Detecting unstable plaques in humans using cardiac CT Can it guide treatments?

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REVIEW

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Can it guide treatments?

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ABSTRACT

Advances in imaging technology have driven the rapid expansion in the use of computed tomography in the assessment of coronary atherosclerotic plaque. Current guidelines recommend coronary CT angiography as the first line diagnostic test for patients presenting with stable chest pain based on a rapidly growing evidence base. There is a growing need to refine current methods for diagnosis and risk stratification to better individualise preventative therapies. Imaging assessments of high-risk plaque with computed tomography can be used to differentiate stable from unstable patterns of coronary atherosclerosis and potentially to improve patient risk stratification. This review will focus on coronary imaging with computed tomography with a specific focus on the detection of coronary atherosclerosis, high-risk plaque features, and the implications for patient management.

KEYWORDS

1. Coronary CT angiography
2. Atherosclerosis
3. High-risk Plaque
4. Positron Emission Tomography

ABBREVIATIONS

1. CT: Computed Tomography
2. TCFA: Thin Cap Fibrous Atheroma
3. PET: Positron Emission Tomography

4. TPSO : Translocator proteins
5. LDL: Low Density Lipoproteins
6. PKS9: Proprotein convertase subtilisin–kexin type 9

INTRODUCTION

Cardiovascular disease remains the leading causes of death globally, placing a huge economic burden on health services worldwide (Mendis et al., 2015). Subsequently, there remains major interest in refining our current methods for diagnosis and risk stratification to better individualise preventative therapies. Atherosclerosis is the main pathophysiological process responsible for cardiovascular disease. It is a systemic multifocal process that starts early in life and has a long quiescent phase prior to the manifestation of clinically overt disease. The majority of patients presenting acutely with a thrombotic cardiovascular event have no previous manifestation of their disease (Ambrose et al., 1988; Myerburg et al., 1992). This silent disease process presents a tremendous diagnostic challenge, underpinning the global burden of cardiovascular disease.

Coronary computed tomography (CT) angiography has emerged as a powerful tool for the diagnosis of coronary artery disease. As well as the assessment of luminal stenosis, it allows direct plaque visualisation and potential identification high-risk plaque. Myocardial infarction is most commonly caused by rupture of atherosclerotic plaque and plaques that rupture have certain common characteristics that together define the vulnerable plaque (Kolodgie et al., 2001). Vulnerable plaques have played an integral role in of our understanding of atherosclerosis and cardiovascular disease, with extensive research conducted to better characterise and identify these lesions. This identification, in combination with timely intervention prior to the occurrence of an acute event, could potentially comprise a treatment

strategy for reducing the morbidity and mortality of atherosclerotic disease. This review will focus on the use of computed tomography to detect coronary atherosclerosis, high-risk plaque features, and the implications for patient management.

THE CONCEPT OF THE VULNERABLE PLAQUE

The coronary artery plaque that lies at the core of coronary heart disease has been the subject of intensive research. Pathological intimal thickening is the first progressive stage of atherosclerosis and is characterised by extracellular lipid accumulation. Macrophage infiltration into the lipid pool heralds the formation of fibroatheroma, with associated necrotic core and overlying nascent fibrous cap (Stary et al., 1994). Foam cell death promotes atheroma expansion, and extracellular binding of lipids to collagen fibres and proteoglycan. As the fibroatheroma progresses, the extracellular accumulation of lipids causes severe inflammatory reactions in the arterial wall, with lymphocytic infiltration and depletion of extracellular matrix with subsequent expansion of the lipid core. The secretion of proteases by macrophages and other immune cells can cause weakening of connective tissue in the atheroma with disruption of the fibrous cap and formation of a thin cap fibrous atheroma (Burke et al., 1997). The vulnerable plaque is thus characterised by a large necrotic core, a thin (<65 μm) and inflamed fibrous cap, large plaque volume, inflammatory cell infiltration and spotty calcification (Burke et al., 1997).

As atherosclerotic plaques progress, the affected vessel may undergo positive remodelling with degradation and reorganisation of the extracellular matrix (ECM) scaffold of the vessel wall, a process regulated by matrix metalloproteinases (MMPs) (Bonnans et al., 2014) which also have an established role in the pathophysiology of plaque rupture (Schoenhagen et al., 2000). Positive remodelling may be a sign of an early proliferative process, allowing

expansion of the plaque contents in an outward direction, that mitigates stenosis and preserves blood flow. These plaques, are thought to be particularly "vulnerable" to rupture (Varnava et al., 2002) (Schoenhagen et al., 2000)

Plaque rupture is the commonest complication of atherosclerosis, accounting for 60-70% of culprit lesions in acute myocardial infarction (Naghavi et al., 2003). The majority of clinical events caused by plaque rupture arise from non-obstructive plaques (Virmani et al., 2002). This may explain why percutaneous coronary intervention in optimally treated patients with stable angina may relieve chest pain symptoms but without reducing the risk of death, non-fatal myocardial infarction or major adverse cardiovascular events (Boden et al, 2007; Sedlis et al, 2015). Indeed, plaques prone to rupture share similar morphological characteristic to the aforementioned thin cap fibrous atheroma (TCFA) (Virmani et al., 2006) (Kolodgie et al., 2001). These findings and their imaging equivalents are found in patients who appear to be at increased risk of future adverse clinical events, forming the basic rationale of vulnerable plaque imaging. However, this prognostic information does not appear to hold true at the level of plaque, with data from the PROSPECT trial (A Prospective Natural-History Study of Coronary Atherosclerosis) suggesting that the vast majority of high-risk thin-capped fibroatheromatous plaques did not result in clinical events (Stone et al, 2011). Indeed, most plaque rupture events appear clinically silent, resulting in a healing response and plaque growth rather than infarction (Davies, 2000).

This raises questions about the value of identifying the vulnerable plaque. If the majority of such plaques do not in fact cause clinical events and more likely to heal silently rather than rupture, what is the value in their detection? Some have argued that this concept may work better at the patient level (Naghavi et al., 2003) – giving rise to the concept of the "vulnerable

patient". Patients with a predisposition to develop high-risk plaque characteristics will tend to form many over time. Whilst the majority of individual plaques will heal, the patient will be at greater risk of a plaque ultimately rupturing at a moment of increased thrombogenicity and causing an acute myocardial infarction. Therefore, our approach to CT assessment of coronary plaque needs to take into account this complex interaction between the anatomical, molecular and biomechanical factors that determine sudden symptomatic plaque disruption, the overt patient burden, and its downstream sequelae.

