High-Risk Coronary Plaques and Cardiovascular Prevention: Insights from Coronary Computed Tomography Angiography and Real-World Data

A dissertation submitted to Swansea University for the degree of Doctor of Philosophy

Ahmed Mohamed Salem, M.B.B.S, MRCP (UK)

Swansea University 2025

Summary

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide, necessitating improved methods for early detection and risk stratification. Coronary CT angiography (CCTA) has emerged as a powerful, non-invasive imaging modality capable of identifying high-risk coronary plaque features that may predict future cardiovascular events. This thesis explores the role of CCTA in assessing plaque vulnerability, guiding risk factor optimisation, and influencing clinical outcomes in patients with stable and acute coronary syndrome (ACS).

The methodology section outlines the study designs, data collection strategies, and analytical approaches used across multiple clinical studies, integrating both CCTA-based imaging assessments and real-world national cohort analyses. The thesis then presents several key investigations, beginning with a real-world analysis of secondary prevention in high-risk patients with type 2 diabetes, evaluating the achievement of European Society of Cardiology (ESC) guideline-recommended risk factor targets. This is followed by a detailed characterisation of high-risk coronary plaques, including the novel CT-defined thin-cap fibroatheroma (CT-TCFA), in patients undergoing CCTA for stable chest pain.

Further, the research assesses how high-risk plaque features identified on CCTA influence cardiovascular risk optimisation, medication intensification, and clinical decision-making. The spatial distribution of vulnerable plaques within the coronary tree is also analysed to provide insights into the patterns of plaque progression and rupture potential. Lastly, as a future work, I'm planning to explore the potential impact of oral semaglutide on coronary artery disease progression following ACS, evaluating its role in modulating atherosclerotic plaque burden and stabilizing high-risk lesions.

Collectively, this body of work highlights the critical role of CCTA in refining cardiovascular risk assessment, facilitating early intervention, and guiding therapeutic strategies to improve patient outcomes. The findings underscore the need for a more personalised approach to cardiovascular prevention, leveraging advanced imaging and targeted pharmacotherapy to mitigate the burden of ASCVD.

Declarations and Statements

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed 

Date. 01/06/2026

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s). Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed 

Date. 01/06/2026

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed 

Date. 01/06/2026

Contents Page

Table of Contents

List Of Figures

List Of Tables

Definitions Or Abbreviations

Acute coronary syndrome	ACS
American Heart Association	AHA
Angiotensin-converting enzyme	ACE
Anonymous Linking Field	ALF
Antioxidant status	AOS
Atherosclerotic cardiovascular disease	ASCVD
Aortic carotid-femoral pulse wave velocity	cfPWV
British Medical Association	BMA
C-reactive protein	CRP
Cardiovascular Disease	CVD
Cardiovascular Magnetic Resonance	CMR
Cardiovascular Outcome Trials	CVOT
Coronary flow velocity reserve	CFR
Chronic kidney disease	CKD
Coronary Artery Calcium	CAC
Coronary Artery Disease	CAD
Coronary Artery Smooth Muscle Cells	CASMCs
Coronary CT Angiography	CCTA
Diabetes Mellitus	DM
Diastolic BP	DBP
Electrocardiographic	ECG
Electronic health record	HER
Emergency department	ED
Endothelial shear stress	ESS
European Society of Cardiology	ESC
Final Appraisal Document	FAD
Fractional flow Reserve	FFR
General Practitioner	GP
Glucagon-like peptide 1 receptor agonists	GLP-RAs
Haemoglobin A1c	HbA1c
Heart failure with reduced ejection fraction	HFrEF
High-density lipoprotein	HDL
High-intensity statin	HI-statin
High-risk plaque	HRP
Hounsfield units	HU
Index of microcirculatory resistance	IMR
Information governance review panel	IGRP
Informed consent form	ICF
Institute of Life Science 2	ILS2
Interleukin-6	IL-6
Intravascular ultrasound	IVUS

Invasive coronary angiography	ICA
Investigational Medicinal Products	IMP
Islet-derived interleukin-1β	IL-1β
Joint Clinical Research Facility	JCRF
Kawasaki disease	KD
Left anterior descending coronary	LAD
Left ventricular ejection fraction	LVEF
Lipid-lowering therapy	LLT
Low attenuation plaque	LAP
Low-density lipoprotein	LDL
Major adverse cardiac events	MACE
Multi-detector CT	MDCT
Multiple Endocrine Neoplasia syndrome type 2	MEN 2
Multiplanar Reconstructions	MPRs
Myocardial Infarction	MI
Napkin Ring sign	NRS
National Cardiovascular Data Registry	NCDR
National Institute for Health and Care Excellence	NICE
National Research Ethics Committee	NREC
Necrotic Core	NC
New York Heart Association	NYHA
NHS Wales Informatics Service	NWIS
Once daily	OD
Optical coherence tomography	OCT
Patient Episode Database for Wales	PEDW
Percutaneous coronary intervention	PCI
Photon-counting computed tomography	PCCT
Positron Emission Tomography	PET
Project-encrypted	PE
Proprotein convertase subtilisin/kexin type 9	PCSK9
SAIL and Swansea Bay University Health Board	SBUHB
Secure Anonymised Information Linkage	SAIL
Smooth muscle cells	SMCs
Sodium-glucose co-transporter 2 inhibitors	SGLT2
ST-segment elevation myocardial infarctions	STEMIs
Swedish Cardiopulmonary Bioimage Study	SCAPIS
Systolic BP	SBP
Thin-capped fibroatheroma	TCFA
Total cholesterol	TC
Tumour necrosis factor	TNF
Very low-density lipoprotein	VLDL
Virtual histology intravascular ultrasound	VH-IVUS

Welsh Demographic	WDS
Welsh Demographic Service Dataset	WDSD
Welsh Index of Multiple Deprivation	WIMD
Welsh Longitudinal General Practice	WLGP

Acknowledgements

I would like to express my deepest gratitude to Dr. Daniel Obaid, Dr Daniel Harris, Professor Jeffrey Stephens, and Professor Julian Halcox for their indispensable guidance and support throughout my time in Swansea and beyond. I could not have wished for better supervisors and friends.

A special thanks to the wonderfully supportive team at the Research Unit at Swansea Bay, especially the unit manager, Kathie Wareham, for all the help, laughter, and cherished memories.

I dedicate this work to my Father and Mother, who have always believed in me, even at my lowest moments. Their unconditional support and encouragement made this journey possible.

Hala and Radwa—my sisters and lifelong companions—this is for you. I truly don't think I would have completed this without the joy of Radwa's loud laughter and Hala's endless hours of counsel and care.

Marwan and Dondon, my nephew and niece—I'm sorry this took so long, and that I haven't been around as much as I should have. But watching you grow (even if only through a mobile screen) gave me the motivation I needed to push through and complete this Ph.D.

Finally, my heartfelt appreciation goes to Dr. Amr Khaled and the Ehsan Project. That experience provided me with spiritual strength, inspiring me to strive for the best version of myself and to see this work through to completion.

And to you, who came into my life at the very end of this journey, thank you for making its final chapter one I will always remember.

Publications During The Period Of This Ph.D.

At the time of submission of this thesis, papers from chapters 1, 3, 4, and 7 were published, and papers from Chapter 5 and 6 are in the process of submission. The references to the published manuscripts are as follows:

1. **Salem AM,** Davis J, Gopalan D, Rudd JHF, Clarke SC, Schofield PM, Bennett MR, Brown AJ, Obaid DR. Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain. **Clin Imaging. 2023** Sep;101:69-76. doi: 10.1016/j.clinimag.2023.06.009. Epub 2023 Jun 8. PMID: 37311397.

2. **Salem AM**, Harris D, Bray JJH, Obaid DR, Stephens JW, Halcox J. Achievement of the ESC recommendations for secondary prevention of cardiovascular risk factors in high-risk patients with type 2 diabetes: A real-world national cohort analysis. **Int J Cardiol. 2023** Apr 15;377:104-111. doi: 10.1016/j.ijcard.2023.02.004. Epub 2023 Feb 9. PMID: 36764610.

3. **Salem AM**, Bain SC, Obaid DR. Glucagon-like peptide-1 receptor agonists as anti-inflammatory agents: A potential mode of cardiovascular benefits. **Atherosclerosis**. 2022 Jul;352:83-84. doi: 10.1016/j.atherosclerosis.2022.05.010. Epub 2022 May 18. PMID: 35662526.

4. Bray JJH, Foster-Davies H, **Salem A**, Hoole AL, Obaid DR, Halcox JPJ, Stephens JW. Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomised controlled trials. **Diabetes Obes Metab**. 2021 Aug;23(8):1806-1822. doi: 10.1111/dom.14399. Epub 2021 May 6. PMID: 33830637.

COVID-19 Impact Statement

The research presented in this thesis was conducted during the period of the COVID-19 pandemic, which had a significant impact on clinical research activity and study delivery.

In particular, the POST-ACS study described in Chapter 7 was originally designed as a central component of this doctoral research, with the aim of prospectively evaluating the impact of oral semaglutide on coronary plaque progression using serial coronary CT angiography. However, the initiation and early phases of this study coincided with the COVID-19 pandemic, which led to substantial disruption in clinical trial recruitment, patient follow-up, and research infrastructure.

These challenges included reduced elective clinical activity, limitations on patient contact, delays in imaging studies, and redeployment of clinical and research staff. As a result, the study timeline was significantly affected, and full completion with outcome data was not possible within the timeframe of the doctoral programme.

In response to these constraints, the focus of the thesis was adapted to emphasise complementary observational and imaging-based studies (Chapters 3–6), which provide the scientific and clinical foundation for the POST-ACS trial. Chapter 7 is therefore presented as a mechanistic, hypothesis-driven study design representing the translational extension of this work.

Despite these challenges, recruitment and follow-up for the POST-ACS study have progressed, and completion of this work remains an important component of ongoing research beyond the PhD.

CHAPTER 1: Introduction

1.0: Atherosclerosis

Atherosclerosis is defined by the Oxford English Dictionary as "a disease of the arteries in which fatty material is deposited on their inner walls".[1] The term was first introduced in 1904 by Felix Marchand, who suggested that atherosclerosis was responsible for almost all obstructive processes in the arteries.[2] Although it has been a defined disease entity for only over 100 years, computed tomography (CT) imaging reports identified evidence of definite or probable atherosclerosis present in Egyptian mummies who lived in the era of ancient Egypt, a time span of >2,000 years.[3]

Atherosclerosis is currently a leading cause of death worldwide. Those fatty streaks in arterial walls gradually develop into atheroma and characteristic plaques. The acute rupture of these atheromatous plaques causes local thrombosis, leading to partial or total occlusion of the affected artery.[4] The clinical hazard of these plaques depends on the degree and the speed of vessel narrowing, and according to the distribution, atherosclerosis can manifest as cerebrovascular disease, reno-vascular disease, peripheral vascular disease and coronary artery disease.

1.1: The Classification of Atherosclerosis

The phases of atherosclerotic plaque development have been divided into six stages by the American Heart Association (AHA)[5], first published in 1994, with the aim of better understanding the atherosclerosis process and preventing its devastating effects worldwide. These are separated into early stages I-III (adaptive intimal thickening, fatty streak and pathological intimal thickening) and late stages IV-VI (including fibroatheroma, calcified fibroatheroma, and disrupted plaques with haemorrhage and thrombosis – Figure 1). Some of those steps are described in more detail below.

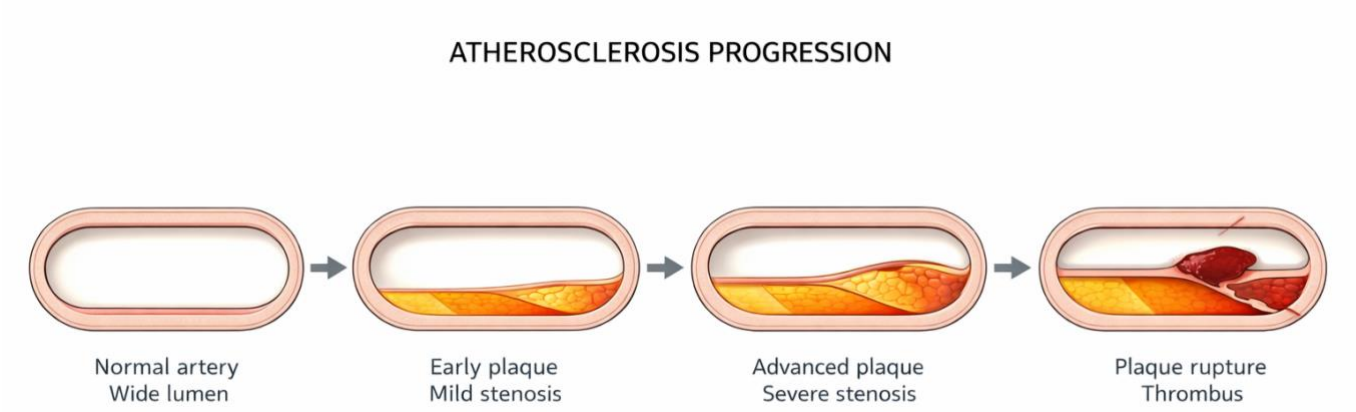


Figure 1: Schematic illustration of coronary atherosclerosis progression in a longitudinal arterial view, demonstrating plaque formation with progressive luminal stenosis, plaque destabilisation and rupture, and subsequent thrombus formation leading to reduced coronary blood flow.

1.1.2: Intimal Thickening and Fatty Streaks

The earliest vascular change described microscopically is intimal thickening (AHA Type I lesion), which consists of layers of smooth muscle cells and extracellular matrix. In autopsy specimens from 17 weeks of gestation to 23 months, it has been reported to occur in 35% of neonates where the intima/media ratio at birth is 0.1 and increases progressively to reach 0.3 by two years of age.[6]

A study of coronary arteries of 63 hearts obtained from deceased foetuses, infants, children, and adolescents found that coronary intimal thickening begins in foetuses and progresses to atherosclerosis in the paediatric population and adolescents.[7] The most common sites of intimal thickening were near bifurcation sites in the Left Anterior Descending Coronary (LAD) Artery (55.6%) and in areas free of bifurcation in the Right Coronary Artery (RCA) (75%). The extent of intimal thickening was significantly associated with older ages in this population.[7]

1.1.3: Pathologic Coronary Intimal Thickening

Besides the adaptive type, pathological coronary intimal thickening is associated with atherosclerosis and other cardiovascular diseases. Pathologic intimal thickening is often observed in various clinical contexts, including Kawasaki disease (KD), where it can occur even in arteries that do not exhibit aneurysms. Studies have shown that intimal thickening in KD is associated with inflammatory damage and can lead to significant coronary artery changes over time.[8]

The mechanisms underlying pathological intimal thickening involve a complex interplay of cellular processes, including the proliferation of smooth muscle cells (SMCs) and the accumulation of extracellular matrix components. In early atherosclerosis, medial hypertrophy often accompanies intimal thickening, driven by growth factors and cytokines that promote SMC proliferation.[9] This pathological process is not limited to atherosclerosis; it can also occur in conditions such as coronary vasospasm, where diffuse intimal thickening can lead to reduced lumen area and coronary events.[10]

Moreover, the implications of coronary intimal thickening extend beyond mere structural changes in the arteries. The presence of intimal thickening creates a substrate for plaque formation and subsequent rupture.[11] In paediatric populations, for instance, the identification of significant intimal changes can lead to improved patient care and monitoring strategies, as these changes may precede more severe complications.[12] Furthermore, the role of molecular mechanisms, such as the regulation of vascular smooth muscle cell behaviour, is crucial in understanding how coronary intimal thickening progresses to more advanced stages of atherosclerosis.[11]

1.2: Coronary Artery Disease Progression

Cardiovascular diseases (CVD) cause approximately one-third of deaths worldwide.[13] Among cardiovascular illnesses, coronary artery disease (CAD) ranks as the most prevalent and is acknowledged as an important threat to sustainable development in the 21st century.[14]

Plaques in the coronary arteries become clinically apparent when their intrusion into the lumen causes a flow-limiting stenosis, leading to symptoms of myocardial ischaemia such as angina. The plaque rupture is the consequent acute cardiovascular complication; however, the coronary disease progression is a complex biological dynamic cellular process, and our knowledge of coronary plaque biology is constantly expanding.

1.2.1: Endothelial Dysfunction and Immune Response

Atherosclerotic vascular disease is believed to be far more than a passive accumulation of cholesterol in the arterial wall. The starting point of atheroma formation is understood to be an endothelial dysfunction or activation, which is the underlying pathology of CVD.

When endothelial cells lose the ability to maintain their delicate structure and protective function, this allows lipid and leukocyte infiltration, representing the early stages of the atheromatous plaque formation.[15] Endothelial dysfunction triggers vascular damage-associated processes, considered the hallmark of CAD.[16] The role of systemic and localised inflammation is now recognised as an active part of this process and contributes to the pathophysiology of atherosclerosis.[17] C-reactive protein (CRP - an acute-phase protein and an essential marker of systemic inflammation) was expressed in coronary atherosclerotic plaque specimens and coronary vasculature detected by directional coronary atherectomy and in situ hybridisation, respectively.[18]

On the other hand, prospective epidemiological studies indicate that high levels of inflammatory markers are associated with an increased risk of coronary events.[19,20] Additionally, Statins, which have been approved to reduce coronary risk, are reported to decrease serum inflammatory marker levels.[21,22] Thus,

local and systemic inflammation might play important roles in plaque instability and risk of coronary events. While these biological processes underpin the development and progression of atherosclerosis at the vascular level, their clinical manifestation is strongly influenced by a range of systemic cardiovascular risk factors. Large epidemiological studies have established a number of key non-modifiable and modifiable risk factors—including age, sex, dyslipidaemia, hypertension, diabetes mellitus, and smoking—that contribute to the initiation and progression of coronary artery disease.[23] However, these risk factors alone do not fully account for the heterogeneity in plaque behaviour or the occurrence of acute coronary events. This highlights the complex interaction between systemic risk profiles and local vascular pathology. A summary of the established and emerging risk factors for coronary artery disease is provided in Table 1.

Table 1: Established Risk Factors for Coronary Artery Disease

Category	Risk Factor	Mechanism / Clinical Relevance
Non-modifiable	Age	Progressive endothelial dysfunction and plaque accumulation
	Male sex	Higher lifetime exposure to atherogenic risk factors
	Genetic predisposition / family history	Early-onset CAD risk; inherited lipid disorders
Metabolic	Dyslipidaemia (↑ LDL-C, ↓ HDL-C)	Lipid accumulation in arterial wall, necrotic core formation
	Diabetes mellitus	Endothelial dysfunction, inflammation, accelerated atherosclerosis
	Obesity	Pro-inflammatory state, insulin resistance
Haemodynamic	Hypertension	Endothelial injury, increased shear stress
Lifestyle	Smoking	Oxidative stress, endothelial damage, thrombosis
	Physical inactivity	Associated with obesity, insulin resistance
	Poor diet	High saturated fats, refined sugars → dyslipidaemia
Inflammatory / Emerging	Chronic inflammation (↑ CRP)	Plaque instability and rupture risk
	Lipoprotein(a)	Pro-atherogenic and pro-thrombotic
	Psychosocial stress	Neurohormonal activation, indirect behavioural effects

1.3: Morphological Features of Plaques Responsible for Clinical Events

According to the 2024 Global Cardiovascular Disease Statistics Report, the prevalence of CVD among adults aged 20 years and older is 48.6 % (127.9 million in 2020), with the rates increasing with age in both males and females.[24] It impacts over 17 million adults in the United States and contributes to over 500,000 deaths each year.[25]

Given that each patient with coronary disease will have multiple plaques, it is evident that most coronary plaques will not be responsible for an acute event. Most acute coronary syndromes (ACS) are thought to be the result of sudden luminal thrombosis, which, from post-mortem studies, have been described to arise from three distinct morphologic entities: rupture, erosion, and calcified nodules.[26]

In a pooled analysis of post-mortem studies that included over 400 patients who had died from coronary thrombosis, rupture of thin-capped fibroatheroma was implicated in 60-70% of cases, plaque erosion in 30-35% and calcified nodules in 2-7%.[27] Therefore, identifying these plaque types is crucial in identifying potentially vulnerable plaques.

1.3.1: Calcified Nodule

These lesions consist of dense eruptive calcified nodules that disrupt the fibrous cap, resulting in an overlying thrombus, and are usually seen in elderly male patients with tortuous arteries.[26] In a post-mortem study, calcified nodules have been shown to have characteristics that can be distinguished by conventional intra-coronary imaging[28]; however, the clinical utility of this finding is limited given the rarity of clinical events (2-7%) for which these lesions are responsible.

1.3.2: Plaque Erosion

Although plaque rupture is the principal cause of coronary thrombosis, the importance of superficial plaque erosion has gradually been recognised in recent years. Plaque erosion exhibits a luminal thrombus with an underlying base rich in proteoglycans and smooth muscle cells, accompanied by minimal inflammation. Most erosion lesions are devoid of a necrotic core. Still, when present, the core does not communicate with the lumen because of a thick fibrous cap.[27] The precursor lesion can be either a fibroatheroma or pathological intimal thickening, making pre-emptive identification of the plaque before erosion virtually impossible. Even when utilizing the highest image resolution, the extremely thin layer of the endothelium cannot be identified. Although the underlying mechanism of local thrombosis on eroded plaques remains unclear, local flow perturbation and changes in endothelial shear stress (ESS) may lead to upregulation of toll-like receptor 2, resulting in endothelial damage, neutrophil extracellular traps formation, and thrombosis on eroded plaque.[29]

Compared to plaque rupture, five independent clinical and laboratory parameters have been shown to be associated more with plaque erosion: age <68 years, anterior ischemia, no diabetes mellitus, a haemoglobin level >15.0 g/dL, and normal renal function.[30]

Furthermore, smoking has been shown to be independently associated with fibrin-rich thrombi in plaque erosion.[31] Thrombogenicity caused by the blood modification effects of smoking may accelerate the ACS onset in plaque erosion.[32]

Generally, the prevalence of plaque erosions among ACS patients has increased in recent decades. This shift is due to improvements in CAD primary detection and prevention measures, which led to a relevant increase of the NSTE-MI (plaque erosion is more common) than STE-MI clinical presentation.[33,34] Also, microscopic plaque examination sheds light on the unique characterisations of plaque erosion. This was historically done in the post-mortem stages; however, presently, intra-coronary ultrasound provides high-resolution cross-sectional imaging of atheromatous plaques, allowing for the detection and examination of plaque erosions in vivo.[35]

Unlike plaque rupture, plaque erosions are associated with negative remodelling and less plaque burden.[33] It's vital to identify plaque erosions, especially in younger patients presenting with a clinical picture of ACS, as they usually have better clinical outcomes when compared with traditional plaque rupture patients.[33,36,37] Therefore, this should be considered in the risk stratification of patients in the context of ACS.

The management of plaque erosions is also different. Recently, the EROSION (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography–Based Management in Plaque Erosion) study suggested that ACS patients with plaque erosions can be safely treated solely with antithrombotic therapy without the need for stenting.[38] In addition, up to a 1-year follow-up, there was a decrease in thrombus volume, with the majority of patients with plaque erosions who were managed with dual antiplatelet without stenting remaining free of major adverse cardiac events.[38] However, more prospective randomised control trials are needed to lend further credibility to this conclusion for consideration of broader utilisation.

1.3.3: Vulnerable Plaques

The term "vulnerable plaque" was initially introduced by Muller et al. during the late 1980s to describe a specific type of plaque that possesses a high likelihood of rupturing and subsequently triggering clinical events, such as heart attacks or strokes.[39] Among individuals who experience sudden cardiac death, the most commonly observed finding during autopsy is plaque rupture.[26] Detailed autopsy studies have revealed an inverse relationship between the thickness of the fibrous cap that overlays the lipid-rich plaque and the risk of plaque rupture.[26] This means that as the fibrous cap becomes thinner, the likelihood of rupture increases significantly.

Rupture typically occurs in plaques that exhibit a large necrotic core, which generally constitutes more than 30% of the plaque's overall area. These plaques are characterised by having a thin and disrupted fibrous cap, usually measuring <65 μm in thickness. This cap is often heavily infiltrated by immune cells

such as macrophages and T-lymphocytes. When rupture occurs, it exposes the highly thrombogenic necrotic core to the flowing blood, which leads to the formation of a platelet-rich luminal thrombus.[40] Falk examined 47 patients dying from CAD preceded by chest pain (suspected MI) and found 103 ruptured plaques, 40 contained occlusive thrombus, and the remainder had grossly discernable intimal haemorrhage with a tiny mural thrombus at the rupture site.[41] The key feature common to plaques that rupture appears to be a thin cap of fibrous tissue separating the necrotic core from the lumen, defining what has been called a "thin-capped fibroatheroma" (TCFA).

TCFA represents the most prevalent form of what is often termed a vulnerable plaque. It is responsible for approximately 60–70% of cases of acute coronary thrombosis and is recognised as the leading cause of death in both young men under the age of 50 and older women over the age of 50.[26] The primary risk factors associated with the development of these lesions include elevated levels of low-density lipoprotein (LDL) cholesterol, reduced levels of high-density lipoprotein (HDL) cholesterol, and a high ratio of total cholesterol to HDL cholesterol.[42]

1.3.4: Healed Plaques

Not all cases of thrombi on disrupted plaques (ruptured or eroded plaque) lead to a clinical event, and a non-occlusive thrombus may heal asymptomatically.[32] Flow-limiting thrombus formation on disrupted plaque causes ACS but otherwise could remain symptomatically silent and ultimately heals. Subsequent developments in terms of these plaque disruptions may depend on the balance between thrombogenicity and protective fibrinolysis mechanisms.

The healing process is characterised by extended plaque fibrosis and may be associated with moderate to severe cross-section area luminal stenosis.[43] The necrotic core may be empty and leave a cavity filled with distinct layers of collagen-rich scars containing fibrin and platelets, which can be seen on coronary imaging as "ulcerated plaque".[26]

The clinical significance of healed plaque ruptures remains an area of controversy. Burke et al. identified healed plaque ruptures in 142 men who died of sudden coronary death.[43] In a total of 265 patients and using optical coherence tomography (OCT) imaging, Kurihara et al. associated the presence of healed plaque with a higher incidence of revascularisation, as compared to those without healed plaque after 2 years of follow-up.[44] On the other hand, a recent study showed that healed coronary plaques were rarely observed in patients with multiple recurrent acute coronary syndromes. At the same time, their prevalence was significantly higher in patients with long-term clinical stability.[45] In the clinical setting, plaque imaging has enabled the characterisation of the culprit plaque that is more in line with the above-mentioned diagnosis of the three pathologies in the autopsy studies.

1.4: Coronary Angiography and Invasive Imaging of Vulnerable Plaques

Evidence from therapeutic trials in patients who have had ACS event such as PROVE IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) indicates that systemic therapy that may potentially reduce inflammation and stabilise plaques may reduce clinical events to a more significant effect than conventional risk factor management alone[46]. An imaging modality that could identify the vulnerable patients who may potentially benefit from intensive treatment could alter the way patients are risk-assessed and subsequently managed. Also, the recent ISCHEMIA (Initial Invasive or Conservative Strategy for Stable Coronary Disease) trial has demonstrated a disappointing lack of mortality benefit in patients undergoing symptom-driven percutaneous coronary intervention (PCI).[47] In view of this, an ability to identify vulnerable plaques in vivo is mandatory if attempts at local treatment such as "plaque sealing" are to be successful.

1.4.1: Coronary Angiogram

In the early 1960s, the investigation of coronary artery disease changed dramatically following the first selective coronary angiography by Dr F Mason Soans in 1958. This technique opened up a new avenue in the diagnosis and evaluation of coronary atherosclerosis in vivo. Although the storage and processing of the data have changed, the technology is fundamentally the same with the acquisition of an x-ray projection taken during the injection of radio-opaque contrast dye into the coronary arteries. This provides a silhouette of the arterial lumen with good spatial (200μm) and temporal resolution (8ms). This allows effective quantification of the luminal stenosis. Although eccentric stenosis or overlapping vessels can hinder this, it can usually be remedied by taking multiple projections. Angiographic assessment of luminal stenosis does provide some important prognostic information, and patient mortality differs depending on whether there is obstructive stenosis in 1,2 or 3 vessels.[48]

Initial work comparing post-mortem histology and angiography revealed that plaque rupture was a precipitating event in coronary thrombosis; however, it was felt that the extent of the pre-existing stenosis was the decisive factor in determining whether the thrombosis would be occlusive.[41] It has become apparent from a larger series that plaque rupture with subsequent myocardial infarction can occur at sites without previously significant (<50%) stenosis.[49] In fact, as plaques that cause <50% stenosis significantly outnumber those that cause >50% stenosis, the culprit lesion in 60-70% of acute coronary syndromes has been found to cause <50% stenosis.[50] Studies in post-mortem arteries and patients undergoing intra-coronary thrombolysis for myocardial infarction have shown that ruptured plaques with overlying thrombus show a moderate correlation with some angiographic features such as eccentric stenosis, irregular margins, intra-plaque lucencies and filling defects.[51] Unfortunately, these features have not been correlated with vulnerable plaques before they have ruptured. Contrast angiography is unsuitable for this purpose as it gives little or no information about the sub-plaque anatomy or the constituent tissues within the plaque. Another limitation is the inability to quantify the arterial geometry

outside of the lumen, which is an important factor, particularly in regard to the presence of positive or negative remodelling.

1.5: Invasive Coronary Imaging

The European Society of Cardiology (ESC) guidelines for the management of chronic coronary syndromes provide a recommendation (class I and level of evidence A) for the use of intra-coronary imaging to guide implantation of coronary drug-eluting stents mainly in anatomically 'complex' lesions[52], especially after the release of large randomised control trials which showed prognostic benefit and superior outcomes in using intra-coronary imaging, particularly on the left main stem, true bifurcations, and long lesions when compared with angiography guidance alone.[53,54]

1.5.1: Intravascular Ultrasound (IVUS)

IVUS examination is an invasive procedure that requires cardiac catheterisation to perform. Unlike coronary angiography, IVUS provides tomographic information on the plaque. The equipment required consists of 3 components: the IVUS catheter, a motorised pull-back device and a console to reconstruct the image. The IVUS catheter uses a tiny ultrasound transducer, which is miniaturised (0.87-1.17mm) and is compatible with a 6-French guiding catheter. The IVUS catheters use either a fixed array of mini transducers or a single rotating transducer.

In the U.S., Boston Scientific and Volcano Therapeutics are the two manufacturers with current FDA-cleared IVUS systems. Volcano offers two systems, the s5 and s5i, and Boston Scientific's system is the iLab. The systems are available on a cart that can be moved around to different cardiac catheterisation labs or as an integrated system where a controller is permanently mounted on a table in the lab. The catheter is introduced on a guide wire, usually 0.36 mm, and the IVUS-tipped catheter is then fed over the guide wire. Transducers operate in the 10-20 MHz range, and the echo return is sent to an external

computer so images can be reconstructed on a screen, usually displayed at 30 frames/second. Angiography is used to guide the IVUS catheter to the area of the vessel to be imaged. It is placed farthest away from the area to be imaged and is then pulled back through the area of stenosis.

The transducer produces the ultrasound signal by passing an electrical current through a piezoelectrical crystal. In conventional IVUS, the ultrasound signal is reflected from the surrounding tissue and sent back to the transducer, which is converted into a grey-scale image. It can be used to assess vessel/lumen diameter and lesion length, help determine the amount of plaque burden in a vessel and its composition, and check to ensure stents have been properly placed and fully deployed.

Grayscale IVUS uses miniaturised crystals, which generate high-resolution, cross-sectional images of the vessel wall and lumen. Axial resolution is approximately 150 μm, and the lateral resolution is 300 μm.[55] Grayscale IVUS allows robust quantitative measurements, including those of the lumen, vessel, and plaque area. Furthermore, Grayscale IVUS imaging enables the assess procedural outcomes after PCI. Moreover, IVUS has been increasingly used to evaluate the natural history of coronary plaque morphology and the underlying mechanism of cardiac events.

Virtual histology intravascular ultrasound (VH-IVUS) is a catheter-based technology where IVUS is generated from the transducer on the catheter tip, and the reflected signals from the artery wall produce a colour-coded map of the arterial disease. The colours assigned to the pixels are dark green for fibrotic tissue, light green for fibro-fatty tissue, red for necrotic core and white for dense calcium. This invasive imaging modality uses radiofrequency ultrasound backscatter data to identify plaque components, including necrotic core, calcification, fibrous, and fibrofatty tissue. In ex vivo studies, VH-IVUS has predictive accuracies of >93.5% to characterise coronary plaque composition.[56]

The colour-coded tissue maps give information about plaque architecture and the relative volume of different plaque constituents. It has been proposed that this information can be used to classify the plaque and that the vulnerability of the plaque can be inferred from this.[57] Post-mortem studies demonstrate that human atherosclerotic plaques that undergo rupture manifest a particular morphology and are often not flow-limiting. The highest risk plaques are the TCFA, where a fibrous cap of <65um separates a

relatively large necrotic core from the lumen.[42,58] Whilst histology can identify risk after an event, plaque classification in vivo prior to an event is required if this knowledge is to be clinically useful. There is now an expanding body of literature utilizing VH-IVUS, some of which is summarised in Table 2.

Table 2: summarizing clinical trials utilizing IVUS to identify different plaque morphology.

Catheter	***Tissue***	***Necrotic core***	***Fibrous***	***Fibro-fatty***	***Calcium***	***Study***
VH-IVUS Volcano 20MHZ	*Ex-vivo human coronaries*	*95.8%*	*93.5%*	*94.1%*	*96.7%*	*Nair et al.*[59]
VH-IVUS Volcano 20MHZ	*Human Atherectomy samples*	*88.3%*	*87.1%*	*87.1%*	*96.5%*	*Nasu et al.*[60]
VH-IVUS Volcano 20MHX	*Ex-vivo human coronaries*	*65%*			*92%*	*Obaid et al.*[61]

% = The percentages relate to diagnostic accuracy, VH-IVUS: Virtual histology intravascular ultrasound

The PROSPECT (predicting future adverse coronary events within the framework of the Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study assessed the potential significance of VH IVUS-derived plaque types. The study focused on ACS patients, and all participants initially underwent PCI for a culprit lesion. Subsequently, angiograms and VH IVUS analyses of the three primary coronary arteries were conducted.[62]

Throughout the follow-up period, clinical events were attributed equally to recurrence at the site of the culprit lesion and non-culprit lesions. Even though non-culprit lesions associated with unforeseen events often appeared angiographically mild, they typically exhibited distinctive characteristics, including a significant plaque burden (≥70%), a small luminal area (≤ 4.0 mm^2), or TCFA. TCFA was defined as a lesion meeting specific criteria in at least three consecutive frames: necrotic core ≥10% without evident overlying fibrous tissue and per cent atheroma volume ≥40%.

The study also found a correlation between plaque composition and the occurrence of distal embolisation after PCI. Observational findings highlighted a clear link between the amount of necrotic core and distal embolisation, suggesting the potential need for additional pharmacological or device-based interventions to mitigate the incidence of distal embolisation.[63]

Other growing evidence illustrates how IVUS improves the clinic outcome when used during PCI to evaluations of the stent under expansion, malposition, incomplete lesion coverage, and residual plaque contribute to reducing not only restenosis but also thrombosis when compared to angiographic-only guided PCI (Table 3).

1.5.2: Optical Coherence Tomography (OCT)

OCT utilises back-scattered pulsed light waves to create the image. Current OCT images are obtained at a peak wavelength between 1280-1350 nm, enabling a spatial resolution of 4-20μm (10 times greater than IVUS), with a penetration depth of 2 to 3 mm.[64] This spatial resolution means that discrimination of a thin cap (<65μm) is possible. OCT has been proven to be successful in visualizing some aspects of plaque structure, and in vivo studies have demonstrated a significant difference in the number of TCFAs between patients with stable angina and acute MI.[65]

Despite OCT's inferior penetration compared to IVUS, it offers a superior evaluation of vulnerable plaque by furnishing detailed images of endoluminal borders, higher lipid core detection rates, fibrous cap measurement, and macrophage detection. In comparative assessments of culprit lesions among patients with acute Mis, OCT demonstrated greater sensitivity in detecting plaque rupture, plaque erosion, and TCFA compared to IVUS or coronary angioscopy.[66]

Table 3: Clinical outcome trials after IVUS-guided PCI.

Study or subgroup	***MACE***	***IVUS***		***Angiogram***		***Odd ratio***	***95% CI***
		Events	***total***	***Events***	***Total***		

Excellent[67]	*Cardiac death, MI and T.L.R.at 12 months*	*34*	*619*	*31*	*802*	*1.4*	*0.88-2.38*
RESET[68]	*Cardiac death, MI, T.V.R. at 12 months*	*12*	*269*	*20*	*274*	*0.59*	*0.28-1.2*
AVIO[69]	*Death, MI, T.V.R. at 2 years*	*24*	*142*	*33*	*142*	*0.67*	*0.37-1.21*
Hur et al.[70]	*Death, MI, T.V.R., S.T.at 3 years*		*2765*		*1816*	*0.85*	*0.71-1.03*
ADAPT-DES[71]	*Cardiac death, MI, S.T.at 12 months*	*103*	*3349*	*238*	*5234*	*0.67*	*0.53-0.84*

IVUS: intravascular ultrasound, PCI: percutaneous coronary intervention, MACE: major adverse cardiac event, CI: confidence interval, D.E.S: drug-eluting stent, MI: myocardial infarction, T.L.R. target lesion revascularisation, T.V.R. target vessel revascularisation, S.T. stent thrombosis

In another head-to-head trial, using two hundred fifty-eight regions of interest from autopsied human hearts with plaque composition and classification assessed by histology and compared with coregistered ex vivo VH-IVUS and OCT, both VH-IVUS and OCT reliably identified TCFA. However, OCT accuracy may be improved using lipid arc ≥80° and fibrous cap thickness ≤85 μm over three continuous frames.[72]

Although OCT facilitates precise evaluation of plaque types, stent strut positioning, and endothelialisation owing to its superior spatial resolution and rapid data acquisition, its limited axial penetration hinders optimal visualisation of the arterial wall. Additionally, its reliance on contrast injection during image capture means it cannot be conducted in scenarios lacking coronary flow, such as complete occlusion situations.

