clinical outcomes, increase diagnostic accuracy and reduce cost in the low to intermediate risk cohort. Indeed, utilizing CTCA in the post-ACS cohort could identify patients who are most likely to benefit from therapy with proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors or other novel therapies, resulting in a reduction in MACE (major adverse cardiovascular events) and/or mortality.\textsuperscript{197} However, it remains less likely that such a benefit in clinical outcomes would translate to the post-ACS
cohort given that most contemporary interventions and medical therapies are applied broadly to all within this patient group.

**CTCA for the risk stratification and diagnosis of patients presenting with suspected ACS**

Several randomised control trials have evaluated the role of CTCA in the risk stratification of patients with chest pain presenting to the emergency department. For example, the randomised control ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography) trial enrolled 1,000 patients without ischaemic changes on ECG or elevated initial troponin into either assessment with early CTCA or standard evaluation. There was an 7.5% rate of observed myocardial infarction in this group, representing a population of intermediate cardiovascular risk. Patients randomised to the early CTCA group had a significant reduction in their mean length of hospital stay (23.2 vs 30.8 hours; p<0.001) with significantly more patients discharged directly from the hospital department (47% vs 12%; p<0.001). However, there was no evidence of a reduction in the mean cumulative cost of care between groups ($4,289 vs $4,060; p=0.65) and there was increased downstream testing and radiation exposure in the CTCA group. Importantly, there were no undetected acute coronary syndromes and no difference in MACE (major adverse cardiac events) between groups at 1 month.

Two other trials examining CTCA in the emergency department, The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial and ACRIN-PA (CT Angiography for Safe Discharge of Patients with Possible Acute Coronary Syndromes) trial, also demonstrated a significant reduction in the time to diagnosis and decreased length of stay. A meta-analysis compared the utilisation of CTCA versus usual care in the emergency department, demonstrating decreased length of stay and cost savings with the use of CTCA, although with a significant increase in the rate of
ICA (OR: 1.36, 95% CI 1.03-1.80; p=0.030) and revascularisation (OR: 1.81, 95% CI 1.20-2.72, p=0.004). However, the BEACON (Better Evaluation of Acute Chest Pain with Computed Tomography Angiography) trial suggested that in the era of hs-CTN, CTCA does not shorten hospital stay, allow for increased direct discharge from ED or identify patients with significant CAD requiring revascularisation. Nevertheless, the use of CTCA was associated with less outpatient testing (4% vs. 10%, p < 0.01) and reduced costs (€337 vs. €511, p < 0.01) compared with contemporary standard of care.

In a retrospective analysis of 472 patients presenting with acute chest pain from the CTCA arm of the ROMICAT-II trial, Puchner et al. demonstrated that high risk plaque features on CTCA were more frequent in those who were ultimately diagnosed with ACS and remained a significant predictor of ACS after adjustment for ≥50% arterial stenosis and clinical risk evaluation (OR: 8.9, 95% CI 1.8-43.3; p<0.006). The presence of arterial stenosis ≥50% on CTCA was also a significant predictor of ACS (RR: 34.4, 95% CI 16.7-70.7, p<0.001). In another observational, retrospective analysis of 160 patients from the ROMICAT-II trial who had both hs-cTN measured and CTCA performed, the CTCA assessment of high-risk plaque features, coronary artery stenosis ≥50% and measurement of hs-cTN significantly improved discriminatory ability for ACS when compared to conventional troponin and traditional CTCA assessment (AUC: 0.74 to 0.84; p <0.001). The use of CTCA reclassified 71.9% of those with intermediate hs-cTN, decreasing the fraction of patients remaining at intermediate risk of ACS from 43.8% to 24.4%. The assessment of HRP features on CTCA when compared to traditional CTCA assessment, improved the specificity for the diagnosis of ACS from 48.2% to 68.1%. The exclusion of HRP and arterial stenosis in this setting has been hypothesised to decrease downstream testing such as ICA. Further studies are needed to confirm if the use of CTCA and hs-cTN in the emergency department could translate into reduced utilisation of ICA for patients with suspected ACS.
Model for CTCA and the risk stratification of the post-ACS population

The utilisation of CTCA may have an important role in identifying patients post-ACS who are at increased risk of a recurrent event. The quantification of plaque burden, plaque composition and the identification of HRP characteristics, may provide incremental benefit when combined with current models of risk estimation (i.e. GRACE and SYNTAX scores) in this high-risk cohort, allowing for improved risk stratification and the identification of individuals most likely to benefit from more expensive or novel therapeutics (see Figure 4). While there are only several studies examining the long-term prognostic utility of CTCA assessment of plaque burden in the post-ACS population, additional inference can be made from extensive research in the low to intermediate risk population and in patients with suspected ACS presenting to the emergency department.

CTCA as a gatekeeper for invasive angiography for patients with troponin-positive ACS

For the assessment of patients with confirmed troponin-positive ACS, the integration of CTCA into contemporary clinical practice remains problematic. An additional CTCA scan following ICA is not feasible due to additional radiation and contrast exposure. It is unlikely that the identification of HRP and plaque quantification for risk stratification could justify such an approach. However, the adoption of a role as a gatekeeper for ICA in lower risk ACS patients could potentially represent a viable alternative for the integration of CTCA into contemporary workflow.

ICA, in combination with OCT and IVUS, remains the gold-standard for the anatomical assessment of coronary arterial stenosis, with excellent spatial and temporal resolution. However, more frequently ICA is used in combination with FFR, with OCT and IVUS typically utilised in academic centres. Perhaps even more significantly, ICA facilitates the performance of PCI immediately following imaging. Yet, diagnostic ICA is invasive, resource intensive,
Figure 1.4: Potential model for the role of CTCA in defining risk in the post-ACS cohort

This figure demonstrates a theoretical pathway for the integration of CTCA for risk stratification following ACS into clinical practice.