IMAGING TARGETS

Obstructive vs Non-Obstructive Disease

Our clinical approach to coronary atherosclerosis has, for many decades, been based around the detection and treatment of obstructive luminal stenoses and the myocardial ischemia that can ensue (Neumann et al., 2019). Invasive coronary angiography with or without invasive functional assessments is perceived to be the gold standard, although cardiac computed tomography is increasingly being employed for the same purpose, avoiding the need for an invasive procedure **(Figure 1)**. Technical advances, such as more sensitive detectors, faster gantry speed rotation, and superior image reconstruction software, have resulted in improved temporal and spatial resolution with better imaging quality and fewer partial volume effects and motion artefacts. Furthermore, recent breakthroughs in post-processing and analysis, such as radiomics (quantitative measures of image texture), allow us to obtain more information from scans. Using novel data analytic techniques, such as machine learning, distinct patterns in radiological images (Kolossváry et al., 2019) can be identified that would

otherwise go undetected. This has the potential to revolutionise imaging and the field of precision medicine.

Assessment of luminal stenosis by coronary CT angiography has demonstrated powerful prognostic capability (Min et al., 2007). Current clinical interpretation, and quantification of coronary arterial stenosis are based on the 2014 Society of Cardiovascular Computed Tomography (SCCT) reporting guidelines (Wu and Wu, 2015) . Obstructive disease is defined as a luminal stenosis of over 70%, a definition that has been adopted in landmark CT trials. Coronary Artery Disease-Reporting and Data System (CAD-RADS) is a newer standardised reporting system for coronary CT angiography which classifies results based on the severity of stenosis and to link these data to clinical patient management. Degree of stenosis, plaque morphology, image quality, stents, and coronary artery bypass grafts are evaluated to decide the final CAD-RADS category (CAD-RADS 0- CAD-RADS 5). Whilst the CAD-RAD scoring provides important prognostic information in patient undergoing evaluation for coronary artery disease (Xie et al., 2018) , this needs to be confirmed using larger registries, and all analysis should incorporate the presence of modifiers (vulnerability, stent and CABG) in addition to stenosis severity. Whilst this scoring system has been endorsed by the SCCT, ACR and NASCI (Cury et al., 2016), it remains mainly a research tool and requires further refinement prior to routine clinical implementation.

Coronary CT angiography carries important prognostic information in addition to the detection of obstructive disease. It also detects non-obstructive disease which is the dominant cause of major adverse cardiovascular events, and would benefit from early risk modification (Jespersen et al., 2012). In the largest randomised trials to date, approximately half of

patients with subsequent adverse clinical events did not have obstructive coronary artery disease (Douglas et al., 2015; SCOT-HEART investigators, 2015). This is in fact consistent with the pathological studies described above and also well-established data demonstrating that the majority of myocardial infarctions arise from non-obstructive lesions on antecedent angiography (Farb et al., 1996). One explanation for this is that as atherosclerotic plaques progress the affected vessel may undergo positive remodelling with expansion of the plaque contents in an outward direction, that mitigates stenosis and preserves blood flow even in lesions with a high plaque burden: so called Glagovian remodelling (Hadamitzky et al., 2013). In fact, the magnitude of coronary atherosclerosis on coronary CT angiography is an important prognostic factor with multiple studies confirming the predictive value of segmental plaque burden above and beyond the degree of stenosis (Min et al., 2007); (Hadamitzky et al., 2013).

Landmarks trials documenting the mortality benefit of coronary artery bypass grafting for extensive obstructive disease, are based on the premise that prognosis is related to the presence and number of obstructive stenosis (Min et al., 2011). However, patients with widespread non-obstructive coronary artery disease have similar event rates when compared with patients with localized obstructive disease (Bittencourt et al., 2014). Moreover, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) (Boden et al., 2007) and BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) (Boden et al., 2007; BARI 2D Study Group et al., 2009) trials demonstrated that percutaneous coronary intervention failed to reduce the risk of myocardial infarction despite effective relief of obstructive disease and consequent ischemia. As a consequence, questions are being asked about the central role that assessments of luminal stenosis and myocardial ischemia play in the management of patients with suspected

coronary artery disease. Accordingly, there has been growing interest in alternative imaging strategies targeting different aspects of the atherosclerotic disease process.

Recent advanced in computational fluid dynamics, such as fractional flow reserve (FFR)-CT and endothelial shear stress-CT, can enable physicians to gather not only anatomical but also morphologic and derived physiologic data using one non-invasive imaging test (Choi et al., 2015) (Norgaard et al., 2014). These novel CT-based approaches have been validated in clinical trials and are associated with atherosclerotic plaque characteristics and may be helpful to assess the future risk of plaque rupture and to determine treatment strategy (Nakazato et al., 2016).

Plaque Burden

One strategy has been to quantify the total atherosclerotic plaque burden. The rationale being that the more plaques a patient has, the more likely it is that a plaque rupture will occur and cause a clinical event. Coronary artery calcium scoring measures macroscopic calcification in the coronary arteries and provides an reliable surrogate marker of coronary plaque burden. It has repeatedly been shown to correlate with clinical outcome (Greenland et al., 2004); (Budoff et al., 2007). There have been multiple studies examining the very low event rates in patients with coronary artery calcium scores of zero (Sarwar et al., 2009); (Blaha et al., 2016). In asymptomatic patients, the absence of calcium reliably excludes obstructive coronary artery stenosis, although more caution is required in symptomatic patients where non-calcific plaques are observed with greater frequency. On this basis, the most recent National Institute of Clinical Excellence (NICE) chest pain guidelines recommend coronary

CT angiography rather than coronary artery calcium scoring in symptomatic patients (NICE CG95, 2016).