The updated coronary revascularisation guidelines were released after the recent publication of three large randomised trials that evaluated the clinical benefits of intra-coronary imaging in the context of

complex PCI. The RENOVATE-COMPLEX PCI (Intravascular Imaging–Guided or Angiography-Guided Complex PCI) trial[53] primarily assessed the utility of IVUS, with a patient cohort consisting of 74% IVUS and 26% OCT usage. In contrast, the OCTOBER (OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions)[54] and ILUMIEN IV(Optical Coherence Tomography–Guided versus Angiography-Guided PCI)[73] trials focused on the efficacy of OCT. Notably, the OCTOBER trial focussed on true bifurcation lesions, while RENOVATE-COMPLEX PCI encompassed a broader range of anatomically complex lesions, including true bifurcation lesions, long lesions, and chronic total occlusion lesions. The ILUMIEN IV trial, however, adopted a more comprehensive approach to defining complexity, incorporating both clinical factors—such as Diabetes Mellitus and ST or non-ST elevation myocardial infarction—and anatomical characteristics of the lesions.

While these trials underscore the value of advanced intra-coronary imaging modalities in complex PCI, they also highlight the evolving paradigm of imaging in cardiology. This progression naturally raises the question of how non-invasive imaging techniques might complement or further advance the understanding and management of coronary artery disease.

1.6: Non-Invasive Imaging of Vulnerable Plaques

Although several intra-coronary imaging techniques exist to accurately visualise various high-risk plaque characteristics, the ideal scenario for screening would involve the detection of vulnerable plaques using non-invasive imaging modalities, eliminating the need for invasive catheterisation. Moreover, non-invasive imaging of vulnerable plaques could also serve as a means to assess plaque regression in trials evaluating treatment strategies. While non-invasive cardiovascular imaging modalities are well-established in demonstrating the presence of CAD (such as coronary calcium) or its consequences (like ischemia or infarction on perfusion imaging), efforts are now being directed towards detecting asymptomatic, non-obstructive, vulnerable plaques as well. Table 4 provides a summary of the features of available non-invasive imaging modalities.

Table 4: summary of the features of non-invasive imaging modalities

	Computed Tomography Coronary Angiography (CCTA)	***Cardiovascular Magnetic Resonance (CMR)***	***FF.D.G.Positron Emission Tomography (PET)***
Spatial resolution, mm	*0.4*	*0.5-1*	*4-5*
Radiation exposure	*Yes*	*No*	*Yes*
Iodine contrast	*Yes*	*No*	*No*
Detection of vulnerable plaque features			
Lipid-rich core	++	+++	-
Fibrous cap thickness	-	-	-
Spotty calcifications	+++	++	-
Positive vessel remodeling	+++	+	-

Spotty calcifications are calcifications <3 mm. Indicator — means not distinguishable; + barely distinguishable; ++ moderately distinguishable; +++ well delineated

1.7: Computed Tomography Coronary Angiography (CCTA)

Nearly 30 years ago, Godfrey Hounsfield introduced the concept of "computerised transverse axial scanning," which involves reconstructing an image of an internal structure using the attenuation pattern of an X-ray beam passing through the object at various angles.[74] X-rays emitted from a source pass through the patient positioned in the field of view before reaching a detector array. This array comprises elements that measure the intensity of attenuated X-rays, with the electrical intensity signal converted into digital data by an analog-digital converter. The resulting attenuation profile is termed a "projection." Through continuous movement of the X-ray source and detector elements around the patient, numerous projections are generated. These projections are commonly reconstructed using a method known as "filtered back projection" to create a transaxial slice.[75] During this reconstruction, a high-pass filter referred to as a "reconstruction kernel" is applied, allowing for varying degrees of image sharpness. The

transaxial slice is then mapped onto a pixel matrix typically sized at 512x512. Each pixel represents the X-ray attenuation coefficient of the underlying structure, with different anatomical structures attenuating X-rays to varying degrees. This attenuation coefficient is translated into Hounsfield units (HU), a grayscale where each pixel is assigned a shade based on the material's attenuation characteristics relative to water. Water has an HU value of 0, blood typically ranges from 30 to 70 HU, and bone exceeds 500 HU.

1.7.1: Development of Cardiac CT

In the early stages of CT scanning, the acquisition of a single image could take up to 300 seconds, resulting in poor temporal resolution that limited its application to static structures like the brain.[76] Given the constant movement of coronary arteries during the cardiac cycle, with velocities reaching up to 69.5mm/sec, gating the scan with the electrocardiogram to acquire data specifically during diastole, when coronary motion is minimal, was proposed in 1977. This technique, even on early machines, enabled sufficient image quality to assess bypass graft patency.[77]

The introduction of electron beam CT scanning in the 1980s, wherein the detector remained stationary while an electron beam rotated around the patient, significantly improved temporal resolution to 50-100msec per slice, allowing for reliable detection of coronary calcification.[78] However, spatial resolution remained inadequate for accurate quantification or characterisation of coronary plaque. Advancements in conventional CT technology have since enhanced both temporal and spatial resolution. The development of the "slip ring" enabled continuous gantry rotation without the need for resetting, facilitating "spiral" scanning, while gantry rotation speeds have increased up to 280 msec.[79] Multi-detector CT allows simultaneous acquisition of multiple slices, with increased slice count enhancing spatial resolution without compromising temporal resolution.

The introduction of a 320-slice CT scanner represents a significant advancement. The Siemens Somatom Definition 64-slice dual-source CT scanner utilised in this project features two X-ray tubes and

corresponding 32-slice detector arrays with a 90-degree offset. While the gantry rotation time is 330msec, dual-segment reconstruction achieves a temporal resolution of 83 msec and spatial resolution of up to 400μm. Although this profile was among the best available at the project's commencement, it's worth noting that the temporal resolution of coronary angiography is 8ms, with a spatial resolution of 200μm.

Across the studies included in this thesis, radiation exposure varied according to scanner generation, acquisition mode, and patient characteristics. The reported dose–length product (DLP) ranged approximately from 120 to 450 mGy·cm per scan, with lower doses observed in prospectively gated acquisitions and newer-generation scanners. These values are consistent with contemporary clinical CCTA practice

1.7.2: CT Coronary Angiography

The introduction of intravenous X-ray contrast enables visualisation of the coronary lumen, offering the potential for a non-invasive coronary angiogram. Data from the National Cardiovascular Data Registry (NCDR) CATH-PCI indicates that nearly 37% of cardiac catheterisations performed in the United States show no significant evidence of coronary disease. CCTA may play a role in reducing this number due to its high negative predictive value.[80]

Recent guidelines from the National Institute for Health and Care Excellence (NICE) suggest that CCTA is a suitable investigation for evaluating patients with stable chest pain and a low-to-intermediate pre-test probability of CAD.[81] The utilisation of CCTA in the United Kingdom rose by 268% from 2011 to 2017. However, regional variances persist, with Scotland and Northern Ireland exhibiting only modest increases in CCTA usage.[82]

The ISCHEMIA (Initial invasive or conservative strategy for stable coronary disease) trial concluded that among patients with stable coronary artery disease and moderate or severe ischemia, an invasive strategy,

when compared to an initial conservative management approach, did not lead to a reduction in the risk of ischemic cardiovascular events or death over a 2-year period.[47] It is noteworthy that during the trial, following stress testing to confirm at least moderate ischemia, the majority of patients (73%) underwent CCTA to exclude left main coronary disease and non-obstructive coronary disease, highlighting the importance of CCTA in ruling out significant coronary disease. Additionally, CCTA has been shown to have the highest diagnostic accuracy for detecting angiographically significant stenosis compared to all other available non-invasive tests. [83] Critics often label CCTA as merely an 'anatomical' test; however, this criticism can be somewhat alleviated by utilizing fractional flow reserve assessment (CT-FFR), a computer-based technology that provides functional information using computational fluid dynamics to determine the functional significance of atherosclerotic plaque.[84] Despite its strengths in anatomical assessment, CCTA does not directly evaluate coronary vasomotor function. Coronary microvascular dysfunction (CMD) is diagnosed by excluding obstructive epicardial coronary artery disease using anatomical imaging and, where appropriate, fractional flow reserve, and by demonstrating abnormal microvascular indices such as an elevated index of microcirculatory resistance (IMR) and/or reduced coronary flow velocity reserve (CFR). This can be assessed invasively using functional coronary angiography with vasoreactivity testing or non-invasively using PET-CT, stress perfusion cardiovascular magnetic resonance, or Doppler-based transthoracic echocardiographic assessment of distal LAD CFR.

1.7.3: CT Imaging of Calcified Plaque

In most coronary CT studies, plaques are typically categorised into calcified, non-calcified (soft), and mixed types. Calcification is defined as a density greater than 220 HU, with lesions containing 50% or more calcium classified as calcified and those with less as mixed.[85] However, this classification is considered overly simplistic for describing the complex composition of advanced plaques.

Coronary artery calcification serves as a recognised marker for atherosclerotic coronary artery disease, with its onset possible in patients as young as 10 to 20 years old. The calcification primarily consists of calcium phosphate (hydroxyapatite), a compound similar to that found in bone, which makes it relatively easy to detect because it has much higher attenuation than other tissue in the vicinity.[86] The amount of calcified plaque can be calculated without the requirement for iodinated contrast using scanners with poor spatial resolution (3mm slices) and with low radiation dose (1-2mSv). The Coronary Artery Calcium (CAC) is expressed as an "Agatston" score, which defines a calcified lesion as having a density equal to or greater than 130 HU and an area equal to or greater than 3 pixels. Each lesion was assigned a score (the product of density and area), and the total score was obtained by summing the scores of all calcified lesions. A semi-automated method, which adheres to the same principles, is now commonly employed for CAC Scoring.[87]

Cardiovascular risk stratification using calcium scoring has been widely studied, and standard categories according to cardiovascular prognosis and total mortality are as follows:[88]

CAC = 0: very low risk of death (<1% at 10 years)

CAC = 1-100: low risk of death (<10% at 10 years)

CAC = 101-400: intermediate risk of death (10-20% at 10 years)

CAC = 101-400 and >75th percentile for age, sex, and ethnicity: moderately high risk of death (15-20% at 10 years)

CAC >400: high risk of death (>20% at 10 years)

In the MESA (Multi-Ethnic Study of Atherosclerosis) study, a calcium score exceeding 300 indicated a 9.5 times higher risk of a cardiac event compared to a calcium score of 0 across four distinct ethnic groups.[89] In a study involving more than 25,000 patients, a calcium score of 0 was associated with a notably low occurrence of events, with a 12-year survival rate of 99.4%.[90]

Spotty calcification is an established marker of plaque instability. It is defined as the presence of calcified plaque with a diameter of <3 mm in any direction, length (extent in the longitudinal direction of the

vessel) of the calcium less than 1.5 times the vessel diameter, and width (extent of the calcification perpendicular to the longitudinal direction of the vessel) of the calcification less than two-thirds of the vessel diameter (Figure 2).[91]

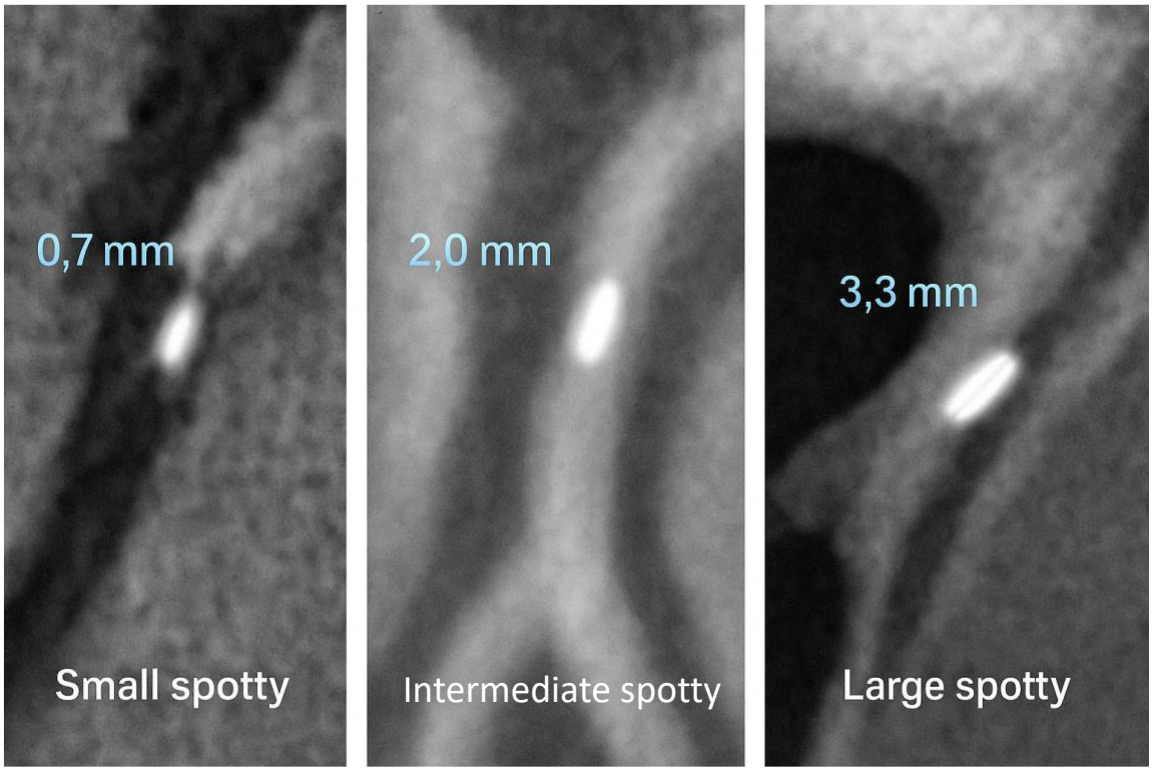


Figure 2: Illustration of the different types of spotty calcification. A: Small spotty calcification (<1 mm). B: Intermediate spotty calcification (1-3 mm). C: Large spotty calcification (>3 mm). Figure adapted from Van Velzen JE et al. J Nucl Cardiol.[92]

In a head-to-head comparison trial between plaque classification on CCTA and VH-IVUS, plaques with small spotty (<1 mm) rather than intermediate spotty (1-3 mm) or large spotty calcifications (>3 mm) calcifications on CT were related to plaque deemed more high-risk on IVUS-V.[92]

Solely measuring calcified plaque presents significant limitations. Extensive calcification may indicate a less biologically active stage of the atherosclerotic disease process, often termed "burnt out." Despite notable reductions in serum lipids and cardiovascular events seen with statin therapy, the progression of CAC scores remains unaffected. This makes CAC an inappropriate endpoint for treatment trials.[93] The discrepancy likely arises from the fact that statins not only reduce cholesterol levels but also may lower

inflammation, potentially inhibiting the progression from inflammation to calcification—a process not captured by calcium scoring using CT.[94]

Moreover, calcified plaque accounts for only 20% of the atherosclerotic burden. Therefore, relying solely on CAC measurement does not exclude the presence of CAD. In a study investigating the association of CAC with the presence of significant CAD, 15% of the participants with zero CAC who presented to the emergency department (ED) with acute chest pain and non-diagnostic ECG had at least ≥50% CAD made up of non-calcified plaque on CCTA.[95] This non-calcified plaque could pose a risk of future events, underscoring the importance of detecting, quantifying, and characterizing its composition.

1.7.4: CT Imaging of Non-Calcified Plaque

Recent efforts by various researchers have aimed at a more detailed assessment of coronary plaques in symptomatic patients. For instance, Motoyama et al. subdivided non-calcified plaques into those with a lipid core, with a cut-off point of less than 30 HU and fibrous plaques (30–150 HU).[85] Similarly, Leber et al. defined lipid pool spots as structures larger than 2 mm^2 with at least 20 HU less than the average value of surrounding non-calcified plaque tissue.[96] In a meta-analysis comparing CCTA and IVUS for plaque detection, the sensitivity and specificity for diagnosing non-calcified plaque (soft or fibrous) were reported as 88% and 92%, respectively.[97] However, distinguishing between soft and lipid-rich plaques versus more stable fibrous plaques remains challenging, with significant overlap in attenuation values between individual plaques observed.[96]

Average values of mixed plaques have been reported between 67 and 104 HU, while for non-calcified plaques, they range from 14 to 51 HU.[98,99] In an ex vivo study by Maurovich-Horvat et al., a qualitative approach was adopted for characterizing non-calcified plaques, with visual classification into homogeneous and heterogeneous attenuation patterns.[100] This approach stems from earlier investigations demonstrating that heterogeneous non-calcified plaques, indicated by a ring sign, are more suggestive of

high-risk plaques containing a lipid core, whereas homogeneous plaques without calcification are stable fibrous plaques.

1.7.5: CT Imaging of Vulnerable Plaques

In vivo, the use of VH-IVUS for the invasive identification of vulnerable TCFA plaques has demonstrated prospective prediction of clinical outcomes.[101] However, directly visualizing TCFA non-invasively is currently not feasible due to the small diameter of vulnerable thin caps (65 μm or less), which exceeds the spatial resolution capabilities of even the most advanced multi-detector CT (MDCT) scanners (approximately 400 μm). Additionally, identifying small lipid cores is challenging due to their low attenuation values, leading to significant noise interference and a low signal-to-noise ratio.

A study focusing solely on large proximal coronary segments using 64-slice CT revealed that only 70% of lipid pools were detected as defined by greyscale IVUS.[96] Comparatively, Pundziute et al. compared 64-slice CT with VH-IVUS and discovered that mixed plaques containing both calcified and non-calcified elements on CT were more likely to contain VH-IVUS-defined TCFA.[102] Another study involving patients with ACS or stable angina who underwent VH-IVUS and CT highlighted that non-calcified and mixed plaques were more prevalent in ACS patients. In contrast, calcified plaques were more common in stable patients.[103]

Interestingly, Velzen et al. observed that plaques with more significant stenosis did not necessarily exhibit significantly larger necrotic cores or a higher prevalence of TCFAs on VH-IVUS. Moreover, they found that CT plaque types (non-calcified, calcified, and mixed) were equally distributed between significant and non-significant stenosis cases, suggesting that features of vulnerability as detected by CT or VH-IVUS were not more prevalent in plaques with more significant stenosis.[104]

CT can identify other indicators of vulnerability as well. Positive arterial remodelling (PR), which has been linked to vulnerable plaques through histological and IVUS analyses[105], can be detected using CT. The presence of positively remodelled plaque segments on CT correlates well with IVUS findings.[106]

These plaques tend to have a higher proportion of necrotic core and are more frequently associated with TCFAs defined by VH-IVUS.[107] Additionally, CT-detected "spotty" calcification in plaques, defined as calcified plaque less than 3mm, has been associated with increased necrotic core and TCFA frequency on VH-IVUS.[92]

In a prospective study involving over 1000 patients followed for two years, the presence of positive remodelling or low attenuation (<30 HU) on CT was associated with subsequent ACS events. Furthermore, the presence of both features together had a high hazard ratio, indicating an increased risk of ACS.[108] Studies have also outlined a distinct pattern of attenuation in atherosclerotic plaques on coronary CT images. This pattern involves a plaque core with low CT attenuation encircled by a rim-like area of higher CT attenuation, resembling the appearance of a napkin ring sign (NRS).[109]

NRS has been described in patients with ACS events, potentially representing a culprit coronary lesion.[109,110] Currently, NRS is considered as a CT signature of high-risk coronary atherosclerotic plaques with histopathological correlate.[100] NRS, along with features like PR, low attenuation plaque and spotty calcification, are predictive markers of plaque vulnerability and instability.[111] These features are shown below in Figure 3.

1.7.6: CT Characterisation of Coronary Plaque and Future Developments

With the advancements in MDCT technology, there is a growing interest in characterizing non-calcified plaque components in human coronaries. Studies using phantoms have demonstrated the potential to differentiate soft and intermediate components of non-calcified plaque based on their attenuation values. The attenuation values play a crucial role in accurately differentiating plaque tissues, although factors like intra-coronary attenuation can influence the measurements.[112] Studies comparing CT with IVUS and post-mortem histology have confirmed that lipid-rich plaque has lower attenuation than fibrous plaque.[113] Calcified plaques have very high attenuation values relative to other plaques, and because of this, CT tends to overestimate their volumes. In the reconstruction process, every voxel (3D pixel) is given an

average HU value depending on the structures it depicts. If there are nearby areas with calcium, the average value assigned to structures will be high, even if there's just a bit of calcium within that voxel.

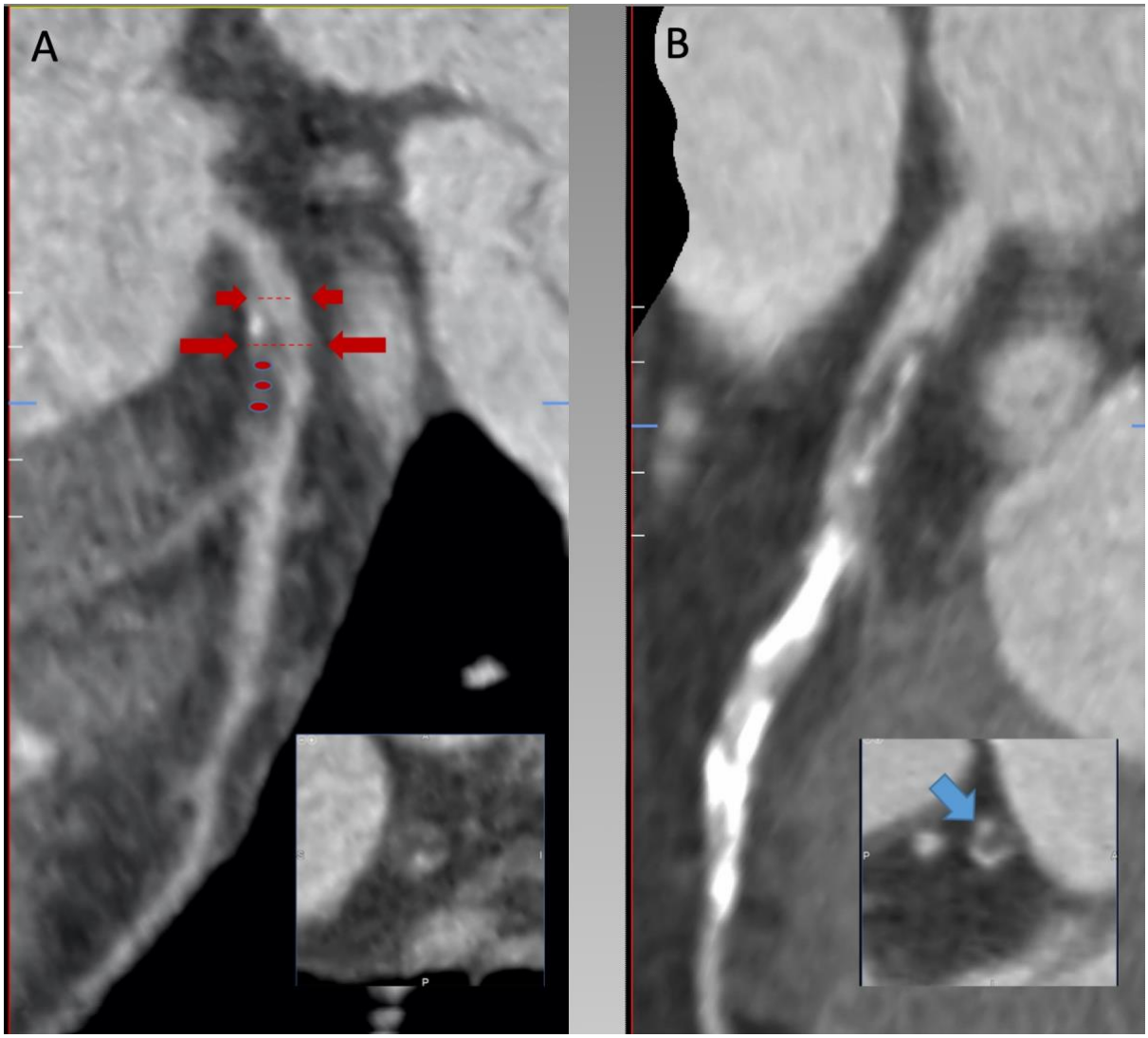


Figure 3: Atherosclerotic plaques showing CT features of vulnerability. A: An atherosclerotic plaque showing positive remodelling (red arrows) and low attenuation (red dots) plaque in the proximal left anterior descending artery on CCTA. B: An atherosclerotic plaque showing a Napkin ring sign in the right coronary artery. Figure adapted from SALEM AM. et al. Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain.[114]

This occurrence is termed "partial volume," causing an overestimation of the calcified plaque's size, known as a "blooming artefact". Blooming artefacts in calcified plaque on CCTA is a well-recognised challenge that can lead to overestimation of coronary stenosis severity and false-positive studies.[115]

Various studies have explored methods to reduce blooming artefacts in CT imaging. For instance, a novel de-blooming algorithm has shown promise in decreasing blooming artefacts caused by coronary calcified plaques, thereby improving diagnostic accuracy.[116] Additionally, the acquisition of dual-energy images has been proposed as a technique to reduce blooming artefacts and enhance the quantification of calcified plaque.[117] Moreover, modified dual-energy algorithms have been developed to address blooming artefacts and improve the accuracy of stenosis grading.[118]

Previous work has been done to use CT attenuation ranges to measure volumes of fatty, fibrous and calcified plaque for comparison with VH-IVUS. Obaid et al. demonstrate that by utilizing CT to define plaque composition, particularly focusing on the percentage of necrotic core and the ratio of necrotic core to fibrous plaque, it could be possible to differentiate between culprit plaques in patients with ACS and those with stable angina. Moreover, CT-defined plaque composition successfully distinguished different levels of vulnerability as defined by VH-IVUS (fibroatheroma vs non-atheroma and thin-cap vs thick cap atheroma) in living organisms, a capability not achieved by traditional markers of CT plaque vulnerability such as spotty calcification, remodelling index, and low attenuation plaque.[61,119]

Their research also introduced a new method for visualizing plaque on CT scans called "Plaque Maps" generated based on contrast/plaque attenuation ratios. These maps allow to visualise ruptured plaque and confluent necrotic core. CT-defined rupture accurately identified ACS culprit plaques with a specificity of 94%, while CT-defined fibroatheroma identified VH-IVUS-defined fibroatheroma in living organisms with a specificity of 100%. These high specificity values suggest potential utility in clinical settings.[61,119]

Ultimately, tissue differentiation by CCTA is limited by the overlap of the attenuation ranges between plaque components, especially necrotic core and fibrous tissue, which is crucial for the identification of vulnerable plaques. One possible solution to overcome this is by using Photon-counting CT, a cutting-edge technology with the potential to revolutionise CT. By tallying individual X-ray photons that engage with the detector, photon-counting CT presents several advantages over traditional energy-integrating CT systems. These advantages encompass superior spatial resolution, improved noise levels, and visualisation of complex structures such as calcified coronary plaques, as well as providing a more

accurate assessment of diameter stenosis.[120] Despite these advantages, the photon-counting technology faces some challenges, like pile-up issues (overlap of multiple signals) and charge sharing between neighbouring pixels, which can affect image quality.[121] Additionally, motion artefacts can significantly degrade the diagnostic performance of X-ray CT images, particularly in photon-counting CT systems, impacting spatial resolution and quantitative imaging capabilities.[122] This thesis further utilises this "Plaque Maps" methodology across high-risk populations in stable and acute settings. While advances in imaging technologies continue to enhance our ability to characterise coronary artery disease at an anatomical and functional level, the clinical expression and progression of atherosclerosis are strongly influenced by systemic risk factors. Among these, metabolic disorders—particularly diabetes mellitus—play a central role in accelerating atherosclerotic processes and increasing cardiovascular risk. The following section therefore focuses on diabetes as a key modifier of coronary artery disease.

1.8: Diabetes Mellitus (DM)

Individuals with Type 2 Diabetes Mellitus (T2DM) face a two- to three-fold higher risk of CV events compared to those without diabetes, with CV mortality accounting for approximately 80% of all deaths in this population.[123] As such, reducing cardiovascular risk is a central therapeutic objective. However, current evidence indicates that hyperglycaemia is only a modest contributor to CV risk, and intensive glycaemic control has limited impact on reducing macrovascular events or CV-related mortality.[124]

1.8.1: Endothelial Dysfunction, Inflammation, Oxidative Stress and Arterial Stiffness in DM

DM leads to significant macro- and microvascular complications. These complications can encompass a range of issues, such as coronary artery disease, peripheral vascular disease, and diabetic retinopathy, among others.[125] Risk factors for these complications include advanced age, duration of diabetes, male

sex, hypertension, body mass index, and atherosclerosis.[125] As mentioned before, atherosclerosis leads to a cascade of endothelial cell dysfunction, which subsequently translates into adverse clinical events. Patients with diabetes, in general, are more prone to endothelial injury and dysfunction as chronic hyperglycaemia and insulin resistance are associated with high inflammatory response.[126] There is some evidence linking the production of islet-derived interleukin-1β (IL-1β) and tumour necrosis factor (TNF) to hyperglycaemia states.[126] Furthermore, some clinical studies have shown that patients with T2DM usually have higher than normal markers of chronic systemic inflammation levels, including CRP, IL-1β and interleukin-6 (IL-6).[127,128] Endothelial dysfunction and inflammation-related processes are now assumed to play an essential role in diabetic macro and microvascular complications.[128] About 90% of diabetic and pre-diabetic individuals are known to have endothelial dysfunction.[129]

An oxidative stress environment arises as a result of an imbalance between free radical production, also known as reactive oxygen species (ROS) and antioxidant vasodilator factors.[130] Excessively high ROS levels cause damage to cellular proteins, membrane lipids and nucleic acids, and eventually cell death.[130] Considerable interest has developed in the role of free radical-mediated cell damage and coronary artery disease.[131] LDL is an important marker of oxidation. Oxidative modification of LDL (Ox-LDL) results in the production of immunogenic molecules which attack the arterial intima and provoke endothelial dysfunction, platelets aggregation, and predispose to atherosclerosis.[15] Plasma total antioxidant status (TAOS) is another practical and inexpensive assay that inversely correlates with plasma oxidation. Both TAOS and Ox-LDL have been studied in vivo and showed a strong association between baseline plasma measures and coronary artery disease risk.[132] Moreover, CRP was frequently colonised with p22phox, an essential component of NADH/NADPH oxidase, an important ROS source in vasculature. Furthermore, CRP directly enhanced p22phox expression as well as the generation of intracellular ROS in cultured human coronary artery smooth muscle cells (CASMCs).[18] Hyperglycemia augments oxidative stress status by upgrading free radicals and impairing antioxidant defence, which is believed to play an active role in developing and progressing the vascular complications of diabetes.[133–135]

1.8.2: Hyperlipidaemic Control in DM

Efforts to mitigate the risk of vascular complications in diabetes involve controlling factors such as hypertriglyceridemia and hyperglycemia. The relationship between hyperlipidaemia and CVD has been well established.[136] Most international guidelines and expert recommendations use LDL-C as the predictor marker for dyslipidaemia and a primary target of lipid-lowering therapy (LLT) for CVD. However, non-high-density lipoprotein cholesterol (non-HDL-C) has recently gained clinical attention in treating patients with hypertriglyceridaemia or cardiometabolic abnormalities.

The LDL-C indicates the cholesterol mass within LDL particles, which is strongly related to the atherosclerotic risk, while non-HDL-C quantifies all atherogenic apolipoprotein B-containing lipoproteins, including LDL and very low-density lipoprotein (VLDL) which as well is a risk factor coronary atherosclerosis.[137] Non-HDL-C is simply calculated by subtracting HDL-C from total cholesterol (TC) regardless of the fasting status, which can be more convenient in clinical practice.[138] The NICE is currently advocating the usage of non-HDL-C as (but not LDL-C) a primary therapeutic target for CVD, especially in high-risk patients with DM, perhaps owing to its practicality.[139] However, a large prospective comparison trial is needed to assess the sensitivity of LDL-C versus non-HDL-C in predicting CAD.

The dyslipidaemia accompanying T2DM contributes to a 2- to 3-fold increased risk of CV events compared to the non-diabetes counterparts.[123,140] Therefore, LLTs, particularly statins, remain one of those patients' most important primary and secondary prevention strategies. Paradoxically, statin use has been found to increase the risk of DM; this observation was initially reported with Rosuvastatin in 2008.[141] Subsequently, meta-analyses of statins randomised clinical trials have confirmed this effect and suggest that statin treatment is associated with a 10%–12% increase in the risk of incident diabetes compared with placebo.[142,143] Those trials mainly comprised individuals with low DM risk, and the diagnosis was not always based on laboratory testing, limiting the sensitivity of evaluating this relationship. Crandall et al. were the first to confirm the association between statin and diabetes in

subjects at high risk for diabetes.[144] Some theoretic mechanisms of this action were proposed, like statin-related modifications to insulin sensitivity and signals; others suggested metabolic changes related to the progression to diabetes among those high-risk individuals. To date, the mechanism by which statins increase DM risk is still not well understood. Practically, a potential increase in DM risk should be balanced against the significant and established CV benefit of statin treatment.

Reports from European and American health systems showed that statin alone (even at the highest tolerated doses) might not be enough to reach the optimal lipid targets for patients with diabetes.[145,146] Additionally, whether real or perceived, statin intolerance remains a real clinical obstacle that can prevent high-risk patients from reaching guideline-recommended LDL-C treatment levels associated with clinical benefits. Therefore, using adjunctive therapies to mitigate sub-optimisation risk is warranted. Agents that either block cholesterol synthesis (ezetimibe) or neutralise the effects of proprotein convertase subtilisin/kexin type 9 (PCSK9) protein have been commonly used in clinical practice. Both agents have impressively improved LDL-C levels and CV outcomes when used instead or as a 'step-up' therapy to statins.[147,148] However, the high cost of PCSK9 inhibitors has raised concerns about their actual net worth. Initial cost-effectiveness data on evolocumab integrating the results of the FOURIER (Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease) trial showed that it exceeds the generally accepted thresholds.[149] Those cost concerns may also be reflected in the current NICE guidelines. While the ESC guidelines recommend adding PCSK9 inhibitors to the background LLT in high and very high-risk patients if the LDL-C levels remain above 1.8 mmol/L or 1.4 mmol/L[150], the NICE had set less stringent LDL-C targets for adding PCSK9 inhibitors to above 4 mmol/L or 3.5 mmol/L in high and very high-risk patients respectively.[151]

Bempedoic acid is a less expensive, novel, oral (180mg - once/day) molecule that reduces LDL-C by inhibiting ATP-citrate lyase (an enzyme in the cholesterol biosynthesis pathway) and subsequently increases LDL receptor activity. It is relatively safe and well tolerated. Although it shares a similar mechanism of action with the statin, it is a prodrug and is converted predominately in the liver into the active form (bempedoic acid-coenzyme A)[152], so the lack of active metabolite exposure in the muscles

limits the potential for myotoxic effects that could be seen with statins. Phase III trials tested it in patients with DM and showed an LDL-C reduction of 21% when used as monotherapy and ~ 30% when used in combination with ezetimibe.[153] Very recently, the results of the CLEAR (first CV outcome of bempedoic acid) trial showed that among statin-intolerant patients, besides significant LDL-C reduction, bempedoic acid was associated with a lower risk of major adverse CV events (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation) over a follow-up period of ~ 41 months when compared to placebo.[154] The NICE guidelines currently recommend using bempedoic acid with ezetimibe when statins are contraindicated or not tolerated.[155]

All those agents mentioned above do not have substantial effects on lipid fractions other than LDL-C. Since elevated CV risks can also be seen with raised triglyceride levels[156], attention has been drawn to agents which lower triglyceride levels, aiming to assess their effect on long-term prognosis; however, the outcome has been somehow ambiguous.

The PROMINENT (Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk) study assessed the effect of pemafibrate in patients with DM and hypertriglyceridemia, a low HDL cholesterol level, and a well-controlled LDL cholesterol level on CV events. It showed no significant difference in the incidence of CV events compared to placebo despite an over 25% reduction in triglyceride levels.[157] Interestingly, there were lower numbers of total hepatic adverse events and non-alcoholic fatty liver disease with pemafibrate than with placebo, which could have a future therapeutic interest out of the context of CVD.

Omega-3 fatty acids (eicosapentaenoic acid [EPA] and/or docosahexaenoic acid [DHA]) are traditionally used to treat hypertriglyceridemia. A number of trials investigating omega-3 fatty acids demonstrated equivocal effects on CV risk despite an efficient decrease in triglyceride levels.[158] Those trials comprised different characteristic baseline cohorts and utilised various omega-3 doses and formulations.

Recently, the NICE released a Final Appraisal Document (FAD) on icosapent ethyl (a highly purified form of fish oil) for reducing the risk of CV events in people with raised triglycerides.[159]

The main prognostic evidence of icosapent ethyl is derived from the REDUCE-IT (Reduction of Cardiovascular Events with icosapent Ethyl-Intervention) trial, where there was a 25% risk reduction in CV events and a 20% reduction in death due to CV causes with icosapent ethyl (2 g twice/day with food) over a median follow-up of nearly 5 years when compared with placebo.[160] The trial exclusively included statin-treated patients with established cardiovascular risk factors, and icosapent ethyl was mainly used as a secondary prevention measure when triglyceride levels were moderately elevated.

The beneficial mechanism of the icosapent ethyl is unclear. The reduction in CV risk observed was more prominent than what would be expected from a reduction in triglycerides alone, which might suggest additional non-lipid effects. There was a higher rate of bleeding events with icosapent ethyl compared to placebo (although non-significant, 2.6% vs 2.1%; p = 0.06), which might indicate a potential antithrombotic effect. Some exploratory thoughts also hypothesised an atherosclerotic plaque stabilisation role, especially since the survival curves suggest a delayed onset of benefit, which perhaps is the time needed for a reduction in triglyceride levels. Additionally, the observed difference in high-sensitivity C-reactive protein level in REDUCE-IT hints towards anti-inflammatory properties. A dedicated mechanistic trial is required for a better understanding of the mechanism of benefit and broader utilisation. Nevertheless, unlike other triglyceride-lowering agents, icosapent ethyl has strong evidence of outcome protection. On this basis, the NICE guidelines recommend icosapent ethyl if fasting triglycerides are 1.7 mmol/litre or above as secondary prevention in high-risk patients with established CV disease or as primary prevention in patients with DM and other CV risk factors.[161] As per the REDUCE-IT trial, icosapent ethyl is to be given once LDL-C levels are well controlled on statin therapy with or without Ezetimibe.