ACS = acute coronary syndrome, CTCA = computed tomography coronary angiography, DAPT = dual-antiplatelet therapy, PCSK9 = proprotein convertase subtilisin/kexin type 9 inhibitors, NOAC = non-vitamin K antagonist oral anticoagulant
and associated with rare, although serious complications, including vascular complications (0.5%), contrast reactions (0.23%), cerebrovascular accident (0.07%), acute myocardial infarction (0.06%) and death (0.1%). Furthermore, diagnostic ICA has been associated with a higher estimated mean effective radiation dose when directly compared to CTCA (8.5+/-4.4mSv vs 2.1+/-0.7mSv, p<0.001).

Current guidelines mandate emergent ICA for PCI-mediated reperfusion in patients with STEMI or occlusive myocardial infarction and it is unlikely there could be any role for CTCA in this setting as it would lead to unacceptable delays in revascularisation. However, CTCA could potentially act as a gatekeeper in ACS patients with NSTEMI/UA, or more precisely, those with non-occlusive myocardial infarction who are unlikely to require emergent reperfusion, who account for approximately 75% of the ACS population. Particularly in settings where patients with lower risk NSTEMI/UA do not undergo emergent angiography within 24 hours, a transition to utilising CTCA as an ICA sparing measure may be feasible, although some institutions have a policy of an early invasive approach even in this patient group. Based on the estimated radiation doses described above, it can be calculated that if one out of four patients undergoing CTCA did not require a subsequent ICA, overall mean estimated radiation dosage would be lower (33.9mSv vs 34mSv). The development of FFR CT and stress CT perfusion techniques may further define which of these lower risk ACS patients may benefit from ICA and reperfusion.

Furthermore, CTCA may have a role in the diagnosis of the MINOCA patient group, who account for approximately 6% of patients who present with myocardial infarction. The aetiology of MINOCA includes, but is not limited to, coronary vasospasm, myocarditis, pulmonary embolism, cardiomyopathy (takotsubo, dilated, hypertrophic), tachyarrhythmia-mediated, renal impairment, stroke, septic shock, spontaneous coronary artery dissection, Factor V Leiden, Protein C and S deficiency, sympathomimetic-induced spasm (i.e. cocaine)
or microvascular dysfunction/embolization. One suggested approach in determining the aetiology of MINOCA is to first rule out non-ischaemic causes of troponin elevation with clinical evaluation and cardiac magnetic resonance imaging. Secondly, investigation into other causes with thrombophilia screening, coronary microvasculature assessment and coronary vasospasm testing should be considered. The utilisation of CTCA in this setting may not only reduce the use of unnecessary ICA, but also identify radiographic features of pulmonary embolism, aortic dissection and cardiomyopathy. In one study, 36.8% of MINOCA patients had angiographically normal coronary arteries, with 65.2% demonstrating stenosis <50%. CTCA may have a role in the detection of atherosclerotic disease in the vessel wall of patients with angiographically normal coronary arteries, identifying those who would benefit from medical therapy. Furthermore, two-thirds of MINOCA patients present with NSTEMI, representing a group that may be more safely evaluated by CTCA, as emergent ICA is not mandated. Nonetheless, for the evaluation of patients with MINOCA, cardiac magnetic resonance provides a higher diagnostic yield and remains the non-invasive imaging investigation of choice.

**Limitations of CTCA for the evaluation of patients following ACS**

There are several factors which may limit the use of CTCA in the post-ACS setting. Cost and radiation exposure remain the primary concern of healthcare legislators. However, radiation doses of approximately 3mSv are now frequently achieved with the use of modern scanners, with a dose reduction of 70-80% accomplished over the previous 10 years. Furthermore, high contrast volumes are associated with an increased risk of contrast-induced nephropathy. Cost also remains a concern, as randomised trials in the low to intermediate cardiovascular risk groups have failed to clearly demonstrate reduced cost with the use of CTCA.
Clinically, CTCA does not provide substantial information regarding the functional significance of CAD. There is also a concern that the use of CTCA in the post-ACS group may offer less utility than in a lower risk setting. As most ACS patients currently undergo ICA prior to CTCA, CTCA must offer a distinct incremental diagnostic advantage if it is to represent a viable imaging modality in this setting. It is likely that any incremental diagnostic improvement will relate to the identification of HRP characteristics, plaque composition and quantification of plaque burden, however this has not been confirmed.

In addition, molecular imaging modalities, such as 18F-sodium fluoride positron emission tomography (18F-NaF PET), bis-5HT-DTPA-Gd molecular magnetic resonance imaging and near-infrared fluorescence OCT or IVUS, may allow for the early detection of vulnerable high-risk plaque and more active atherosclerotic disease in patients following ACS, although further research is required before defining any role in clinical practice\textsuperscript{215-217}.