The presence of calcium confirms the presence of coronary atherosclerotic plaque, with increasing scores identify increasing plaque burden and increased cardiovascular risk. Moreover, when added to traditional risk scores, coronary artery calcification has the ability to provide incremental risk predictive information to re-classify individuals into higher or lower risk groups (Silverman et al., 2014); (Polonsky et al., 2010). This has the benefit of facilitating more effective healthcare resource utilisation by minimising therapy in low-risk groups and allowing for more appropriate therapy in high-risk groups thereby improving outcomes (Rozanski et al., 2011). Coupled with its non-invasive nature, minimal radiation exposure and no requirement for patient preparation, its powerful predictive ability makes coronary calcium scoring an attractive option for population screening. Despite its many strengths, not least the decades of prognostic data supporting their value for clinical risk prediction, traditional calcium scores using the Agatston score fail to incorporate information about the number and size of calcified lesions, and are weighted for increasing calcium with higher calcium density. This does seem counterintuitive in the context of histological data suggesting that plaques with high calcium density have smaller lipid cores, whilst plaques with low calcium density have large lipid cores and positive remodelling.

Progression in CT calcium scores is more difficult to interpret. Statins, whilst well established in the prevention of coronary events, appear to increase not decrease the CT calcium score (Wong et al., 2004); (Arad et al., 2005). This perhaps reflects a healing response to statins which may play a role a role in the conversion of non-calcified plaque to calcified plaque, thereby stabilising potentially vulnerable plaques. This highlights an

important limitation of CT calcium scoring: namely this approach is actually targeting a more stable form of plaque that itself is less prone to rupture or cause clinical events. The rationale extension of plaque burden imaging is to consider not only how much plaque a patient has but also what kind of plaque they have and whether the disease process in that area is active or not. These two approaches are considered in the following sections.

Plaque Morphology

The sub-millimeter spatial resolution of coronary CT angiography is capable of imaging not only the lumen, but also the coronary artery wall. This makes CT a promising alternative to the more invasive intravascular imaging with studies demonstrating close correlation between coronary CT angiography and intravascular imaging findings of thin-cap fibroatheromas for the detection of high-risk plaque (Voros et al., 2011) (Tanaka et al., 2008). At the very least, CT angiography is able to differentiate between calcific, partially calcified (mixed) and non-calcified coronary plaque, thereby potentially overcoming an important limitation of CT calcium scoring (Plank et al., 2014). Non-calcified coronary plaques identified by coronary CT angiography portend a poorer prognosis (Hulten et al., 2011; Hou et al., 2012).

Coronary CT angiography can provide even more detailed morphological information. There are several well described coronary CT angiographic features of high-risk plaque which reflect the underlying pathological changes **(Figure 2)**. These are low-attenuation (<30 Hounsfield Units), positive remodelling (commonly defined as a remodelling index >1.1), spotty calcification and the napkin-ring sign (low-attenuation plaque core with a rim of higher attenuation). There is a large body of observational evidence demonstrating the prognostic power of coronary CT angiography assessments of high-risk plaque in both stable and acute coronary presentations. Motoyama and colleagues identified that the presence of

high-risk plaque characteristics was associated with acute coronary syndrome (Motoyama et al., 2007). Recent analyses from the two largest randomised trials of coronary CT angiography in patients with suspected stable coronary disease – the Scottish Computed Tomography of the Heart (SCOT-HEART) and Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trials – have added further weight to the prognostic power of CT assessments of high-risk plaque (Ferencik et al., 2018); (Williams et al., 2019). We will explore this further in the following sections.

While these data support the theory that patients with high-risk plaque features are at increased risk of future events, they highlight an important caveat: that no study of high-risk plaque identification has yet demonstrated incremental prognostic benefit over and above the calcium score. As such, there is currently little evidence to support the inclusion of high-risk plaque features in guidelines and recommendations.

Whilst there is overwhelming evidence that higher calcium scores are associated with greater cardiovascular risk, at an individual plaque level, studies have shown that calcified plaques are more stable and less prone to rupture. This paradox raises questions about the role of calcification in the natural history of coronary atherosclerosis and highlights the need to assess disease activity within plaques.

Plaque Activity

Recent advances in hybrid imaging technology combines the high spatial resolution and anatomical detail provided by CT with molecular assessment of disease activity provided by positron emission tomography (PET). This allows identification of high-risk plaque characteristics, the differentiation of active from burnt out stable disease states, with the

potential to improve patient risk stratification. With modern PET-CT scanners, accurate co-registration, improved blood-pool correction and state-of-the-art motion correction have facilitated the measurement of disease activity in the coronary arteries (Kwiecinski et al., 2018; Lassen et al., 2018). This has in turn triggered a growing interest in the development of novel tracers targeting specific aspects of plaque biology.

^{18}F-Sodium fluoride preferentially binds to pathological mineralisation and identifies areas of microcalcification which is thought to be an early adaptive response to cell necrosis and inflammation that precedes the development of larger macroscopic deposits of calcium that can stabilise plaque (Irkle et al., 2013). The increased surface area of microcalcification relative to macrocalcification results in increased tracer uptake (Creager et al., 2019). Recent evidence demonstrates an inverse correlation between plaque calcium density and tracer uptake, with lesions at the lower end of the Hounsfield unit coefficient exhibiting greater radioisotope accumulation whilst denser and more highly calcified plaque had relatively lower fluoride uptake (Dweck et al., 2012).

^{18}F-Sodium fluoride is characterised by very low uptake in the myocardium (roughly half to two-thirds lower than in the blood-pool) which makes this tracer well suited to the detection of signal in the coronary arteries. In patients with stable disease, ^{18}F-sodium fluoride uptake is associated with multiple adverse features on CT and intravascular ultrasound (Joshi et al., 2014) . Following acute myocardial infarction, increased ^{18}F-sodium fluoride uptake is consistently observed within the culprit plaque (Joshi et al., 2014) **(Figure 3)**. To further investigate the clinical utility of 18F-sodium fluoride in the coronary arteries and its role in risk prediction, the prospective multicentre PREFFIR (Prediction of Recurrent Events With ^{18}F-Fluoride) trial is currently underway (ClinicalTrials.gov NCT02278211).