Similarly, those benefits are reflected in the ESC guidelines, which recommend considering icosapent ethyl in combination with statins for treating hypertriglyceridemia in high CV-risk patients.[150]

In conclusion, besides counselling on leading a healthy lifestyle, lipid-lowering drugs remain a key player in preventing the risk of developing CVD. Physicians need to be familiar with the growing list of

novel therapies, their mechanism of action, indications and contraindications for widespread uptake and optimal utilisation

1.8.3: Glucagon-Like Peptide 1 Receptor Agonists and Cardiovascular Disease

New anti-hyperglycemic agents – the glucagon-like peptide 1 receptor agonists (GLP-RAs) have been developed in the last decade. They were shown to have insulin-tropic properties which potentiate incretin effects, including stimulating insulin secretion by pancreatic β- cells in a glucose-dependent manner, modulation of gut motility, satiety stimulation and inhibition of glucagon secretion by the pancreatic α-cells[162] (Figure 4). Presently, GLP-1RAs are approved worldwide, including in Europe, to improve glycaemic control in patients with T2DM, owing to their ability to reduce haemoglobin A1c (HbA1c) without significant hypoglycaemia risk.

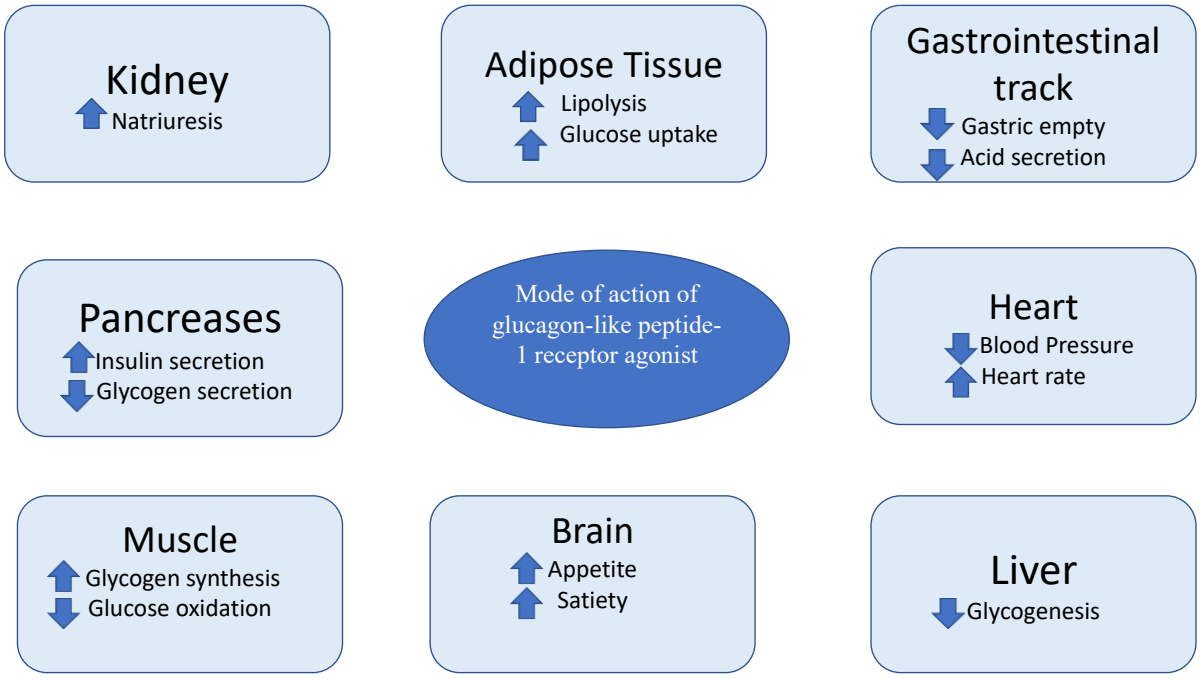


Figure 4: Mode of action of glucagon-like peptide-1 receptor agonist. Figure adapted from Meier JJ. Nat Rev Endocrinol.[163]

Several large cardiovascular outcome trials have examined the effects of GLP1-RAs on CV events in patients with T2DM and shown a reduction in major adverse cardiac events (MACE), including cardiovascular death, non-fatal MI and non-fatal stroke.[164–166] Interestingly, GLP1-RA appears to have pleiotropic effects with cardiovascular benefits that are not directly related to their glucose-lowering action[167]. However, the mechanism of reducing CV events does not appear to stem wholly from their impact on blood pressure or weight loss either. The potential proposed means for CV benefit include reducing systemic inflammation, protecting ischemia/reperfusion injury, and improving endothelial dysfunction.[168,169] Given this evidence, the ESC now recommends GLP-1RA therapy as first-line therapy in T2DM patients (Figure 5).

1.8.4: Glucagon-Like Peptide 1 Receptor Agonists Effect on Inflammation and Oxidative Stress Biomarkers

The CV benefits of the GLP1-RAs are driven from multiple cardiovascular outcome trials[170–174], making it an ideal diabetes therapy due to the reduction in morbidity and mortality independent from its glycaemic control property. Currently, the European Cardiology and Nephrology societies recommend the usage of GLP-1RAs either as monotherapy or in addition to other antidiabetic drugs for patients with T2DM who had either a previous CV event or CV risk factors in light of their demonstrated CV benefit, high efficacy, and low potential for hypoglycemia.[175,176]

Despite the extensive exploratory analyses, the exact mechanisms of the salutary effects of GLP-1RAs remain elusive. The published CVOTs didn't specifically examine the effect of GLP-1RAs on the inflammation and oxidative stress biomarkers, an essential contributing factor in developing diabetes and its complications.[177]

Arteries in diabetic people, in general, are more prone to endothelial damage and atherosclerosis due to the prolonged hyperglycemia state and insulin resistance.[177] Inflammation mediates insulin resistance and

beta-cell damage by high glucose and fatty acid released from adipose tissues[178], making it an active factor in the pathogenesis of diabetes. In addition to predisposing to diabetes, chronic inflammation is a well-known risk factor for atherosclerosis.[15] Atherosclerotic cardiovascular disease arises from endothelial dysfunction caused by proinflammatory stimuli in the vascular endothelial cells and is associated with increased plasma levels of TNF-α, IL-6, and CRP.[179] On the other hand, oxidative stress has an essential role in developing and progressing diabetes in cardiovascular complications. It generates ROS, AGEs, and oxidised LDL, causing coronary microvascular dysfunction and subsequently ischemic heart disease.[180]

Emerging data summarised below in Table 5 illustrated the therapeutic tactics of GLP-1RAs on reducing inflammatory markers and balancing oxidative stress, leading to islet preservation and improvement of insulin sensitivity in addition to its protective properties against atherosclerosis and diabetes complications, all independent of its glucose-lowering effect.

GLP-1 receptors are also distributed in the renal cortex and vasculature.[181] Various clinical trials tried to explain the mechanism by which GLP-1RAs positively influence the kidneys. GLP-1RAs have very little significance on the eGFR. Avgerinos et al. demonstrated through a meta-analysis of 60 clinical trials that GLP-1RAs marginally reduced the Urine albumin-to-creatinine ratio compared to placebo and other antidiabetic agents but resulted in no clinical changes in eGFR.[182]

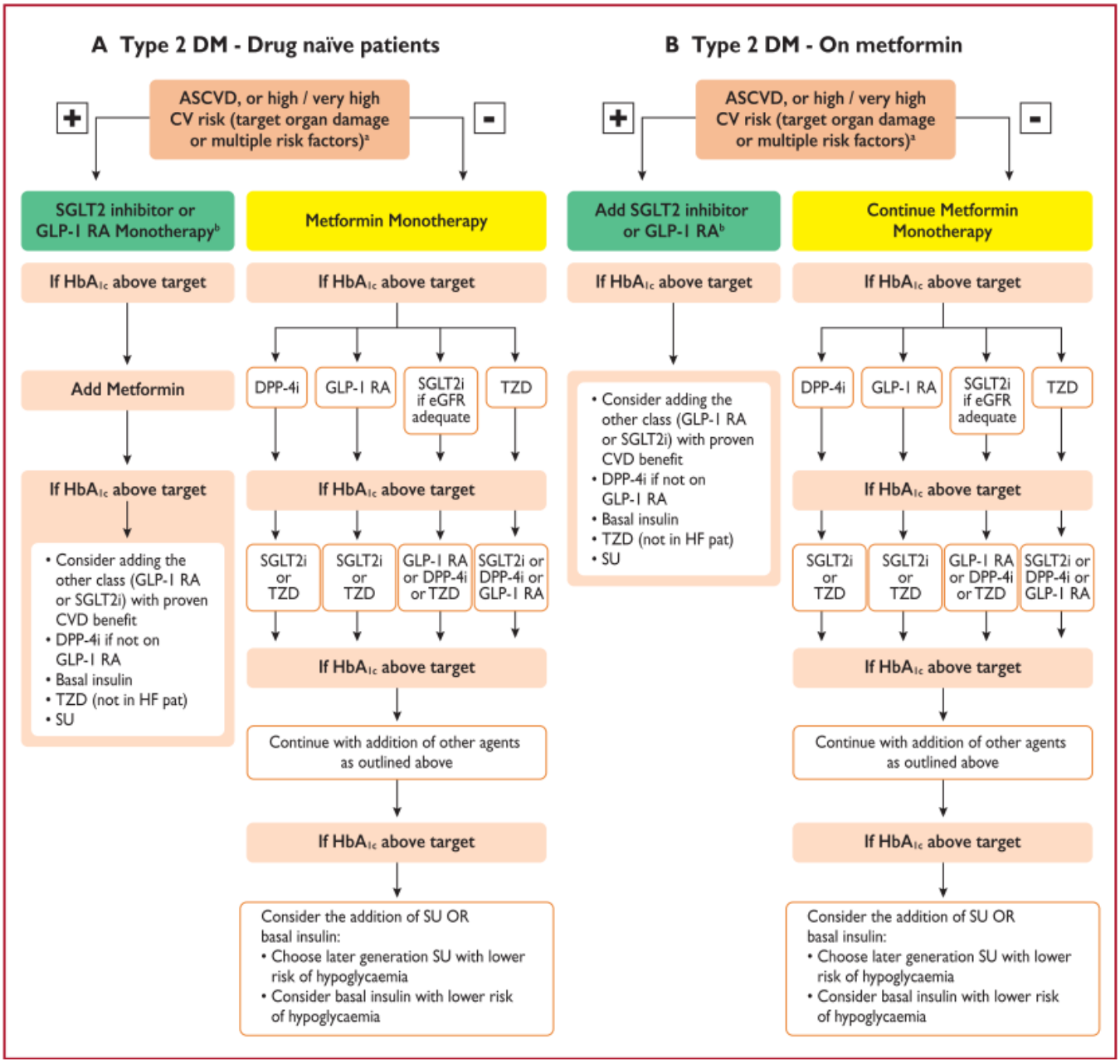


Figure 5: ESC Treatment algorithm in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.[175] *For high/very high CV risk Treatment algorithms for (A)drug-naive and (B) metformin-treated patients with diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease: CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP1- RA = glucagon-like peptide-1 receptor agonist; HbA1c = haemoglobin A1c; HF = heart failure; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione*

Diabetic nephropathy is believed to be associated with chronic low-grade inflammation[183,184]; various human and animal trials proposed the reno-protective effect of GLP-1RAs is secondary to its ability to suppress inflammation pathways and oxidative stress signalling.[185–188] It's also worth noting that patients with diabetes who have severe renal impairment are not eligible for some of the diabetic therapy, which

makes GLP-1RAs an important therapeutic option for these patients. The potential anti-atherosclerotic role of GLP-1RAs will be discussed in detail throughout this thesis.

Table 5: summarizing the effect of GLP-1RA on inflammation and oxidative stress markers.

Trial	***Biomarker***	***Randomisation***	***Number of patients***	***Study duration (weeks)***	***Population***	***Mean difference, 95% CI***
			Inflammatory biomarkers			
Courreges 2008[189]	*hs-CRP*	*GLP1RA vs. placebo*	*165*	*14*	*Denmark*	*- 0.98 (-3.43, 1.47)*
Pavithra 2019[190]	*hs-CRP*	*GLP1RA vs DPP-4*	*80*	*26*	*India*	*- 0.5 (-7.03, 6.03)*
Anholm 2019[191]	*hs-CRP*	*GLP1RA vs. placebo*	*41*	*26*	*Sweden*	*-1.16 (-3.72, 1.40)*
Li 2019[192]	*TNF-α*	*GLP1RA vs sulfonylurea*	*23*	*26*	*China*	*- 0.33 (-1.16, 0.50)*
Wang 2019[193]	*TNF-α*	*GLP1RA vs Insulin*	*25*	*52*	*China*	*- 0.41 (-1.20, 0.39)*
Von Scholten 2017[194]	*TNF-α*	*GLP1RA vs. placebo*	*32*	*12*	*Denmark*	*- 0.55 (-1.25, 0.16)*
Yao 2020[195]	*IL6*	*GLP1RA vs Insulin*	*65*	*2*	*China*	*- 0.22 (- 0.73, 0.29)*
Li 2019[192]	*IL6*	*GLP1RA vs sulfonylurea*	*23*	*26*	*China*	*- 1.85 (- 2.87, - 0.84)*
			Oxidative stress biomarkers			
Wang 2019[193]	*Serum 8-iso-prostaglandin F2 alpha*	*GLP1RA vs Insulin*	*25*	*52*	*China*	*3.64 (-3.62, 10.90)*
Li 2019[192]	*Serum 8-iso-prostaglandin F2 alpha*	*GLP1RA vs sulfonylurea*	*23*	*26*	*China*	*1.30 (-5.24, 7.84)*
Lambadiari[196]	*Serum malondialdehyde*	*GLP1RA vs biguanide*	*60*	*26*	*Greece*	*- 0.09 (- 0.05, 0.42)*

hs-CRP high-sensitivity C-reactive protein, TNF-α: Tumor necrosis factor alpha, IL6: Interleukin-6

1.9: Research Hypothesis and Project Aims

While CCTA is well-established in diagnosing CAD, its emerging role in characterising plaque composition and vulnerability presents a promising avenue for earlier risk identification and therapeutic optimisation. However, there is limited evidence regarding how these imaging findings translate into

clinical decision-making, modification of cardiovascular risk factors or the assessment of pharmacological interventions aimed at plaque stabilisation.

This thesis aims to address key gaps in the literature by exploring the utility of advanced CCTA techniques, such as plaque mapping and high-risk plaque feature identification, in influencing clinical outcomes, risk management strategies, and the evaluation of novel therapeutic agents in both stable and post-ACS populations.

1.9.1: Research Hypotheses

1. Advanced plaque Mapping using CCTA improves the identification of vulnerable atherosclerotic plaques in high-risk patient populations.
2. Identifying coronary plaques through CCTA positively influences the management of risk factors.
3. CCTA can be effectively used to evaluate the impact of novel therapies, such as new hypoglycaemic agents, on coronary plaque morphology and burden.

1.9.2: Project Aims

Aim 1 – Chapter 3:

To evaluate the real-world achievement of ESC-recommended secondary prevention targets (lipids, HbA1c, and BP) in patients with T2DM and high cardiovascular risk and to identify gaps in risk factor control.

Aim 2 – Chapter 4:

A) To describe the inter-observer variability of conventional high-risk plaque features and plaque

mapping (novel CT-TCFA) in a cohort of patients with chest pain and a high likelihood of coronary disease undergoing CCTA.

B) To identify the rate of MACE in a cohort of patients with chest pain and a high likelihood of coronary disease undergoing CCTA in the presence of conventional high-risk plaque features and novel CT-TCFA

Aim 3 – Chapter 5:

A) To determine how the results of CCTA influence the optimisation of cardiovascular risk factors and guide treatment decisions in a large, multi-centre cohort of stable patients with a low likelihood of coronary artery disease.

B) To identify the rate of MACE in a cohort of stable patients with a low likelihood of coronary disease undergoing CCTA in the presence of conventional high-risk plaque features and novel CT-TCFA

Aim 4 – Chapter 6:

To assess the distribution and anatomical patterns of vulnerable plaques within the coronary tree using advanced CT plaque analysis among three patient cohorts: stable patients with a low likelihood of coronary artery disease, patients with chest pain and a high likelihood of coronary artery disease and very high-risk patients who have undergone an ACS.

Aim 5 – Chapter 7:

To explore the potential impact of oral semaglutide, a novel hypoglycaemic agent, on the progression of coronary artery disease following acute coronary syndrome, using CCTA as a non-invasive imaging biomarker.

1.9.3: Candidate Contribution

The candidate played a central role in the conception, design, and execution of the research presented in this thesis. This included leading the development of study protocols, performing CCTA analysis and interpretation, conducting statistical analyses, and drafting manuscripts for publication. Collaborative contributions, including data acquisition and clinical oversight, are acknowledged where appropriate in each chapter. This work was conducted within a multidisciplinary research environment integrating imaging, clinical cardiology, and translational research.

CHAPTER 2: Methodology

This section provides details on how I collected, processed, and analysed the data used in this Ph.D. project. In addition to identifying and recruiting patients for clinical studies, a significant proportion of time was dedicated to acquiring, processing and reporting CCTA scans. These components were foundational to the integrity and outcomes of the research, particular emphasis is placed on describing them in this section.

Methodologies specific to each study are detailed within the respective results chapters (Chapters 3–7), where study-specific data sources, statistical methods, and analytic techniques are presented.

2.1: Patient Recruitment for Clinical Studies

Three distinct cohorts were included in this thesis: (1) patients with stable chest pain and high likelihood of CAD (Chapter 4), (2) a large real-world cohort with low-intermediate risk (Chapter 5), and (3) a high-risk post-ACS cohort (Chapter 7). These cohorts were intentionally selected to reflect different stages of cardiovascular risk and to evaluate the role of CCTA across the disease spectrum.

Cohort 1 – Chapter 4: Patients with stable chest pain and a high likelihood of coronary disease.

The data from this prospective, observational cohort of patients was obtained from collaborators (Dr Deepa Gopalan and Dr Adam Brown) at Royal Papworth Hospital.

Following Research Ethical Committee approval (Ref number 14/LO/2130) approval, One hundred patients with stable chest pain were previously recruited by the Papworth team from outpatient chest pain assessment clinics. All patients who were considered to have a high likelihood of coronary artery disease were scheduled for routine invasive coronary angiography. The study protocol was approved by the Cambridgeshire Research and Ethics Committee and involved all patients undergoing routine CCTA prior to invasive angiography and follow-up with a structured interview via telephone and postal data collection in the subsequent seven years following recruitment to determine MACE (a composite of all-cause mortality and non-fatal myocardial infarction (MI)).

Inclusion criteria:

A) Patients aged ≥18 years

B) There is a high likelihood of coronary artery disease requiring invasive coronary angiography (as judged by the physician in the outpatient chest pain assessment clinic).

Exclusion criteria:

A) Patient aged <18 years

B) History of renal insufficiency with estimated glomerular filtration rate <30mL/min/1.73m2

Previous diagnosis of coronary artery disease

CCTA acquisition:

Patients underwent a prospective-gated CT at the Royal Papworth Hospital with ECG-dependent tube current modulation using a Somatom Definition 64-slice dual-source system (Siemens Medical Systems, Forchheim, Germany) with the following scan parameters: pitch 0.20-0.48, collimation 32 x 0.6 mm, tube voltage 120 kV and tube current 360 mA. In addition, intravenous contrast was injected in a triphasic protocol following a 20 ml timing bolus to assess circulation time. Patients with a heart rate >70 beats/min received metoprolol intravenously, and all patients received 0.6 mg of sublingual Nitroglycerin.

Cohort 2 – Chapter 5: Patients with stable chest pain and a low likelihood of coronary disease.

This was a retrospective observational cohort study using linked anonymised electronic health record (EHR) data for 2,072 consecutive stable patients with chest pain and a low probability of CAD and referred for CCTA. They presented to the outpatient chest pain assessment clinics across South-West Wales, UK, between January 2012 and December 2019. I identified the patients using the South West

Wales CCTA results archive (maintained using Sharepoint by Swansea Bay University Health Board) and followed up their 3-year progress after the CCTA scan.

Inclusion criteria:

A) Patients aged ≥18 years

B) There is a low likelihood of coronary artery disease (as judged by the physician in the outpatient chest pain assessment clinic) requiring CCTA.

Exclusion criteria:

A) Patient aged <18 years

B) Previous diagnosis of coronary artery disease

CCTA acquisition:

Patients underwent a prospective ECG-gated CCTA at one of three centres in South-West Wales using a 320-slice Aquilion One, Toshiba Medical Systems, Japan or a 256-slice Revolution, GE, USA, according to local acquisition protocols.

Patients with a heart rate >65 beats/min received metoprolol intravenously, and all patients received 0.6 mg of sublingual Nitroglycerin.

Cohort 3 – Chapter 7*:* Very high-risk patients who have undergone a coronary event.

Following Research Ethical Committee approval (Ref number 21/WA/0176) and the Medicines and Healthcare Products Regulatory Agency (Ref number CTA 35930/0005/001-0001) approval, I recruited a prospective cohort of patients as part of the POST-ACS (Potential Impact Of Oral Semaglutide On Coronary Artery Disease Progression Following Acute Coronary Syndrome) randomised, placebo-controlled trial which is described in detail in Chapter 7. The group comprised 100 patients with a recent history of PCI following an ACS. I recruited the patients from the cardiology centre at Swansea Bay

University Hospital between September 2022 and March 2024, and then they underwent CCTA one-month post-hospital discharge.

Detailed inclusion and exclusion criteria is provided in Chapter 7

CCTA acquisition:

Patients underwent a prospectively-gated CT at the Clinical Imaging Facility, Institute of Life Science 2, Swansea University, with ECG-dependent tube current modulation using a Somatom Definition 128-slice scanner. Patients with a heart rate >65 beats/min received metoprolol intravenously, and all patients received 0.6 mg of sublingual Nitroglycerin.

2.2: CCTA analysis

After completing the CCTA scans, I performed a per-plaque analysis to identify the prevalence and location of CCTA- high-risk plaque (HRP) features using the different currently accepted definitions. I also examined the correlation between those plaque definitions and quantitative plaque metrics, including plaque burden, necrotic core and fibrous plaque volumes and percentages. All CCTA analysis was supervised by Dr Daniel Obaid, who is a level 3 (Advanced Practitioner) trained reporter with >10 years of experience.

2.2.1: CCTA Qualitative Plaque Analysis

I classified each plaque into calcified - a plaque with a CT attenuation of ≥130 Hounsfield units (HU) on a non-contrast image, or non-calcified plaque (<130 HU on a non-contrast image) - a plaque with lower density compared with the contrast-enhanced vessel lumen.

I then analysed every plaque containing non-calcified elements for any of the following HRP features as shown in Figure 3 in Chapter 1:

Positive remodelling (PR) – (ratio of vessel diameter at lesion site to reference vessel >1.1).[197]

Low attenuation plaque (LAP) – a focal area of plaque <30 Hounsfield units {HU}.[198,199]

Napkin ring sign (NRS) – central area of low attenuation surrounded by higher attenuation rim <130HU.[200]

Plaques were classified by CCTA as vulnerable if they had either PR and LAP combined or the NRS, as these are the plaques most strongly associated with future acute coronary syndrome (ACS) risk in prospective studies.[108,200,201]

Although spotty calcification is recognised as a vulnerable plaque feature, it was not included in the quantitative vulnerability index in this thesis due to its lower inter-observer reproducibility and its dependence on spatial resolution and partial-volume effects, particularly in smaller vessels.

2.2.2: CCTA Quantitative Plaque Analysis

I divided the coronary arteries into 18 segments according to the Society of Cardiovascular Computer Tomography modified classification[202] and analysed if >1.5 mm in diameter as measured on CCTA. A coronary plaque was defined as a tissue structure of >1 mm within the vessel wall that could be discriminated from surrounding pericardial tissue, epicardial fat, and the vessel lumen itself.

For pragmatic grouping, plaques were classified as non-obstructive (<50% luminal stenosis) or obstructive (≥50% luminal stenosis). However, stenosis severity was interpreted in accordance with SCCT CAD-RADS definitions, whereby 50–69% stenosis represents moderate disease and ≥70% severe disease.[203]

I set multi-vessel disease as obstructive lesions in >1 coronary artery (2-vessel and 3-vessel CAD).

I used Vitrea (Vital Images, US) to perform plaque quantification. The software utilises semi-automated segmentation with manual correction of vessel contours if required. Total plaque volume, defined as the entire volume of a coronary plaque, including calcified and non-calcified, was reported in mm^3. Coronary

plaque burden was calculated as [cross-sectional vessel area – cross-sectional lumen area] / cross-sectional vessel area.

While several alternative validated software solutions exist (including Medis QAngio CT and Autoplaque), inter-vendor variability in plaque quantification remains a recognised limitation. A formal inter-vendor comparison was beyond the scope of this thesis but represents an important future validation step to support broader clinical adoption.

Additionally, Emerging photon-counting CT technology offers improved spatial resolution and material decomposition, which may enhance plaque characterisation and reduce calcium blooming artefact. However, re-analysis and re-validation of quantitative vulnerability thresholds would be required before direct translation of the current findings to photon-counting platforms.

2.2.3: Plaque Mapping and CT TCFA

The Vitrea software separates plaques into constituent parts, assigning each plaque voxel depending on its attenuation to create a colour-coded Plaque Map overlays representing plaque components of differing densities (dark green-low attenuation plaque, light green-intermediate attenuation plaque, orange-contrast and pink-high attenuation plaque), allowing visualisation of the plaque components (Figure 6). To create patient-specific plaque maps, I calculated each plaque's mean attenuation HU of luminal contrast by measuring luminal attenuation proximal and distal to each plaque. The attenuation cut-offs for each plaque component were calculated according to ratios of luminal contrast and plaque attenuation (necrotic core <0.197, fibrous plaque 0.197–0.470, calcified plaque >1.295) derived using the histologically validated method described previously.[61,119] This sets attenuation thresholds for plaque components individualised to each patient and allows the volumes of the necrotic core, fibrous plaque, and calcified plaque to be calculated. Plaques with a necrotic core/fibrous plaque ratio (NC/Fib) >0.9 were classified as CT-TCFA.

I then determined the frequency, location and patient characteristics associated with these different plaque types. To create the curved Multiplanar Reconstructions (MPRs) of the coronary arteries, Vitrea employs a semi-automatic vessel edge definition that I reviewed and manually corrected when needed. I often performed measurements (e.g. arterial dimensions or size of calcifications) and attenuation sampling on these curved MPRs. I also used cross-sections through the MPRs to determine the attenuation values (HU) of plaque components on CT. This also was used to define HU ranges for plaque components pre-classified by VH-IVUS and has been histologically validated previously.[61,119] The Plaque Map software then has the facility to assign colour maps to arterial segments using these defined HU ranges with different colours representing different tissue types. These colour maps allow quantification of relative volumes of plaque components (necrotic core, fibrous plaque, and calcified plaque) on CT. Finally, I divided the patients into groups according to the presence of any vulnerable features and subsequently recorded the rate of MACE events that occurred.

2.3: Secure Anonymised Information Linkage Databank

Data used in Chapters 3 and 5 were primarily sourced from the Secure Anonymised Information Linkage (SAIL) Databank[204], a national research infrastructure for Wales that hosts routinely collected, anonymised health and social care data. The following linked datasets within SAIL were utilised in this PhD:

- Patient Episode Database for Wales (PEDW): Contains data on hospital admissions, discharges, diagnoses, procedures, and patient demographics, including date of death, where applicable.
- Welsh Longitudinal General Practice (WLGP): Provides demographic, clinical, and prescribing data from approximately 80% of general practices in Wales.
- Welsh Demographic Service (WDS): Includes demographic information and residency history for individuals registered with a Welsh GP.

These datasets enabled robust longitudinal tracking of clinical outcomes, comorbidities, and treatment patterns in large, real-world patient populations.

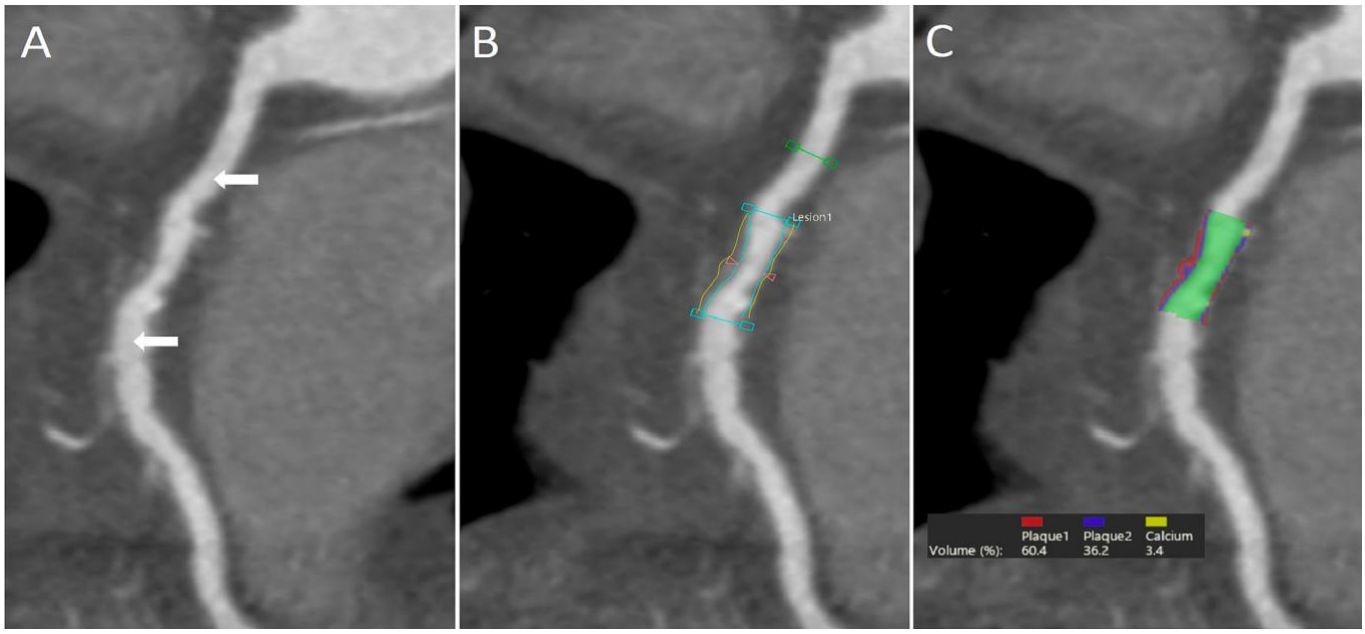


Figure 6: Defining a CT-TCFA (necrotic core/fibrous plaque ratio >0.9). (A) Measurement of luminal contrast attenuation proximal and distal to plaque (white arrows). (B) Creation of vessel and lumen borders. (C) Quantification of plaque constituent volumes (red = necrotic core, blue = fibrous plaque, yellow = calcified plaque) using attenuation cut-offs for each plaque component calculated according to ratios of luminal contrast and plaque attenuation. Figure adapted from SALEM AM. et al. Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain[114].

2.3.1: Governance, Ethics and Approvals

All data processing and analysis within this PhD adhered strictly to ethical and data governance protocols. The SAIL Databank operates within a secure, privacy-protecting framework that prohibits access to identifiable information. Projects are only approved if they demonstrate potential public benefit and pass review by the Information Governance Review Panel (IGRP) — an independent committee comprising members from the National Research Ethics Committee (NREC), the British Medical Association (BMA), and public representatives.

Chapters 3 and 5 utilised anonymised, routinely collected patient data and, therefore, did not require separate ethics approval. Both studies received clearance from the SAIL IGRP prior to data access and analysis.

Permission to use the Cardiac Intervention Dataset, held at Swansea Bay University Health Board (SBUHB), was granted by the data custodian, Dr James Barry. Additionally, the SBUHB Caldicott Guardian approved the secure transfer of the cardiac intervention and discharge medication datasets to SAIL for research purposes.

2.3.2: Processing of Data within the Thesis

The following sections outline the methodology used to identify, access, process, and analyse the datasets employed throughout this PhD. Particular emphasis is placed on the methodological approach undertaken in Chapter 3; this was the first study I undertook using SAIL. This study formed a subgroup analysis of a larger research project led by a senior PhD candidate, Dr Daniel Harris. I focused specifically on individuals with T2DM who had undergone percutaneous coronary intervention (PCI), intending to evaluate the extent to which their cardiovascular risk factors were managed in line with the most recent ESC guidelines.

Details of the methods specific to Chapter 5 are presented later in the thesis. However, many of the data extraction and classification techniques developed during the Chapter 3 analysis formed the foundation for subsequent work. These included the development of code lists for diagnoses, comorbidities, cardiovascular risk factors, and prescribed medications, which were applied consistently throughout the two chapters.

2.3.3: Anonymisation of Personal Data

For the study presented in Chapter 3, the dataset—including intervention and prescribing information—was anonymised and transferred to SAIL by Dr Daniel Harris. For the study in Chapter 5, I personally undertook the anonymisation process and dataset transfer. This process involved separating demographic data from all clinical (CT results) and event-related information and assigning each participant a unique identifier. The demographic data were sent to NHS Wales Informatics Service (NWIS), while the clinical dataset (containing only the unique identifiers) was transferred to SAIL.

NWIS anonymises and encrypts the demographic data and assigns an Anonymous Linking Field (ALF) to each individual. These anonymised demographic records are then sent to SAIL, where they are linked with the corresponding clinical data. To enhance security, SAIL further encrypts the ALF to produce a project-specific Anonymous Linking Field (ALF_PE), which enables secure longitudinal linkage across datasets while preserving anonymity.

All participants included in Chapter 3 & 5 were over 18 years of age and had at least 90 days of follow-up data available within the WLGP dataset. In Chapter 3, I only included participants with a documented history of T2DM who had undergone PCI in South Wales, including the Regional Cardiac Centre at Morriston Hospital. Patients were identified using the regional Coronary Intervention Dataset, which includes demographic, procedural, and clinical data—such as antithrombotic strategies, procedural indications, comorbidities, and risk factors. This information was entered at the time of intervention by the clinical team performing the procedure. Using the PEDW, I collected discharge prescribing data related to the index hospital admission.

I defined the index date as the date of the first PCI during the study period. Follow-up was set at one year from the date of discharge from the index admission.

In Chapter 5, I set the index date as the date of the coronary CT scan, with follow-up periods at both one and three years post-scan.

2.3.4: WLGP

WLGP dataset contains demographic, clinical and prescribing data for approximately 80% of primary care practices across Wales. This dataset was joined to the patients of interest (ALF_PE), with the date of admission and discharge. Events recorded in the WLGP were denoted as occurring before or after the index admission. Events entered in the WLGP are recorded using Read codes, a thesaurus of clinical terms and provide the standard vocabulary by which clinicians can record patient findings, procedures and prescriptions. All coding was created and checked by a data analyst with experience in cardiac datasets, Dr Arron Lacey.

I used the WLGP dataset to identify comorbidities and risk factors using Read codes, including hypertension, ischaemic heart disease, and chronic kidney disease (stage IV or higher), as well as recorded lipids, HbA1c, and blood pressure levels. It also provided information on prescriptions for glucose-lowering, lipid-lowering, and anti-hypertensive agents. Additional diagnostic history—such as prior myocardial infarction, heart failure, and ischaemic stroke—was extracted using linked data from both WLGP and PEDW.

To ensure the veracity of the data, a number of checks were made. During each stage of the data processing, I performed simple counts of patients and lines of data to ensure there were no unintended loss or gain of data.

2.4: Statistical Analysis

The statistical methodologies applied across the individual studies are described in full within the respective methods sections of each chapter. However, this section outlines the overarching analytical approaches, statistical tools, and rationale employed throughout the thesis.

I conducted all the statistical analyses using IBM SPSS Statistics (Version 26.0, IBM Corp., Armonk, NY). Where appropriate, additional analyses were validated using R (version 4.1.0) to ensure robustness and reproducibility of findings.

Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of histograms. For normally distributed variables, data are presented as means ± standard deviations (SD). For non-normally distributed variables, medians with interquartile ranges (IQR) were reported.

Comparative analyses between two independent groups were performed using either the independent-sample t-test for parametric data or the Mann-Whitney U test for non-parametric data. Where repeated measures were available within the same group, the paired t-test or Wilcoxon signed-rank test was used accordingly.

Categorical variables were expressed as counts and percentages. Group differences were evaluated using the Chi-square test or Fisher's exact test when expected frequencies were less than five.

A two-sided p-value < 0.05 was considered to indicate statistical significance for all analyses.

Missing data were addressed through complete-case analysis unless otherwise specified. Sensitivity analyses were performed where relevant to assess the impact of data imputation or exclusion criteria.

CHAPTER 3: Achievement Of The ESC Recommendations For Secondary Prevention Of Cardiovascular Risk Factors In High-Risk Patients With Type 2 Diabetes: A Real-World National Cohort Analysis

This Chapter is based on the following published article:

Salem, A. M. et al. Achievement of the ESC recommendations for secondary prevention of cardiovascular risk factors in high-risk patients with type 2 diabetes: A real-world national cohort analysis. Int. J. Cardiol. (2023) https://doi.org/10.1016/j.ijcard.2023.02.004.

3.0: Rationale:

This chapter provides real-world evidence of gaps in the implementation of guideline-directed secondary prevention in patients with type 2 diabetes, a population at particularly high risk of cardiovascular events. While the primary focus of this thesis is the use of coronary CT angiography (CCTA) to refine cardiovascular risk stratification, understanding baseline deficiencies in risk factor control is essential to contextualise the potential clinical impact of advanced imaging.

These findings therefore establish the clinical rationale for subsequent chapters, which explore how detailed plaque characterisation using CCTA may help identify high-risk patients and guide more targeted and effective preventive strategies.

3.1: Introduction

Patients with DM and previous ASCVD are at very high risk of future cardiovascular disease (CVD), with a quoted 10-year risk of CVD death >10%.[150] To mitigate against this risk, the ESC guidelines advocate optimal glycaemic control post-percutaneous coronary intervention (PCI) along with associated risk factors. A near-normal HbA1c level of <7.0% (<53 mmol/mol) is the recommended target to reduce vascular complications. [175] These guidelines recommend adding the relatively newer agents, GLP-1RA and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) to the standard glucose-lowering regime due to CV benefits demonstrated in several Cardiovascular Outcome Trials (CVOT).[172,173,205,206] In addition, there is also an emphasis on controlling the lipid profile and blood pressure (BP) to prevent CVD. Currently, for very high-risk patients, the ESC recommends a therapeutic regime that will achieve a 50% reduction in low-density lipoprotein cholesterol (LDL-C) from the baseline with an LDL-C target level of <1.4 mmol/L and non-high-density lipoprotein cholesterol (non-HDL- C) targets of <2.2 mmol/L.[150] Furthermore, patients with hypertension and DM should be treated in an individualised manner. The BP target is a systolic BP (SBP) of 130 mmHg in patients with DM and <130 mmHg if

tolerated. In older adults (aged >65 years), the SBP target is 130 - 139 mmHg. The recommended diastolic BP (DBP) target is <80 mmHg.[175]

Approximately 8% of the population in Wales aged 17 years and over are living with DM - the highest prevalence in the UK[207] - with 4% known to have coronary artery disease (CAD).[208] Little is known about the proportion of those patients who achieve the ESC targets of HbA1c, lipids and blood pressure. A better understanding of these relationships will offer a valuable opportunity to optimise CVD risk factors. Therefore, this study aims to examine the achievement of the ESC guideline recommendations in a contemporary national cohort of patients from Wales with DM and known CAD.