Another limitation is that most patients in the high-risk post-ACS group are already prescribed adequate secondary prevention therapy. This means that unlike the low to intermediate risk group, clinical outcomes may not be meaningfully improved with changes in medication prescription. Therefore, improving risk stratification in this patient group may not alter clinical management significantly.
CHAPTER TWO – ASSOCIATION BETWEEN COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY (CTCA)-DERIVED RESIDUAL PLAQUE BURDEN COMPOSITION AND CLINICAL AND ANGIOGRAPHIC RISK SCORES IN PATIENTS FOLLOWING AN ACUTE CORONARY SYNDROME

Numerous studies have demonstrated the value of CTCA for the risk stratification of low and intermediate cardiovascular risk patients, where in addition to providing an evaluation of luminal patency, it can identify, quantify and characterise plaque within the vessel wall.\textsuperscript{17,58} However, despite extensive research supporting clinical use in low and intermediate cardiovascular risk patients,\textsuperscript{190} there is limited research investigating the value of CTCA for the risk stratification of the high-risk post-ACS cohort. Likewise, the utility of quantifying non-culprit lesion plaque on CTCA has not been thoroughly investigated. Indeed, although providing an inferior evaluation of luminal patency when compared to ICA, CTCA could theoretically improve risk-stratification following an ACS through the characterisation and quantification of plaque within the vessel wall by visualising anatomy not seen on ICA.

The development of software for the semi-automatic and automatic quantification of plaque burden on CTCA has improved feasibility, reproducibility and accuracy,\textsuperscript{218} with several studies demonstrating the incremental advantage of automated plaque quantification beyond conventional CTCA analysis in patients with stable coronary artery disease.\textsuperscript{111-113} Currently, the use of risk scores are recommended to identify the risk of death and recurrent MACE following an ACS, including the SYNTAX\textsuperscript{158} score, derived from ICA, and the GRACE\textsuperscript{159} score, derived from a composite of clinical parameters.\textsuperscript{171,180} However, there are a limited data on the association between CTCA quantified plaque and these risk scores used for prognostication.

Therefore, the present study aimed to explore the association between CTCA-derived residual plaque burden components and risk scores that have been validated as predictors of mortality and MACE (GRACE and SYNTAX scores) in patients following an ACS.
A. METHODS

Study design and population

All patients enrolled in the MOTIVATOR (Multi-modality imaging and biomarkers to improve risk stratification for secondary prevention after acute coronary syndrome) study who underwent CTCA within 40 days of ICA were selected. Patients aged 18 years or older were eligible if they were admitted to hospital with a NSTEMI, STEMI or unstable angina and proceeded to inpatient ICA, and if all three major epicardial coronary arteries (left anterior descending, left circumflex, right coronary artery) were suitable for analysis by OCT. Exclusion criteria included: A calculated eGFR <40 ml/min or <60 ml/min with diabetes mellitus, unlikely to survive for at least three years due to comorbidity, coronary anatomy unsuitable for OCT, pregnancy, or previous coronary artery bypass grafting. This study was approved by the Royal Perth Hospital Human Research Ethics Committee (approval number: REG 15-033). All participants provided written informed consent.

Demographic variables, comorbidities and medication were recorded by questionnaire. Height, weight, pulse rate, systolic and diastolic blood pressure were also documented. Additionally, the GRACE score, derived from a combination of patient age, Killip class, systolic blood pressure, the presence of ST segment deviation, cardiac arrest during presentation, serum creatinine concentration, serum cardiac markers and heart rate, was calculated for all participants at the baseline visit.

Invasive coronary angiography

ICA was performed as part of clinical care during the index hospitalization via the transradial or transfemoral route, according to local best practice. The angiographic views obtained, visual interpretation and decisions regarding the need for revascularization and revascularization strategy, were at the discretion of the interventional cardiologists responsible for the clinical
care of each patient on the day of their procedure. Coronary angiography images were independently reviewed by a cardiologist, who calculated the SYNTAX score for each patient, while blinded to the CTCA analysis. The SYNTAX score was calculated using the online calculator http://www.syntaxscore.com.

CTCA data acquisition

All CTCA images were acquired by a 64-multidetector row scanner (Phillips iCT with IMR, or Siemens Definition AS+) within 40 days of ICA. Isotropic voxel size was 0.5 x 0.5 x 0.5 mm or smaller, gantry rotation time 330 ms or less, with a temporal resolution of ≤ 165 ms and collimation of 0.625 mm. The target heart rate for CTCA was < 65 beats per minute. Heart rate was controlled according to local protocol, with oral metoprolol 50 mg, or in the case of beta-blocker intolerance, ivabradine 7.5 mg. Additional medication was given if required to reach the target heart rate. Radiation dose was minimised through the utilization of prospective ECG-triggered tube current modulation, limiting the maximum dose to the diastolic phase of the cardiac cycle resulting in an average radiation dose received of 3 mSv per scan. Image slices were reconstructed at 0.5 mm slice thickness at an increment of 0.5 mm. The contrast volume was adjusted according to body size and the mean contrast volume was 122 (±31) ml.

Quantification of residual plaque burden on CTCA

Semi-automatic quantification of coronary plaque burden was performed utilizing previously validated, dedicated CTCA software (QAngio CT RE, Version 3.1, Medis, Leiden, the Netherlands) by a single reader, S.B, who was blinded to clinical data and ICA results.\textsuperscript{220,221} Initially, an automatic tree extraction algorithm was used to derive straightened and curved MPR volumes for each coronary vessel. Each coronary artery was then divided into segments according to the Society of Cardiovascular Computed Tomography guidelines.\textsuperscript{222} Luminal and
vessel wall contours were then analysed in 0.5 mm transverse cross-sections perpendicular to derived centrelines (Figure 1). Classification into low attenuation, fibro-fatty, fibrotic and dense calcified plaque was performed automatically using dynamic adaptive HU thresholds adjusted according to an algorithm based on luminal contrast densities, a method previously validated by IVUS. Plaque quantification was performed in all coronary vessels until luminal diameter was less than 2 mm. Plaque burden was calculated by the formula: (plaque area / vessel area) X 100. To define residual plaque burden, stented sections of each segment were excluded from the final analysis. Five parameters of residual plaque burden were derived:

1. Total residual plaque burden (%): defined as the total plaque burden of all analyzed coronary segments excluding stented sections.