There are some emerging novel tracers that target more specific inflammatory pathways. For example, there have been recent reports describing the use of ^{68}Ga-dotatate which targets somatostatin type 2 receptors that are abundant on the surface of pro-inflammatory macrophages. This has been successfully used to identify inflamed coronary artery plaque with higher uptake noted in culprit vessel than in the non-culprit vessels (Tarkin et al., 2017). Novel agents that target translocator proteins (TPSO) in macrophages localize to atherosclerotic plaques and can quantify plaque macrophage content (Gaemperli et al., 2012). In contrast to ^{18}F-sodium fluoride, these approaches target the pathological processes and pathways that mediate the disease process itself and may therefore be a better indicator of disease activity and treatment response. Further clinical research is needed to confirm the role of these tracers in the assessment and characterisation of atherosclerotic disease.

One emerging technique for identifying areas of coronary artery inflammation is the assessment of perivascular adipose tissue that is thought to interact with adjacent coronary atherosclerotic plaque in a bidirectional manner (Antonopoulos et al., 2017). Coronary artery and plaque inflammation is thought to alter the composition of the adjacent perivascular adipose tissue, an effect that can be detected by subtle changes in CT attenuation (Antonopoulos et al., 2017); (Goeller et al., 2018) **(Figure 4)**. In effect, the composition of the perivascular fat provides a proxy of underlying inflammation in the coronary arteries and may allow assessment of coronary plaque instability (Antonopoulos et al., 2017). Indeed, the technique does correlate well with 18F-sodium fluoride coronary uptake (Kwiecinski et al., 2019), and appears to identify patients at elevated cardiovascular risk (Mahabadi and Rassaf, 2018) and predict cardiovascular mortality (Oikonomou et al., 2018). The appeal of cardiac a

single coronary CT angiography providing details about coronary anatomy, plaque morphology, plaque burden as well as disease activity is undeniable.

CLINICAL CONTEXT

Asymptomatic Individuals

At present, coronary artery calcium scoring is superior to any combination of traditional risk factors and serum biomarkers. In asymptomatic patients, a calcium score of zero has a negative predictive value of 95-99% (Sarwar et al., 2009). In these patients, the absence of calcium reliably excludes obstructive coronary artery stenosis. Equally, scores >0 confirm the presence of coronary atherosclerotic plaque, and increasing scores identify increasing plaque burden and increased cardiovascular risk (Detrano et al., 2008). The 2017 Society of Cardiovascular Computed Tomography (SCCT) guidelines recommend performing calcium scoring in selected patients with a CVD risk between 5 and 20% in the context of shared decision-making (Hecht et al., 2017). Calcium scoring should also be considered in patients with CVD risk <5% who have a with family history of premature coronary heart disease (Hecht et al., 2017). Calcium scores can guide the need for lipid lowering therapy. A coronary artery calcium score >300 Agatston units is associated with a four-fold higher risk of cardiovascular events compared to a calcium score of zero (Lauer, 2007). On this basis, the 2013 ACC/AHA Guideline on the Management of High Cholesterol (Ray et al., 2014) recommended that an Agatston Score of >300 units be used as a modifier to justify statin therapy for primary prevention in adults between 40-75 years old without diabetes and with LDL-C 70-189 mg/dL. Furthermore, evidence suggests that CAC may also promote long-term compliance to preventative therapy (Nasir et al., 2010).

Although the majority of data to date has focused on symptomatic patients with suspected coronary artery disease, the prognostic utility of coronary CT angiography has also been assessed in asymptomatic patients. The CONFIRM Registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) is the largest observational study looking at the associations between coronary CT angiography findings and their ability to predict mortality and major adverse cardiac events. In a cohort of asymptomatic individuals with no previous history of coronary artery disease, the addition of coronary CT angiography did not add any incremental benefit over and above the coronary artery calcium score and traditional risk score (p=0.423) (Cho et al., 2012). As such, coronary CT angiography is not currently recommended as a screening tool in asymptomatic patients who are in at low absolute risk of major adverse cardiac events. The current European guidelines generally do not recommend routine non-invasive imaging to for risk assessment in asymptomatic patients, but suggest that assessment of disease burden (using calcium score and carotid ultrasound) may be considered as a risk modifier in cardiovascular risk assessment (Piepoli et al., 2016). Conversely, the latest American guidelines for detection and risk assessment of coronary artery disease state that calcium scoring and coronary CT angiography use "may be appropriate" in asymptomatic patients with high global risk (Greenland et al., 2010).

To date there has been only one randomised controlled trial of coronary CT angiography in the setting of primary prevention. In the FACTOR 64 trial, 900 high-risk asymptomatic patients with long-standing diabetes mellitus were randomised to screening with coronary CT angiography (n=452) or guideline-based optimal diabetes care (n = 448) (Muhlestein et al., 2014). Despite a high prevalence of obstructive disease (23 % with moderate to severe luminal stenosis on coronary CT angiography), intention-to-treat analysis showed similar

rates of the composite of death, non-fatal MI, and hospitalisation for unstable angina after a mean follow-up of 4 years. The majority of patients had well controlled cardiovascular risk factors at baseline, with haemoglobin A_{1C}, serum low-density lipoprotein cholesterol concentrations, and systolic blood pressure near or exceeding target levels in all participants. The addition of coronary CT angiography had no effect on these risk factors although there was a very modest greater reduction in serum cholesterol concentrations which may have reflected an increase in the use and intensity of statins. Thus, the role of coronary CT angiography in primary prevention needs to established and will be the focus of the SCOT-HEART 2 trial.

Patients with Stable Chest Pain

Contrast coronary CT angiography is being increasingly used in the clinical assessment of patients with suspected coronary artery disease, supported by a growing evidence base. Current American College of Cardiology guidelines for stable ischaemic heart disease suggest that in symptomatic patients with low to intermediate pre-test probability of CAD, CT coronary angiography should be reserved for those with contraindications to stress testing (Fihn et al., 2014), and the European Society of Cardiology guidelines recommend the use of CTA as the first line test in symptomatic patients at low-intermediate pre-test probability for CAD (Task Force Members et al., 2013). The most recent National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom recommend coronary CT angiography as the first line imaging assessment in all patients presenting with typical or atypical angina, as well as patients with non-anginal chest pain with associated ECG changes (Padley et al., 2017). The clinical utility of coronary CT angiography in the treatment of patients presenting with stable chest pain has been investigated in the setting of two major randomised controlled trials (Douglas et al., 2015; SCOT-HEART investigators, 2015).