This chapter provides population-level context regarding secondary prevention gaps in high-risk patients with type 2 diabetes and serves as a clinical and healthcare-system framework for the subsequent CCTA-based studies exploring plaque vulnerability and treatment optimisation.

3.2: Methods

I undertook a retrospective, observational cohort study of glycaemic control and CVD risk factor management for patients with DM who had a PCI in Wales, UK, between January 2012 and December 2017 and had a one-year follow-up period. Data linkage was performed using the SAIL data bank.[204] Details on how data was filtered and analysed through the SAIL data bank are listed in detail in Chapter 2: Methodology.

In summary, SAIL is part of the national e-health records research infrastructure for Wales; the following linked data sources are held within SAIL: secondary care hospital admission data within the PEDW, GP data within the WLGP, demographic data and GP registration history within the WDSD.

All study subjects were >18 years of age, with at least 90 days of follow-up data available in the WLGP with a documented history of DM. The index date was assigned to the date of the first PCI

during the study period for each patient. The follow-up duration was set at 1 year from the discharge date of the index hospital admission. The WLGP data was used to describe the presence of hypertension, ischemic heart disease, chronic kidney disease (CKD) stage IV+, chronic liver disease, dementia, recorded lipid levels, HbA1c and blood pressure levels, prescriptions of glucose-lowering agents, lipid-lowering therapy and anti-hypertensive agents. In addition, PEDW and WLGP data were used to describe a prior history of myocardial infarction, heart failure and ischaemic stroke.

3.2.1: HbA1c Levels and Glucose-Lowering Agents

Medical prescriptions of all the glucose-lowering agents were documented in the first 90 days after discharge following the index PCI. These medications were grouped a priori as - (i) oral anti-diabetic agents (including Metformin, Gliclazide, and Dipeptidyl peptidase-4 [DPP-4] inhibitors), (ii) newer anti-diabetic agents (SGLT2 inhibitors or GLP-1 RAs) with or without any other oral anti-diabetic agents, (iii) insulin-based therapy (any type of insulin with or without oral agents – excluding SGLT2 inhibitors and GLP-1 RAs), (iv) other treatments (including acarbose, meglitinides and thiazolidinedione), (v) no treatment.

We identified the number (and proportions) of patients achieving the ESC HbA1c target of <53 mmol/mol (controlled group) or above target HbA1c ≥53 mmol/mol (non-controlled group) and their respective glucose-lowering regimen.

3.2.2: Lipid Profile Levels and Lipid-Modifying Therapies

An optimised LDL-C was defined as a level <1.4 mmol/L and <1.8 mmol/L (according to the 2019 and 2016 ESC guidelines for dyslipidaemias, respectively).[150,209] Similarly, an optimised non-HDL level was defined as <2.2 mmol/L and <2.6 mmol/L (according to 2019 and 2016

guidelines, respectively).[150,209] Patients with lipid targets outside these ranges were counted as having a non-controlled lipid profile. Lipid-lowering therapy (LLT) was documented within 90 days following discharge after a PCI and classified as described in our previous study[210] as (i) high-intensity statin (HI-statin; atorvastatin ≥40 mg/d and rosuvastatin ≥20 mg/d), (ii) non-high-intensity statin (NI-statin; any other statin prescription), (iii) combination therapy (e.g. combination of ezetimibe with either HI- or NI-statin), (iv) other monotherapy treatment (e.g. ezetimibe or fibrate), (v) no treatment.

3.2.3: Blood Pressure Readings and Anti-Hypertensive Therapies

Since the mean age group of all patients was 66 ± 11 years, patients with SBP <140 mmHg and/or DBP <80 mmHg were categorised as meeting the ESC recommended BP targets and labelled as the controlled BP group.[175] Patients with BP recordings above this range were classified as the non-controlled BP group. The medical prescription of all the anti-hypertensive agents was documented in the first 90 days following PCI.

3.2.4: Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and differences were assessed by independent t-test. Categorical variables were described as a number (n) with percentage (%), and differences were analysed by Pearson $\chi 2$ or Fisher exact tests. Comparisons between groups during follow-up were performed using a two-sample t-test as appropriate. All tests were 2-tailed, and $p < 0.05$ was considered statistically significant. Model selection for all analyses was conducted using a forward stepwise approach in SPSS (v22.0).

3.3: Results

3.3.1: Baseline Characteristics of The Study Participants with Diabetes

The sample size during the study consisted of 25,690 patients admitted to the hospital for PCI. 18,302 (71%) patients had linked primary care data available. Of those, 4,184 (23%) patients had a documented history of DM. Altogether, 3,478 (83%) patients with diabetes had available information on SAIL at a 1-year follow-up. Out of the 706 patients with no data at 1 year, 351 (50%) had died, and the remaining 355 patients were counted as follow-up loss.

Figure 7 summarises the study population cohort selection and numbers excluded.

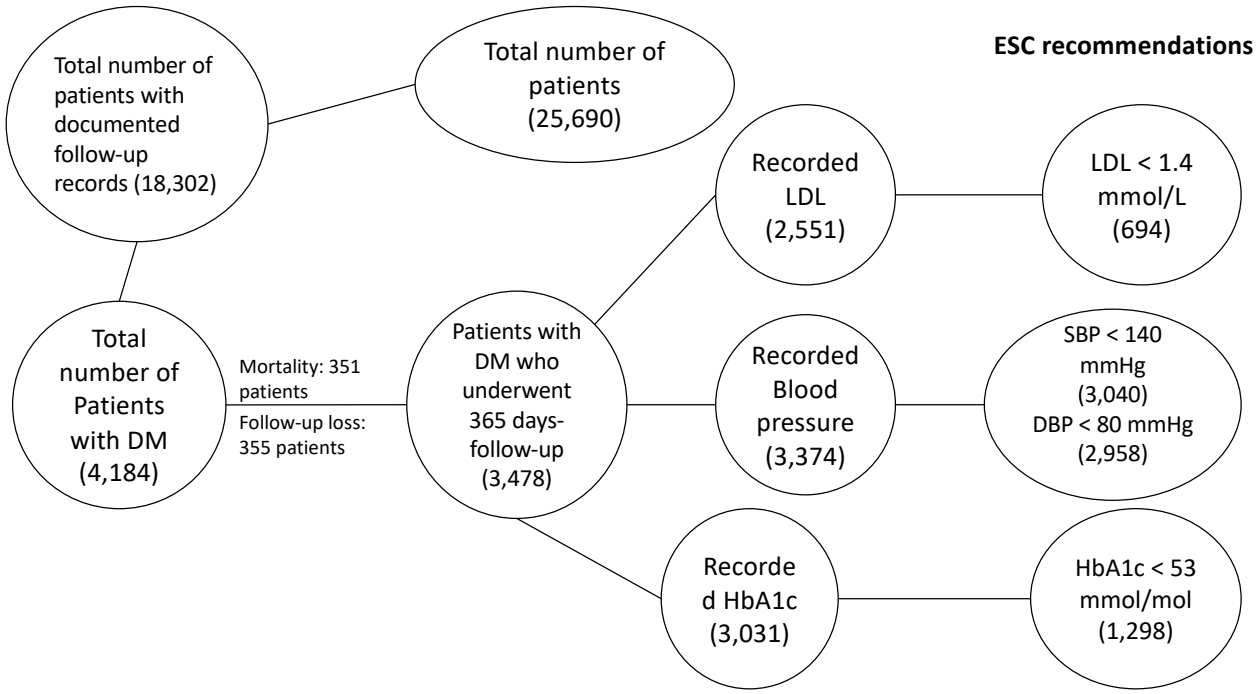


Figure 7: Selection of study population. DM = Diabetes mellitus, LDL = low-density lipoprotein, SBP = systolic blood pressure and DBP = diastolic blood pressure

Patients who completed the follow-up period were more likely to be males and had a younger age ($p < 0.001$ and 0.02, respectively) compared to their counterparts. In addition, a history of heart failure with reduced ejection fraction (HFrEF), CKD stage IV and previous stroke were more

common in the group of patients without 1-year follow-up ($p < 0.001$, 0.03 and < 0.001, respectively). The other variables were comparable.

Table 6 summarises the characteristics of patients with diabetes with and without 1-year available follow-up data.

Table 6: Cohort characteristics and comparison between patients with diabetes who have or don't have follow-up data at one-year post-index admission.

	All patients with DM (4184)	***Patients with DM with one-year follow-up (3478)***	***Patients with DM without 1-year follow-up (706)***	***p-value***
Mean Age – years (SD)	*66 ± 11*	*66 ± 11*	*70 ± 11*	*< 0.001*
Male n (%)	*2949 (71%)*	*2477 (71%)*	*472 (70%)*	*0.02*
Hypertension	*2346 (56%)*	*1941 (56%)*	*405 (57%)*	*0.44*
Dyslipidaemia	*1023 (24.5%)*	*858 (25%)*	*165 (23%)*	*0.46*
Previous MI	*894 (21%)*	*734 (21%)*	*160 (23%)*	*0.35*
Previous stroke	*438 (11%)*	*339 (10%)*	*99 (14%)*	*< 0.001*
HF	*873 (21%)*	*683 (20%)*	*190 (27%)*	*< 0.001*
CKD stage 4	*121 (3%)*	*92 (3%)*	*29 (4%)*	*0.03*
Liver disease	*106 (2.5%)*	*83 (2%)*	*23 (3%)*	*0.17*
COPD/asthma	*830 (20%)*	*692 (20%)*	*138 (20%)*	*0.83*

Value of p for comparison between those with and without follow-up data. DM = diabetes mellitus, MI = myocardial infarction, HF = heart failure, CKD = chronic kidney disease and COPD = chronic obstructive pulmonary disease.

3.3.2: HbA1c Levels and Glucose-Lowering Agents

In total, 3,031 (87%) of the cohort had at least one documented HbA1c during the follow-up period (mean HbA1c 59 ± 16 mmol/mol), of which 1,298 (43%) had controlled glucose levels with at least one HbA1c reading <53mmol/L (Figure 8). The median time between discharge

post-PCI and the lowest recorded HbA1c level was 113 days. These patients were more likely to be older or have a history of hypertension compared to the non-controlled group ($p < 0.001$ and < 0.001, respectively). Patients with a history of a previous MI (prior to the index admission) and CKD stage IV were more likely to have uncontrolled HbA1c ($p = 0.04$ and 0.003, respectively).

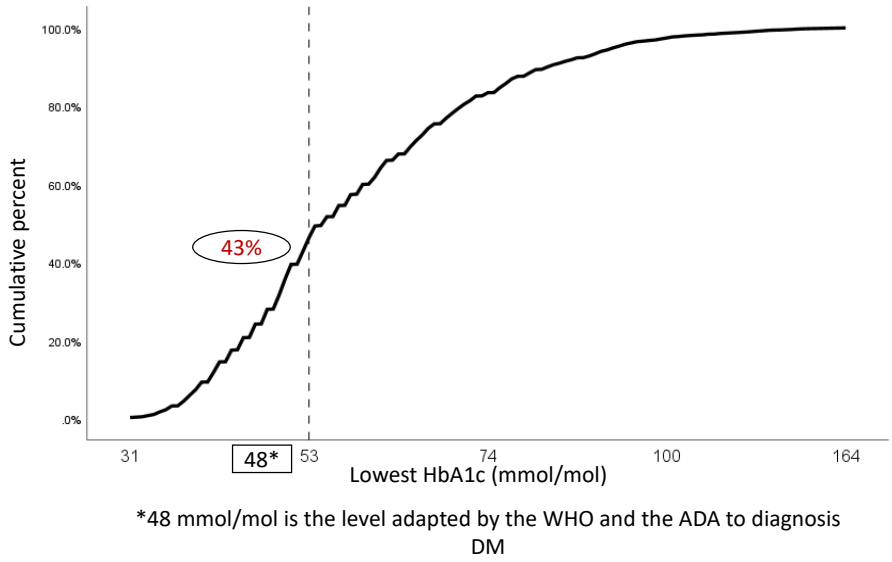
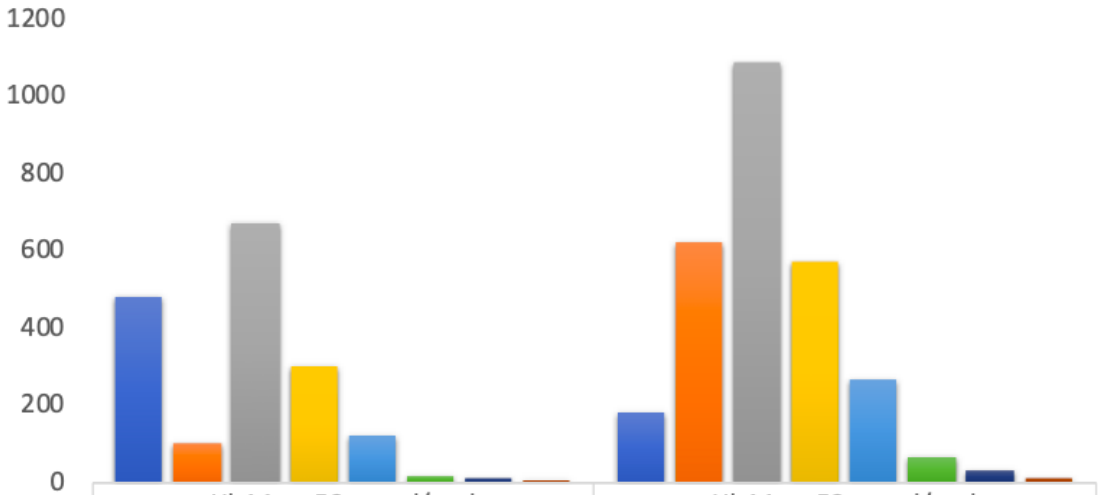


Figure 8: Lowest HbA1c after discharge following the index PCI in 3031 patients. The dotted line represents the recommended level set in the European Society of Cardiology guidelines for diabetes regarding optimal glycaemic control.

In total, 180 (10%) patients in the non-controlled group did not receive any hypoglycaemic drug treatment compared to 482 (37%) patients in the controlled group ($p < 0.001$). There were 619 (36%) patients receiving insulin therapy in the non-controlled group, compared to 101 (8%) patients in the controlled group ($p < 0.001$).

There were 934 (54%) patients treated with non-insulin-based therapy compared to 715 (55%) in the controlled group. Of these, only 85 (8%) patients from the non-controlled group received either an SGLT2 inhibitor or GLP-1 RA (33 patients on SGLT2 inhibitor and 56 patients on GLP-1 RA, 4 patients were on both agents). In comparison, 28 (2%) patients in the controlled group

were treated with those agents (11 patients on SGLT2 inhibitor and 16 patients on GLP-1 RA, $p < 0.001$). Figure 9 shows the frequency distribution of prescribed hypoglycaemic medications among both groups.



	HbA1c < 53 mmol/mol	HbA1c ≥ 53 mmol/mol
No treatment	482	180
Insulin	101	619
Metformin	670	1085
Gliclazide	304	573
DDP-4 inhibitors	124	268
GLP1-RAs	16	65
SGLT-2 inhibitors	11	33
Others	5	12

Figure 9: Prescribed glucose-lowering therapy in patients at or above European Society of Cardiology for diabetes mellitus guidelines HbA1c targets. Other treatment indicates a prescription for acarbose, meglitinides and thiazolidinedione.

3.3.3: Lipid Profile Levels and Lipid-Modifying Therapies

Of 3,478 diabetes individuals, 2,551 (73%) patients had LDL-C recorded during the 1-year follow-up (mean LDL-C 1.9 ± 0.8 mmol/L). Of these, 300 (8.5%) patients had their first lipid profile checked within 30 days of discharge (Figure 10).

The median time between discharge post-PCI and the last recorded lipid profile was 130 days.

In total, 1313 (51%) patients had achieved LDL-C levels below the 2016 ESC target of 1.8 mmol/L, but only 694 (27%) were below the 2019 target of 1.4 mmol/l (Figure 11A). Females were less likely to achieve the 2016 LDL-C recommended target <1.8 mmol/L (23.5% vs 76.5% male patients, $p < 0.001$). This percentage was reduced with further stringent of the LDL-C target to <1.4 mmol/L in the 2019 guidelines (21% vs 79% male patients, $p < 0.001$).

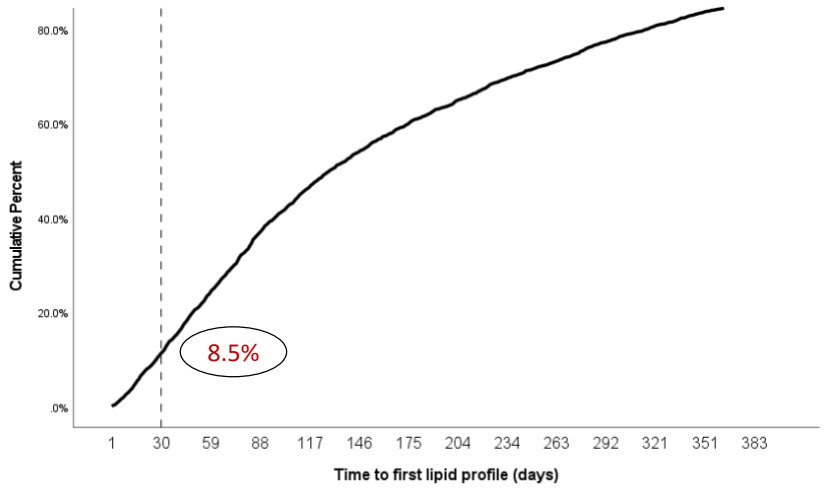


Figure 10: Time to first post-discharge lipid profile.

Regarding patients with documented LDL-C levels ≥1.4 and 1.8 mmol/L, only 774 (42 %) and 438 (35%) respectively, were prescribed HI-statins; 77 (4%) and 57 (5%) respectively were prescribed a combination of ezetimibe and/or fibrate plus a statin, with 54 (3%) and 52 (4%) prescribed ezetimibe and/or fibrate without a statin ($p < 0.001$) (Figure 12A & B).

Non-HDL-C levels were documented in 1171 patients (mean Non-HDL-C 2.1 ± 1.1 mmol/L), of whom 401 (34%) patients had non-HDL-C levels <2.2 mmol/L (2019 guidelines) and 639 (55%) had non-HDL-C levels <2.6 mmol/L (2016 guidelines) (Figure 11B). Among patients with non-HDL-C levels ≥2.2 mmol/L and ≥2.6 mmol/L, only 366 (48%) and 439 (69%), respectively, were

prescribed high-intensity statins. Furthermore, 35 (4.5%) and 27 (5%), respectively, received combination therapy with ezetimibe and/or fibrates in addition to a statin, while 22 (3.0%) and 21 (4%), respectively, were prescribed ezetimibe and/or fibrates without a statin ($p < 0.001$) (Figure 13).

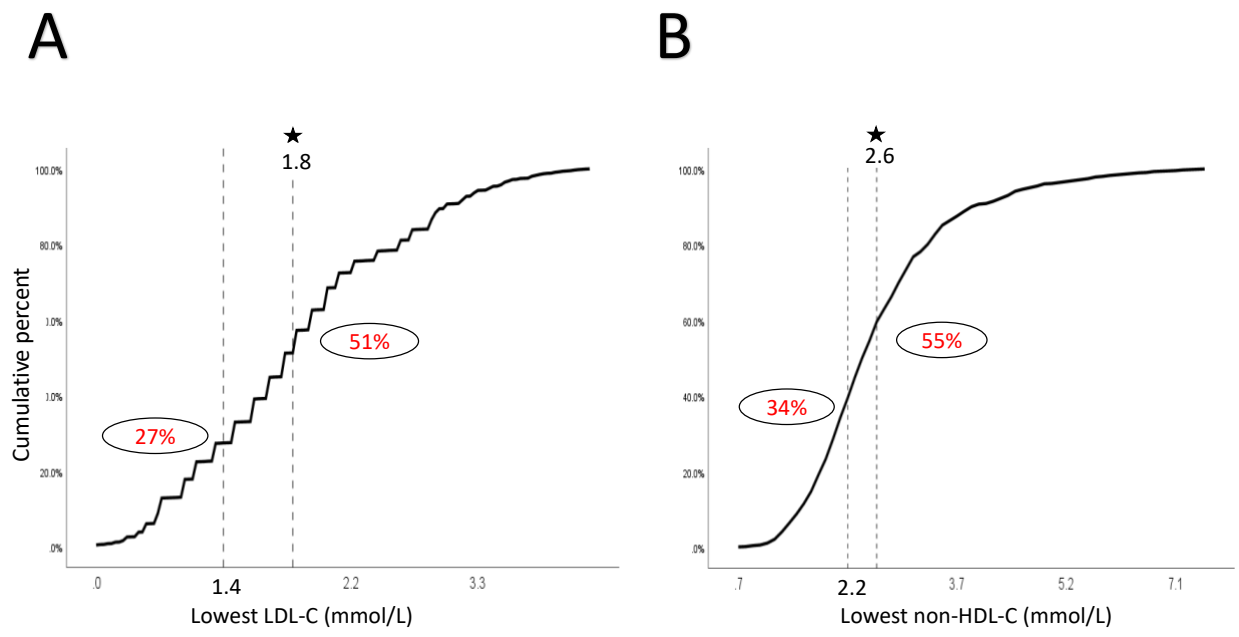


*Figure 11: (A) Lowest LDL-C and (B) non-HDL after discharge following the index PCI. The dotted lines represent the recommended level set in the most up-to-date (2019) European Society of Cardiology guidelines for the management of dyslipidaemias. *The optimal LDL-C and non-HDL-C targets set in 2016 European Society of Cardiology guidelines for the management of dyslipidaemias*

3.3.4: Blood Pressure Readings and Anti-Hypertensive Therapies

In total, 3,374 (97%) patients had at least one recorded BP reading during the 1-year follow-up period (mean ± SD: SBP 121 ± 14 mmHg, DBP 67 ± 12 mmHg). 3,259 (97%) had controlled BP (3,040 (90%) with controlled SBP; 2,958 (88%) with controlled DBP; and 2,739 (81%) with both controlled SBP and DBP) (Figure 14).

Figure 15 shows the frequency distribution of prescribing anti-hypertensive medications among both groups.

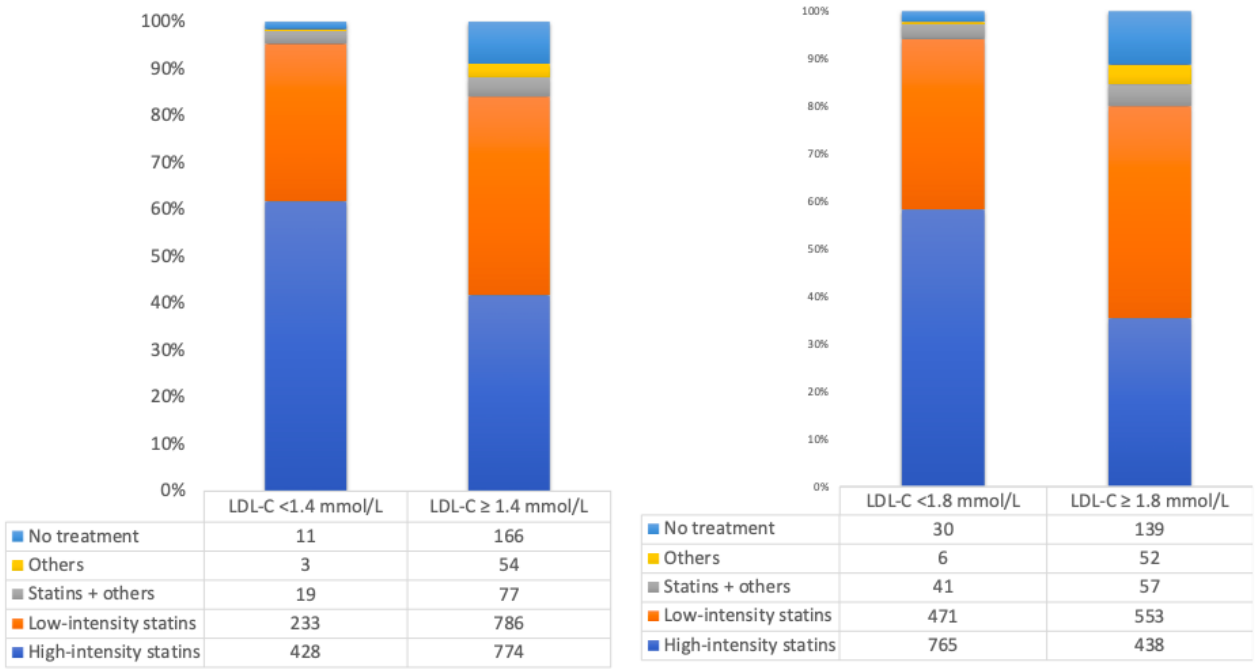


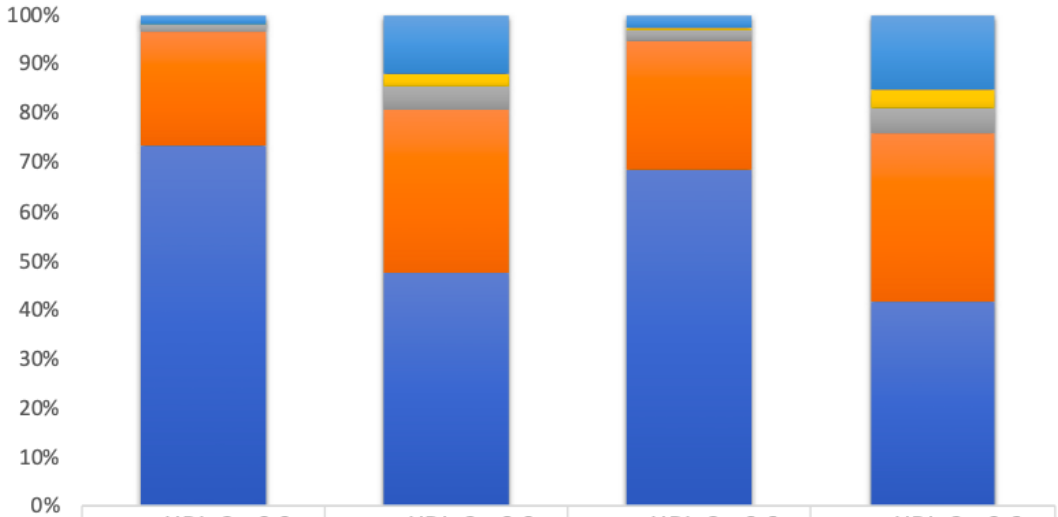
Figure 12: Prescribed lipid-lowering therapy in patients at or above the targets set for LDL-C in the 2019 (A) & 2016 (B) European Society of Cardiology guidelines for the management of dyslipidaemias. Other treatment indicates a prescription for Fibrate or Omega-3 fatty acids.

3.4: Discussion

This study examined the achievement of the ESC recommendations in a contemporary post-PCI Welsh population with DM. Notably, less than half achieved the target HbA1c, and just over a quarter achieved the target LDL-C. Achievement of the BP target was high at 81%. Only 7% of patients met the recommended targets for three parameters combined.

Of the three main CV risk factors, achievement of LDL-C was the lowest overall. In the 2019 ESC guidance, the recommended lipid level targets in patients with DM and CAD were an LDL-C reduction of ≥50% from baseline and a level of <1.4 mmol/L (<55 mg/dl)[150], reduced from the level of <1.8 mmol/L (<70 mg/dl) in 2016.[211] This class I recommendation was made based on

convincing evidence of improved CV outcomes with further reduction in LDL (9,10). Registry-based data has subsequently supported these 2019 LDL-C target recommendations.[214,215] However, the above results show that very few patients within this national sample (27%) achieved this target during one year of follow-up post-PCI. Even considering the less stringent targets suggested by the 2016 guidelines that were used at the time this data was collected, only 51% of our patients met the target of <1.8 mmol/L. These are similar observations to a previously published study examining a larger cohort of post-PCI patients with and without diabetes. [210]



	non-HDL-C < 2.2 mmol/L	non-HDL-C ≥ 2.2 mmol/L	non-HDL-C < 2.6 mmol/L	non-HDL-C ≥ 2.6 mmol/L
No treatment	7	90	17	80
Others	1	22	2	21
Statins + others	6	35	14	27
Low-intensity statins	92	257	167	182
High-intensity statins	295	366	439	222

Figure 13: Prescribed lipid-lowering therapy in patients at or above the targets set for non-HDL-C in the 2019 & 2016 European Society of Cardiology guidelines for the management of dyslipidaemias. Other treatment indicates a prescription for Fibrate or Omega-3 fatty acids.

Moreover, I found that the female sex was consistently associated with a lower probability of achieving optimal LDL-C control (whether according to 2016 or 2019 guidelines targets). This finding was also observed in an Italian retrospective study examining cholesterol control of a

larger population cohort[216], highlighting the possibility of underestimation of CV risk in these patients.

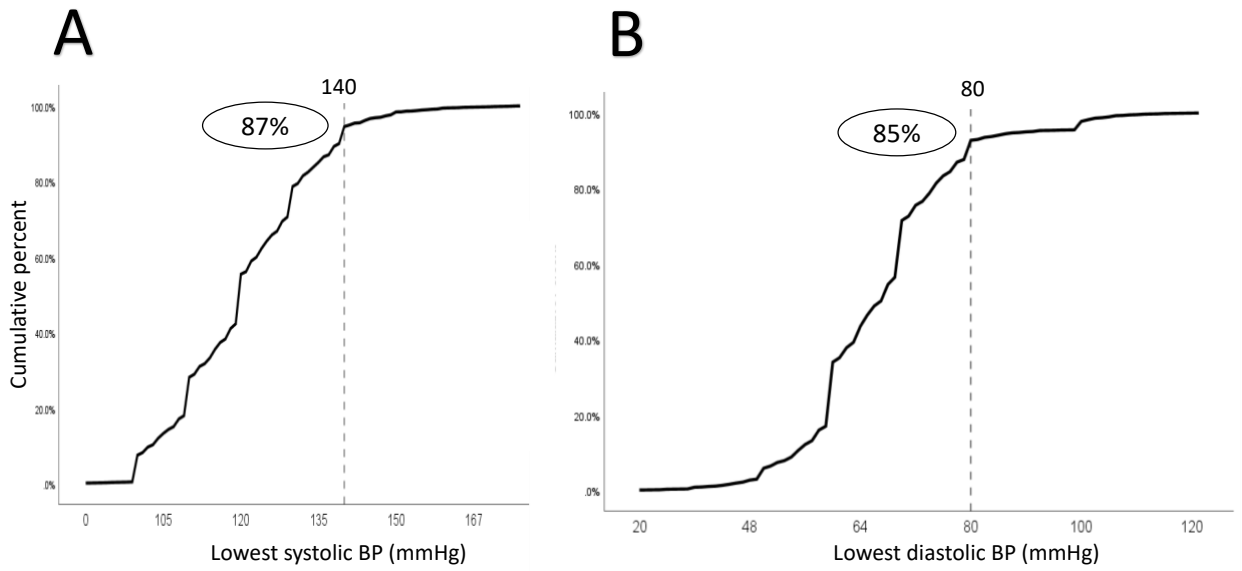
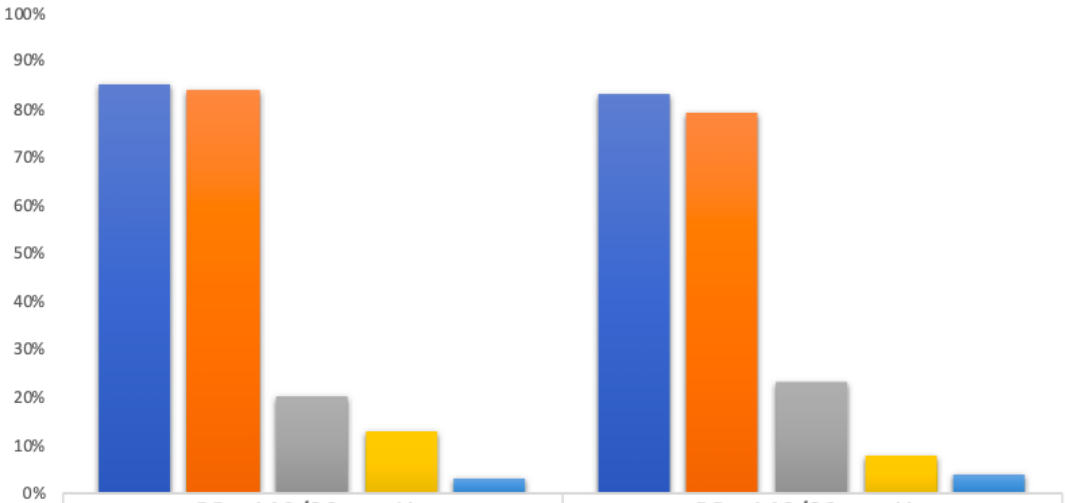


Figure 14: Lowest systolic and diastolic blood pressure recorded after discharge following the index PCI. The dotted lines represent the recommended blood pressure levels set in the European Society of Cardiology guidelines for the management of hypertension.

Globally, previous studies in other populations investigating the proportion of patients with DM and CAD meeting the LDL-C target of <1.8 mmol/L showed mixed results, with achievement rates between 14%-45%.[217,218]

Cross-sectional study data of very-high risk patients with and without diabetes in the United States has demonstrated a similarly high proportion of patients to be taking statin therapy, with the prevalence of patients taking lipid-lowering therapies to be as high as >90%[146], confirming that a high rate of statin use is feasible. However, LDL-C goal attainment is not always achievable, even when prescribed the highest tolerated statin doses.



	BP <140/80 mmHg	BP ≥140/80 mmHg
ACE-I or ARBS	85%	83%
Beta blockers	84%	79%
CCB	20%	23%
MRAs	13%	8%
No treatment	3%	4%

Figure 15: Prescribed anti-hypertensive therapy in patients at or above the targets set in the European Society of Cardiology guidelines for the management of hypertension. ACE-I = Angiotensin-converting enzyme inhibitors, ARBs = Angiotensin receptor blockers. CCB = calcium channel blockers and MRAs = Mineralocorticoid receptor antagonists

Even prior to the 2019 ESC guidance update, there has been a gap in the attainment of LDL guideline recommendations in those at very high risk.[219,220] Whilst uptake and persistence with statins have generally been poor historically[221,222], this has been particularly concerning in patients with DM as they may have the most to gain from statin therapy.[223] Whilst poor adherence to statin treatment is mostly due to concerns over adverse effects, the prevalence of intolerance has been reported to be 10-20%.[224,225] Therefore, it is unlikely to account for most of the discrepancies I have identified. Recently, it has become more apparent that whilst self-reported symptoms from statins may be high, the objective risk of clinically confirmed adverse events is low.[226] Moreover, another trial has demonstrated that the ratio of symptom intensity from a placebo versus a statin was only 0.9, suggesting a large proportion of symptoms to be attributable to a placebo effect.[227] On a promising note, contemporary data are, however, more encouraging,

showing that patients with DM may now be more likely to attain LDL guidance than in earlier studies.[228]

Current consensus indicates that glycemic control should be individualised according to the duration of DM, comorbidities, age and the impact of these features on the risk of therapy side effects (e.g., hypoglycemia and weight gain).[229] Nevertheless, the ESC guidelines (2013 & 2019) recommend tight glucose control in high-risk patients, targeting HbA1c <53 mmol/mol (<7.0%) to decrease microvascular complications.[175,230]

Relatively few of the participants (43%) met the 2019 ESC guidance of HbA1c <53 mmol/mol, compared to similar studies in the last 5 years of patients with CAD and DM that range from approximately 50% to 60%.[231–233] I also noted low usage rates of SGLT2 inhibitors and GLP-1RAs of only 10% in both groups. This is despite the clear cardioprotective impact highlighted in the cardiovascular Outcome Trials (CVOTs), especially in patients with DM and CAD.[164,234] The 2019 ESC diabetes guidelines give an 'I A' recommendation for using either SGLT2 inhibitors or GLP-1RAs in patients with DM and at high/very high risk of coronary disease as a first-line therapy – even before metformin. This data (2012-2017) was collected before the release of these updated guidelines; however, experimental and early clinical observation data indicated favourable effects of these agents on myocardial performance before they were examined in randomisation trials[164], and this was reflected in the 2013 DM guidelines.[230]

Moreover, results from the EMPA-REG OUTCOME and LEADER trials (two of the CVOTs pillars) were published during the data-collection phase of this study and encouraged physicians to utilise those agents in a 'treat-to-benefit' fashion.[164,235]

According to national registry data from Denmark, this gap has been noted globally; however, the prescription of those new agents is far less across Europe than in the US.[236] This 22-year Danish registry data showed congruent results with our report, with only 12% prescription shares for SGLT-2 inhibitors and GLP-1RAs among hypoglycaemic drugs across all patients with T2DM by 2017.

Pharmacy cost doesn't seem to be a barrier to the suboptimal prescription rate of those agents. SGLT-2 inhibitors and GLP-1RAs are similarly priced as DPP-4 inhibitors, whether in Denmark or US[236,237]; however, DPP-4 inhibitors still have a higher prescribing rate despite their neutral CV effects.[238] In this report, DPP-4 inhibitors had a 25% prescription rate (versus 10% for SGLT-2 inhibitors and GLP-1RA) across all patients with DM.