2. Residual low attenuation plaque burden (%): defined as the total low attenuation plaque burden of all analyzed coronary segments excluding stented sections.

3. Residual dense calcified plaque burden (%): defined as the total dense calcified plaque burden of all analyzed coronary segments excluding stented sections.

4. Residual fibro-fatty plaque burden (%): defined as the total fibro-fatty plaque burden of all analyzed coronary segments excluding stented sections.

5. Residual fibrotic plaque burden (%): defined as the total fibrotic plaque burden of all analyzed coronary segments excluding stented sections.
Figure 2.1: Examples of the calculation of residual plaque burden on CTCA

Panel A demonstrates a curved MPR image of the RCA. The orange contour represents the outer vessel wall, while the yellow contour represents the luminal wall. Panel B demonstrates a transverse slice of the RCA seen in panel A. The area in between the orange and yellow contours is calculated as plaque area, while vessel area is calculated as the area within the orange contour. Residual plaque burden is then calculated as: (plaque area / vessel area) X 100 for each transverse slice and summated for each segment, excluding stented sections. Panel C demonstrates a curved MPR image of the LM and LAD for a different patient, with a transversal slice seen in panel D. There are no stented sections in this example, so residual plaque burden is equal to plaque burden.

CTCA = Computed tomography coronary angiography, dLAD = Distal left anterior descending coronary artery, dRCA = Distal right coronary artery, LAD = Left anterior descending coronary artery, LM = Left main coronary artery, mLAD = Mid-left anterior descending coronary artery, MPR = Multiplanar reformatted, mRCA = Mid-right coronary artery, pLAD = Proximal left anterior descending coronary artery pRCA = Proximal right coronary artery, RCA = Right coronary artery
Statistical analysis

Categorical variables are expressed as numbers and percentages. The Kolmogorov–Smirnov test and visual assessment of histograms were used to examine for adherence to a normal distribution. Normally distributed continuous variables are presented as mean ± standard deviation whilst variables that are non-normally distributed are presented as median and interquartile range. Categorical variables were compared using the $\chi^2$ test. Continuous variables were compared using the Student $t$-test if normally distributed, while the Mann-Whitney $U$-test was utilized for non-normally distributed variables. Pearson correlation was used to investigate the relationship between normally distributed variables, whereas Spearman correlation was used if parameters were not normally distributed. Ten random individuals were selected for evaluation of intraobserver agreement using scatter plots, intraclass correlation coefficients (ICCs) and Bland Altman analysis. Intraobserver measurements were performed offline after a two-week interval. All tests were two-sided and $p$-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL).

B. RESULTS

Clinical Characteristics

A total of 75 patients were recruited from the department of cardiology at Royal Perth Hospital according to the study protocol. Of these, 62 patients underwent CTCA within 40 days of enrolment (Figure 2). One patient was excluded from CTCA analysis due to inadequate image quality (feasibility, 98%). The mean age of participants was 61.3 ($\pm$9.2) years, 85% were of male sex, 7% had a previous history of myocardial infarction, 54% of patients had hypertension, 44% dyslipidemia, 18% diabetes mellitus, 8% chronic kidney disease and 31% were current smokers. The mean GRACE score was 123 ($\pm$25), the median SYNTAX score
was 11 (interquartile range, 5.5 to 19), while the median number of stents per patient was 2, with 52 patients (85%) receiving at least one stent. Additional clinical characteristics are summarized in Table 1.

Figure 2.2: Study Flow Chart

CTCA = Computed tomography coronary angiography, ICA = Invasive coronary angiography, MOTIVATOR study = Multi-modality imaging and biomarkers to improve risk stratification for secondary prevention after acute coronary syndrome study
Table 2.1: Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population (n=61)</th>
<th>GRACE Score &lt;123 (n=30)</th>
<th>GRACE Score ≥123 (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.3 (±9.2)</td>
<td>57.5 (±8.0)</td>
<td>67.0 (±8.9)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>52 (85%)</td>
<td>28 (93%)</td>
<td>24 (77%)</td>
<td>p=0.080</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30kg/m²)</td>
<td>23 (38%)</td>
<td>15 (50%)</td>
<td>8 (26%)</td>
<td>p=0.051</td>
</tr>
<tr>
<td>CKD (eGFR &lt;60ml/min/1.73m²)</td>
<td>5 (8%)</td>
<td>1 (3%)</td>
<td>4 (7%)</td>
<td>p=0.173</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (18%)</td>
<td>5 (17%)</td>
<td>6 (19%)</td>
<td>p=0.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (54%)</td>
<td>18 (60%)</td>
<td>15 (48%)</td>
<td>p=0.36</td>
</tr>
<tr>
<td>Previous history of MI</td>
<td>4 (7%)</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>p=0.97</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (31%)</td>
<td>15 (50%)</td>
<td>4 (13%)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (44%)</td>
<td>13 (43%)</td>
<td>14 (45%)</td>
<td>p=0.89</td>
</tr>
<tr>
<td>Number of stents</td>
<td>2 (1 to 2)</td>
<td>1 (1 to 2)</td>
<td>2 (1 to 2)</td>
<td>p=0.50</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>11 (5.5 to 19)</td>
<td>7.5 (5.75 to 16.25)</td>
<td>13.0 (5 to 22)</td>
<td>p=0.13</td>
</tr>
</tbody>
</table>