The Scottish Computed Tomography of the Heart (SCOT-HEART) trial was a multicentre randomised controlled trial of 4,146 patients across Scotland who presented to the cardiology clinic with suspected angina pectoris due to coronary heart disease (Douglas et al., 2015; SCOT-HEART investigators, 2015). In this trial, the addition of coronary CT angiography was compared with standard care alone which included unrestricted access to stress testing and invasive angiography in both groups. It demonstrated that the use of coronary CT angiography increased diagnostic certainty and improved clinical management. At a median of 4.8 years, the primary endpoint of coronary heart disease death or non-fatal MI was reduced by a 41% in patients who underwent CT imaging compared to standard care alone (2.3% vs. 3.9%, HR 0.59, 95% CI 0.41-0.84) (SCOT-HEART, 2018). This difference was principally driven by a lower rate of non-fatal MI which is most likely due to the more accurate diagnosis of both obstructive and non-obstructive coronary heart disease, resulting in the more appropriate initiation of preventative therapies and a subsequent reduction in adverse events (Williams et al, 2019).

The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) randomised 10,003 participants to coronary CT angiography or functional stress testing in a head-to-head comparison (Douglas et al, 2015). It recruited a lower risk population and showed that there was no difference in the composite primary outcome (death, non-fatal myocardial infarction, hospitalisation for unstable angina, or major procedural complication) after a median of 25 months (Douglas et al., 2015). However, at 12 months, there was a reduction in the rate of death and non-fatal myocardial infarction of a similar magnitude to the SCOT-HEART trial (34% relative risk reduction). In both these trials, a half or more of

the observed myocardial infarctions occurred in patients with non-obstructive disease on their baseline scan (Hoffmann et al., 2017).

Further analyses of both the PROMISE and SCOT-HEART cohorts have explored the associations between high-risk plaque characteristics and outcomes. In SCOT-HEART, the presence of at least one high-risk plaque feature (positive remodelling or low attenuation plaque) conferred a 3-fold higher risk of coronary heart disease death or nonfatal myocardial infarction (HR 3.01, 95% CI 1.61 – 5.63) (Williams et al., 2019). Similarly, PROMISE data showed that even after adjusting for risk factors and stenosis severity, the presence of high-risk plaque features is associated with an increased risk of major adverse cardiac events (HR 1.72, 95% CI 1.89 – 3.93) (Hoffmann et al., 2017). Whilst there is growing evidence confirming the association between high-risk plaque characteristics and outcomes (Nerlekar et al., 2018), it is important to keep this in perspective. The positive predictive value of high-risk plaque is in fact very low as only a minority of patients with high-risk plaque will experience major adverse cardiovascular event (Stone et al., 2011; Otsuka et al., 2013).

Patients with Acute Chest Pain

Whilst the role of cardiac CT in the assessment of stable chest pain is well established, its role in improving clinical outcomes in patients with acute chest pain remains unclear. Acute chest pain accounts for 6% of all attendance to the emergency department (Goodacre et al., 2005), and represents a challenge for attending clinicians due to its broad differential diagnosis, and risks of serious morbidity and mortality. Although most patients will be admitted for measurement of serial biomarkers and electrocardiograms, less than a quarter of these will ultimately be diagnosed with acute coronary syndrome (Body et al., 2011). In light of its high negative predictive value, coronary CT angiography may prove useful in this

setting. There have been several trials assessing the role of coronary CT angiography in the safe and effective discharge of low risk chest pain patients from the emergency department (Hoffmann et al., 2012); (Litt et al., 2012).

The ROMICAT II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography II) trial is a multicentre, randomized controlled which enrolled 1000 patients with low-risk chest pain presenting to the emergency department and randomised them to either coronary CT angiography (n = 501) or standard care (n = 499) (Hoffmann et al., 2012). Whilst there were no differences in cardiovascular outcomes, the use of coronary CT angiography results in more direct discharges from the emergency department and a lower mean length of stay in the hospital. In the CT arm, over a fifth of acute coronary syndrome were observed in patients with non-obstructive disease, highlighting once more the prognostic significance of non-obstructive disease and the added value of CT imaging of high-risk plaque features in these patients. In patients presenting with acute chest pain, the presence of any high-risk plaque features is an independent predictor of the presence of acute coronary syndrome (Puchner et al., 2014). Furthermore, in patients with confirmed myocardial infarction, the non-calcified plaque volume is an independent predictor of further major adverse cardiovascular events (Hammer-Hansen et al., 2009). The role of coronary CT angiography in high-risk patients including those with changes on the electrocardiogram or elevations in cardiac troponin, is the subject of the ongoing RAPID-CTCA trial (ISRCTN19102565).

In the era of high sensitivity troponin assays, we are seeing the identification of more patients with raised cardiac biomarkers but no evidence of coronary thrombosis. This may be related to other cardiac conditions, such as myocarditis, arrhythmia and type 2 myocardial infarction.

CT coronary angiography may reduce the need for invasive intervention in some of these patients who may otherwise have gone to the catheterisation laboratory. Growing evidence supports that non-invasive anatomic testing by coronary CTA alone may prove advantageous for promptly and accurately identifying candidates for downstream procedures (Lee et al., 2017) (Dewey et al., 2016).

TREATMENT STRATEGIES

Antithrombotic Therapy

The role of antiplatelet therapies in the management of atherothrombotic disease is well established and has been extensively studied. An acute coronary event is often heralded by an acute plaque rupture, exposing the subendothelium and activating the clotting cascade, thereby leading to localised thrombus formation. Antiplatelet therapies are part of the routine standard of care for patients with or at risk of acute coronary events. In addition to its antiplatelet effect, aspirin may prevent coronary thrombotic disease through systemic effects resulting in a reduction in pro-inflammatory cytokines (Cyrus et al., 2002). Furthermore, aspirin also seems to reduce C-reactive protein level in patients with coronary artery disease, a blood biomarker that has been linked to worsening outcomes following myocardial infarction (Heeschen et al., 2000). Raised C-reactive protein levels following a myocardial infarction may reflect the inflammatory activity of a ruptured plaque (Rioufol and Finet, 2004) and intensive dual anti-platelet therapy in this setting may have a stabilising effect.