Schernthaner G. et al. argued that the slow uptake of SGLT2i and GLP-1 RA following CVOT disclosures is attributed to clinical inertia among clinicians with limited knowledge of the current evidence and a preference for agents with more personal clinical experience.[239]

Reassuringly, I observed effective BP control in 81% of patients. One explanation for this is the fact that those patients had undergone recent PCIs; therefore, the blood pressure is mainly managed by cardiology specialists rather than primary care physicians, with the majority of the patients prescribed the guideline-recommended medications for ischaemic heart disease, including beta blockers and Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin Receptor Blockers, as well as other anti-hypertensive medications on discharge as a standard of care management. This was also shown in similar studies, where CVD risk factors were better managed if treatment was initiated by specialist physicians rather than PCP.[240]

Another explanation is that I aimed for higher blood pressure targets (systolic pressure <140 mmHg and diastolic pressure <80 mmHg), considering the mean age of our cohort group being >65 years old. Interestingly, this ratio is considerably higher than in other studies of patients with CAD and DM, ranging from 13% to 67%.[218,241–244] In a German/Austrian population with T2DM and CVD, the prevalence of achieving the target BP was as high as 90%. However, higher target values were set for patients (70–90 mmHg for diastolic and 120–140 mmHg for systolic blood pressure).[243]

In a large European registry (which recruited 20,588 symptomatic patients with established CAD from 18 European countries), 59% of the patients had optimal control of 3 or more risk factors combined.[245] Disappointingly, the number of patients meeting the three recommended targets for

HbA1c, LDL, and BP combined in our study is much lower than this (7%, n = 241). Although this is far from optimal, it is still relatively better than other European healthcare systems, which follow the same guidelines.[246]

It is possible that the lack of awareness by many physicians regarding the benefits of effectively controlling CVD risk factors might contribute to the observed suboptimal results across the population. Another barrier to full optimisation may be an inaccurate perception of how well-controlled the patients' risk factors are in a stable outpatient compared to a more acute setting, e.g. acute coronary syndrome. Healthcare economics and patients' compliance may also influence the level of care provided.

Regardless of the reasons, there is a need for a positive change in practice level and perhaps beyond pharmacological therapy to avoid missed opportunities for optimal medical care and prevent unnecessary morbidity and mortality.

3.5: Strengths and Limitations

The major strength of this study is the use of a large, nationwide sample owing to the data-linkage nature of the SAIL database. It is clinically relevant, representative data that is directly used by clinicians and can be used to optimise relevant upstream decision-making.

The main limitation is that this is a retrospective, observational study. Nonetheless, these data represent real-world assessments and analyses. This study uses relatively older data (from 2012 to 2017), reflecting the clinical practice against the guidelines available when these data were collected (i.e., according to ESC 2013-2016 Guidelines). Nevertheless, it may offer a 'snapshot' of the current patient management in the Welsh clinical settings and assess the attainment of the ESC guidance. It is possible that prescription rates and lipid, glucose and BP control may have improved in the interim, so a more up-to-date analysis is warranted. Still, previous amendments to guidelines have not rapidly changed practice in the past.[247] I couldn't make an assessment on

unmeasured variables such as medication compliance or the quantity of medications taken, as well as other potential confounders such as patients' socio-economic class. Although, it is unlikely that adjustment for these factors would change this study's conclusions significantly. Similarly, it was not possible to differentiate patients with type 1 and type 2 DM from the SAIL data set. Since SGLT2 inhibitors and GLP-1 RA are not currently licenced to use in type 1 DM, I only analysed the prescription rate of those new agents in patients receiving non-insulin-based therapy in both groups, assuming they all have type 2 rather than type 1 DM. Nevertheless, it's unlikely that the prescription rate would differ much if the percentage of patients with T2DM were known.

Finally, reports from the Welsh healthcare system may not be generalisable to other healthcare systems as prescriptions are free, abolishing the affordability barrier that may be relevant in different settings.

3.6: Conclusion

Although not imaging-based, this chapter highlights substantial gaps between guideline recommendations and real-world clinical practice in high-risk patients. These findings provide a foundation for the subsequent CCTA-based analyses presented in this thesis, which aim to address this unmet need by improving risk stratification through detailed assessment of coronary plaque characteristics and their impact on clinical decision-making. This work therefore serves as a systems-level context for the imaging-based investigations that follow.

CHAPTER 4: Characteristics Of Conventional High-Risk Coronary Plaques And A Novel CT Defined Thin-Cap Fibroatheroma In Patients Undergoing CCTA With Stable Chest Pain

This Chapter is based on the following published article:

Salem, A. M. et al. Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain. Clin. Imaging 101, 69–76 (2023) https://doi.org/10.1016/j.clinimag.2023.06.009

4.1: Introduction

CCTA is a validated diagnostic imaging modality for investigating patients with suspected coronary artery disease (CAD).[248] Beyond identifying luminal stenosis, CCTA enables plaque visualisation, a capability not available during routine invasive coronary angiography (ICA) without intravascular imaging.[198,249,250] HRP features on CCTA, such as low-attenuation plaque (LAP), positive remodelling (PR), and Napkin ring sign (NRS), have been recognised as potentially valuable for identifying patients at increased risk of cardiovascular events.[108,200] However, the utility of these features in routine practice may be limited by inter-observer variability, especially among less experienced CCTA practitioners.[251]

Histologically, vulnerable plaques (i.e., those prone to rupture) typically have larger necrotic cores with less overlying fibrous tissue.[26] Advances in image quality and software tools mean quantitative assessment of coronary plaque components is now feasible.[61,252] A histologically validated 'plaque map' analysis using CCTA has been described before. This novel analysis identifies different plaque constituent volumes with x-ray attenuation cut-offs derived from the relationship of plaque to luminal contrast attenuation, automatically adjusting for inter-patient variation in contrast intensity.[61] A vulnerability index, which calculates a necrotic core/fibrous plaque ratio, has been proposed. This index, with a cut-off of >0.9, identifies plaques analogous to Virtual Histology Intravascular Ultrasound (VH-IVUS)-defined TCFA, potentially introducing a new vulnerable plaque identifiable on CCTA, termed the ‘CT-TCFA’.

4.2: Aims

This study aims to investigate the prevalence and inter-observer variability of both traditional CT-defined vulnerable plaques and the new CT-TCFA among a cohort of patients who presented with stable chest pain and demonstrate their significance on cardiovascular outcomes.

4.3: Participant Recruitment

I used pre-existing data for this prospective observational cohort study, which included patients with stable chest pain and a high pre-test probability of coronary artery disease at Royal Papworth Hospital. Patient characteristics and follow-up information were obtained through collaboration with Dr Deepa Gopalan and Dr Adam Brown.

A total of 100 patients were consecutively recruited from outpatient chest pain assessment clinics. All participants were deemed to have a high likelihood of coronary artery disease and were scheduled for routine invasive coronary angiography.

As part of the study protocol, all patients underwent CCTA prior to invasive angiography. The study received ethical approval from the Cambridgeshire Research and Ethics Committee.

The team at Cambridge assessed the long-term clinical outcomes via structured telephone interviews and postal questionnaires over a seven-year follow-up period. MACE—defined as a composite of all-cause mortality and non-fatal myocardial infarction—were recorded to evaluate the prognostic significance of CCTA findings in this high-risk population.

4.4: CCTA Acquisition

Patients underwent a gated CT with ECG-dependent tube current modulation at Royal Papworth Hospital using a Somatom Definition 64-slice dual-source system (Siemens Medical Systems, Forchheim, Germany) with the following scan parameters: pitch 0.20-0.48, collimation 32 x 0.6 mm, tube voltage 120 kV and tube current 360 mA. CCTA acquisition was performed using prospective ECG-gated protocols where feasible; retrospective gating was employed in selected cases to optimise image quality, acknowledging the associated increase in radiation exposure. More details regarding the dual source data set are listed below in Table 7. In addition, intravenous contrast was injected in a triphasic protocol following a 20 ml timing bolus to assess

circulation time. Patients with a heart rate >70 beats/min received metoprolol intravenously, and all patients received 0.6 mg of sublingual Nitroglycerin.

Table 7: Acquisition Parameters for the CCTA

Premedication	*Nitrates sublingual (0.4mg SL)*
Rotation time	*Temporal resolution 83 msec*
Collimation	*64mm X 0.6mm*
Pitch	*0.20–0.48 (heart rate adaptive)*
ECG-dependent tube current modulation	*35%–75%*
Tube voltage	*120 kV*
Tube current	*360 mAs*
Contrast agent	*Routine triphasic injection protocol*
Contrast timing	*20 cc test bolus with ROI in ascending aorta*

4.4.1: CCTA Qualitative and Quantitative Plaque Analysis

Detailed information on qualitative and quantitative plaque analysis methods is provided in Chapter 2. The initial analysis was originally done by Dr Daniel Obaid, who is a senior CT reporter with >5 years of experience, and carries level 3 (Advanced Practitioner) accreditation at the Society of British Cardiovascular CT.

I divided the patients into groups according to the presence of any vulnerable features and calculated the rate of MACE events that occurred and were previously recorded. I then determined the frequency and patient characteristics associated with these different plaque types.

To assess inter-observer variability in a real-world setting, a randomly selected subset of 40 plaques (approximately 11% of the total plaque cohort) was independently re-analysed by a second reader. Each plaque was evaluated for vulnerability features, as previously defined, to determine the consistency and reproducibility of interpretation.

4.5: Statistical Analysis

Categorical variables are presented as numbers and percentages, while continuous variables are shown as mean ± standard deviation. The chi-square test was used to compare categorical variables. Between-group comparisons were conducted using the independent-samples t-test. Inter-observer variability was measured using the kappa coefficient (k). Event rates were estimated with Kaplan–Meier curves and compared using log-rank tests. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 26.

4.6: Results

4.6.1: Characteristics of Different CT-Defined Vulnerable Plaque Types

After CCTA examination, 3 patients were discovered to have had previous coronary artery bypass grafting; in 2 patients, CT images were too poor for plaque analysis. A further 8 patients were lost to long-term follow-up, giving a final study population of 87 patients (patient demographics are shown in Table 8).

The total number of plaques present in all 87 patients was 346, of which 244 (70%) contained only calcified plaque. The remaining 102 (29%) plaques contained non-calcified elements. Of the 346 plaques, forty-one plaques (12%) were obstructive (luminal stenosis >50%). There were 93 (27%) plaques that exhibited at least one conventional high-risk CCTA feature (LAP, PR, NRS). The most frequent feature was LAP, which was present in 87 (25%) plaques, while there were 64 (18%) plaques with PR and 46 (13%) plaques with NRS.

Table 8: Baseline patient characteristics.

Patient Demographics	*(n = 87)*
Male	*58 (68%)*
Age (years)	*63 ± 13*
Hypertension	*54 (62%)*
Diabetes	*11 (13%)*
Current smoker	*6 (7%)*
BMI, (Kg/ m2)	*30 ± 6*
Hyperlipidemia (TC>5 or LDL>3 mmol/L)	*28 (32%)*
Family history of CAD	*39 (45%)*
Multi-vessel disease	*11 (13%)*
Calcium score (Agatston units)	*596 ± 1109*

Multi-vessel disease= Obstructive lesions in >1 coronary artery. BMI = body mass index, CAD = coronary artery disease. Values are n (%) or mean ± SD

The kappa coefficient of inter-observer variability (*k*) for PR was 0.7, and for LAP was 0.3. There were 59 plaques with LAP and PR combined. Seventy-two (21%) of all plaques were classified by conventional CT parameters as vulnerable (either NRS or PR and LAP combined), and 80 (23%) of plaques were considered vulnerable using either conventional parameters or the new CT-TCFA definition. The kappa coefficient of inter-observer variability (*k*) for NRS was 0.4, and for PR and LAP, was combined 0.4. Using the novel CT-TCFA definition of (NC/fib ratio of >0.9) led to 43 (12%) of plaques being classified as vulnerable. The kappa coefficient of inter-observer variability (*k*) for CT-TCFA was 0.7. There was considerable overlap of plaques between all 3 definitions of vulnerable plaque. Eight (19%) and 10 (23%) plaques with NC/fib ratio >0.9 overlapped with the vulnerable plaques showing NRS and LAP & PR, respectively. Seventeen plaques exhibited all 3 features (Figure 16).

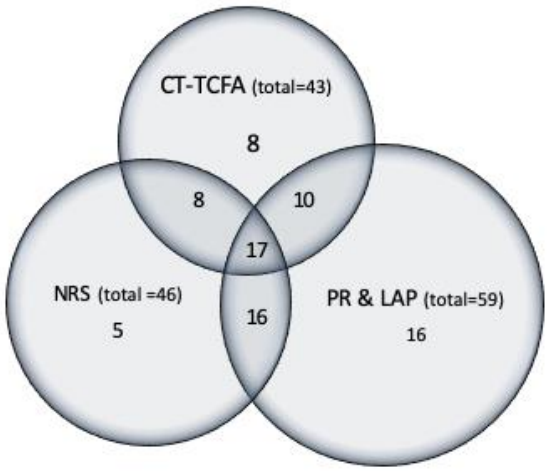


Figure 16: NRS and PR&LAP plaques overlapping with the novel coronary CT vulnerability index. CT-TCFA: CT-defined thin-cap fibroatheroma NRS = Napkin ring, LAP = Low attenuation and plaque PR = Positive remodelling. Numbers represent plaque counts. Discrepancies reflect overlapping classification using conventional and CT-TCFA criteria.

Plaque map quantification of constituent plaque volumes of the three vulnerable plaque types (LAP&PR, NRS and CT-TCFA) are shown in Table 9. Compared with non-vulnerable plaques, I found that all 3 plaque types had greater NC volumes and percentages than non-vulnerable ones (p-values < 0.001). In addition, the percentage of calcified plaque was lower in all 3 vulnerable types when compared to the non-vulnerable ones (p-values < 0.001). Luminal stenosis >50% was significantly more frequent in all 3 vulnerable plaque types than in the non-vulnerable plaques.

Table 9: Quantitative analysis for each CCTA vulnerable plaque feature.

	Non-vulnerable plaques (23)	***Low attenuation and positive remodelling plaques (59)***	***p value***	***Napkin ring plaques (46)***	***p value***	***CT TCFA (43)***	***p value***
NC volume, mm^3	*40 ± 25*	*83 ± 61*	*< 0.001*	*93 ± 63*	*< 0.001*	*91 ± 62*	*< 0.001*
NC %	*24 ± 8*	*37 ± 12*	*< 0.001*	*38 ± 13*	*< 0.001*	*46 ± 11*	*< 0.001*
Fibrous plaque volume, mm^3	*63 ± 36*	*97 ± 71*	*0.01*	*106 ± 71*	*0.004*	*75 ± 49*	*0.1*
Fibrous plaque, %	*40 ± 9*	*42 ± 10*	*0.2*	*41 ± 10*	*0.2*	*37 ± 8*	*0.09*
Ca volume, mm^3	*71.5 ± 58*	*76 ± 136*	*0.4*	*76 ± 131*	*0.4*	*36 ± 44*	*0.007*
Ca %	*36 ± 14*	*21 ± 18*	*< 0.001*	*21 ± 18*	*< 0.001*	*17 ± 15*	*< 0.001*
NC/Fib ratio	*0.6 ± 0.2*	*0.9 ± 0.3*	*< 0.001*	*1 ± 0.3*	*< 0.001*	*> 0.9*	
NC/Fib > 0.9	*1 (40%)*	*27 (46%)*	*< 0.001*	*25 (54%)*	*0.04*	*43 (100%)*	
Plaque burden %	*58 ± 17*	*62 ± 10*	*0.06*	*66 ± 10*	*0.006*	*62 ± 11*	*0.1*
Luminal stenosis >50%	*3 (10%)*	*26 (90%)*	*0.006*	*31 (67%)*	*< 0.001*	*20 (46.5%)*	*0.007*

NC = Necrotic core, Fib = Fibrous plaque, Ca = calcium. Values are n (%) or mean ± SD

I then compared the characteristics of the patients (41/87 - 46%) who had at least one conventional (NRS or LAP & PR) or novel defined vulnerable plaque (NC/fib > 0.9) and those without. I found those patients with vulnerable plaques were more likely to have hyperlipidaemia (p = 0.01), greater prevalence of multi-vessel CAD (p = 0.002), and higher coronary artery calcium scores (p = 0.005) when compared with those patients without vulnerable plaques. All other variables in the two groups were comparable (Table 10).

Table 10: Patient characteristics in relation to vulnerable plaques.

	Patients with VP (41)	***All other patients (46)***	***p Value***
Male	*30 (73%)*	*28 (61%)*	*0.2*
Age (years)	*64 ± 10*	*64 ±13*	*0.4*
Hypertension (mmHg)	*27 (66%)*	*27 (59%)*	*0.5*
Diabetes	*7 (17%)*	*4 (9%)*	*0.3*
Current smoker	*4 (10%)*	*2 (4%)*	*0.4*
BMI, (Kg/m2)	*29 ± 5*	*30 ± 6*	*0.3*
Hyperlipidemia (TC>5 or LDL>3 mmol/L)	*11 (27%)*	*2 (4%)*	*0.01*
Family history of CAD	*17 (49%)*	*22 (56%)*	*0.5*
Multivessel disease	*10 (24%)*	*1 (2%)*	*0.002*
Calcium score (Agatston units)	*970 ± 1345*	*310 ± 793*	*0.005*

Multivessel disease = Obstructive lesions in >1 coronary artery. BMI = body mass index, CAD = coronary artery disease. Values are n (%) or mean ± SD

4.6.2: Plaque-Based Analysis of CCTA Findings Associated with MACE

I examined the survival outcomes after a mean follow-up period of 7 ± 0.8 years. Among the 87 patients who were successfully followed up, 17 patients (19%) experienced MACE. These events included 10 deaths and 7 cases of ACS. Notably, patients who had no coronary plaque detected on CCTA experienced no MACE events during the subsequent 7 years.

When comparing patients with no coronary plaque to those with conventional CT-defined vulnerable plaques—characterised by LAP combined with PR and the NRS—a significant association with MACE was observed (Figure 17A). This indicates that the presence of these conventional CT-defined vulnerable plaques markedly increases the likelihood of MACE.

A similar pattern emerged when comparing patients with no coronary plaques to those with the newly proposed CT-TCFA. The Kaplan-Meier survival curve demonstrated a significant

difference in MACE events, suggesting that the new CT-TCFA metric is also a strong predictor of adverse cardiovascular outcomes (Figure 17B).

In contrast, there was no significant difference in the occurrence of MACE between patients with no coronary plaque and those with non-vulnerable plaques (Figure 17A).

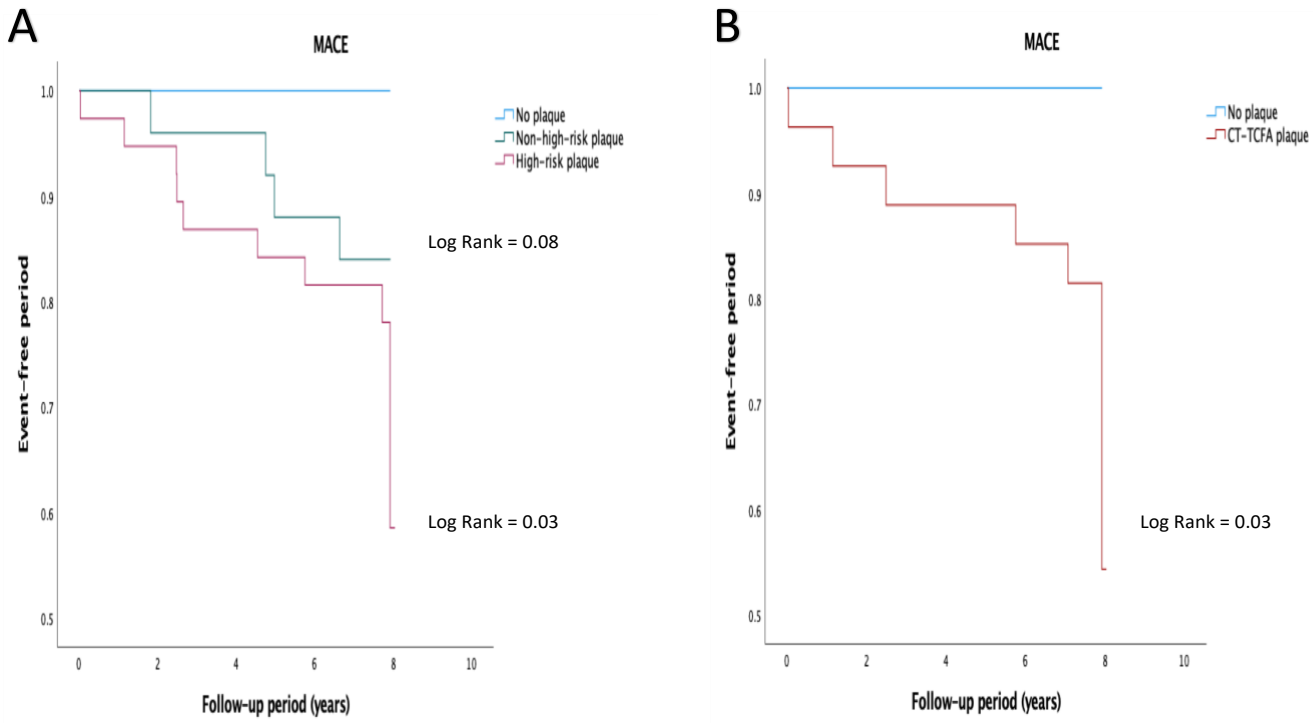


Figure 17: Kaplan-Meier Curves for MACE events in (A) patients with conventionally defined high-risk plaques vs non-high-risk plaques and no plaques, (B) patients with CT-TCFAs vs no plaques on CCTA

4.7: Discussion

In this study, I used CCTA in a cohort of stable patients with a high suspicion of CAD to examine the characteristics and prevalence of both conventionally defined high-risk plaque and a new potential CT-defined high-risk plaque – the CT-TCFA. CT-TCFA is determined using colour-coded plaque map analysis to identify different plaque characteristics using the X-ray attenuation ratio of the plaque and the luminal contrast. This has been validated against post-mortem

histology and can discriminate fibrous tissue, necrotic core and calcification with minimal overlap.[61]

I found that these high-risk plaques occurred more commonly in patients with hyperlipidemia. This mirrors pathological studies which have demonstrated an association between the incidence of TCFA in patients dying suddenly from acute MI and hyperlipidemia.[27] The clinical importance of conventional high-risk plaque features, particularly the presence of LAP&PR and NRS, is well established.[108,200] In addition, quantitative plaque measures such as total plaque volume, non-calcified plaque volume and volume of low attenuation plaque may also provide further prognostic information.[253,254] In a subgroup of the ICONIC (Incident COroNary Syndromes Identified by Computed Tomography) study, CT-defined necrotic core and fibrofatty plaque volumes significantly correlated with future cardiac events independent from lesion stenosis diameter.[255] I found that conventional CCTA-defined high-risk plaque had higher percentages of necrotic core and lower percentages of calcified plaque, in keeping with previous findings showing constituent plaque volumes correlate with high-risk plaque features.[256] The most powerful predictor of cardiac risk may be a combination of adverse plaque characteristics, including quantitative measures of plaque burden and high-risk features.[257] In addition to predicting future events, CT assessment of high-risk plaque improves the diagnosis of ACS in patients with acute chest pain who otherwise had no ECG or enzymatic evidence of ischemia.[258] Furthermore, when correlated against coronary lesions with positive Fractional Flow Reserve (FFR), high-risk CCTA plaque characteristics improved the identification of coronary lesions that cause ischemia.[259]

It is now recommended that high-risk plaque features should be routinely reported.[260] However, there are concerns that the subjective nature of these features raises issues with inter-observer variability.[251,261] In this study, the kappa co-efficient of inter-observer variability (k) for the conventional high-risk plaques of NRS was 0.4 and for LAP combined with PR was 0.4. In contrast, the CT-TCFA is based on plaque volumes calculated in a semi-automated fashion, and

the early career reader and the expert reader demonstrated a strong concordance ($k = 0.7$). I found significant morphological overlap between both the conventional high-risk plaques (LAP&PR and NRS) and the newly introduced 'plaque map' (CT-TCFA), with 51/80 high-risk plaques meeting more than one definition. Some conventional high-risk plaques were not classified as CT-TCFA after plaque map analysis. This was not affected by overall plaque burden or luminal stenosis. Conventional high-risk plaques that met the criteria for CT-TCFA did have a higher percentage of necrotic core; this is not surprising given a necrotic core/ fibrous plaque ratio > 0.9 is the criteria used to define CT-TCFA. Interestingly, high-risk plaques were more likely to be classified as CT-TCFA in plaques with less calcification. Possible explanations for this include that partial volume effects from heavily calcified lesions may affect the attenuation of adjacent plaque components, limiting the use of plaque map quantitative plaque volume analysis. Another possibility is that in plaques with high calcium burden, the partial volume artefact may affect the identification of LAP, PR and NRS. In this study, over the 7 year follow-up period, I found the rate of MACE for patients with conventional high-risk plaques (26%) and CT-TCFA (22%) was similar to that of conventional high-risk plaque found in a previous study (23%) undergoing mid-term (4 years) follow up.[197] While this study was relatively small, the Kaplan-Meier curves showed similar survival from MACE over an extended follow-up period for conventional high-risk plaque and CT-TCFA. This, combined with the fact that there was considerable overlap of plaques within these definitions, means that CT-TCFA is likely identifying a broadly similar group of patients with atherosclerotic coronary disease to conventional high-risk plaques, but with the potential advantage of lower inter-observer variability. Interestingly, patients with no high-risk plaques were initially free of MACE for 18 months but did not have an identical course to patients with no plaques and subsequently began having MACE events. This may be because some MACE events are caused by plaques other than TCFAs (plaque erosions and calcified nodules).[26] Another possibility is that given the dynamic nature of coronary plaque[262], some non-high-risk plaque may have progressed to a more high-risk phenotype over the time course of the

study. Given this, overall atherosclerotic disease burden remains a determinant of coronary artery risk assessment, and the focus should not be on individual plaque features alone.[263] It is possible that in the future, risk assessment will be further enhanced by radiomics - enhanced image analysis of large amounts of quantitative information from digital imaging not distinguishable to the human eye.[264] Further validation is required before clinical use, but preliminary research has shown that radiomics-based machine learning analysis can improve the discriminatory power of coronary CT angiography in the identification of advanced atherosclerotic lesions.[265]

4.8: Limitations

This study has several limitations that should be acknowledged. Firstly, due to constraints in spatial resolution, CT cannot directly identify TCFA. Instead, the CT-TCFA definition relies on a high CT-defined percentage of the necrotic core relative to the fibrous plaque, mirroring what is observed in histological TCFA.[26] This definition has been previously utilised in vivo and has shown favourable comparisons with VH-IVUS.[119] Secondly, the study was conducted at a single centre and involved a relatively small sample size. This limitation precluded the possibility of conducting further survival analysis to compare outcomes between unstable plaques—whether defined by traditional high-risk signs or the CT-TCFA—and stable plaques. The restricted sample size limits the generalizability of the findings and underscores the need for larger, multi-centre studies to validate the utility of CT-TCFA in broader populations.

Additionally, the study population consisted of patients with a high prevalence of coronary artery disease, which may limit the applicability of the findings to other populations with different baseline characteristics. Future research should involve more diverse populations to ensure the findings are widely applicable. Furthermore, the plaque-map analysis approach necessitates the evaluation of coronary plaques throughout the entire coronary tree. This process is time-consuming and requires a certain level of clinical expertise, which could be a barrier to

widespread adoption in clinical practice. Importantly, CT-TCFA analysis in this study was performed using the Vitrea plaque analysis platform. Although several alternative validated software solutions for quantitative plaque characterisation are available, inter-platform variability remains a recognised limitation. As such, the generalisability of the present findings may be influenced by software-specific implementations, and further validation across different analysis platforms and scanner vendors will be required before widespread clinical adoption.

In summary, while this study offers promising insights, these limitations highlight the necessity for further research with larger sample sizes and more diverse populations to confirm the findings and enhance the clinical utility of CT-TCFA.

4.9: Conclusions

This study presents the introduction of a potentially novel CT-defined vulnerable plaque, characterised by a vulnerability index based on the ratio of the necrotic core to fibrous plaque. This new metric demonstrates improved inter-observer variability when compared to the currently established CT-defined vulnerable plaques. The enhanced consistency in measurements suggests that this new index may be more suitable for widespread clinical application, particularly among less experienced operators. This improved reliability could significantly aid in the identification of atherosclerotic plaque composition, thereby enhancing the accuracy of risk stratification for potential future cardiac events. The potential for this new index to streamline and improve the diagnostic process underscores its importance in advancing cardiovascular imaging and patient care.

Chapter 5: High-Risk Plaque Features On CCTA: A Catalyst For Cardiovascular Risk Optimisation

5.1: Introduction

ASCVD remains a leading cause of mortality in Europe, accounting for over 4 million deaths annually.[266] Prevention strategies should be tailored to an individual's total CV risk, with more intensive interventions directed at those at higher risk.

Risk score calculators are widely used in clinical practice to estimate CV risk, guide treatment decisions, and predict outcomes in patients with suspected coronary artery disease (CAD).[150] International guidelines endorse these scores as they provide cumulative risk assessments, particularly for individuals with multiple contributing risk factors. However, the effectiveness of risk scores in influencing treatment decisions remains debated, leading to an increased reliance on non-invasive imaging techniques for improved risk stratification and management.[267]

CCTA is established as a valuable tool in detecting and quantifying ASCVD[268] - providing incremental prognostic value over traditional risk stratification models. Despite its widespread availability, the extent to which physicians integrate CCTA findings into clinical decision-making remains unclear. CCTA also provides additional prognostic value by visualising plaque composition.[85] High-risk plaque features (HRF) such as low-attenuation plaque (LAP), positive remodelling (PR), and Napkin ring sign (NRS) have been associated with an increased likelihood of adverse cardiovascular events.[85,108,200] However, these features are not routinely reported, partly because their detection has significant variability amongst reporters.[251]

5.2: Aims

This study aims to evaluate changes in patients' risk factor profiles—including lipid levels, HbA1c, and blood pressure—as well as statin medication prescriptions following routine CCTA assessment. By analyzing symptomatic patients with a suspicion of CAD, this research will assess

whether patient management based on standard CCTA reports facilitates risk factor modification targeted to individuals with high-risk plaque features.

5.3: Methods

5.3.1: Participants:

I undertook a retrospective observational cohort study using linked anonymised electronic health record (EHR) data for over 2,000 stable patients with chest pain and a low probability of CAD. They attended outpatient chest pain assessment clinics, underwent CCTA in Wales, UK, between January 2013 and 2020. All participants with a diagnosis of coronary artery disease underwent routine clinical treatment, including medical therapy and risk factor modification, in keeping with clinical guidelines at the time. I then collected follow-up data for up to three years post-CCTA through the Secure Anonymised Information Linkage (SAIL) Databank

In summary, SAIL is part of the national e-health records research infrastructure for Wales; the following linked data sources are held within SAIL: secondary care hospital admission data within the Patient Episode Database for Wales (PEDW), primary care General Practitioner (GP) data within the Welsh Longitudinal General Practice (WLGP), demographic data and GP registration history within the Welsh Demographic Service Dataset (WDSD).

Study subjects included those >18 years of age, with at least three years of follow-up available in the WLGP. I assigned the index date to the date of the CCTA scan during the study period for each patient.

The WLGP data was used to describe the presence of hypertension, recorded lipid levels, HbA1c and blood pressure levels, and lipid-lowering therapy. In addition, PEDW and WLGP data were used to describe a prior history of myocardial infarction and ischaemic stroke and urgent or unplanned coronary revascularization. I then set MACE to the composite of all-cause mortality and myocardial infarction, stroke and urgent unplanned revasculisation.

Further details on data filtering and analysis using the SAIL Databank, as well as the recruitment process and inclusion/exclusion criteria, are provided in detail in Chapter 2: Methodology**.**

5.3.2: CCTA Acquisition and Analysis

All the participants underwent prospective ECG-gated coronary CT angiography. Detailed information on qualitative and quantitative plaque analysis methods is provided in Chapter 2. Following imaging, I stratified the participants into three groups based on the presence and morphology of coronary plaques:

No plaque group – Patients with no detectable coronary plaques.

Low-risk plaque group – Patients with calcified plaques only.

Higher-risk plaque group – Patients with non-calcified or mixed plaques. This group underwent further evaluation for the presence of high-risk plaque features, including (LAP, PR or NRS). In addition, plaques were assessed using the the new CT-TCFA derived from plaque 'colour mapping' criteria, as previously described (Figure 18).

5.3.3: Risk Factors Recording

Low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), HbA1c, and blood pressure readings were collected at three time-points: an index measurement taken within 6–12 months prior to the CCTA, followed by two follow-up measurements at 1 year and 3 years post-CCTA. These values were included in the analysis to assess longitudinal changes.

I evaluated the reduction in HbA1c, lipid levels, and blood pressure across the three patient groups, as well as any changes in cholesterol-lowering medication prescriptions following the

CCTA assessment. Additionally, I recorded the incidence of MACE over the 3-year follow-up period and compared the groups based on the CCTA findings.

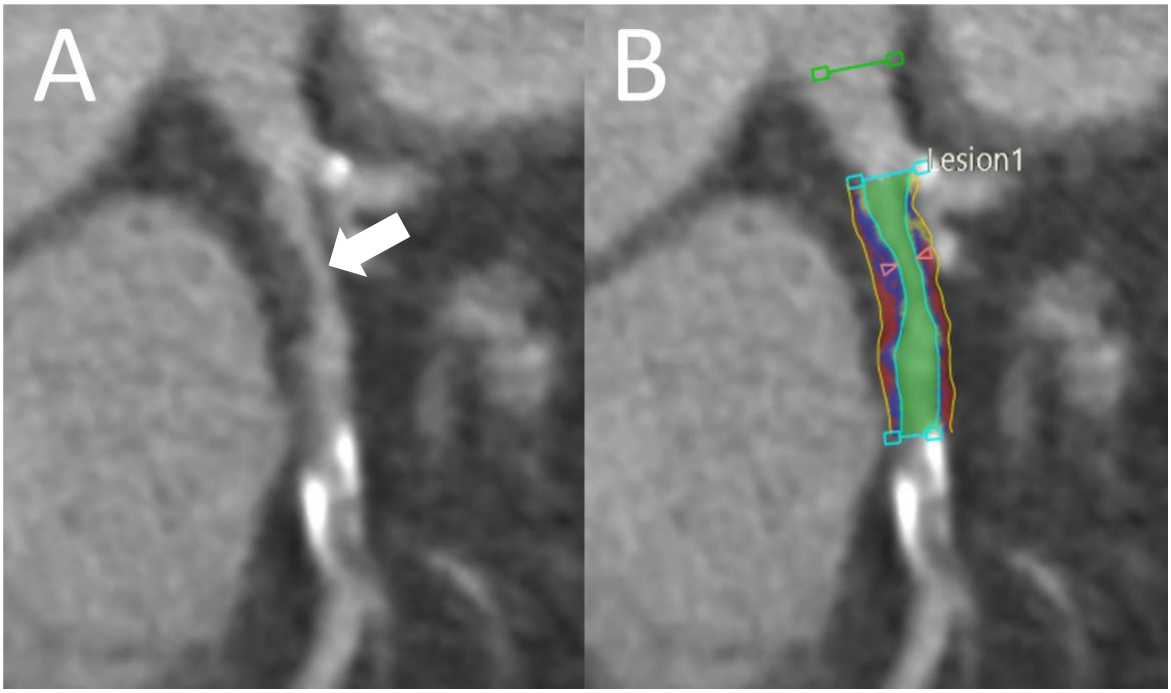


Figure 18: Plaque colour mapping in a proximal LAD. A: Identifying the vessel and lumen borders, luminal contrast attenuation proximal and distal to plaque (white arrows). Then, B: Plaque Map analysis ((red = necrotic core, blue = fibrous plaque, yellow = calcified plaque).

5.3.4: Statistical Analysis

I used the following software programs for data processing: SPSS version 26.0 and Microsoft Excel 2018© (16.16.27). Continuous variables were expressed as mean ± standard deviation and were compared using paired and unpaired Student's t-test, as appropriate. Categorical variables were expressed as amounts and proportions and were compared using the Chi-square and Fisher tests when applicable. Two-way repeated measures ANOVA was used to calculate the changes in the risk factors parameters during the baseline and the follow-up periods. p values < 0.05 were considered significant. Event rates were expressed as Kaplan–Meier curves and compared by log-rank tests. P-value < 0.05 was considered statistically significant.

5.4: Results

5.4.1: Characteristics of Patients According to Different CT-Plaque Types

A total of 2,072 participants were evaluated and included in the study between January 2013 and 2020. Of these, 1,617 patients (78%) had no evidence of coronary plaques on their CT scans (Group 1). A further 307 patients (15%) presented with calcified plaques only (Group 2). The remaining 148 patients (7%) exhibited non-calcified/mixed plaques plaques, all of whom had at least one conventional high-risk feature CCTA (LAP, PR or NRS) and/or the new CT-defined high-risk plaque CT-TCFA (Group 3).

Among the high-risk plaques, the most frequently observed feature was PR, which was present in 74 (50%) patients, while there were 66 (45%) plaques with LAP and 36 (24%) plaques with NRS. Additionally, 89 (60%) patients had at least one plaque exhibiting TCFA (Figure 19).

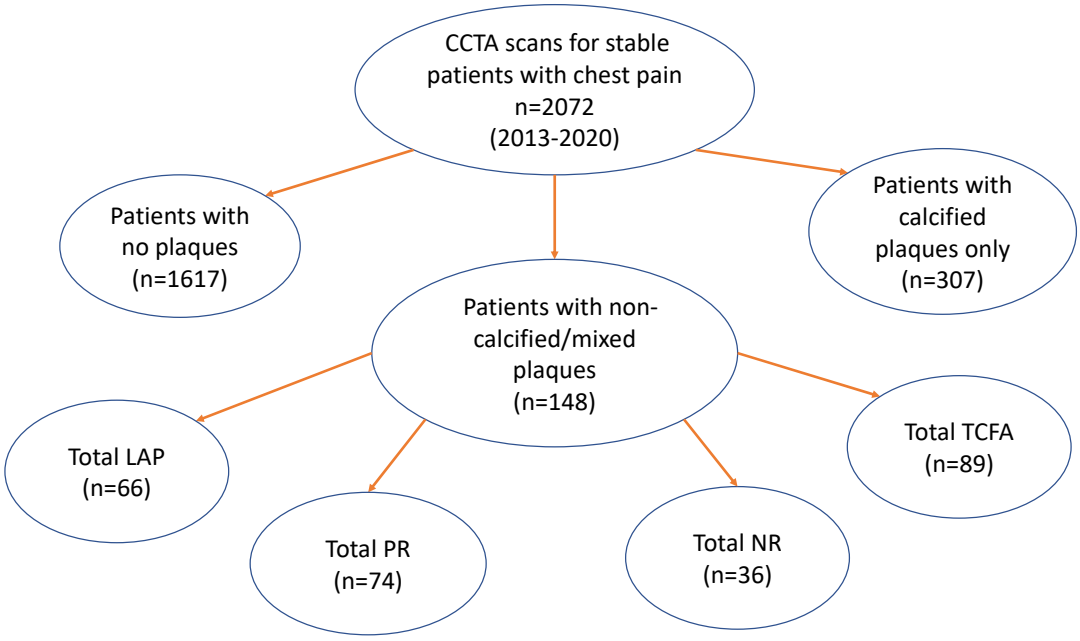


Figure 19: Classification of the CCTA findings of the study population. LAP = Low Attenuation Plaque, PR = Positive Remodeling, NRS = Napkin-Ring Sign, TCFA = thin-cap fibroatheroma

There were 95 (4.5%) patients with at least one vulnerable plaque as classified by conventional CT parameters as high-risk (either NRS or PR and LAP combined), and 101(5%) patients were considered 'vulnerable' using either conventional parameters or the new CT-TCFA definition. There were 46 (2%) patients with at least one obstructive plaque (luminal stenosis >50%). Table 11 summarises the characteristics of patients with different plaque types. Patients with no plaques were more likely to be younger than patients with calcified or non-calcified plaques (p value < 0.001). Patients with no plaques had lower baseline LDL-C values (2.66 ± 1.0 mmol/L) than those with calcified (2.89 ± 1.0 mmol/L) or non-calcified or mixed plaque (2.87 ± 1.0 mmol/L) (p = 0.009). Additionally, a history of heart failure with reduced ejection fraction (HFrEF) was more common in patients with no plaques when compared with the other two groups (p value = 0.02). All the other variables were comparable.