**Blood test results**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population (n=61)</th>
<th>GRACE Score &lt;123 (n=30)</th>
<th>GRACE Score ≥123 (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sensitivity cardiac troponin, ng/L</td>
<td>1180 (162 to 10105)</td>
<td>1330 (163 to 6355)</td>
<td>1100 (148 to 18500)</td>
<td>p=0.59</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>146.0 (135.0 to 154.0)</td>
<td>147.5 (137.8 to 153.0)</td>
<td>140.3 (133.0 to 154.0)</td>
<td>p=0.33</td>
</tr>
<tr>
<td>Total Cholesterol, mmol/L</td>
<td>5.0 (±1.2)</td>
<td>5.2 (±1.3)</td>
<td>4.7 (±1.0)</td>
<td>p=0.11</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.1 (±1.0)</td>
<td>3.2 (±1.1)</td>
<td>2.9 (±0.8)</td>
<td>p=0.32</td>
</tr>
<tr>
<td>WCC, 10⁹/L</td>
<td>10.2 (±2.6)</td>
<td>10.1 (±2.4)</td>
<td>10.2 (±2.8)</td>
<td>p=0.84</td>
</tr>
</tbody>
</table>

Data are presented as mean± SD if normally distributed or median (25th-75th percentile) if not normally distributed

BMI = Body mass index, CKD = Chronic kidney disease, GRACE score = Global Registry of Acute Coronary Events score, Hb = Haemoglobin, LDL = Low-density lipoprotein cholesterol, MI = Myocardial infarction, SYNTAX score = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score, WCC = White cell count

**CTCA**

Quantitative CTCA analysis demonstrated that mean total residual plaque burden was 39.0 (±5.4) %, composed of 60% fibrotic plaque, 25% fibro-fatty plaque, 9% low-attenuation plaque and 6% dense-calcified plaque. Mean non-calcified residual plaque burden was 36.2 (±4.3) %, while median residual dense calcified plaque burden was 1.1 %. Of the non-calcified residual plaque, mean low attenuation plaque burden was 3.5 (±1.0) %, mean fibro-fatty plaque burden was 23.0 (±3.5) % and mean fibrotic plaque burden was 9.7 (±1.8) %. When the population was dichotomized according to median GRACE score, the upper quantile had a higher total
residual plaque burden, a higher residual fibrotic plaque burden and a higher residual dense calcified plaque burden. CTCA characteristics are summarized in Table 2.2 and Table 2.3.

Table 2.2: CTCA characteristics according to GRACE score

<table>
<thead>
<tr>
<th>Variable:</th>
<th>Total population (n=61)</th>
<th>GRACE Score &lt;123 (n=30)</th>
<th>GRACE Score ≥123 (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total residual plaque burden, %</td>
<td>39.0 (±5.4)</td>
<td>36.5 (±4.6)</td>
<td>41.3 (±5.1)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Residual low attenuation plaque burden, %</td>
<td>3.5 (±1.0)</td>
<td>3.2 (±0.9)</td>
<td>3.7 (±1.1)</td>
<td>p=0.051</td>
</tr>
<tr>
<td>Residual dense calcified plaque burden, %</td>
<td>1.1 (0.5 to 3.3)</td>
<td>0.8 (0.4 to 1.8)</td>
<td>2.1 (0.8 to 4.0)</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Residual fibro-fatty plaque burden, %</td>
<td>9.7 (±1.8)</td>
<td>9.4 (±1.8)</td>
<td>10.1 (±1.8)</td>
<td>p=0.15</td>
</tr>
<tr>
<td>Residual fibrotic plaque burden, %</td>
<td>23.0 (±3.5)</td>
<td>22.0 (±3.1)</td>
<td>23.9 (±3.7)</td>
<td>p=0.042</td>
</tr>
<tr>
<td>Contrast volume, ml</td>
<td>122 (±31)</td>
<td>123 (±29)</td>
<td>122 (±34)</td>
<td>p=0.84</td>
</tr>
</tbody>
</table>

Data are presented as mean± SD if normally distributed or median (25th-75th percentile) if not normally distributed

CTCA = Computed tomography coronary angiography, GRACE score = Global Registry of Acute Coronary Events score

Table 2.3: CTCA characteristics according to SYNTAX score

<table>
<thead>
<tr>
<th>Variable:</th>
<th>Total population (n=61)</th>
<th>SYNTAX Score &lt;11 (n=30)</th>
<th>SYNTAX Score ≥11 (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total residual plaque burden, %</td>
<td>39.0 (±5.4)</td>
<td>37.5 (±4.4)</td>
<td>40.4 (±5.9)</td>
<td>0.039</td>
</tr>
<tr>
<td>Residual low attenuation plaque burden, %</td>
<td>3.5 (±1.0)</td>
<td>3.2 (±1.2)</td>
<td>3.6 (±0.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Residual dense calcified plaque burden, %</td>
<td>1.1 (0.5 to 3.3)</td>
<td>0.8 (0.4 to 2.4)</td>
<td>1.5 (0.6 to 3.9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Residual fibro-fatty plaque burden, %</td>
<td>9.7 (±1.8)</td>
<td>9.3 (±2.0)</td>
<td>10.1 (±1.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Residual fibrotic plaque burden, %</td>
<td>23.0 (±3.5)</td>
<td>22.6 (±2.7)</td>
<td>23.4 (±4.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Contrast volume, ml</td>
<td>122 (±31)</td>
<td>119 (±25)</td>
<td>126 (±36)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Data are presented as mean± SD if normally distributed or median (25th-75th percentile) if not normally distributed

CTCA = Computed tomography coronary angiography, GRACE score = Global Registry of Acute Coronary Events score
Relationship between CTCA-derived residual plaque burden, GRACE and SYNTAX scores