Plaque vulnerability is a dynamic process and, at any one time, plaques that were previously stable may become “vulnerable”. As such, the therapeutic effects of anti-platelet therapy are not limited to the acute setting and argue for the early implementation of anti-platelet therapy

in patient with both obstructive and non-obstructive disease. This may reduce plaque progression and reduce events by mitigating the development of occlusive thrombus formation in the presence of a plaque rupture event.

Lipid Lowering Therapy

The use of lipid lowering therapy in the form of statin is advocated for both primary and secondary prevention of cardiovascular disease and has been associated with a mortality benefit (Heart Protection Study Collaborative Group, 2002). Statins achieve these benefits through plaque stabilisation and slowing plaque progression (Nissen et al., 2006); (Nicholls et al., 2010). This is thought to be partly driven by the pro-calcific effects of statin therapy on coronary atheroma that is independent of their plaque-regressive effect (Puri et al., 2015) and explains why statins appear to increase not decrease the CT calcium score (Houslay et al., 2006; Dykun et al., 2016); (Schmermund et al., 2006). Furthermore, in patients with unstable disease, statins have anti-inflammatory effects that may increase fibrous plaque thickness (Komukai et al., 2014); (van der Harst et al., 2004).

Coronary CT angiography studies have shown that initiation of statin therapy reduces progression of noncalcified plaque volume, which accounts for most of the benefits of this therapy (Hoffmann et al., 2010); (Li et al., 2016). This concurs with large randomised trials that have demonstrated that the use cardiac CT is associated with a lower rate of myocardial infarction and is most likely due to the early targeted initiation of preventative therapies, such as statins, in patient with both obstructive and non-obstructive disease (SCOT-HEART investigators, 2015). Based on the increased risk of myocardial infarction in patients with high-risk plaque features, irrespective of the degree of stenosis, the intensification of statin therapy, may be a cost effective and effectual strategy.

Proprotein convertase subtilisin–kexin type 9 (PKS9) inhibitors are a newer class LDL-lowering drugs that reduce LDL cholesterol levels when added to statin therapy (Giugliano and Sabatine, 2015). PCKS9 levels appear to correlate with necrotic core size of non-culprit coronary plaques (Cheng et al., 2016) and their inhibition improves plaque morphology (Kühnast et al., 2014). This has been confirmed by a reduction in intravascular ultrasound-determined plaque atheroma volume in patients treated with PCSK9 inhibitors (Puri et al., 2016). Their modulatory effects on high-risk plaques has yet to be established but would be anticipated to have similar beneficial effects to statins.

Anti-inflammatory Therapy

Various pathways and inflammatory mediators have been implicated in atherosclerotic process. Anti-inflammatory medication is anticipated to reduce atherosclerotic burden and stabilise atherosclerotic plaques. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was a randomized, double-blind trial involving 10,061 patients and it showed that that an anti-inflammatory intervention with the monoclonal antibody canakinumab confers a reduced risk of atherothrombotic events, reducing cardiovascular events in well-treated patients with coronary heart disease (Ridker et al., 2017). This is thought to be driven by the reduction in vascular inflammation - as reflected by the reduction in tumour necrosis factor-alpha, interleukin-6 and c-reactive protein – since it had no effect on serum LDL cholesterol concentrations. However, the Cardiovascular Inflammation Reduction Trial (CIRT) showed that low-dose methotrexate did not reduce inflammatory mediators, or cardiovascular events compared with placebo among patients with established coronary heart disease and diabetes, the metabolic syndrome or both.

These trials are a major step forward in exploring the cardiovascular impact of anti-inflammatory interventions. It is too early to predict how successful these agents will prove in the treatment of coronary plaques. Further research is needed to better elucidate the complex nature of the pathophysiological mechanisms underpinning inflammation and its impact on plaque vulnerability, and consequent clinical events. However, it would be interesting to explore whether CT-derived measures of perivascular adipose tissue inflammation, or plaque vulnerability could be used to guide anti-inflammatory therapies and determine whether they could impact on clinical outcomes.

Localised Invasive Treatment

Our clinical management of coronary atherosclerosis is centred on the identification and revascularisation of obstructive disease. However, whilst stable angina and symptoms of cardiac ischemia are associated with severe coronary artery stenoses, the majority of myocardial infarctions occur at sites of non-obstructive plaque on antecedent angiography. This is supported by a large body of evidence from interventional trials, showing that effective treatment of obstructive disease does not translate to better outcomes through the prevention of myocardial infarction (Boden et al., 2007). This suggests that identification of obstructive coronary lesions is only one aspect of the complex relationship between atherosclerosis and ischaemia. The number of high-risk plaque features appear to increase as stenosis severity increase, but the presence of high-risk plaque also remains an independent predictor of ischaemia regardless of stenosis severity, particularly positive remodelling (Park et al., 2015; Nakazato et al., 2016).

Whilst there is currently no evidence to justify targeted revascularisation of lesions on the basis of high-risk plaque features alone, the question remains as to whether the decision to

undertake percutaneous coronary intervention should take into account not only the haemodynamic significance of the coronary disease but also consider plaque composition. There are ongoing trials (PROSPECT-ABSORB, PREVEVENT, PECTUS) looking at the preventive local treatment of vulnerable plaques that are using bioabsorbable stents which may reduce or eliminate the long-term risk of stent thrombosis: so called "plaque sealing" approaches. Given the low but significant procedural event rates and risks of stent thrombosis or restenosis, the concept of stenting mild to moderate non-obstructive lesions because they contain vulnerable plaques needs to be convincing proven especially as the evidence for stenting obstructive lesions is lacking.

CONCLUSION

With advances in scanner technology, it is now possible to image atherosclerotic plaque composition and disease activity as well as differentiate stable from unstable patterns of disease in the coronary vessels. Coronary CT angiography has proven to be an effective method to improve the detection of coronary heart disease and this has had the downstream consequences of improving and targeting therapies that are associated with improved outcomes such as reductions in non-fatal and fatal myocardial infarction. It is likely that we will see its increasing use in the current and future management of patients with suspected coronary heart disease across a broad range of clinical areas.