Table 11: Cohort characteristics of patients with different types of coronary plaques.

	Patients with no plaques (1617)	Patients with calcified plaques only (307)	Patients with non-calcified/mixed plaques (148)	p value
Age (years)	*61 ± 12*	*66 ± 12*	*65 ± 11*	*< 0.001*
Sex (male)	*959 (59%)*	*179 (58%)*	*92 (62%)*	*0.62*
Baseline LDL-C	*2.66 ± 1.0*	*2.89 ± 1.0*	*2.87 ± 1.0*	*0.009*
Baseline High-intensity statin	*149 (9%)*	*24 (8%)*	*13 (9%)*	*0.73*
BMI	*31 ± 8*	*30.6 ± 7*	*30 ± 7*	*0.33*
Hypertension	*69 (4%)*	*13 (4%)*	*7 (5%)*	*0.9*
HFrEF	*65 (4%)*	*8 (3%)*	*0*	*0.02*
Ischemic stroke	*15 (1%)*	*2 (1%)*	*0*	*0.45*
DM	*20 (1%)*	*7 (2%)*	*2 (1%)*	*0.36*

BMI: Body mass index, HFrEF: Heart failure with reduced ejection fraction, DM = Diabetes Millets.

5.4.2: Changes In Lipid Profile and Lipid-Modifying Therapies

A total of 1,185 patients (57% of the cohort) had documented LDL-C levels during the 3-year follow-up period post-CCTA. The overall mean LDL-C level significantly decreased from 2.76 ± 1.0 mmol/L in the year prior to the scan to 2.3 ± 0.9 mmol/L at the end of the follow-up period, representing an approximate 17% reduction across the study population.

The variation in LDL-C levels between the baseline and follow-up measurements differed by CCTA findings (Figure 20 & Table 12). In the group with normal CCTA, LDL-C levels decreased by 17%, from 2.66 ± 1.0 mmol/L to 2.2 ± 1.0 mmol/L after 3 years ($p < 0.001$). In the group with calcified plaques only, the reduction was 20%, from 2.89 ± 1.0 mmol/L to 2.3 ± 1.0 mmol/L ($p < 0.001$). In the group with non-calcified/mixed plaques, LDL-C levels showed a 34% decrease, from 2.89 ± 1.0 mmol/L to 1.9 ± 1.0 mmol/L ($p < 0.001$). There was no significant difference in LDL-C values between the different CCTA groups at baseline ($p = 0.8$).

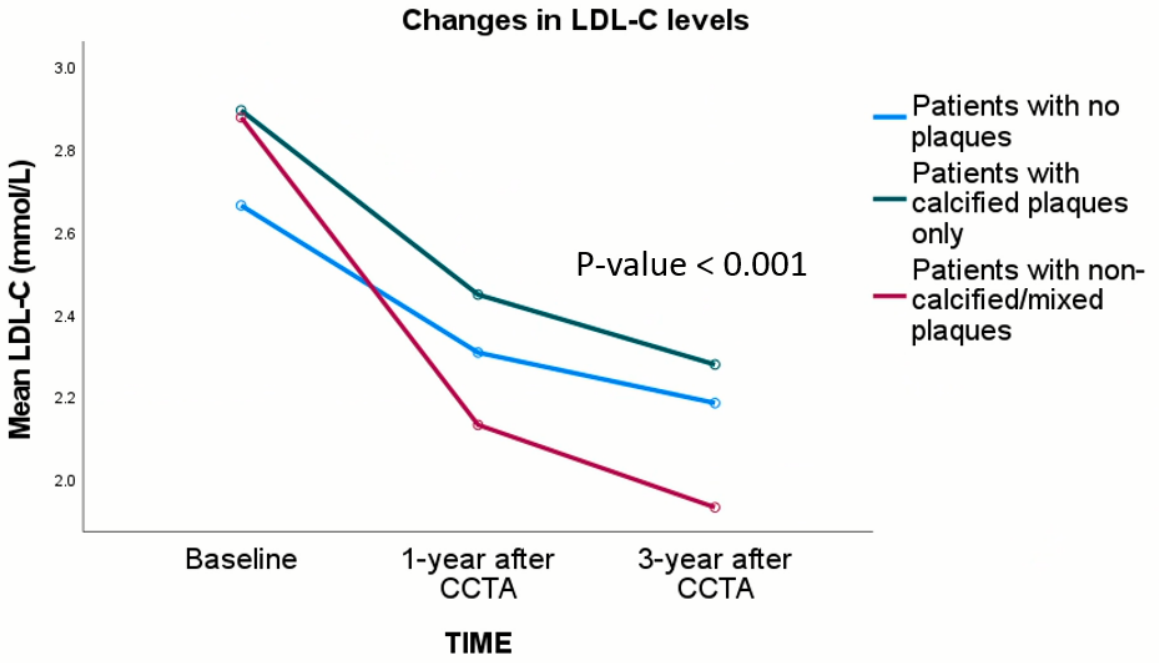


Figure 20: The difference in LDL-C levels pre and post-CCTA when divided into categories according to plaque morphology (No plaque, Calcified plaques only or Non-calcified/mixed plaques).

A total of 1,170 patients, comprising 56% of the cohort, had documented non-HDL-C levels during the 3-year follow-up period after CCTA. There was an overall reduction of approximately 6% in the mean non-HDL-C levels across the study population, decreasing from 3.5 ± 1.1 mmol/L in the year preceding the scan to 3.3 ± 1.1 mmol/L at the end of the 3-year follow-up period. The change in non-HDL-C levels between baseline and follow-up measurements varied according to CCTA findings (Figure 21 & Table 13). In Group 1, non-HDL-C levels decreased by 11%, from 3.5 ± 1.1 mmol/L to 3.1 ± 1.0 mmol/L (p = 0.01). In Group 2, there was an overall reduction of 14%, from 3.5 ± 1.4 mmol/L to 3.0 ± 1.1 mmol/L (p = 0.01). In Group 3, the reduction in non-HDL-C levels was most pronounced, with a 24% decrease from 3.7 ± 1.2 mmol/L to 2.8 ± 1.1 mmol/L (p = 0.01). Notably, there was no significant difference in non-HDL-C levels among the CCTA groups at baseline (p = 0.3).

With regards to lipid-modifying therapy, there was no significant difference in the prescription of high-intensity statins (defined as Atorvastatin ≥40 mg/day or Rosuvastatin ≥20 mg/day) among

the CCTA groups at baseline: 149 patients (9%) with no plaques, 24 patients (8%) with calcified plaques only, and 13 patients (9%) with non-calcified or mixed plaques (p = 0.7). However, over the three-year period following CCTA, the number of patients on high-intensity statins increased significantly in some groups. Specifically, prescriptions increased to 199 patients (12%) in the no plaque group , 30 patients (10%) in the calcified plaque group, and 31 patients (21%) in the non-calcified or mixed plaque group (p = 0.003; Figure 22)

Table 12: Baseline LDL-C and reduction according to CCTA plaque morphology.

Plaque Morphology	***LDL-C baseline (mmol/L)***	***LDL-C 1 year post CCTA***	***LDL-C 3 year Post CCTA***	***Reduction from baseline***
No Plaques	*2.66 ± 1.0*	*2.3 ± 1.0*	*2.2 ± 1.0*	*17% (p < 0.001)*
Calcified Plaques only	*2.89 ± 1.0*	*2.45 ± 1.0*	*2.3 ± 1.0*	*20% (p < 0.001)*
Non-calcified/ mixed plaques	*2.87 ± 1.0*	*2.33 ± 1.0*	*1.9 ± 1.0*	*34% (p < 0.001)*

5.4.3: Changes in HbA1c Levels

In total, 1,184 patients (57% of the cohort) had documented HbA1c during the 3-year follow-up period post-CCTA. The overall mean HbA1c decreased significantly from 43 ± 14 in the year prior to the CCTA to 41 ± 11 at the end of the follow-up period (p < 0.001). There was no variation in HbA1c reduction according to CCTA findings (Figure 23).

In group 1, HbA1c levels decreased by 4%, from 46 ± 16 mmol/mol to 44 ± 13 mmol/mol after 3 years . In the group 2, the reduction was 8%, from 48 ± 16 mmol/mol to 44.5 ± 12 mmol/mol. In the group 3, HbA1c levels showed a 6% decrease, from 47 ± 16 mmol/mol to 43.7 ± 11 mmol/mol (p = 0.2).

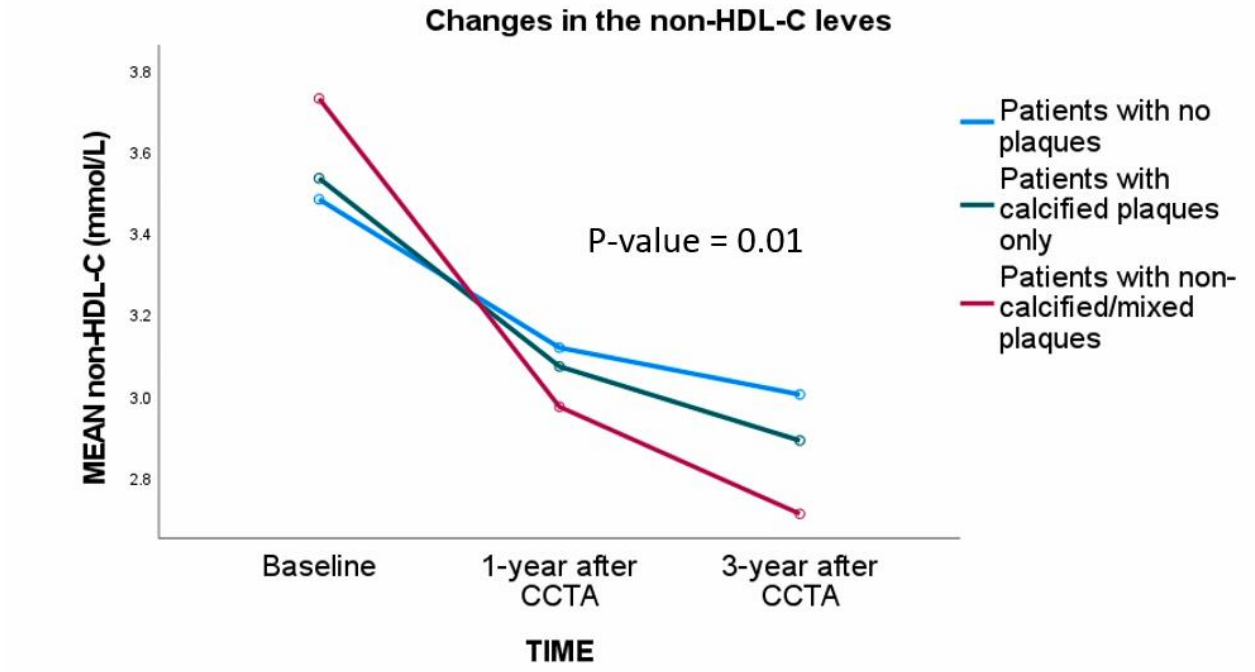


Figure 21: The difference of non-HDL-C levels pre and post-CCTA when divided into categories according to plaque morphology (No plaque, Calcified plaques only or Non-calcified/mixed plaque).

5.4.4: Changes in Blood Pressure Levels

In total, 1,629 (79%) patients had at least one recorded BP reading during the 3-year follow-up period. The overall mean systolic and diastolic blood pressure decreased significantly from 130 ± 17 mmHg and 78 ± 11 mmHg in the year prior to the scan to 121 ± 17 mmHg and 74 ± 11, respectively, at the end of the follow-up period ($p < 0.001$).

The variation in blood pressure levels between the baseline and follow-up measurements didn't significantly differ by CCTA findings (Figure 24).

5.4.5: Plaque-Based Analysis of CCTA Findings Associated with MACE Survival

I analysed the survival outcomes over a mean follow-up period of three years. Among the 2,027 patients included in the follow-up cohort, MACE occurred in 51 individuals (2.5%). These events comprised seven deaths, 31 non-fatal strokes, and 13 urgent coronary revascularisations.

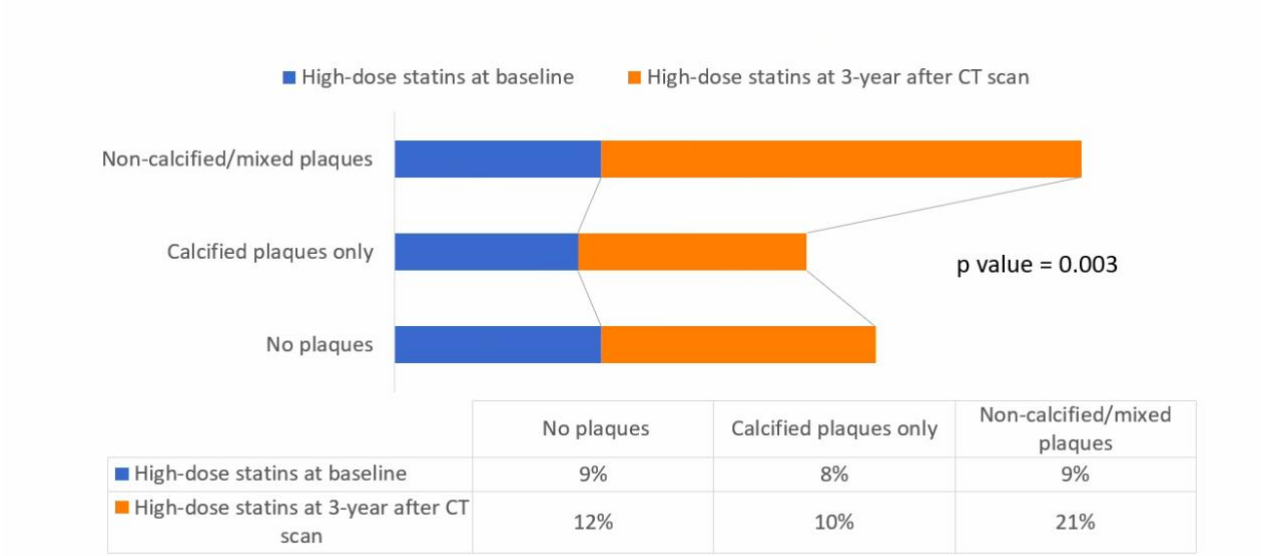
When stratified by plaque type, 38 patients (2.0%) in the group with no detectable plaques experienced MACE, compared to 8 patients (2.6%) in the group with calcified-only plaques and 5 patients (3.0%) in the group with non-calcified or mixed plaques. There were no statistically significant differences in MACE rates among the three groups, as illustrated in Figure 25. However, it is noteworthy that patients with the non-calcified/mixed plaque tended to experience MACE events earlier in the follow-up period compared to those in the other groups.

Table 13: Baseline non-HDL-C and reduction according to CCTA plaque morphology.

Plaque Morphology	***non-HDL-C baseline (mmol/L)***	***non-HDL-C 1 year post CCTA***	***non-HDL-C 3 year Post CCTA***	***Reduction from baseline***
No Plaques	*3.5 ± 1.1*	*3.2 ± 1.2*	*3.1 ± 1.0*	*11% (p = 0.01)*
Calcified Plaques only	*3.5 ± 1.4*	*3.1 ± 1.1*	*3.0 ± 1.1*	*14% (p = 0.01)*
Non-calcified/ mixed plaques	*3.7 ± 1.2*	*2.9 ± 1.1*	*2.8 ± 1.1*	*24% (p = 0.01)*

5.5: Discussion

In this real-world study, I assessed how CCTA results influenced the optimisation of CAD risk factors and the use of drug therapies. Specifically, I analysed changes in lipid profiles, HbA1c levels, and blood pressure measurements over 3 years following the CCTA. Evaluating this impact on clinical management is essential, as optimising risk factors is directly linked to improved patient prognosis.[269,270]



	No plaques	Calcified plaques only	Non-calcified/mixed plaques
High-dose statins at baseline	9%	8%	9%
High-dose statins at 3-year after CT scan	12%	10%	21%

Figure 22: The difference between High-intensity statins prescriptions pre and post-CCTA when divided into categories according to plaque morphology (No plaque, Calcified plaques only or Non-calcified/mixed plaques). High-dose statins: Atorvastatin ≥40 mg/day or Rosuvastatin ≥20 mg/day

I found that patients who have non-calcified plaques with high-risk features on CCTA were the ones who receive the most intensification to their risk factors compared to others with no or calcified plaques.

In the 2019 guidance from the ESC, recommended lipid targets for primary prevention are stratified based on cardiovascular risk, with LDL-C levels ranging from 3.0 mmol/L for low-risk individuals to 1.4 mmol/L for those at high risk. For non-HDL-C, the target levels range from 3.4 mmol/L in moderate-risk patients to 2.2 mmol/L in high-risk patients.[150] This study demonstrated adherence to these targets, as all patients experienced reductions in both LDL-C and non-HDL-C levels over the 3-year follow-up period. Notably, patients with high-risk plaque features saw the most significant decreases compared to baseline, with LDL-C and non-HDL-C reductions of 34% and 27%, respectively ($p < 0.001$).

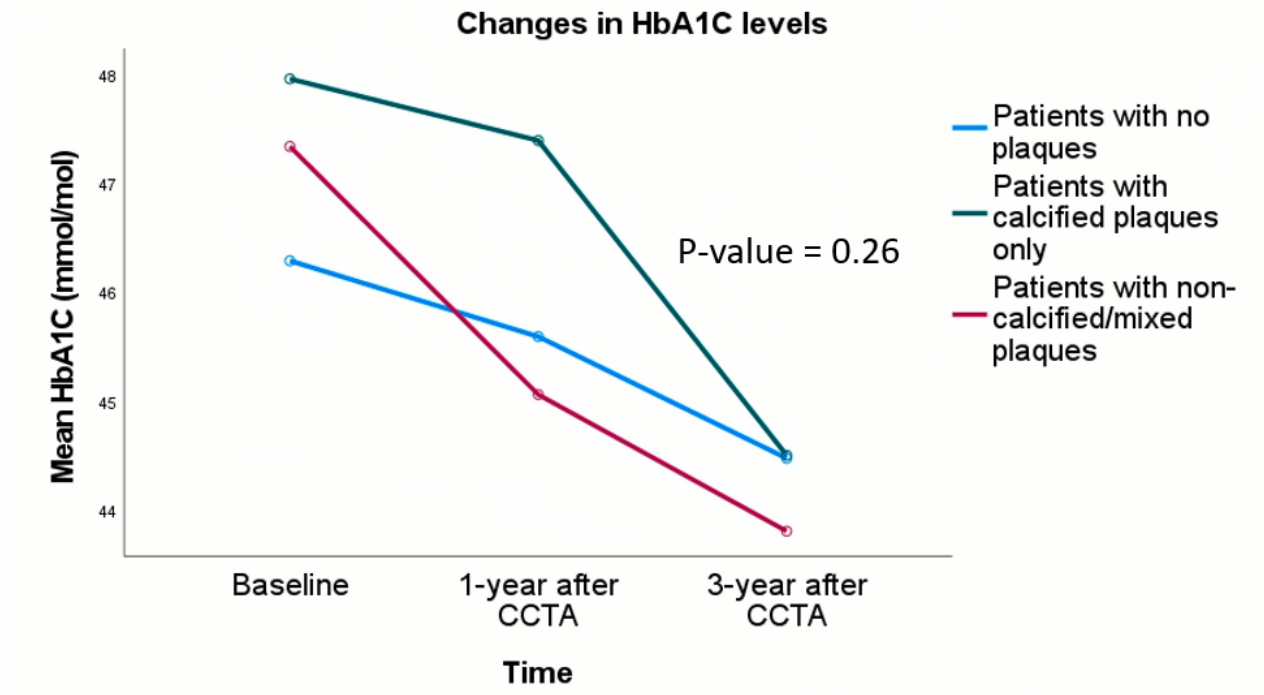


Figure 23: The difference in HbA1c levels pre and post-CCTA when divided into categories according to plaque morphology (No plaque, Calcified plaques only or Non-calcified/mixed plaques).

Moreover, these high-risk patients were the most likely to be prescribed and maintained on high-intensity statin therapy throughout the 3 years.

The ESC guidelines advocate optimal glycaemic control with near-normal HbA1c level of <7.0% (<53 mmol/mol) to reduce vascular complications and even stricter goals [6.0–6.5% (42–48 mmol/mol)] for younger patients without evidence of cardiovascular disease[175]. In this study, the mean HbA1c at the baseline was 43 ± 14 mmol/mol, which was reduced by 5% at the end of the follow-up period to 41 ± 11 mmol/mol. However, no significant differences in HbA1c levels were observed among the three groups. This may be due to the inclusion of mean HbA1c values across all participants, including those without diabetes, given that diabetic patients comprised only a small proportion of the whole cohort (1.4%). Similarly, there was a trend towards lower blood pressure after 3 years, but no significant difference across the study groups. One explanation for this is that patients would have been prescribed the guideline-recommended anti-anginal agents,

including beta blockers and calcium channel blockers, as well as other medications which also have anti-hypertensive properties.

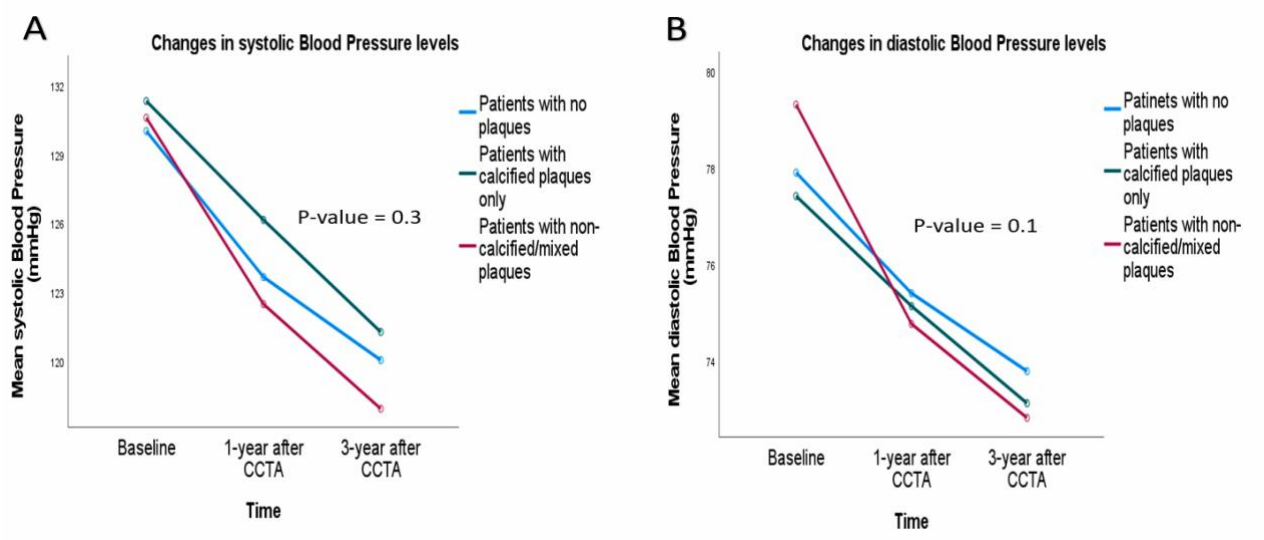


Figure 24: The difference in systolic (A) and diastolic (B) Blood pressure measurements pre and post-CCTA depending on plaque morphology (No plaque, Calcified plaques only or Non-calcified/mixed plaques).

Despite the observed trend toward a higher and an early incidence of MACE in the group with high-risk plaques, there was no statistically significant difference in the overall MACE events among the three groups. This lack of difference may suggest that the stabilisation of those plaques was achieved through optimal risk factor management in group 3. Such tight control of modifiable risk factors, including lipid profile, HbA1c, and blood pressure, might have mitigated the anticipated adverse outcomes typically associated with these high-risk plaques. This is in keeping with the 10-year outcome data from the SCOT-HEART trial which showed a continuous reduction in MACE, predominately non-fatal MIs, for CCTA based care despite no difference in the use of invasive coronary angiography or coronary revascularisation.[271]

These results also mirror other studies from different countries which stratified patients according to coronary luminal stenosis on CCTA[272–274]. Naue et al. investigated the impact of CCTA findings on clinical decision-making, specifically through the prescription of cardiovascular medications and their effect on lipid profiles. Their study demonstrated that patients with

obstructive CAD (≥50% stenosis) had the lowest cholesterol levels and were most frequently prescribed antiplatelet agents and lipid-lowering therapies.[273] Similarly, in 1,125 consecutive patients without known CAD, Cheezum et al. showed that CAD presence and severity were independently associated with increased aspirin, statin, and BP medication use rates.[274] These studies traditionally relied mostly on luminal stenosis to identify high-risk patients. However, emerging evidence suggests that plaque vulnerability, rather than the degree of stenosis, is the key factor predisposing to cardiac events.[275]

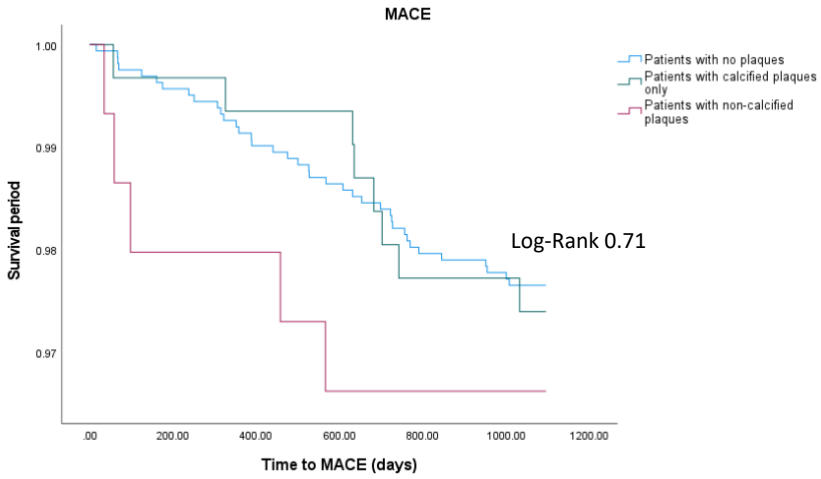


Figure 25: Kaplan-Meier Curve for MACE events between the three patient groups (No plaque, Calcified plaques only or Non-calcified/mixed plaques).

The recently published PREVENT (Preventive Coronary Intervention on Stenosis With Functionally Insignificant Vulnerable Plaque) study highlighted that coronary lesions that did not cause significant flow limitation (fractional flow reserve >0.80) but exhibited vulnerable characteristics on intra-coronary imaging were the most likely to rupture, leading to future events.[276]

The clinical importance of conventional CT high-risk plaque features, particularly the presence of LAP, PR and NRS, is well established.[85,108,200] Furthermore, quantitative plaque metrics, such as total plaque volume, non-calcified plaque volume, and low-attenuation plaque volume, offer additional prognostic insights.[253,254] A subgroup analysis of the ICONIC (Incident Coronary Syndromes Identified By Computed Tomography) study demonstrated that CT-defined necrotic core and fibrofatty plaque volumes were significantly associated with future cardiac events, independent of lesion stenosis severity.[255]

Additionally, the introduction of CT plaque 'colour mapping' – CT-TCFA, has enhanced the identification of plaque vulnerability. This technique has shown better inter-observer reliability, improving diagnostic accuracy even among less experienced CT reporters.[114]

While this study does not develop a formal risk prediction model, it provides important insights into how coronary CT angiography can refine cardiovascular risk assessment in clinical practice. Specifically, the identification of high-risk plaque features offers incremental information beyond traditional risk factors by capturing plaque vulnerability rather than relying solely on clinical characteristics.

This additional layer of risk stratification appears to influence clinician behaviour, as demonstrated by the observed intensification of lipid-lowering therapy and greater reductions in LDL-C among patients with high-risk plaque features. In this context, CCTA-derived plaque assessment may be considered a tool for personalised risk assessment, enabling clinicians to identify patients who may benefit from more aggressive preventive strategies despite otherwise low or intermediate estimated risk.

These findings therefore support the concept that advanced imaging can bridge the gap between population-based risk models and patient-specific disease biology, contributing to a more individualised approach to cardiovascular prevention.

5.6: Study Strengths and Limitations

The major strength of this study is the use of a large, nationwide sample owing to the data-linkage nature of the SAIL database. It is clinically relevant, representative data that is directly used by clinicians and can be used to optimise relevant upstream decision-making.

Nevertheless, several limitations should be acknowledged. The observational design introduces variability in follow-up intervals for post-test risk factors, reflecting real-world clinical practice but also opening the possibility of temporal biases. Furthermore, the extended follow-up duration of three years may have introduced additional confounding influences, such as changes in medication use, adverse effects, or evolving treatment guidelines.

The low representation of patients with diabetes may reflect the NICE guidelines in effect at the time the scans were performed. At that point, CCTA was primarily recommended for individuals with a low pre-test probability of CAD—a group that typically excluded patients with diabetes due to their inherently higher cardiovascular risk.[277]

Furthermore, unmeasured variables, such as medication adherence, dosage, and other potential confounders like socioeconomic status, could not be assessed. While it is unlikely that adjusting for these factors would significantly alter the conclusions, their omission should be acknowledged.

The relatively low rate of MACE observed in this study likely reflects the low-risk nature of the study population, as well as the relatively short duration of follow-up. As a result, the study was not powered to detect differences in clinical outcomes between plaque phenotype groups. Importantly, the absence of a statistically significant difference in outcomes should not be interpreted as a lack of clinical relevance. Instead, the findings highlight that CCTA-derived plaque characteristics may influence clinician behaviour and risk factor optimisation prior to the occurrence of clinical events. This is supported by the observed intensification of lipid-lowering therapy and greater reductions in LDL-C among patients with high-risk plaque features.

Longer-term follow-up and larger, prospective studies will be required to determine whether these changes translate into measurable reductions in cardiovascular events.

Despite these limitations, the findings provide a valuable snapshot of how CCTA results influence physician decision-making and current patient management practices in Welsh clinical settings.

5.7: Conclusions

CCTA led to improved cardiovascular risk factor control in this real-world cohort. In particular, patients with non-calcified or mixed plaque received a doubling of high-intensity statin prescriptions and subsequent greatest LDL-C and non-HDL-C reductions, sustained at 3 years. This may have led to some mitigation of MACE events in this group later in the follow-up period.

CHAPTER 6: Coronary Tree Vulnerable Plaque Distribution And CT Analysis

6.1: Introduction

ACS remains a leading cause of morbidity and mortality globally.[266] For decades, pathological and foundational studies have focused on the concept of 'vulnerable plaque' as a primary contributor to ACS.[32,39,42] Vulnerable plaques are characterised by their higher propensity to rupture, leading to acute thrombotic occlusion.[26]

Given that patients with CAD often harbour multiple plaques, it is evident that the majority of these plaques will not precipitate an acute event. Efforts to mitigate the risk of acute rupture have focused on both patient-specific diagnostic strategies and systemic preventive measures. These include optimal control of blood pressure and diabetes, behavioural modifications such as smoking cessation, regular physical activity, and stress management.[278]

While major cardiovascular risk factors are well-established, the location and prevalence of vulnerable coronary plaques across different risk cohorts remain an area of active research.

In addition to patient-centred approaches, advancements in imaging technologies now enable the direct identification of vulnerable plaques through both invasive and non-invasive techniques, including IVUS, OCT, and CCTA.[108,279] Once identified, evidence suggests that these unstable plaques could be modified or stabilised via percutaneous coronary interventions (PCI).[276]

Our current understanding of the structural characteristics that render an atherosclerotic plaque prone to thrombosis—such as a thin fibrous cap, large lipid core, and heightened inflammatory activity—derives primarily from histopathological studies.[26,40] However, the feasibility of accurately measuring these features in vivo to identify vulnerability before rupture remains unproven.

6.2: Aims

To assess the distribution and anatomical patterns of vulnerable plaques within the coronary tree using advanced CT plaque analysis among three patient cohorts: stable patients with a low

likelihood of coronary artery disease, patients with chest pain and a high likelihood of coronary artery disease and very high-risk patients who had had a cardiac event.

6.3: Methods

6.3.1: Participants

I conducted a retrospective observational study involving three cohorts of patients who underwent CCTA at different timeframes.

These cohorts were drawn from the studies described in Chapters 4, 5, and 7 of this thesis.

Group 1: 2,072 stable patients with atypical chest pain were recruited from outpatient chest pain assessment clinics and underwent CCTA in Wales, UK, between January 2013 and December 2019.

Group 2: 87 symptomatic chest pain patients thought to have a high likelihood of coronary artery disease were recruited from outpatient chest pain assessment clinics and underwent CCTA at the Royal Papworth Hospital between December 2007 and June 2008.

Group 3: Between September 2022 and March 2024, 100 patients with a recent history of PCI following ACS were recruited from the cardiology centre at Swansea Bay University Hospital and underwent CCTA 1 month after the hospital discharge.

All patients with a diagnosis of coronary artery disease underwent routine clinical treatment, including medical therapy and risk factor modification, in keeping with clinical guidelines at the time.

Further details regarding recruitment processes, ethical approvals, inclusion/exclusion criteria, participant matching, and use of primary study populations are comprehensively described in Chapter 2: Methodology.

6.3.2: CCTA Acquisition and Analysis

All patients underwent a prospective-gated CT scan. Details on CT acquisition, as well as qualitative and quantitative analysis, are described extensively in Chapter 2.

I classified plaques as vulnerable if they had (positive remodelling and low attenuation combined or napkin ring sign), or the new CT-TCFA definition as described previously. Those signs were found to be strongly associated with future coronary event risk in prospective studies.[108,114,200,201]

I then determined the frequency, location and patient characteristics associated with these different plaque types.

6.3.3: Statistical Analysis

Categorical variables are presented as numbers and percentages, while continuous variables are shown as mean ± standard deviation. The chi-square test was used to compare categorical variables.

6.4: Results

6.4.1: Patient Characteristics

A total of 2,214 patients were included in the analysis. The average age of the cohort was 63 years, with the majority being male (70%). Among the study groups, patients in Group 3—those with a documented history of CAD—demonstrated the highest prevalence of diabetes mellitus, hypertension, and smoking, as detailed in Table 14.

Across the entire cohort, 998 coronary plaques were identified, of which 332 (33%) exhibited features of vulnerability. Group 3 showed the highest burden of vulnerable plaques, with an average of 1.5 vulnerable plaques per patient, compared to 0.9 in Group 2 and 0.05 in Group 1.

Details of the distribution and characteristics of vulnerable plaque features are provided in Figure 26, offering a comprehensive breakdown of these findings.

Table 14: patient characteristics of each group.

	Group 1 (N = 2027)	***Group 2 (N = 87)***	***Group 3 (N = 100)***
Male	*1419 (70%)*	*58 (67%)*	*74 (74%)*
Age	*62 ± 12*	*63 ± 13*	*63 ± 9*
HTN	*89 (4%)*	*54 (62%)*	*24 (24%)*
DM	*67 (3%)*	*11 (13%)*	*31 (31%)*
Smokers/ex-smokers	*101 (5%)*	*6 (7%)*	*52 (52%)*
Hyperlipidaemia	*49 (2%)*	*28 (32%)*	*15 (15%)*
BMI	*30 ± 6*	*30 ± 6*	*31 ± 6*
FH	*608 (30%)*	*39 (45%)*	*48 (48%)*

HTN: Hypertension, DM: Diabetes Miletus, BMI: body mass index, FH: Family history

6.4.2: Plaque Distributions

Figure 27, Figure 28 and Figure 29 provide a detailed depiction of the distribution patterns of both total and vulnerable plaques within the coronary tree across the three distinct patient cohorts included in the study. The analysis underscores that the majority of vulnerable plaques were predominantly localised in the proximal segments of the major coronary arteries, specifically the Left Anterior Descending (LAD) artery and the Right Coronary Artery (RCA), with a smaller proportion observed in the Left Circumflex (LCx) artery.

In group 1, the proximal segment of the LAD artery exhibited the highest concentration of vulnerable plaques, which accounted for 22% of all vulnerable plaques identified in this cohort. This finding highlights the LAD as the primary site of plaque vulnerability in this group.

In group 2, the distribution pattern shifted, with the proximal RCA emerging as the coronary segment with the highest burden of vulnerable plaques. These plaques represented 24% of the total vulnerable plaques in this group.

In group 3, the distribution of vulnerable plaques was more balanced between the proximal segments of the LAD, RCA, and LCX, with each site contributing approximately 17% to the total number of vulnerable plaques in this cohort.