Correlations between parameters of residual plaque burden, GRACE and SYNTAX scores are presented in Table 3. Total residual plaque burden demonstrated a statistically significant correlation with GRACE and SYNTAX scores ($r=0.40$, $p=0.001$ and $r=0.37$, $p=0.004$, respectively), although there was no significant correlation between SYNTAX and GRACE scores ($r=0.20$, $p=0.13$) (Figure 3). Figure 4 demonstrates that the proportion of patients with total residual plaque burden above the median is higher with higher SYNTAX and GRACE scores. Residual dense calcified plaque burden significantly correlated with GRACE and SYNTAX scores ($r=0.32$, $p=0.013$; $r=0.26$, $p=0.044$ respectively). Residual fibrotic plaque burden also significantly correlated with GRACE scores, although not with SYNTAX scores. There was no statistically significant correlation between residual low attenuation plaque burden and either the GRACE or SYNTAX scores.

Figure 2.3: Correlation of total residual plaque burden, GRACE and SYNTAX scores.

A significant correlation between total residual plaque burden and SYNTAX and GRACE scores is evident. There is no correlation between GRACE and SYNTAX scores.

GRACE score = Global Registry of Acute Coronary Events score, SYNTAX score = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score
<table>
<thead>
<tr>
<th></th>
<th>GRACE score</th>
<th>SYNTAX score</th>
<th>Total residual plaque burden</th>
<th>Residual low attenuation plaque burden</th>
<th>Residual dense calcified plaque burden</th>
<th>Residual fibro-fatty plaque burden</th>
<th>Residual fibrotic plaque burden</th>
<th>Non-calcified residual plaque burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE score</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>0.20</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total residual plaque burden</td>
<td>0.40**</td>
<td>0.37**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual low attenuation plaque burden</td>
<td>0.18</td>
<td>0.14</td>
<td>0.46**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual dense calcified plaque burden</td>
<td>0.32*</td>
<td>0.26*</td>
<td>0.56**</td>
<td>0.06</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual fibro-fatty plaque burden</td>
<td>0.061</td>
<td>0.19</td>
<td>0.36*</td>
<td>0.62**</td>
<td>-0.25</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual fibrotic plaque burden</td>
<td>0.29*</td>
<td>0.23</td>
<td>0.68**</td>
<td>-0.07</td>
<td>0.27*</td>
<td>0.00</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-calcified residual plaque burden</td>
<td>0.31*</td>
<td>0.29*</td>
<td>0.84**</td>
<td>0.49**</td>
<td>0.13</td>
<td>0.58**</td>
<td>0.75**</td>
<td>1</td>
</tr>
</tbody>
</table>

Pearson correlation coefficients are displayed for normally distributed variables, Spearman correlation coefficients are displayed for non-normally distributed variables.

*p<0.05

**p<0.01

GRACE score = Global Registry of Acute Coronary Events score, SYNTAX score = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score
Figure 2.4: Bar graphs depicting the relationship between GRACE and SYNTAX scores above and below the median and the proportion of patients with total residual plaque burden above the median. It is evident from the bar graphs, that with increasing GRACE and SYNTAX scores, an increasing proportion of patients have a total residual plaque burden above the median.

GRACE score = Global Registry of Acute Coronary Events score, SYNTAX score = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery score

**Intra-observer variability**

Bland-Altman analysis and scatter plots for assessing the intraobserver variability for three of the CTCA-derived parameters of residual plaque burden are presented in Figure 5. The ICC for intraobserver variability was 0.878 for total residual plaque burden (p<0.0001) and 0.814 for residual low attenuation plaque burden (p<0.0001), indicating good reliability (Table 4). The ICC for intraobserver variability for residual dense calcified plaque burden demonstrated excellent reliability at 0.942 (p<0.0001).
Figure 5: Scatterplots for intraobserver measurements (A) and Bland-Altman plots for intraobserver agreement (B) for parameters of residual plaque burden. Figure 4A demonstrates scatterplots with a line of best fit (black line), 95% confidence intervals (dotted lines) and r² values, reflecting the good reproducibility of parameters of residual plaque burden. Figure 4B shows the mean difference of intraobserver measurements and the limits of agreement. Intraclass correlation coefficients were 0.88 (0.48 to 0.97), 0.81 (0.01 to 0.96) and 0.94 (0.79 to 0.99) for total residual plaque burden, residual low attenuation plaque burden and residual dense calcified plaque burden, respectively.

LAP = low attenuation plaque, DCP = dense-calcified plaque.

C. DISCUSSION

This pilot study demonstrates the feasibility of quantifying and defining the composition of residual plaque burden using CTCA in individuals following an ACS. We found that total and different types of plaque were associated with the GRACE and SYNTAX scores, raising the possibility that CTCA may play a future role in predicting outcome after MACE.

CTCA-derived residual plaque burden composition in the post-ACS cohort

To the best of our knowledge, this study is the first to examine CTCA-derived residual plaque burden composition in a cohort following an ACS. This study demonstrated a mean total
residual plaque burden of 39%, comprised of approximately 60% fibrotic plaque, 25% fibrofatty plaque, 9% low-attenuation plaque and 6% dense-calcified plaque. These values are consistent with those seen in previous IVUS studies evaluating residual plaque burden composition in ACS patients, despite the fact that CTCA quantifies plaque composition across the entire coronary tree, while IVUS only analyses the proximal components of the major epicardial arteries. For example, using IVUS, McPherson et al. demonstrated a higher total residual plaque burden of 49.6%, with similar plaque composition: 59% fibrotic plaque, 21% fibrofatty plaque, 13% low-attenuation plaque and 7% dense-calcified plaque. These similarities suggest that it may be sufficient to analyse plaque composition in the proximal section of a single, major epicardial artery to obtain a representative sample of total coronary plaque composition. Previously, CTCA-derived non-calcified (defined as any plaque <130 HU) and calcified plaque volume were evaluated in a study of 312 consecutive patients presenting with NSTEMI who underwent CTCA prior to ICA. However, plaque burden and detailed plaque characterisation (i.e. low attenuation, fibrotic, fibro-fatty plaque components) were not reported, precluding comparison with the results of this study.