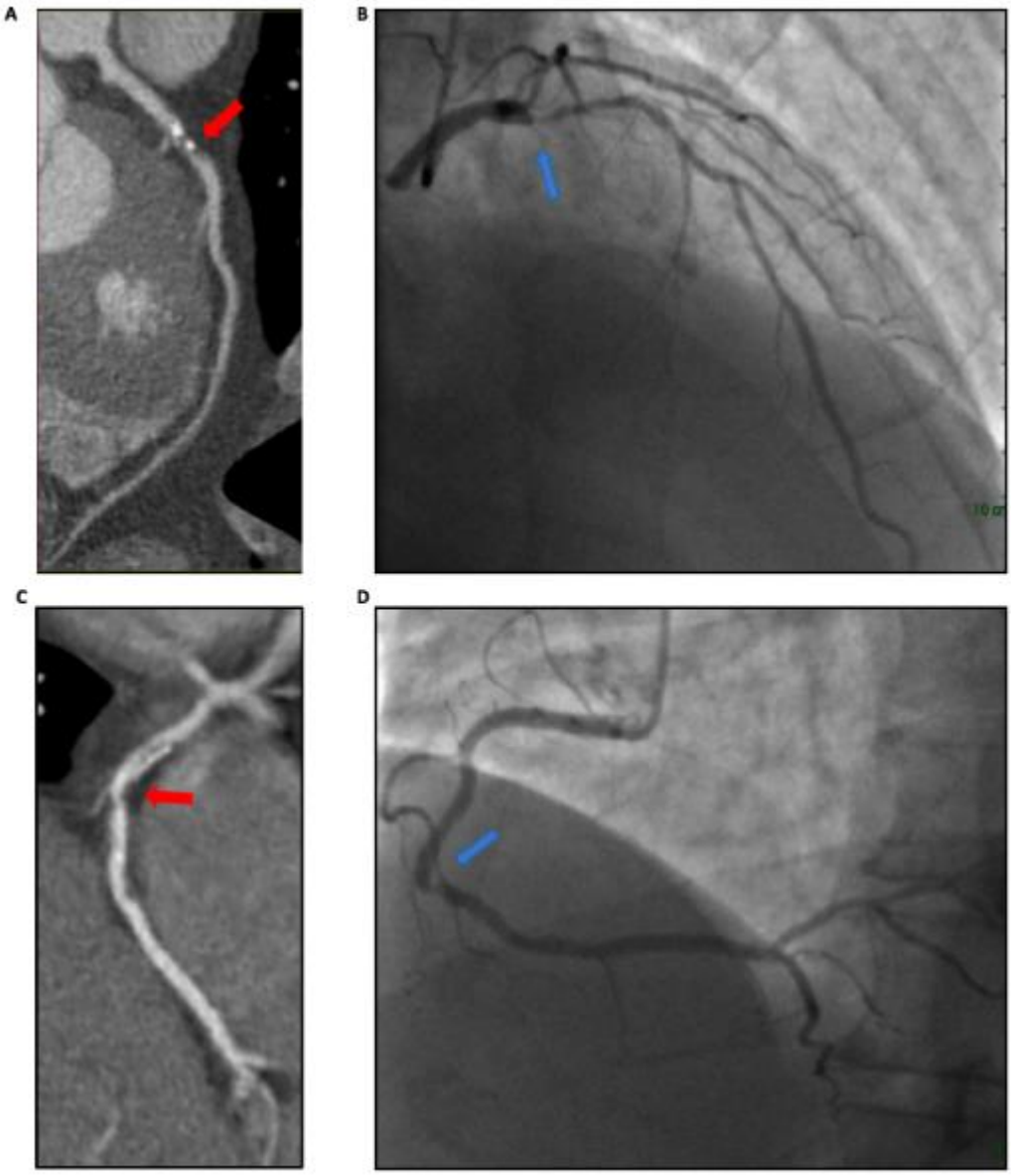

Figure 1: Assessment of Luminal Stenosis

(A)	Coronary CT angiography of a patient with angina showing mixed plaque and luminal stenosis in proximal left anterior descending artery (red arrow).
(B)	Subsequent invasive coronary angiogram demonstrating an obstructive stenosis of the proximal left anterior descending artery (blue arrow).
(C)	Coronary CT angiography of a patient with angina showing a tight stenosis of the mid right coronary artery (red arrow).
(D)	Subsequent invasive coronary angiogram confirmed a tight stenosis of the mid right coronary artery (blue arrow).