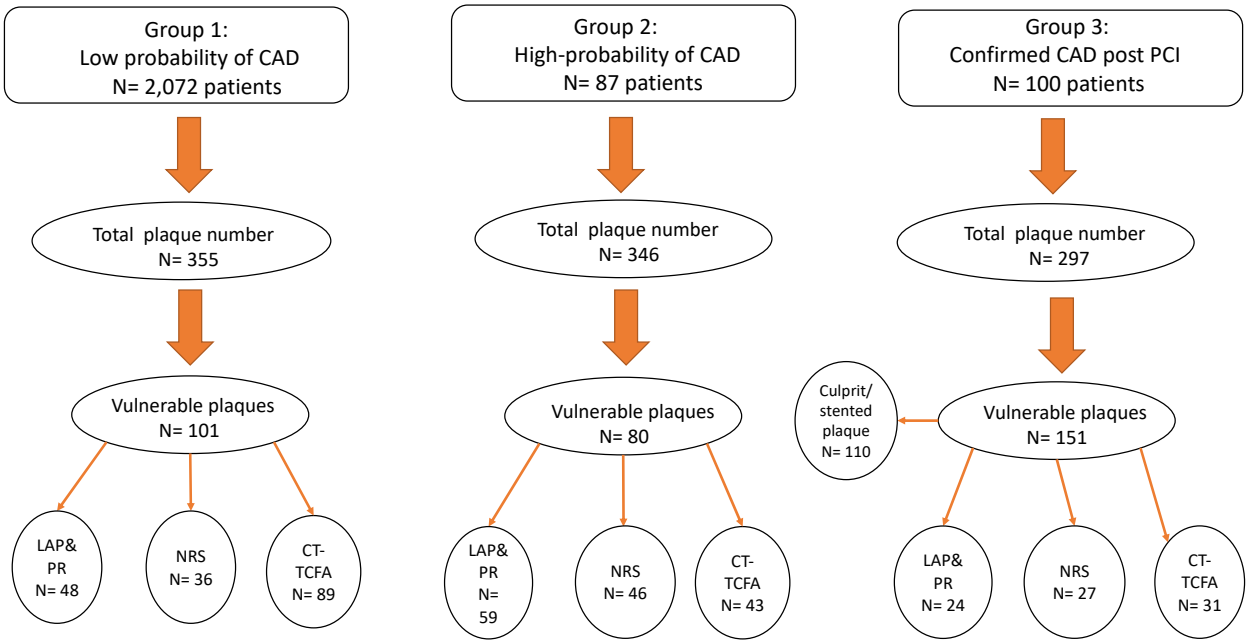


Figure 26:CCTA findings of the study population. LAP = Low Attenuation Plaque, PR = Positive Remodeling, NRS = Napkin-Ring Sign, TCFA = thin-cap fibroatheroma

Across all cohorts, the left main stem (LM) consistently exhibited the lowest frequency of vulnerable plaques among the major epicardial coronary branches. Specifically, vulnerable plaques in the LM accounted for 4% of Group 1, were absent (0%) in Group 2, and constituted 6% in Group 3.

6.5: Discussion

This study provides an in-depth analysis of the geographical distribution of vulnerable plaques within the coronary tree in 3 different patient cohorts. Across all three cohorts, vulnerable plaques were most frequently located in the proximal segments of the coronary arteries, irrespective of overall clinical risk profile. This consistent spatial clustering suggests that plaque vulnerability may be influenced not only by patient-level risk factors but also by local haemodynamic and anatomical factors inherent to proximal coronary segments. Importantly, this pattern was observed even in patients with a low pre-test probability of coronary artery disease, indicating that proximal plaque vulnerability is a recurring anatomical phenomenon rather than a marker confined to high-risk populations.

This finding has practical implications for the interpretation of both CCTA and invasive coronary angiography. In situations where image quality is suboptimal—such as motion artefact, heavy calcification, limited contrast opacification, or incomplete vessel visualisation—heightened attention to proximal coronary segments may be particularly informative. Awareness that vulnerable plaques tend to cluster proximally may assist clinicians in contextualising equivocal findings and in guiding further investigation or management decisions.

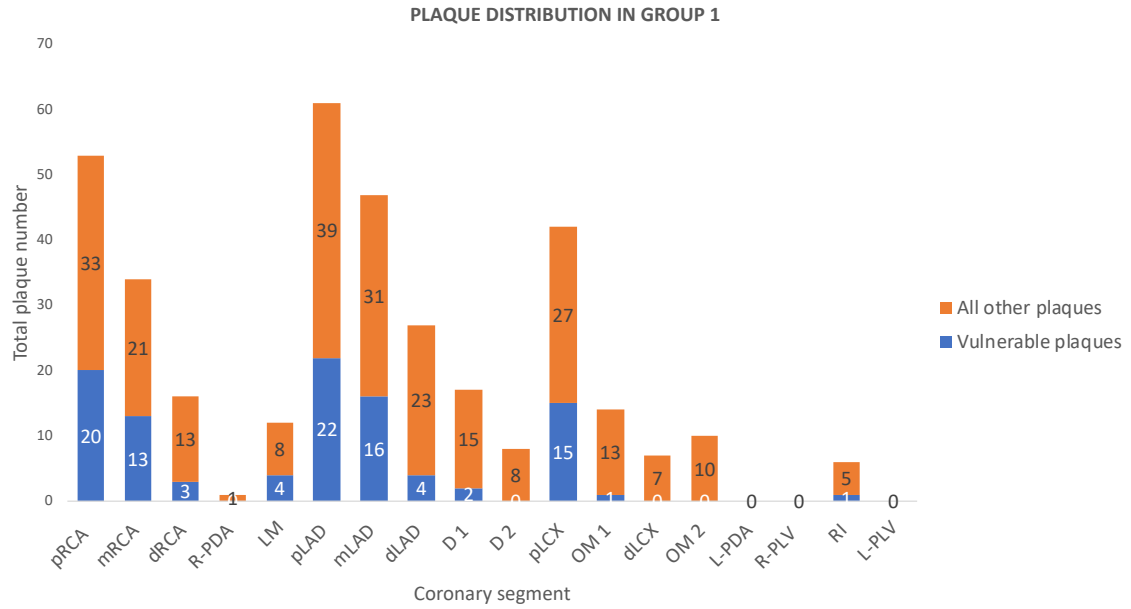


Figure 27: Distribution of atherosclerotic plaques in Coronary Artery Trees in Group 1. P = proximal, m = mid, d = distal, RCA = right coronary artery, R-PDA = right posterior descending artery, LM = left main, LAD = left anterior descending, D = diagonal, LCX = left circumflex, OM = obtuse marginal, L-PDA = left posterior descending artery, R-PLV = right posterior left ventricular, RI = ramus intermedius, and L-PLV = left posterior left ventricular.

Acute coronary events are precipitated by the erosion or rupture of vulnerable plaques.[27] This spatially specific clustering aligns with the concept of a targeted approach to both diagnostic and therapeutic strategies. By focusing on these high-risk coronary segments, clinicians can better identify vulnerable plaques and implement preventive measures to reduce the risk of plaque rupture and subsequent cardiac events. The study underscores the potential benefits of integrating this localised understanding into clinical practices to enhance patient outcomes.

These results also mirror previous findings from invasive angiography and post-mortem studies of the location of plaques deemed responsible for myocardial infarctions.[27,280,281] In 208 patients who presented with ST-segment elevation myocardial infarctions (STEMIs), Wang et al. found that acute coronary occlusions tend to cluster in predictable 'hot spots' within the proximal third of the coronary arteries.[280] Additionally, numerous CCTA studies have consistently reported LAD susceptibility to atherosclerosis.

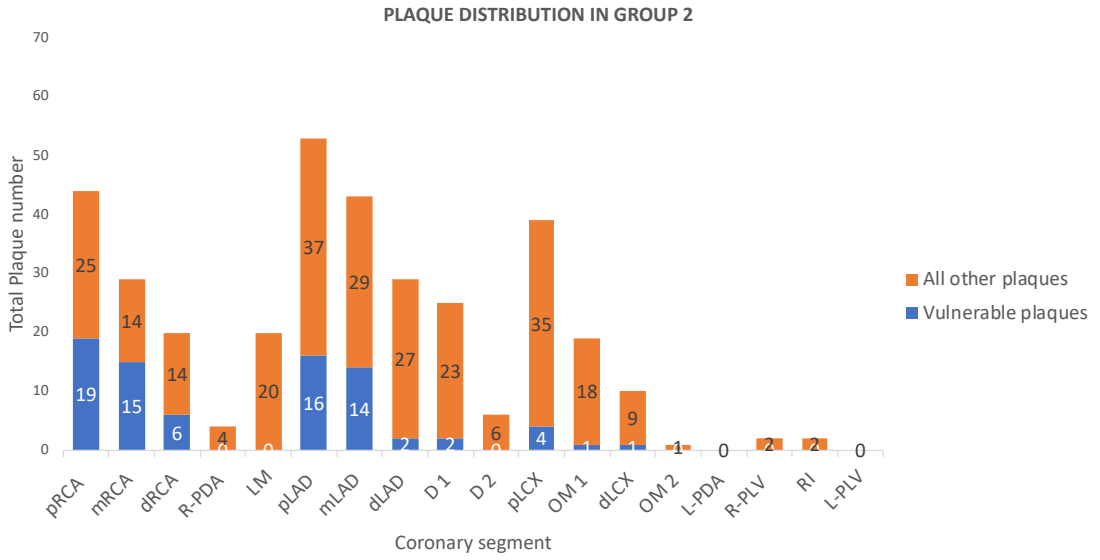


Figure 28: Distribution of atherosclerotic plaques in Coronary Artery Trees in Group 2. P = proximal, m = mid, d = distal, RCA = right coronary artery, R-PDA = right posterior descending artery, LM = left main, LAD = left anterior descending, D = diagonal, LCX = left circumflex, OM = obtuse marginal, L-PDA = left posterior descending artery, R-PLV = right posterior left ventricular, RI = ramus intermedius, and L-PLV = left posterior left ventricular.

Of the 30,154 participants in the SCAPIS (Swedish Cardiopulmonary Bioimage Study) cohort, in the early phase of atherosclerosis, defined as a disease of only one coronary segment, the proximal LAD was most commonly involved.[281] In both patients with diabetes and renal diseases, the LAD was the most frequently involved vessel, and the LM was the least affected.[282,283] When considered alongside demographic factors and disease-related risks that contribute to myocardial infarctions, This spatial model of vulnerable plaque distribution has the potential to significantly refine risk estimation for coronary events. By providing a more precise understanding of where vulnerable plaques are most likely to form, this model could enhance the targeting of both conventional and emerging preventive strategies, ensuring they are more effectively applied.

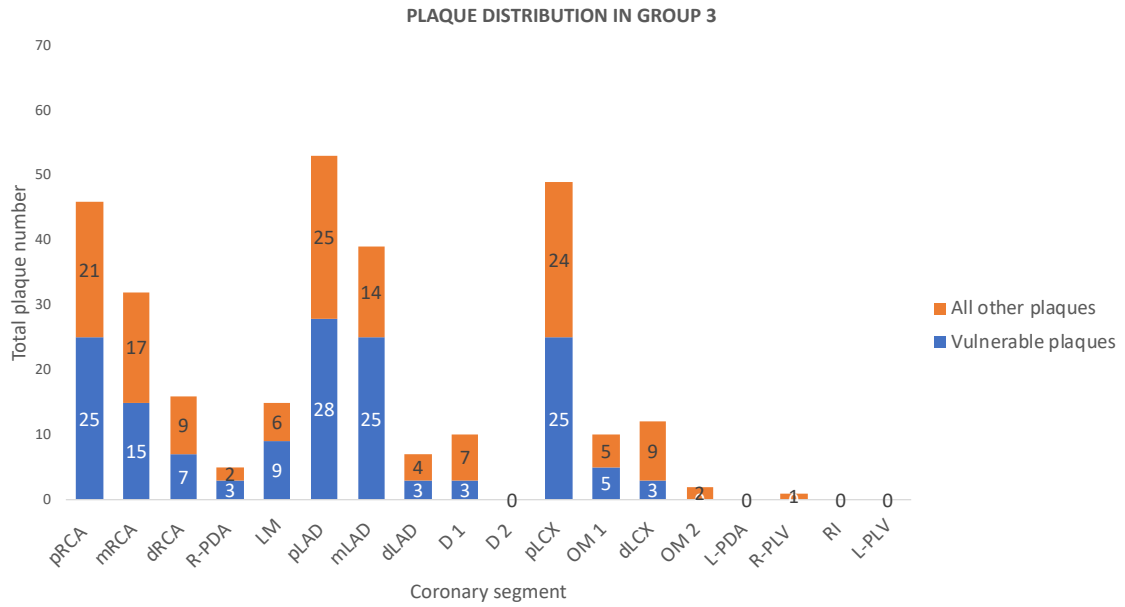


Figure 29: Distribution of atherosclerotic plaques in Coronary Artery Trees in Group 3. P = proximal, m = mid, d = distal, RCA = right coronary artery, R-PDA = right posterior descending artery, LM = left main, LAD = left anterior descending, D = diagonal, LCX = left circumflex, OM =obtuse marginal, L-PDA = left posterior descending artery, R-PLV = right posterior left ventricular, RI = ramus intermedius, and L-PLV = left posterior left ventricular.

Furthermore, the observed clustering of vulnerable plaques in specific coronary segments highlights an opportunity to develop and evaluate novel experimental interventions. These could include the use of standard or modified drug-eluting stents strategically deployed to stabilise plaques and prevent rupture. Such an approach could serve as the basis for designing robust clinical trials aimed at reducing the incidence of acute coronary events by addressing the plaques most likely to cause harm.

Nevertheless, this analysis remains exploratory and hypothesis-generating. The observed distribution patterns should be interpreted cautiously given overlapping clinical characteristics between cohorts and the absence of outcome validation. Further studies integrating multimodal imaging, haemodynamic assessment, and prospective outcome data are required to determine whether proximal plaque vulnerability confers incremental prognostic value beyond established anatomical and clinical risk markers.

6.6: Limitations

This study data were derived from three distinct cohorts of patients, collected at different time points and from various institutions. This heterogeneity could introduce potential bias. However, it is noteworthy that findings from trials with even more diverse populations were broadly consistent with this study.[280]

While the overall sample size was adequate, smaller subgroup sizes—particularly those involving patients with high-risk plaque features—limit the statistical power and generalizability of the findings.

Moreover, the above plaque morphology and location analysis relied solely on CCTA as the imaging modality. This approach may have provided only a partial characterisation of plaque burden and features. Utilising multimodal imaging could offer a more comprehensive understanding of plaque morphology and vulnerability.

Furthermore, the observed lower prevalence of vulnerable plaques in the left main artery was unexpected. However, this may reflect an underestimation due to the often-fatal nature of left main thromboses.

Finally, the study did not account for variability in the intensity of risk factor management, such as lipid-lowering or antihypertensive therapies, across the cohorts. Differences in these factors could influence plaque stability and, consequently, clinical outcomes.

6.7: Conclusion

This exploratory analysis demonstrates that vulnerable plaques are consistently clustered within proximal coronary segments, irrespective of overall patient risk profile. This finding has potential clinical implications, particularly in the interpretation of CCTA or invasive angiography in cases of suboptimal image quality. These results should be considered hypothesis-generating and require validation in larger, prospective studies.

CHAPTER 7: Potential Impact Of Oral Semaglutide On Coronary Artery Disease Progression Following Acute Coronary Syndrome: The POST-ACS Trial, Study Design and Interim Baseline Characteristics (Outcomes Pending)

Part of this Chapter is based on the following published article:

Salem, A. M. et al. Glucagon-like peptide-1 receptor agonists as anti-inflammatory agents: A potential mode of cardiovascular benefits. Atherosclerosis (2022) *doi:10.1016/J.ATHEROSCLEROSIS.2022.05.010.*

7.1: Introduction

Over the past decade, significant advancements have been made in the development of novel anti-hyperglycemic agents, particularly GLP-1RAs. These agents have been shown to possess insulinotropic properties, enhancing the effects of incretin hormones[163]. Their mechanisms of action include stimulating insulin secretion from pancreatic β-cells in a glucose-dependent manner, modulating gut motility, promoting satiety, and inhibiting glucagon secretion from pancreatic α-cells, as illustrated in Figure 4 in Chapter 1.

Currently, GLP-1RAs are approved globally, including in Europe, for the management of T2DM. They are widely recognised for their efficacy in improving glycemic control by significantly decreasing HbA1c levels, all while minimising the risk of hypoglycemia.[284]

In addition to their glycemic benefits, several large-scale cardiovascular outcome trials have assessed the impact of GLP-1RAs on cardiovascular events in patients with T2DM. These studies have demonstrated a notable reduction in MACE, including cardiovascular death, non-fatal MI, and non-fatal stroke.[164–166] These findings underscore the dual metabolic and cardiovascular benefits of GLP-1RAs, making them a pivotal component of modern T2DM management strategies.

The mechanism of the cardioprotective action of GLP-1RAs is incompletely understood. They have pharmacodynamic effects on several cardiovascular risk factors (body weight, blood pressure and lipid profile)[285]; however, the Liraglutide effect on MACE in a subgroup analysis of the LEADER (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes) trial was independent of LDL-lowering.[164] The gradual divergence of the event curves in these trials suggests the cardiovascular benefit is due to a reduction in atherosclerotic-related events. Further research into the mechanisms of this benefit is identified as a key requirement.[175]

Vulnerable coronary plaques are found more commonly in patients with diabetes[286], and their presence greatly increases the risk of future events.[287] The GLP1-RA Liraglutide effects on

atherosclerotic plaque have been studied in murine animal models. It has been shown to promote plaque stability as well as inhibit the progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function.[288] However, the impact on the in-vivo atherosclerotic plaque in humans has not been studied.

Patients with diabetes who suffer ACS are at increased risk of adverse outcomes.[289] Whilst these patients potentially have the most benefit, they are the least studied in the cardiovascular outcome trials. In the ELIXA (Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome) study, Lixisenatide was non-inferior to placebo in patients with a previous ACS. Still, the drug was not initiated until 180 days post-event[290], hence missing any potential benefit in early initiation.

7.2: Aims and Hypothesis

I designed the POST-ACS trial to explore the potential impact of oral semaglutide on the progression of coronary artery disease following ACS, using CCTA as a non-invasive imaging biomarker.

The hypothesis is that compared to placebo, 1-year treatment with semaglutide will result in a regression of necrotic core within potentially vulnerable coronary plaques, which will be detected by the novel "plaque map" CCTA analysis non-invasively.

This study will provide important imaging-derived data and mechanistic insights to elucidate further the favourable clinical cardiovascular outcome data for GLP-1RA therapies, which is crucial to guiding physicians and potentially expanding their role into ACS settings in the future.

7.3: Methods

7.3.1: Trial Design and Participants Recruitment

The POST-ACS study is a randomised placebo-controlled trial evaluating the effect of semaglutide initiated in T2DM and pre-diabetes state patients admitted with ACS. However, there are two other ongoing semaglutide trials - SOUL (Semaglutide Cardiovascular Outcomes Trial in Patients With Type 2 Diabetes (clinicaltrial.gov: NCT03914326), which excludes patients within 60 days of ACS and the semaglutide treatment on coronary progression trial (clinicaltrials.gov: NCT03985384), which excludes patients within 90 days of ACS; The POST- ACS study will be the first study to evaluate the effect of early initiation of a GLP1-RA (30 days from index admission with ACS). We will also utilise Rybelsus (Semaglutide, Novo Nordisk), the first oral GLP-1RA, which has recently been released and shown a reduction in cardiovascular death compared with placebo.[291] This has a key advantage as oral medications are often preferable for patients than subcutaneous ones, with persistence more likely.[292]

I gained Ethics Committee permission (Wales Research Ethics Committee 1/Cardiff – Ref number 21/WA/0176) and The Medicines and Healthcare Products Regulatory Agency (Ref number CTA 35930/0005/001-0001) to initiate the trial. Both approvals have been added to the Supplementary materials at the end of this Chapter (Figure 31and Figure 32, respectively).

I enrolled one hundred forty participants admitted to the cardiac centre with ACS and had raised HbA1c level (>5.7%) in the trial and randomised them in a 1:1 blinded fashion to receive conventional therapy and initiation of oral semaglutide or conventional therapy and placebo OD. The drug was initiated 30 days after the ACS (index admission) following the resolution of all ischemic symptoms. All participants have had a CCTA with Plaque Map analysis to evaluate the presence of any potentially vulnerable plaques and to calculate the plaque burden and volume (including percentage necrotic core) at baseline (before drug initiation – 30 days post index admission) and following 12 months of treatment. In addition, to elucidate further any potential mechanisms for this, I looked at changes in markers of plaque initiation (Lipid profile, LpPLA2),

endothelial activation (MCP-1), plaque inflammation (hs-CRP, IL6, IL18, TNF, advanced glycation end-products), vulnerable transformation (vEGF, PAI-1, BMP-6) and measures of oxidative stress (Ox-LDL, TAOS, TBARs). In addition, I measured the changes in endothelial function and arterial stiffness using applanation tonometry the Vicorder (Skidmore Medical, UK) at baseline and following 12 months of treatment.

Participants have been followed up on regular interval periods post drug initiation at Joint Clinical Research Facility (JCRF) at Swansea University to provide support during the dose-escalation period and maximise compliance.

Site visits occurred more frequently during the first months of the trial to optimise treatment then through telephone consultations. Information on clinical progress, especially hospital readmission, medication compliance and further investigations was documented.

Figure 30 summarises the trial design.

Inclusion criteria

- Patients aged ≥18 years
- Patients with type II DM and pre-diabetic status (HbA1c ≥5.7% within 3 months of the index admission)
- Patients presented with a clinical diagnosis of ACS comprising detection of a rise and/or fall of cardiac troponin (cTn) with at least one value above the 99th percentile and with at least one of the following:
    1. Symptoms of acute myocardial ischemia;
    2. New ischemic electrocardiographic (ECG) changes (ST-T wave changes or new LBBB);
    3. Development of pathological Q waves;
    4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology;

5. Identification of a coronary thrombus by angiography, including intra-coronary imaging

Exclusion criteria

- Patient aged <18 years
- Type 1 DM
- Left ventricular ejection fraction <40%
- Heart failure is classified as being in New York Heart Association (NYHA) Class III-IV.
- A documented history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy.
- History of renal insufficiency with estimated glomerular filtration rate <30mL/min/1.73m^2
- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- History of treatment with GLP-1 within 90 days before screening
- Known or suspected hypersensitivity to semaglutide or related products.
- Female who is pregnant, breastfeeding or intends to become pregnant, or is of child-bearing potential and not using a highly effective contraceptive method.
- Current enrolment in any other clinical trial within 30 days from screening

7.3.2: Trial Drug

The Investigational Medicinal Products (IMP) is named oral semaglutide (Rybelsus®), a member of GLP-RAs and already has a marketing authorisation for the management of T2DM. The marketed Rybelsus® tablets come in 3, 7,14 mg strength and are produced with the tablet debossment '3', '7' or '14' on one side and 'NOVO' on the other side in 10 tablet blisters with coloured forming foil and print on lid foil.

In order to blind the product, a clinic variant of the marketed product was supplied. The clinic variant of oral semaglutide 3 mg, 7 mg, 14 mg and placebo are produced with the tablet

embossment ‘M8’ in 7 tablet blister packs with no colour on forming foil and no print on the lid foil. The differences have no impact on the stability.

The start dose for oral semaglutide is 3 mg once daily for 30 days. The 3 mg dose is intendedfor treatment initiation and is not sufficient for glycaemic control.

A follow-up fixed 30-day dose-escalation regimen was charted until reaching the treatment dose of 14 mg oral Semaglutide/ placebo OD, as illustrated in Table 15.

I assigned eligible participants a unique 3-digit patient number, which remained the same throughout the trial, and I then did the randomisation, assigned in a constant 1:1 allocation ratio to one of two arms:

Group A: Semaglutide + conventional therapy

Group B: placebo (same dose and administration route) + conventional therapy

All the participants and their care providers were blinded to the randomisation results they were assigned to.

All participants have had CCTA using the novel "Plaque Maps analysis" method at baseline (30 days post ACS event) and after 12 months of therapy initiation.

The 30-days dose-escalation interval was applied in order to mitigate the risk of gastrointestinal AEs.

Ideally, participants were asked to remain on the 14 mg dose level until the end of the treatment visit; however,dose reductions, extensions of dose escalation intervals and treatment pauses were allowed, e.g. if treatment with the trial product is associated with unacceptable AEs.

Any change to trial product dose, including date of change or discontinuation, was recorded throughout the trial.

7.3.3: Randomisation and Follow-up

I approached the eligible participants in the cardiac centre at Swansea Bay University Hospital and counselled them about the trial. All the participants were given a patient information sheet to read and were approached again after 24 hours for a final decision. When a participant agreed to participate, they were given an informed consent form (ICF) written in English to sign.

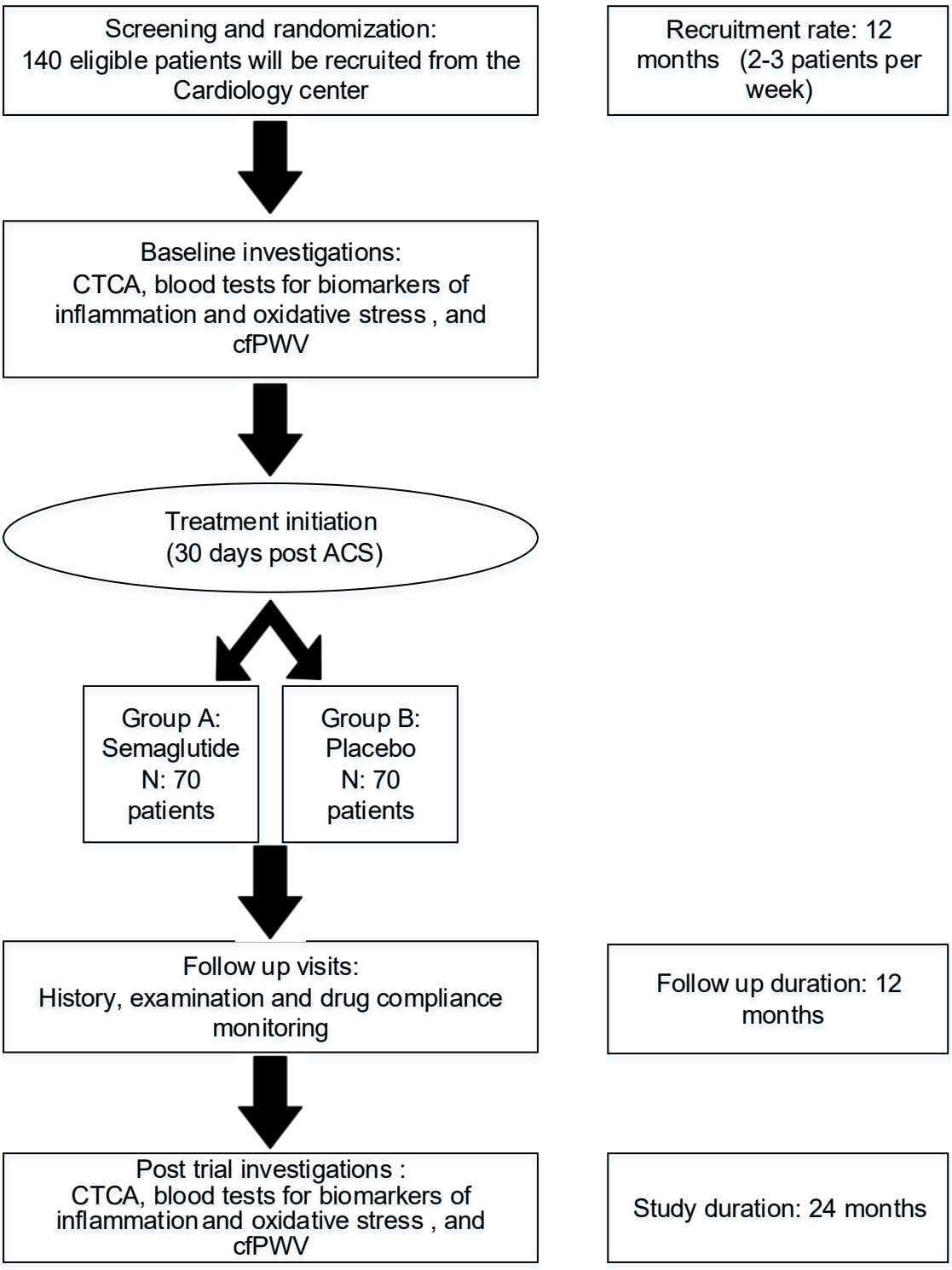


Figure 30: The POST-ACS study design. CCTA: Computed Tomography Coronary Angiography. cfPWV = Aortic carotid-femoral pulse wave velocity

I assigned eligible participants a unique 3-digit patient number , which remained the same throughout the trial, and I then did the randomisation, assigned in a constant 1:1 allocation ratio to one of two arms:

Group A: Semaglutide + conventional therapy

Group B: placebo (same dose and administration route) + conventional therapy

All the participants and their care providers were blinded to the randomisation results they were assigned to. All participants have had CCTA using the novel "Plaque Maps analysis" method at baseline (30 days post ACS event) and after 12 months of therapy initiation.

Table 15:Treatment and visit periods

Trial periods	***Screening***	***Treatment initiation***	***Dose escalation***	***Maintenance***
Visits in each Period	*Visit 0*	*Visit 1*	*Visit 2*	*Visit 3 to end of the trial*
Duration	*During index admission*	*30 days post-index admission*	*60 days post index admission*	*90 days post index admission*
Daily dose	**-**	*3 mg*	*7 mg*	*14 mg*

CCTA Imaging took place at the clinical imaging facility of the Institute of Life Science 2 (ILS2), Swansea University. The ILS2 is a purpose-built, fully equipped trials unit with a Siemens Somatom Definition AS CT Scanner. This facility provides a comfortable setting for trial patients to undergo state-of-the-art imaging by SOR-qualified radiographers without the constraints of a busy NHS clinical workflow.

Contrast-enhanced prospective ECG-gated images were acquired. In addition, the participants have had (non-fasting) blood samples performed to assess serum glucose, lipid profile and serum biomarkers for plaque initiation (Lipid profile, LpPLA2), endothelial activation (MCP-1), plaque inflammation (hs-CRP, IL6, IL18, TNF, advanced glycation end-products), vulnerable transformation (vEGF, PAI-1, BMP-6)

and measures of oxidative stress (Ox-LDL, TAOS, TBARs) at baseline, and at 12 months after therapy initiation.

Furthermore, the participants underwent aortic carotid-femoral pulse wave velocity (cfPWV) through the Vicorder (Skidmore Medical, UK), which was performed by myself. The cfPWV uses oscillometric cuff-based measurements to establish the index of arterial stiffness. The procedure was done at baseline and 12 months after therapy initiation.

After randomisation and initiating the first dose of the drug (semaglutide or placebo), participants have had a formal review by myself. They have been educated on the importance of remaining in the study and attending the scheduled follow-ups up to the end ofthe study.

The following procedures were conducted and documented either by myself or research staff:

- Confirmation of signed ICF
- Confirmation of investigation completion
- Ensuring an adequate supply of the drug (semaglutide or the placebo) has been given

Participants have been followed up in regular time intervals from the drug initiation, as illustrated inTable 16, through formal reviews at the JCRF.

This is a suitable setup designed for research purposes. The staff are familiar with the trial drug, having worked with similar previous cardiovascular semaglutide trials and ongoing ones like SOUL (clinicaltrial.gov: NCT03914326).

Physical examinations have been performed by myself according to local procedures when indicated. A physical examination included assessments of the following:

- General Appearance
- Thyroid gland
- Respiratory system

- Cardiovascular system
- Gastrointestinal system incl. mouth
- Extremities

I also recorded relevant findings prior to randomisation as concomitant illness/medicalhistory. While reported relevant findings occurring after randomisation as an AE. Vital signs, Body measurements (e.g. height, weight and waist circumference), Blood glucoseand HbA1c were recorded and documented by the nursing staff. The measured values were recorded in the eCRF without rounding. Blood pressure and pulse measurements were assessed in a sitting position with a completely automated device. Manual techniques were used only if an automated device was not available.

When applicable, a urine pregnancy test was performed during the trial if a menstrual period was missed or if pregnancy was suspected.

Information on clinical progress, especially on hospital readmission, medication compliance and further investigations, has been documented in every follow-up visit.

Table 16: Trial follow-up timeline.

Trial Periods	***Screening***	***Start of treatment and Randomisation***	***Follow up period***				***End of trial***	***Post-trial care***
Site visit (V)/Phone contact (P)	*V0*	*V1(week 0)*	*V2*	*V3*	*V4 - P4*	*V5 – P5*	*V6*	*P7*
Timing of visit (weeks)	*During and after index admission*	*At least 4 weeks after index admission*	*4 (+/- 3 days)*	*8 (+/- 3 days)*	*12 (+/- 1 week)*	*24 (+/- 1 week)*	*52 (+/- 1 week)*	*56*
PIS/IFC	✓							
Inclusion/Exclusion criteria	✓	✓						
Demography	✓							
Up to date contact list	✓	✓	✓	✓	✓	✓	✓	✓
Medical history/concomitant illness and medications	✓	✓	✓	✓	✓	✓	✓	✓
Drug compliance (counting remaining bills/ empty boxes)			✓	✓	✓	✓	✓	
Trial product dose adjustment			✓	✓				
Physical examination		✓					✓	
Vital signs		✓	✓	✓	✓	✓	✓	
Weight, Height and waist circumference		✓	✓	✓	✓	✓	✓	
Blood glucose		✓	✓	✓	✓	✓	✓	
HbA1c					✓	✓	✓	
Urine pregnancy test, if applicable		✓	✓	✓	✓	✓	✓	
Serum biomarkers and cfPWV		✓					✓	
CCTA		✓					✓	

V = visit, PIS = Patient information sheet, IFC = Informed consent

7.3.4: CCTA Analysis

All patients underwent a prospective-gated CT scan. Details on CT acquisition, as well as qualitative and quantitative analysis, as described extensively in Chapter 2.

Plaques were classified as vulnerable if they had (positive remodelling and low attenuation combined, or napkin ring sign), or the new CT-TCFA definition as described previously. Those signs were found to be strongly associated with future coronary event risk in prospective studies.[108,114,200,201]

The primary CT objective for the trial was to compare the regression of vulnerable coronary plaque (necrotic core) assessed by "Plaque Maps" derived from CT Coronary angiography in participants treated with oral semaglutide or placebo for 12 months.

The secondary CT objectives were to:

- Evaluate the effect of oral semaglutide on atherosclerotic plaque composition.
- Evaluate the effect of oral semaglutide on total coronary atherosclerotic plaque volume and burden.

The secondary non-imaging objectives were to:

- Evaluate the effect of oral Semaglutide on levels of biomarkers of inflammation, atherogenesis and oxidative stress.
- Evaluate any potential effect of oral Semaglutide on vascular function and arterial stiffness by assessing aortic carotid-femoral pulse wave velocity.

7.4: Statistical Analysis

Percent change in plaque between baseline and 12 months is presented as change in plaque divided by baseline plaque. Univariable analysis and multiple linear regression will be used to examine the change in the primary and secondary outcomes between the two treatment arms. All statistical analyses report two-sided P-values for the outcomes.

The baseline value is defined as the latest available measurement from the randomisation visit or the screening visit. Thus, if a randomisation assessment is missing, the screening assessment is used as the baseline assessment, if available. Missing data is defined as data that are planned and can be observed but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring is not considered missing. This data will be estimated using multiple imputations and regression analysis.

Descriptive statistics will be used to summarise the data. Continuous data will be expressed by medians and interquartile range to avoid the assumption of the distribution of the data; categorical data are presented by the numbers with percentages. In the secondary endpoint, the T-test or Mann-Whitney U test is used to compare the differences between the treatment group and the control group.

The clinical trial will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement (http://www.consort-statement.org/).

7.5: Results

As of September 2022, the study successfully enrolled its first participant. By the second quarter of 2023, the targeted enrolment was achieved. By the second quarter of 2024, approximately 70% of the enrolled patients had completed the follow-up period. The trial is anticipated to conclude by the first quarter of 2026. Preliminary data summarising the demographics and clinical characteristics of the participants are presented in Table 17. Continuous variables are reported as means ± standard deviations (SDs), while categorical variables are expressed as counts and percentages. Baseline parameters were analysed using either a Student's t-test for continuous variables or a chi-square test for categorical variables. The average age of participants in the cohort is 63.9 years, with males comprising 74% of the population. The mean body mass index (BMI) for the cohort is 31.6 kg/m². Overall, there were 197 (bystander) plaques in the 100 trial participants at baseline. Out of this, only 11 (8%) were causing significant luminal stenosis

(>50%). There were 33 (18%) plaques exhibiting vulnerable features (PR&LAP, NRS, or CT-TCFA). A breakdown of the percentage of all the high-risk can be found in Table 18.

Table 17: patient characteristics

Patient characteristics	
Male	*74%*
Age	*63 +/- 9*
Hypertension	*24%*
Diabetes Mellitus	*31%*
Smokers/ex-smokers	*52%*
Hyperlipidemia	*15%*
Ejection fraction	*52% +/-6*
Body mass index	*31 +/- 6*
Family history of CAD	*48%*

CAD = Coronary artery disease

7.6: Discussion

This study provides an opportunity to evaluate the anti-atherogenic potential of semaglutide, providing a mechanism of CV benefit.

At the time of thesis submission, recruitment and follow-up were ongoing, and that outcome data were not yet available. No preliminary results are available. Therefore, this study should be interpreted as a mechanistic, hypothesis-generating investigation rather than a completed outcomes trial. The absence of final results reflects delays related to the COVID-19 pandemic, which impacted recruitment timelines and follow-up completion.

GLP-1 RAs improve glycaemic control through their insulinotropic properties. However, the mechanisms by which these agents reduce adverse cardiovascular events remain unclear. Whilst large randomised trials have provided safety and positive outcome data, the

mechanisms of these benefits require further exploration if there is to be broader utilisation and additional applications of these agents.

The Post-ACS trial randomises participants with T2DM and previous ACS who are on a standard-of-care regimen to receive once daily semaglutide or placebo. This is crucial to our understanding of DM treatment and CVD.

Table 18: Characteristics and percentage of different plaque morphologies

Coronary plaques	
Total plaques	*197*
Stenotic plaques	*11 (8%)*
Vulnerable plaques	*33 (18%)*
Total LAP	*32 (16%)*
Total PR	*37 (19%)*
Total NRS	*27 (14%)*
Total CT-TCFA	*31 (16%)*

CT-TCFA = computed tomography defined Thin-cap fibroatheroma, NRS = Napkin ring sign, PR = Positive remodelling, and LAP = Low attenuation plaque.