**CTCA-derived residual plaque burden and risk scores**

The SYNTAX score has been validated for the short- and long-term prediction of MACE in the ACS population. It is derived from ICA and grades luminal obstruction and lesion complexity (including lesion calcification, location, tortuosity, presence of thrombus and length). In contrast to CTCA, the SYNTAX score does not provide an estimate of plaque within the vessel wall that does not contribute to luminal stenosis and does not evaluate plaque composition. The present study demonstrated that CTCA-derived total residual plaque burden is positively correlated with the SYNTAX risk score. Of the quantified plaque components, residual dense-calcified and fibrotic plaque burden were correlated with the SYNTAX score.
The finding that these components were associated with the SYNTAX score is intuitive, as fibrotic plaque burden was the parameter best correlated with total residual plaque burden, while the SYNTAX score includes the presence of calcification in its calculation, explaining the association with dense-calcified plaque burden. However, this study did not find evidence of a correlation between low-attenuation plaque burden and the SYNTAX score, which is in agreement with a previous study of 680 ACS and stable angina patients who were evaluated with ICA, radiofrequency IVUS and near-infrared spectroscopy.227

The present study also demonstrated that residual total, dense-calcified and fibrotic plaque burden were correlated with higher GRACE scores, whereas there was no statistically significant association with residual low attenuation and fibro-fatty plaque burden. A meta-analysis of over 200,000 patients previously demonstrated the excellent predictivity of the GRACE score in post-ACS patients, reporting a c-statistic of 0.82 (95% CI: 0.80-0.89) and 0.84 (95% CI: 0.82-0.87) for the prediction of MACE and mortality at short- and long-term follow-up respectively.171 Therefore, the association between plaque burden components and the GRACE score may suggest a possible future role for the quantification of CTCA-derived residual plaque burden for the risk prediction of the post-ACS population. However, the absence of an association between the GRACE score and residual low-attenuation plaque burden differs from the findings of a recent study of stable chest pain patients from the SCOT-HEART cohort, where low-attenuation plaque burden quantified on CTCA was the strongest predictor of future MACE and mortality.58 Similar to the present study, they utilized semi-automatic plaque quantification with scan-specific thresholds for plaque components, although low-attenuation plaque was defined differently, by a fixed threshold of <30 HU. Importantly, this study only evaluated lower cardiovascular risk patients and did not include patients with a history of ACS. Further research is required to delineate the most important plaque components for defining risk in the post-ACS population.
SYNTAX score and GRACE score

There was no significant correlation between the SYNTAX and GRACE scores in this study, which was unexpected given that clinical determinants of cardiovascular risk (age, systolic blood pressure and renal function) are usually at least moderately related to the extent of atherosclerotic disease visualised on ICA. The closer relationship between CTCA-derived residual plaque burden and the clinical risk factors comprising the GRACE score, may reflect the capability of CTCA to quantify plaque within the vessel wall in addition to plaque causing luminal narrowing. Indeed, that CTCA-derived residual plaque burden correlates with both validated risk scores, while the risk scores do not correlate with each other, suggests that it may have a role in the future in facilitating risk prediction for patients following an ACS.

Previous studies utilizing a variety of imaging modalities have demonstrated an association between residual plaque burden and cardiovascular risk in the post-ACS cohort. For example, the investigators of the PROSPECT trial demonstrated that higher residual plaque burden (as estimated by IVUS) was associated with an increased risk of MACE. In another study of 697 ACS patients who underwent successful PCI, greater IVUS-derived lesion-based residual plaque burden was significantly associated with MACE. In one of the few studies examining the prognostic value of CTCA following an ACS, residual plaque burden index was demonstrated to be significantly associated with MACE at a median of 4.8 years of follow-up of 169 patients. Residual plaque burden index was defined as total plaque volume divided by vessel length (rather than the standard calculation of plaque burden, which divides by vessel area instead of length), excluding stented coronary segments. Additionally, the study did not report on the composition of quantified plaque burden or the association of different plaque components with cardiovascular risk.
**Clinical implications**

The association between CTCA-derived residual plaque burden composition and validated risk scores observed in this study, suggests that CTCA may provide an insight into the risk profile of individuals following an ACS event. Theoretically, the quantification of low-attenuation plaque burden would provide the optimal evaluation of the activity and extent of coronary atherosclerosis,\textsuperscript{44, 58} although a strong relationship between this parameter and validated clinical and angiographic risk scores was not observed in this study. Furthermore, intraobserver variability for the measurement of residual low-attenuation plaque burden was more marked when compared to other CTCA-derived parameters, an important consideration if this parameter is to be utilized clinically to evaluate individual patient risk. Nonetheless, it is possible that in the future, CTCA may improve risk stratification, allowing clinicians to target ACS patients at the highest risk with more intense risk factor modification therapies, such as newer blood pressure and lipid regulating therapies, or prolonged dual anti-platelet therapy.\textsuperscript{197, 229} However, further research demonstrating that CTCA incrementally improves prognostication of the post-ACS cohort beyond that of current models is required before integration into clinical practice.