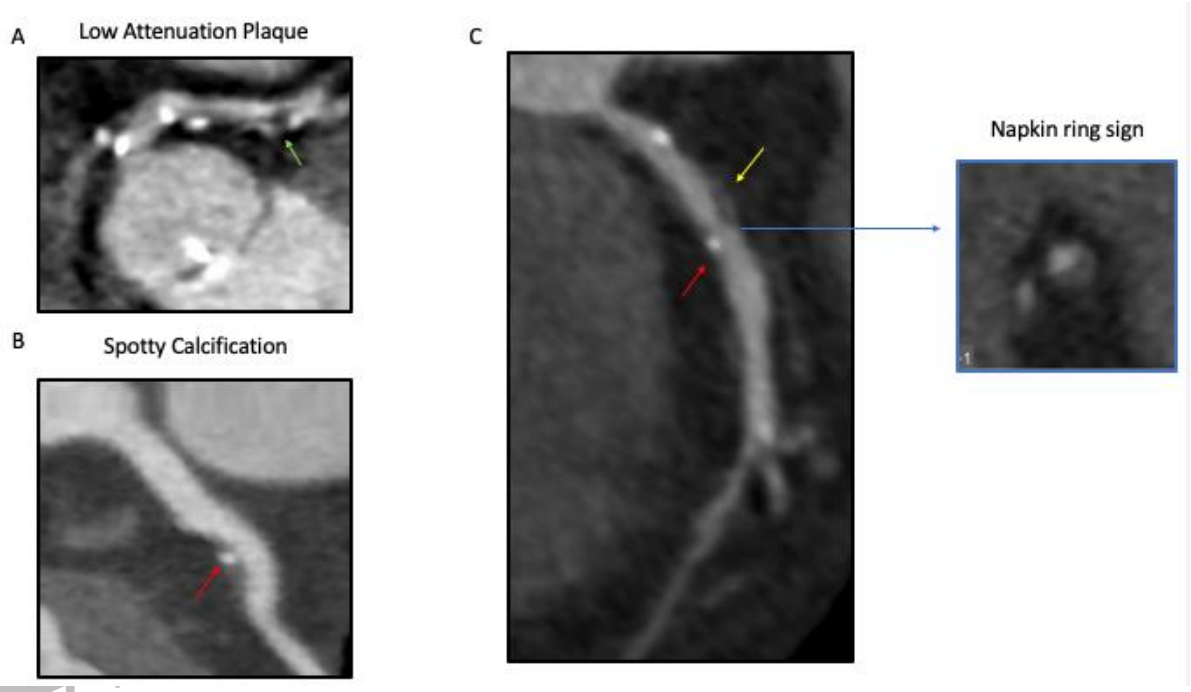

Figure 2: Assessment of High-risk Plaque Features

(A)	Low attenuation plaque (green arrow) in the proximal left anterior descending artery with spotty calcification and associated vessel stenosis
(B)	An atherosclerotic plaque in the right coronary artery with positive remodelling (yellow arrow), napkin-ring sign (blue arrow) and spotty calcification (red arrow).
(C)	Non-obstructive plaque in proximal left anterior descending artery with spotty calcification (red arrow).

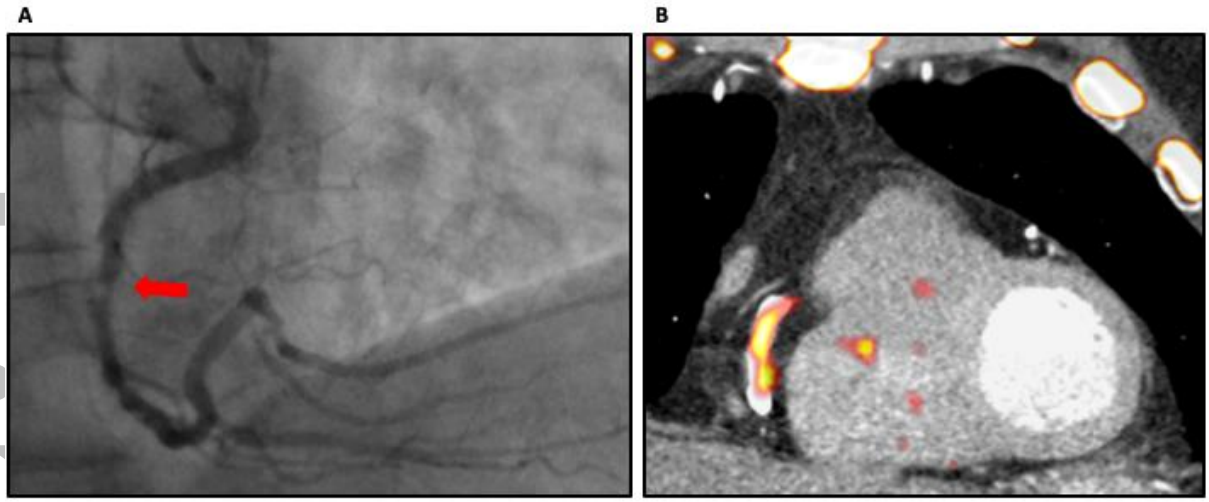

Figure 3: Assessment of Disease Activity using Positron Emission Tomography

(A)	Invasive coronary angiography showing a culprit stenosis of the right coronary artery (red arrow).
(B)	Intense focal ^{18}F-fluoride uptake (^{18}F-NaF, tissue-to-background ratios 2.1) is observed at the site of the culprit plaque on the combined positron emission and computed tomogram (PET-CT).

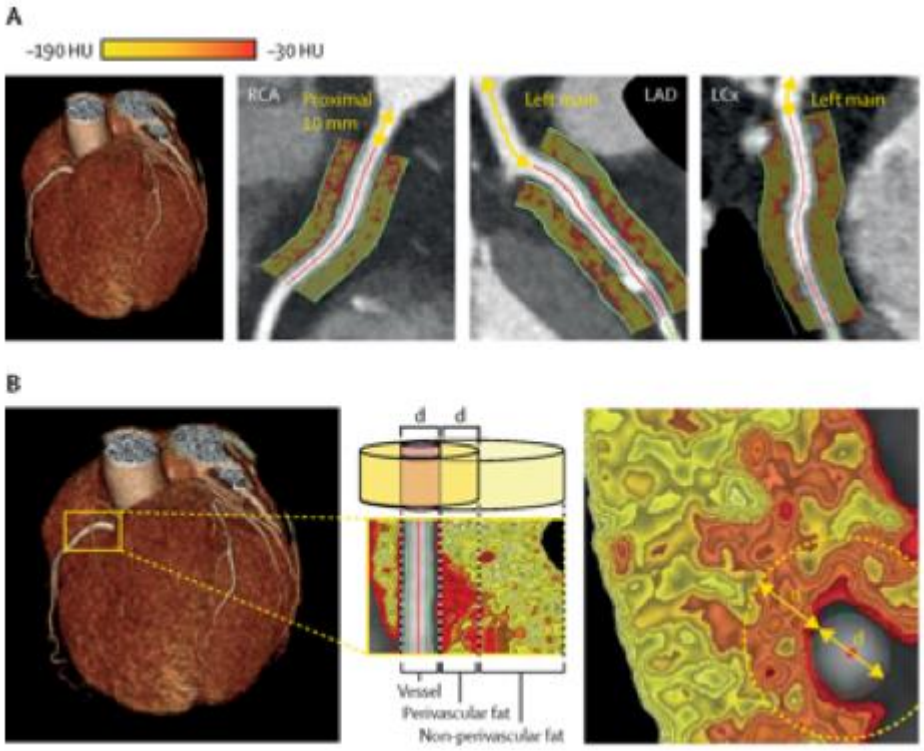

Figure 4: Perivascular Fat Analysis Around Epicardial Coronary Vessels

Image reproduced from (Oikonomou et al., 2018)

(A)	Perivascular fat attenuation index phenotyping of the proximal segments of all three major epicardial coronary vessels, with corresponding fat attenuation index colour maps
(B)	Example of perivascular fat attenuation index phenotyping around the proximal right coronary artery. Perivascular fat was defined as fat within a radial distance equal to the diameter (d) of the vessel.

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