While in this study, CTCA plaque quantification was semi-automated, recent data demonstrates that quantification of plaque burden on CTCA can be automated, providing a reproducible, standardised estimation of plaque burden composition that correlates well with IVUS.\textsuperscript{218, 230} Indeed, while previously time-consuming and cumbersome to perform, continued improvements in automation may allow for plaque burden quantification to be seamlessly integrated into clinical practice.\textsuperscript{58}
Limitations

This study is subject to all of the limitations of a single centre, observational design. Additionally, only a small number of patients were enrolled, and it was not powered to evaluate hard clinical endpoints. While validated, risk scores associated with MACE and mortality (such as the GRACE and SYNTAX scores) are imperfect substitutes for hard CVD outcomes.\textsuperscript{172, 231} Importantly, due to the absence of cardiovascular outcome data, this study was unable to evaluate any incremental benefit of CTCA over these contemporary risk scores. Another limitation is the quantification of plaque burden excluding stented sections (residual plaque burden), rather than the quantification of total plaque burden prior to intervention. However, while stented sections were excluded, plaque burden is adjusted for the area of the segment assessed. Furthermore, it is likely that a representative sample of plaque burden composition can be obtained through the evaluation of a representative proximal coronary segment, as previously discussed. Additionally, several prior studies have already demonstrated the prognostic value of the quantification of residual plaque burden following ACS.\textsuperscript{225, 228}
CHAPTER THREE: CONCLUSION AND FUTURE DIRECTIONS

The investigation of the role of CTCA in the post-ACS cohort is a highly topical field of research, with studies such as the PREFFIR\textsuperscript{232} trial currently recruiting patients in order to better identify those at higher risk of recurrent events. However, at this time there is insufficient data to define the role of CTCA in the post-ACS setting. Indeed, there has been minimal research and advances in the analysis of the post-ACS cohort with CTCA over the previous decade. While it is less likely that improved risk stratification with CTCA will translate directly into improved clinical outcomes as seen in lower-risk groups, the ability to more accurately stratify the heterogeneous risk profile of the post-ACS patient group may allow for targeted interventions for those at highest risk. For example, future trials may be able to define which post-ACS patients should receive concurrent PCSK9 inhibitor-statin therapy or prolonged dual-anti-platelet therapy. Introduction of CTCA as a gatekeeper to ICA in the lower-risk NSTEMI or UA patient group could allow for integration of this theoretically improved risk stratification (i.e. through the assessment of plaque burden and plaque composition) into contemporary workflow whilst decreasing the rates of unnecessary ICA.

The study presented in chapter two demonstrates that total residual plaque burden and plaque components can be quantified by CTCA after ACS and are associated with clinical and angiographic risk scores. However, determining the clinical significance of these CTCA-derived plaque components will require a large clinical study powered for hard clinical endpoints. In addition, further studies directly comparing CTCA-derived coronary plaque burden with conventional risk stratification models, such as the GRACE and SYNTAX scores, are required to demonstrate any incremental benefit in prognostication for this patient group.
REFERENCES


68. Danciu SC. Usefulness of multislice computed tomographic coronary angiography to identify patients with abnormal myocardial perfusion stress in whom diagnostic catheterization may be safely avoided. Am J Cardiol. 2007;100(11):1605-8.


140. Kitagawa T, Yamamoto H, Ohhashi N, Okimoto T, Horiguchi J, Hirai N, et al. Comprehensive evaluation of noncalcified coronary plaque characteristics detected using 64-


APPENDICES

Appendix A – Ethics approval letter from UNDA

28 August 2019

Professor David Playford
School of Medicine
The University of Notre Dame Australia
P.O.Box 944
Broadway NSW 2007

Dear David,

Reference Number: 019121F
Project title: “What is the prognostic value of Computed Tomography Coronary Angiography (CTCA) in the evaluation of the post-acute coronary syndrome (ACS) population group?”

Thank you for submitting the above project for review. It is noted that you have ethics approval for this project from Royal Perth Hospital HREC, reference number REG 15-033. Your application has been assessed as qualifying for a Cross-Institutional approval and is therefore exempt from HREC review. I am pleased to advise that ethical clearance has been granted for this proposed study.

Other researchers identified as working on this project are:

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<th>Name</th>
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<th>Role</th>
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<tr>
<td>Steele Butcher</td>
<td>School of Medicine</td>
<td>MD student</td>
</tr>
<tr>
<td>Prof Carl Schultz</td>
<td>Royal Perth Hospital</td>
<td>Co-Supervisor</td>
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All research projects are approved subject to standard conditions of approval.
Please read the attached document for details of these conditions.

Should you have any queries about this project, please contact me at #2964 or Natalie.Giles@nd.edu.au.
Appendix B – Ethics approval letter from Royal Perth Hospital HREC

20 June 2018

Professor Carl Schultz
Cardiology
Royal Perth Hospital

Dear Professor Schultz

Project Title: *Multi-modality imaging and biomarkers to improve risk stratification for secondary prevention after acute coronary syndrome The MOTIVATOR Study*

REG Number: 2015-033

HREC: Royal Perth Hospital Human Research Ethics Committee (EC00270)

Site: Royal Perth Hospital

The following amendment(s) (and associated documents) have been approved by the RPH HREC and the EMHS site(s):

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<td>Extension of Approval:</td>
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Change to Project Investigators:  
Addition of Steele Butcher as Associate Investigator  
Addition of Claire Siedovskas as Associate Investigator

If this project is also being conducted at non-EMHS sites, please submit a copy of this approval letter to the Research Governance Office of those sites, as evidence of approval by the HREC.