The focus on individual demographic, clinical, and plaque factors that may influence a differential coronary plaque response to medications will add to our understanding of therapy for T2DM. The major aim of this study is to assess the impact of semaglutide on the progression of coronary artery atherosclerosis. Potentially, some benefits of GLP-1 RAs could be explained by better control of non-glycemic CV risk factors such as blood pressure and weight.[293] However, in the HARMONY trial, albiglutide was associated with a

significant reduction in MACE without substantial differences in body weight or blood pressure compared to placebo.[166] Whilst there might be some positive effects of GLP-1RAs on heart failure (HF), the data are inconsistent. None of the CVOTs included heart failure in the primary composite outcome, and details about baseline left ventricular ejection fraction (LVEF) or concurrent HF therapies during the trials weren't clear.[294] Furthermore, one can argue that other GLP-1RA's favourable hemodynamic effects may contribute to this finding. On the other hand, in a recent network meta-analysis, which included seven hundred and sixty-four trials, GLP-1RAs reduce cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. There was a remarkable benefit in non-fatal stroke, which has not been observed with the sodium-glucose co-transporter-2 (SGLT2) inhibitors (the other class of glucose-lowering drugs to have shown CV benefit).[295] Those outcomes suggest that GLP-1RAs may exhibit CV protection through anti-atherosclerotic properties.

Systemic and localised inflammation is now recognised as an active part of atherosclerosis pathophysiology and plays an essential role in plaque instability and the risk of myocardial infarction.[17] Chronic hyperglycemia and insulin resistance are associated with higher-than-normal inflammatory responses, putting people with T2DM at higher risk for CV adverse outcomes than their non-diabetic counterparts.[126,128]

Currently, some of the available biomarker data points toward an anti-inflammatory role of GLP-1-based therapies. Within this context, liraglutide, in combination with metformin, was found to decrease plasma CRP levels in patients with CAD and newly diagnosed T2DM.[191] Similarly, liraglutide treatment in people with T1DM resulted in a decrease in the levels of IL-6, IL-8, IL-10, and INF-γ after 26 weeks of treatment versus placebo, although this decrease was only significant for IL-6.[296] To explore this anti-inflammatory role further, Jensen et al. examined the impact of the long-acting GLP-1RA semaglutide on the atherosclerotic burden in a rabbit model using multimodality positron emission tomography

and computed tomography(PET/CT).[297] The authors report a significantly decreased uptake of [^{18}F]FDG and [^{64}Cu]Cu-DOTATATE tracers imaging activated macrophages and cellular metabolism within the aorta in the semaglutide group when compared to the saline placebo group. The animal models used in the trial did not have diabetes, and fasting blood glucose did not differ between groups either at baseline or at follow-up. This is further evidence that the cardiovascular benefits of GLP-1RAs are not directly related to glucose-lowering. This was the first in vivo CT PET study to investigate the anti-inflammatory role of GLP-1RAs. Although these anti-inflammatory effects may have beneficial cardioprotection in people with diabetes mellitus, supporting data in humans are neither extensive nor consistent.

The localised role of GLP-1RA on coronary arteries has been investigated recently. In a sub-study of the LIRAFLAME trial, the authors examined the anti-inflammatory effect of liraglutide on coronary arteries using a combined [64Cu]Cu-DOTATATE PET and CT coronary angiogram in 30 participants with T2DM.[298] After 26 weeks of treatment, there was a significant reduction in [64Cu]Cu-DOTATATE uptake in the coronary arteries in the liraglutide group compared to placebo. In an ongoing randomised control study, Hamal et al. aim to investigate the impact of 1-year treatment with subcutaneous semaglutide on coronary plaque volumes and progression rate using CT coronary angiography in patients with T2DM.[299]

Interestingly, patients' baseline characteristics appear to be an essential determining factor in detecting the anti-atherosclerotic prosperities of GLP-RAs. In two recent large randomised controlled trials, liraglutide and semaglutide showed remarkable CV benefits compared to placebo when added to people with T2DM.[165,172] In both trials, participants either had established CV disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease) or had a high CV risk profile. In a more low to moderate risk-population with T2DM, liraglutide had little effect on vascular inflammation assessed as [18F]-

fluorodeoxyglucose uptake compared with placebo.[300] This supports the hypothesis that GLP-1RAs' anti-atherosclerotic benefits are best utilised in populations at high CV risk.

In line with this, consensus statements from the American Diabetic Association and the American College of Cardiology now acknowledge the role of GLP-1RAs in people with T2DM and those who are at high risk of developing atherosclerotic cardiovascular disease[301,302]. The most up-to-date ESC guidelines (2019) have gone a step further and recommended either GLP- 1RAs or SGLT-2 inhibitors as a first-line therapy – even before metformin to people with T2DM and prevalent ASCVD or high/very high CV risk profile.[175] However, these recommendations are not universal. The National Institute of Clinical Excellence in the United Kingdom advocate a stepwise, personalised approach in T2DM in which GLP-1RAs can be introduced as an 'add-on' after a number of standard therapies if required to achieve adequate glycaemic control.[303] One reason for this heterogenicity is the absence of a clear, defined mechanism for the cardiovascular protection of the GLP-1 mimetic agents.

The POST-ACS trial is the first dedicated mechanistic study designed to evaluate the impact of oral semaglutide on atherosclerotic burden in high-risk patients with a prior history of ACS.

The trial is not powered for clinical endpoints, however, the changes observed in CCTA scans, including plaque volume, severity, and calcification, will provide insights into the anti-atherosclerotic effects of semaglutide. Biomarker analysis and evaluation of new and existing vulnerable plaques will shed light on their potential biological effects on vascular health, such as reducing inflammation and promoting plaque stabilisation. Additionally, CT-based observations, such as the transition of soft plaques into fibrous or calcified forms, will offer valuable information on the potential for long-term stabilisation of atherosclerosis associated with semaglutide treatment.

It is important to acknowledge that the POST-ACS study was initiated during the COVID-19 pandemic, which significantly affected recruitment, follow-up, and research delivery. As a result, complete outcome data were not available within the timeframe of this thesis. This study is therefore presented as a mechanistic, hypothesis-driven randomised controlled trial design, forming the translational extension of the preceding imaging and observational work. Completion of this study will provide important prospective data linking pharmacological intervention to changes in coronary plaque characteristics.

7.7: Conclusions

This study is the first to investigate the effects of semaglutide on atherosclerotic plaque progression using CCTA in individuals with T2DM while also examining the correlation of these effects with changes in HbA1c and inflammatory markers. The findings will offer valuable insights into the anti-atherosclerotic mechanisms of long-acting GLP-1, potentially contributing to the prevention of coronary events in T2DM patients.

7.8: Supplementary Materials

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

Wales Research Ethics Committee 1
Cardiff

Mailing address:
Health and Care Research Wales
Castlebridge 4
15-19 Cowbridge Road East
Cardiff, CF11 9AB

email: Wales.REC1@wales.nhs.uk
website: ww.hra.nhs.uk

Please note:

This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites until you receive HRA/HCRW Approval

09 July 2021
Dr Daniel Obaid
Swansea Bay UHB-Cardiology
Swansea
SA6 6NL

Dear Dr Obaid

Study title:	**THE POTENTIAL IMPACT OF ORAL SEMAGLUTIDE ON CORONARY ARTERY DISEASE PROGRESSION FOLLOWING ACUTE CORONARY SYNDROME: THE POST-ACS STUDY**
REC reference:	**21/WA/0176**
Protocol number:	**0.3**
EudraCT number:	**2020-004700-34**
IRAS project ID:	**275165**

Thank you for your letter of 08 July 2021, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Figure 31: A copy of an email confirming favourable ethical opinion to start the POST-ACS study

Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Mr Ahmed Salem
SWANSEA BAY UNIVERSITY HEALTH BOARD
ONE TALBOT GATEWAY,
BAGLAN ENERGY PARK, BAGLAN
PORT TALBOT
SA12 7BR
UNITED KINGDOM

07/10/2021

Dear Mr Ahmed Salem,

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	CTA 35930/0005/001-0001
Eudract Number:	2020-004700-34
Product:	Rybelsus
Protocol number:	6

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 11/08/2021.

MEDICAL - Remarks: Remarks:

The following comments are for future consideration / information only and do not affect the approval status of your study. No response is required.

The Sponsor is encouraged to send any evidence of patient engagement activities undertaken specific to the trial in question to the CTU helpline for our records and to support the drug development programme moving forward.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

You are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed, changes made as part of your amended request may need to be notified to the Ethics Committee. If not already provided, please follow the guidance on our website on informing us of the registration status of your trial (where applicable).

Figure 32: A copy of acceptance from Medicines and Healthcare products Regulatory Agency.

CHAPTER 8: Summary and Conclusions

8.1: Discussion of Key Findings

This thesis represents a coherent and progressive research programme aimed at improving cardiovascular risk stratification through the integration of real-world evidence, advanced imaging, and translational clinical investigation. The work follows a structured trajectory: identifying gaps in cardiovascular prevention, developing imaging-based tools to better characterise disease, evaluating their impact on clinical decision-making, and ultimately translating these insights into a prospective mechanistic trial.

The thesis provides a comprehensive exploration of contemporary cardiovascular disease prevention, with a particular focus on patients with T2DM, the evolving role of CCTA, and the potential of novel pharmacological therapies to modify atherosclerotic disease. Across a series of interrelated studies, several key insights have emerged:

In **Chapter3,** I conducted an in-depth analysis of real-world data from a large, population-based cohort in Wales and identified persistent gaps in the implementation of secondary prevention measures among individuals with T2DM. Despite the existence of robust clinical guidelines, there were notable deficiencies in achieving recommended targets for lipid levels, blood pressure, and glycaemic control. These discrepancies highlight a substantial disconnect between guideline-directed care and actual clinical practice. While the dataset had inherent limitations—such as the inability to account for medication adherence or distinguish between diabetes subtypes—this work nevertheless offers a valuable benchmark for current practice in a healthcare system with minimal access barriers (e.g., no prescription costs). The findings underscore the need for improved care delivery systems, better integration of multidisciplinary approaches, and the potential utility of digital tools to bridge these critical care gaps.

I then utilised CT "Plaque Maps" methodology across different population cohorts in stable and acute settings**.** In **Chapter4,** I tested the reproductivity of the proposed CT-TCFA index

(a novel CT-based plaque vulnerability metric), which is based on the necrotic core-to-fibrous plaque ratio, and demonstrated improved reproducibility and superior inter-observer reliability compared to existing CT high-risk metrics. This holds promise for broader application, especially among less experienced readers. These findings also suggest that the use of CCTA extended beyond anatomical assessment to the characterisation of plaque composition and distribution, offering enhanced granularity in cardiovascular risk stratification and that with appropriate tools, plaque assessment using CCTA could aid in risk stratification and management.

In **Chapter 5**, I explored the clinical significance of these imaging findings by conducting a large, real-world outcomes study involving over 2,000 low-risk patients in Wales. This study examined the impact of CCTA-derived plaque characteristics—particularly high-risk features—on physician decision-making, cardiovascular risk factor modification, and adverse cardiovascular outcomes. The results indicate that the presence of high-risk plaque features may influence clinician behaviour, as evidenced by a doubling in high-intensity statin prescriptions and greater reductions in LDL-C and non-HDL-C among affected patients. These findings advocate for more identification and reporting of high-risk features when interpreting CCTA scans.

In **Chapter 6**, I extended this analysis by exploring the anatomical distribution of vulnerable plaques across different clinical populations. The observed lower prevalence of high-risk features in the left main artery, while potentially artefactual, points to the need for further studies with multimodal imaging and post-mortem validation.

Then, in **Chapter 7**, I have designed and led a **first-of-its-kind** randomised control trial exploring the impact of semaglutide on plaque progression using CCTA, providing early evidence of its potential anti-atherosclerotic effects in high-risk patients with and without DM. The POST-ACS trial will offer a prospective, mechanistic exploration of semaglutide's

role in modulating atherosclerotic plaque characteristics. By correlating changes in CCTA-derived plaque features with metabolic and inflammatory markers, this work lays the foundation for future trials integrating imaging and pharmacological interventions.

The thesis integrates a series of complementary studies spanning real-world data analysis, advanced imaging-based plaque characterisation, and the design of a prospective mechanistic clinical trial. The work presented reflects the candidate's primary contribution to study design, imaging analysis, data interpretation, and manuscript preparation across all chapters.

Collectively, these studies highlight persistent shortcomings in current clinical practice and demonstrate how advanced imaging modalities and novel pharmacological interventions can be leveraged to improve cardiovascular risk stratification and management in high-risk populations, particularly those with T2DM.

Taken together, these findings demonstrate a clear progression from identifying gaps in real-world cardiovascular care to developing and applying advanced imaging tools, and ultimately to designing targeted therapeutic strategies. This integrated approach supports a shift from population-based risk assessment towards a more personalised, imaging-guided model of cardiovascular prevention.

8.2: Future Directions

A key priority for future research is the completion and analysis of the POST-ACS trial described in Chapter 7. This study represents the translational extension of the work presented in this thesis and is designed to evaluate whether pharmacological modulation of atherosclerosis leads to measurable changes in plaque characteristics as assessed by coronary CT angiography. Completion of this trial will provide important prospective, mechanistic

insights linking imaging findings with therapeutic intervention and will be essential in determining the clinical relevance of imaging-defined plaque modification.

Furthermore, building on the insights generated by this work, several important avenues for future investigation emerge. First, larger, multicentre trials are necessary to validate the CT-TCFA metric and determine its prognostic significance across diverse clinical populations. Such studies will help establish its reproducibility, clinical utility, and potential role in routine risk stratification. The advancement of automation and artificial intelligence (AI)-enhanced tools for plaque characterisation also holds significant promise. These technologies could streamline image interpretation, reduce inter-observer variability, and enable real-time integration of advanced imaging metrics into clinical decision-making pathways.

In parallel, further mechanistic trials exploring the vascular effects of glucagon-like peptide-1 (GLP-1) receptor agonists and other emerging cardiometabolic agents are needed. Such studies should employ both imaging-based and circulating biomarker endpoints to better understand the mechanisms underlying atherosclerotic disease modification.

An exciting frontier in cardiovascular imaging is the emergence of photon-counting computed tomography (PCCT), a next-generation CT technology that offers superior spatial resolution, improved tissue contrast, and material decomposition capabilities. Photon-counting detectors allow for more precise characterisation of coronary plaque components and may overcome some limitations of conventional energy-integrating detectors, such as blooming artefacts from calcification. Incorporating PCCT into future research could significantly enhance the detection of high-risk plaque features and improve the quantification of treatment response, making it a valuable tool for both clinical practice and research applications. Collectively, these future directions offer promising pathways to advance precision cardiovascular prevention and optimise outcomes in high-risk populations.

References

1. Oxford Reference - Answers with Authority. https://www.oxfordreference.com/.
2. Konstantinov, I. E., Mejevoi, N. & Anichkov, N. M. Nikolai N. Anichkov and His Theory of Atherosclerosis. *Texas Hear. Inst. J.* **33**, 417 (2006).
3. Allam, A. H. *et al.* Atherosclerosis in ancient Egyptian mummies: the Horus study. *JACC. Cardiovasc. Imaging* **4**, 315–327 (2011).
4. Bentzon, J. F., Otsuka, F., Virmani, R. & Falk, E. Mechanisms of Plaque Formation and Rupture. *Circ. Res.* **114**, 1852–1866 (2014).
5. Stary, H. C. *et al.* A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler. Thromb. Vasc. Biol.* **15**, 1512–1531 (1995).
6. Ikari, Y., McManus, B. M., Kenyon, J. & Schwartz, S. M. Neonatal intima formation in the human coronary artery. *Arterioscler. Thromb. Vasc. Biol.* **19**, 2036–2040 (1999).
7. Guerri-Guttenberg, R. *et al.* Coronary Intimal Thickening Begins in Fetuses and Progresses in Pediatric Population and Adolescents to Atherosclerosis. *Angiology* **71**, 62–69 (2020).
8. Tsuchihashi, T. *et al.* Intimal thickening and disruption of the media occur in the arterial walls of coronary arteries not associated with coronary arterial aneurysms in patients with Kawasaki disease. *BMC Cardiovasc. Disord.* **21**, (2021).
9. Nakamura, T., Horikoshi, T. & Kugiyama, K. Relationship of a thinned medial layer to the attenuated contractile response in atherosclerotic coronary arteries. *Am. J. Physiol. Heart Circ. Physiol.* **318**, H135–H142 (2020).
10. Uchida, Y. *et al.* Functional medial thickening and folding of the internal elastic lamina in coronary spasm. *Am. J. Physiol. Heart Circ. Physiol.* **300**, (2011).
11. Riches, K. *et al.* Elevated expression levels of miR-143/5 in saphenous vein smooth

muscle cells from patients with Type 2 diabetes drive persistent changes in phenotype and function. *J. Mol. Cell. Cardiol.* **74**, 240–250 (2014).

12. Duncombe, S. L., Hosking, M. C. K., Coté, A. T., Voss, C. & Harris, K. C. Intimal thickening at coronary bifurcations in pediatric heart transplant recipients. *Pediatr. Transplant.* **22**, (2018).
13. Mozaffarian, D. *et al.* Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **133**, e38–e48 (2016).
14. Prabhakaran, D. *et al.* The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990-2016. *Lancet. Glob. Heal.* **6**, e1339–e1351 (2018).
15. Esper, R. J. *et al.* Endothelial dysfunction: A comprehensive appraisal. *Cardiovasc. Diabetol.* **5**, 1–18 (2006).
16. Monnink, S. H. J. *et al.* Endothelial dysfunction in patients with coronary artery disease: A comparison of three frequently reported tests. *J. Investig. Med.* **50**, 19–24 (2002).
17. Libby, P. & Hansson, G. K. Inflammation and immunity in diseases of the arterial tree: Players and layers. *Circulation Research* vol. 116 307–311 (2015).
18. Kobayashi, S. *et al.* Interaction of oxidative stress and inflammatory response in coronary plaque instability: Important role of C-reactive protein. *Arterioscler. Thromb. Vasc. Biol.* **23**, 1398–1404 (2003).
19. Ferreiró, E. R. *et al.* Independent prognostic value of elevated C-reactive protein in unstable angina. *Circulation* **100**, 1958–1963 (1999).
20. Lagrand, W. K. *et al.* C-reactive protein as a cardiovascular risk factor more than an epiphenomenon? *Circulation* vol. 100 96–102 (1999).
21. S. Antonopoulos, A., Margaritis, M., Lee, R., Channon, K. & Antoniades, C. Statins as

Anti-Inflammatory Agents in Atherogenesis: Molecular Mechanisms and Lessons from the Recent Clinical Trials. *Curr. Pharm. Des.* **18**, 1519–1530 (2012).

22. Taqueti, V. R. & Ridker, P. M. Lipid-Lowering and Anti-Inflammatory Benefits of Statin Therapy: More Than Meets the Plaque. *Circulation: Cardiovascular Imaging* vol. 10 2195–2207 (2017).

23. Yusuf, P. S. *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)* **364**, 937–952 (2004).

24. Kaminsky, L. A. *et al.* The importance of healthy lifestyle behaviors in the prevention of cardiovascular disease. *Prog. Cardiovasc. Dis.* **70**, 8–15 (2022).

25. Benjamin, E. J. *et al.* Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* **137**, E67–E492 (2018).

26. Virmani, R., Kolodgie, F. D., Burke, A. P., Farb, A. & Schwartz, S. M. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler. Thromb. Vasc. Biol.* **20**, 1262–1275 (2000).

27. Virmani, R., Burke, A. P., Farb, A. & Kolodgie, F. D. Pathology of the Vulnerable Plaque. *Journal of the American College of Cardiology* vol. 47 (2006).

28. Lee, S. Y. *et al.* Attenuated plaque detected by intravascular ultrasound: clinical, angiographic, and morphologic features and post-percutaneous coronary intervention complications in patients with acute coronary syndromes. *JACC. Cardiovasc. Interv.* **2**, 65–72 (2009).

29. Partida, R. A., Libby, P., Crea, F. & Jang, I. K. Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. *Eur. Heart J.* **39**, 2070 (2018).

30. Yamamoto, E. *et al.* Clinical and Laboratory Predictors for Plaque Erosion in Patients

With Acute Coronary Syndromes. *J. Am. Hear. Assoc. Cardiovasc. Cerebrovasc. Dis.* **8**, (2019).

31. Barua, R. S. & Ambrose, J. A. Mechanisms of coronary thrombosis in cigarette smoke exposure. *Arterioscler. Thromb. Vasc. Biol.* **33**, 1460–1467 (2013).

32. Kurihara, O., Takano, M., Miyauchi, Y., Mizuno, K. & Shimizu, W. Vulnerable atherosclerotic plaque features: findings from coronary imaging. *J. Geriatr. Cardiol.* **18**, 577 (2021).

33. Kwon, J. E. *et al.* Multimodality Intravascular Imaging Assessment of Plaque Erosion versus Plaque Rupture in Patients with Acute Coronary Syndrome. *Korean Circ. J.* **46**, 499 (2016).

34. Pasterkamp, G., den Ruijter, H. M. & Libby, P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. *Nat. Rev. Cardiol. 2016 141* **14**, 21–29 (2016).

35. AC, F. & IK, J. Plaque erosion and acute coronary syndromes: phenotype, molecular characteristics and future directions. *Nat. Rev. Cardiol.* (2021) doi:10.1038/S41569-021-00542-3.

36. G, N. *et al.* Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur. Heart J.* **36**, 1377–1384 (2015).

37. Yonetsu, T. *et al.* Plaque morphologies and the clinical prognosis of acute coronary syndrome caused by lesions with intact fibrous cap diagnosed by optical coherence tomography. *Int. J. Cardiol.* **203**, 766–774 (2016).

38. Xing, L. *et al.* EROSION Study (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography–Based Management in Plaque Erosion). *Circ. Cardiovasc. Interv.* **10**, (2017).

39. Muller, J. E., Tofler, G. H. & Stone, P. H. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* **79**, 733–743 (1989).

40. Burke, A. P. *et al.* Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N. Engl. J. Med.* **336**, 1276–1282 (1997).

41. Falk, E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br. Heart J.* **50**, 127 (1983).

42. Llen, A. *et al.* Coronary Risk Factors and Plaque Morphology in Men with Coronary Disease Who Died Suddenly. *https://doi.org/10.1056/NEJM199705013361802* **19**, 678–680 (1997).

43. Burke, A. P. *et al.* Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. *Circulation* **103**, 934–940 (2001).

44. Kurihara, O. *et al.* Clinical significance of healed plaque detected by optical coherence tomography: a 2-year follow-up study. *J. Thromb. Thrombolysis* **50**, 895–902 (2020).

45. Vergallo, R. *et al.* Coronary Atherosclerotic Phenotype and Plaque Healing in Patients With Recurrent Acute Coronary Syndromes Compared With Patients With Long-term Clinical Stability: An In Vivo Optical Coherence Tomography Study. *JAMA Cardiol.* **4**, 321 (2019).

46. Ray, K. K. & Cannon, C. P. The Potential Relevance of the Multiple Lipid-Independent (Pleiotropic) Effects of Statins in the Management of Acute Coronary Syndromes. *J. Am. Coll. Cardiol.* **46**, 1425–1433 (2005).

47. Maron, D. J. *et al.* Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N. Engl. J. Med.* **382**, 1395–1407 (2020).

48. Proudfit, W. L., Bruschke, A. V. G. & Sones, F. M. Natural history of obstructive coronary artery disease: ten-year study of 601 nonsurgical cases. *Prog. Cardiovasc.*

Dis. **21**, 53–78 (1978).

49. Little, W. C. *et al.* Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* **78**, 1157–1166 (1988).

50. Falk, E., Shah, P. K. & Fuster, V. Coronary plaque disruption. *Circulation* **92**, 657–671 (1995).

51. Levin, D. C. & Fallon, J. T. Significance of the angiographic morphology of localized coronary stenoses: histopathologic correlations. *Circulation* **66**, 316–320 (1982).

52. Vrints, C. *et al.* 2024 ESC Guidelines for the management of chronic coronary syndromes: Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **45**, 3415–3537 (2024).

53. Lee, J. M. *et al.* Intravascular Imaging–Guided or Angiography-Guided Complex PCI. *N. Engl. J. Med.* **388**, 1668–1679 (2023).

54. Holm, N. R. *et al.* OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. *N. Engl. J. Med.* **389**, 1477–1487 (2023).

55. Honda, S. *et al.* Characterization of coronary atherosclerosis by intravascular imaging modalities. *Cardiovasc. Diagn. Ther.* **6**, 368 (2016).

56. Campos, C. M. *et al.* Ex vivo validation of 45 MHz intravascular ultrasound backscatter tissue characterization. *Eur. Heart J. Cardiovasc. Imaging* **16**, 1112–1119 (2015).

57. Nair, A., Kuban, B. D., Obuchowski, N. & Geoffrey Vince, D. Assessing spectral algorithms to predict atherosclerotic plaque composition with normalized and raw intravascular ultrasound data. *Ultrasound Med. Biol.* **27**, 1319–1331 (2001).

58. Davies, M. J. & Thomas, A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N. Engl. J. Med.* **310**, 1137–1140 (1984).

59. Nair, A. *et al.* Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation* **106**, 2200–2206 (2002).

60. Nasu, K. *et al.* Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. *J. Am. Coll. Cardiol.* **47**, 2405–2412 (2006).

61. Obaid, D. R. *et al.* Atherosclerotic plaque composition and classification identified by coronary computed tomography: Assessment of computed tomography-generated plaque maps compared with virtual histology intravascular ultrasound and histology. *Circ. Cardiovasc. Imaging* **6**, 655–664 (2013).

62. Stone, G. W. *et al.* A prospective natural-history study of coronary atherosclerosis. *N. Engl. J. Med.* **364**, 226–235 (2011).

63. Claessen, B. E. *et al.* Plaque composition by intravascular ultrasound and distal embolization after percutaneous coronary intervention. *JACC. Cardiovasc. Imaging* **5**, (2012).

64. Raffel, O. C., Akasaka, T. & Jang, I. K. Cardiac optical coherence tomography. *Heart* **94**, 1200–1210 (2008).

65. Jang, I. K. *et al.* In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* **111**, 1551–1555 (2005).

66. Kubo, T. *et al.* Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J. Am. Coll. Cardiol.* **50**, 933–939 (2007).

67. Park, K. W. *et al.* Impact of intravascular ultrasound guidance in routine percutaneous coronary intervention for conventional lesions: data from the EXCELLENT trial. *Int.*

J. Cardiol. **167**, 721–726 (2013).

68. Kim, J. S. *et al.* Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. *JACC. Cardiovasc. Interv.* **6**, 369–376 (2013).

69. Chieffo, A. *et al.* A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. *Am. Heart J.* **165**, 65–72 (2013).

70. Hur, S. H. *et al.* Impact of intravascular ultrasound-guided percutaneous coronary intervention on long-term clinical outcomes in a real world population. *Catheter. Cardiovasc. Interv.* **81**, 407–416 (2013).

71. Witzenbichler, B. *et al.* Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* **129**, 463–470 (2014).

72. Brown, A. J. *et al.* Direct Comparison of Virtual-Histology Intravascular Ultrasound and Optical Coherence Tomography Imaging for Identification of Thin-Cap Fibroatheroma. *Circ. Cardiovasc. Imaging* **8**, (2015).

73. Ali, Z. A. *et al.* Optical Coherence Tomography–Guided versus Angiography-Guided PCI. *N. Engl. J. Med.* **389**, 1466–1476 (2023).

74. Hounsfield, G. N. Computerized transverse axial scanning (tomography). 1. Description of system. *Br. J. Radiol.* **46**, 1016–1022 (1973).

75. Ohnesorge, B. M. Multi-slice and dual-source CT in cardiac imaging : principles, protocols, indications, outlook. 369 (2007).

76. Hounsfield, G. N. The E.M.I. scanner. *Proc. R. Soc. London. Ser. B, Biol. Sci.* **195**, 281–289 (1977).

77. Lackner, K. & Thurn, P. Computed tomography of the heart: ECG-gated and

continuous scans. *Radiology* **140**, 413–420 (1981).

78. Agatston, A. S. *et al.* Quantification of coronary artery calcium using ultrafast computed tomography. *J. Am. Coll. Cardiol.* **15**, 827–832 (1990).

79. Kröpil, P. *et al.* Prospectively ECG-triggered high-pitch spiral acquisition for cardiac CT angiography in clinical routine: initial results. *J. Thorac. Imaging* **27**, 194 (2012).

80. Poon, M. *et al.* Consensus update on the appropriate usage of cardiac computed tomographic angiography. *J. Invasive Cardiol.* **19**, 484–490 (2007).

81. Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis. *Recent. chest pain suspected Card. Orig. Assess. diagnosis* (2016).

82. Asher, A. *et al.* UK perspective on the changing landscape of non-invasive cardiac testing. *Open Hear.* **6**, (2019).

83. Coronary CTA Should Be the Initial Test in Most Patients With Stable Chest Pain: PRO - American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2018/05/21/06/37/coronary-cta-pro.

84. Devuyst, S. *et al.* Impact of non-invasive anatomical testing on optimal medical prescription in patients with suspected coronary artery disease. *Cardiovasc. Diagn. Ther.* **9**, 221–228 (2019).

85. Motoyama, S. *et al.* Multislice Computed Tomographic Characteristics of Coronary Lesions in Acute Coronary Syndromes. *J. Am. Coll. Cardiol.* **50**, 319–326 (2007).

86. Abazid, R. M. *et al.* Visceral adipose tissue influences on coronary artery calcification at young and middle-age groups using computed tomography angiography. *Avicenna J. Med.* **05**, 83–88 (2015).

87. Panh, L. *et al.* Coronary artery calcification: From crystal to plaque rupture. *Arch. Cardiovasc. Dis.* **110**, 550–561 (2017).

88. Liew, G. *et al.* Cardiac Society of Australia and New Zealand Position Statement:

Coronary Artery Calcium Scoring. *Hear. Lung Circ.* **26**, 1239–1251 (2017).

89. Detrano, R. *et al.* Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N. Engl. J. Med.* **358**, 1336–1345 (2008).

90. Budoff, M. J. *et al.* Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J. Am. Coll. Cardiol.* **49**, 1860–1870 (2007).

91. Kitagawa, T. *et al.* Characterization of Noncalcified Coronary Plaques and Identification of Culprit Lesions in Patients With Acute Coronary Syndrome by 64-Slice Computed Tomography. *JACC Cardiovasc. Imaging* **2**, 153–160 (2009).

92. Van Velzen, J. E. *et al.* Comprehensive assessment of spotty calcifications on computed tomography angiography: comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis. *J. Nucl. Cardiol.* **18**, 893–903 (2011).

93. McCullough, P. A. & Chinnaiyan, K. M. Annual Progression of Coronary Calcification in Trials of Preventive Therapies: A Systematic Review. *Arch. Intern. Med.* **169**, 2064–2070 (2009).

94. Joshi, F. R., Lindsay, A. C., Obaid, D. R., Falk, E. & Rudd, J. H. F. Non-invasive imaging of atherosclerosis. *Eur. Hear. J. - Cardiovasc. Imaging* **13**, 205–218 (2012).

95. Yoon, Y. E. *et al.* The absence of coronary artery calcification does not rule out the presence of significant coronary artery disease in Asian patients with acute chest pain. *Int. J. Cardiovasc. Imaging* **28**, 389–398 (2012).

96. Leber, A. W. *et al.* Accuracy of 64-Slice Computed Tomography to Classify and Quantify Plaque Volumes in the Proximal Coronary System: A Comparative Study Using Intravascular Ultrasound. *J. Am. Coll. Cardiol.* **47**, 672–677 (2006).

97. Gao, D. *et al.* Computed tomography for detecting coronary artery plaques: A meta-

analysis. *Atherosclerosis* **219**, 603–609 (2011).

98. Leschka, S. *et al.* Ex vivo evaluation of coronary atherosclerotic plaques: Characterization with dual-source CT in comparison with histopathology. *J. Cardiovasc. Comput. Tomogr.* **4**, 301–308 (2010).

99. Galonska, M. *et al.* Characterization of Atherosclerotic Plaques in Human Coronary Arteries With 16-Slice Multidetector Row Computed Tomography by Analysis of Attenuation Profiles. *Acad. Radiol.* **15**, 222–230 (2008).

100. Maurovich-Horvat, P. *et al.* The napkin-ring sign: CT Signature of high-risk coronary plaques? *JACC Cardiovasc. Imaging* **3**, 440–444 (2010).

101. Calvert, P. A. *et al.* Association between IVUS findings and adverse outcomes in patients with coronary artery disease: The VIVA (VH-IVUS in vulnerable atherosclerosis) study. *JACC Cardiovasc. Imaging* **4**, 894–901 (2011).

102. Pundziute, G. *et al.* Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. *JACC. Cardiovasc. Interv.* **1**, 176–182 (2008).

103. Pundziute, G. *et al.* Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. *Eur. Heart J.* **29**, 2373–2381 (2008).

104. Van Velzen, J. E. *et al.* Plaque type and composition as evaluated non-invasively by MSCT angiography and invasively by VH IVUS in relation to the degree of stenosis. *Heart* **95**, 1990–1996 (2009).

105. Filardo, S. D. *et al.* Acute myocardial infarction and vascular remodeling. *Am. J. Cardiol.* **85**, 760–762 (2000).

106. Gauss, S. *et al.* Assessment of coronary artery remodelling by dual-source CT: a head-

to-head comparison with intravascular ultrasound. *Heart* **97**, 991–997 (2011).

107. Kröner, E. S. J. *et al.* Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. *Am. J. Cardiol.* **107**, 1725–1729 (2011).

108. Motoyama, S. *et al.* Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome. *J. Am. Coll. Cardiol.* **54**, 49–57 (2009).

109. Narula, J. & Achenbach, S. Napkin-ring necrotic cores: defining circumferential extent of necrotic cores in unstable plaques. *JACC. Cardiovasc. Imaging* **2**, 1436–1438 (2009).

110. Tanaka, A. *et al. Non-Invasive Assessment of Plaque Rupture by 64-Slice Multidetector Computed Tomography Comparison With Intravascular Ultrasound*. *Circulation Journal* vol. 72 (2008).

111. Márton, E. *et al.* Cardiovascular Imaging Techniques for Detection of Vulnerable Plaques. *J. Interdiscip. Med.* **6**, 21–26 (2021).

112. La Grutta, L. *et al.* Comparison of iodinated contrast media for the assessment of atherosclerotic plaque attenuation values by CT coronary angiography: observations in an ex vivo model. *Br. J. Radiol.* **86**, 20120238 (2013).

113. Pohle, K. *et al.* Characterization of non-calcified coronary atherosclerotic plaque by multi-detector row CT: comparison to IVUS. *Atherosclerosis* **190**, 174–180 (2007).

114. Salem, A. M. *et al.* Characteristics of conventional high-risk coronary plaques and a novel CT defined thin-cap fibroatheroma in patients undergoing CCTA with stable chest pain. *Clin. Imaging* **101**, 69–76 (2023).

115. Sun, Z., Ng, C. K. C., Wong, Y. H. & Yeong, C. H. 3D-Printed Coronary Plaques to Simulate High Calcification in the Coronary Arteries for Investigation of Blooming

Artifacts. *Biomolecules* **11**, (2021).

116. Li, P. *et al.* Blooming Artifact Reduction in Coronary Artery Calcification by A New De-blooming Algorithm: Initial Study. *Sci. Rep.* **8**, (2018).

117. Williams, M. C. *et al.* Cardiac and coronary CT comprehensive imaging approach in the assessment of coronary heart disease. *Heart* **97**, 1198–1205 (2011).

118. Mannil, M. *et al.* Modified Dual-Energy Algorithm for Calcified Plaque Removal: Evaluation in Carotid Computed Tomography Angiography and Comparison With Digital Subtraction Angiography. *Invest. Radiol.* **52**, 680–685 (2017).

119. Obaid, D. R. *et al.* Coronary CT angiography features of ruptured and high-risk atherosclerotic plaques: Correlation with intra-vascular ultrasound. *J. Cardiovasc. Comput. Tomogr.* **11**, 455–461 (2017).

120. Mese, I., Altintas Taslicay, C. & Sivrioglu, A. K. Synergizing photon-counting CT with deep learning: potential enhancements in medical imaging. *https://doi.org/10.1177/02841851231217995* **65**, 159–166 (2023).

121. Byl, A. *et al.* Photon-counting normalized metal artifact reduction (NMAR) in diagnostic CT. *Med. Phys.* **48**, 3572–3582 (2021).

122. Huang, R., Larsson, K. & Persson, M. U. Deep-learning-based motion artifact reduction for photon-counting spectral cardiac CT. *https://doi.org/10.1117/12.3006362* **12925**, 23–27 (2024).

123. Sarwar, N. *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet* **375**, 2215–2222 (2010).

124. Gerstein, H. C. *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* **358**, 2545–2559 (2008).

125. Kosiborod, M. *et al.* Vascular complications in patients with type 2 diabetes:

Prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovasc. Diabetol.* **17**, 1–13 (2018).

126. Donath, M. Y. Targeting inflammation in the treatment of type 2 diabetes: Time to start. *Nature Reviews Drug Discovery* vol. 13 465–476 (2014).

127. Lee, C. H., Changchien, C. Y. & Hung, Y. J. Targeting inflammation in type 2 diabetes by antibody-mediated Tyro-3, Axl, Mer receptor activation. *Journal of Diabetes Investigation* vol. 6 491–494 (2015).

128. Williams, M. D. & Nadler, J. L. Inflammatory mechanisms of diabetic complications. *Current Diabetes Reports* vol. 7 242–248 (2007).

129. DeFronzo, R. A. The triumvirate: β-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* vol. 37 667–687 (1988).

130. Maritim, A. C., Sanders, R. A. & Watkins, J. B. Diabetes, oxidative stress, and antioxidants: A review. *Journal of Biochemical and Molecular Toxicology* vol. 17 24–38 (2003).

131. Harrison, D., Griendling, K. K., Landmesser, U., Hornig, B. & Drexler, H. Role of oxidative stress in atherosclerosis. in *American Journal of Cardiology* vol. 91 7–11 (Elsevier Inc., 2003).

132. Stephens, J. W. *et al.* Increased plasma markers of oxidative stress are associated with coronary heart disease in males with diabetes mellitus and with 10-year risk in a prospective sample of males. *Clin. Chem.* **52**, 446–452 (2006).

133. Baynes, J. W. & Thorpe, S. R. Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. *Diabetes* vol. 48 1–9 (1999).

134. Baynes, J. W. Role of oxidative stress in development of complications in diabetes. *Diabetes* vol. 40 405–412 (1991).

135. Hunt, J. V., Dean, R. T. & Wolff, S. P. Hydroxyl radical production and autoxidative

glycosylation. Glucose autoxidation as the cause of protein damage in the experimental glycation model of diabetes mellitus and ageing. *Biochem. J.* **256**, 205–212 (1988).

136. Stein, E. A. Management of dyslipidemia in the high-risk patient. *Am. Heart J.* **144**, (2002).

137. Contois, J. H., Warnick, G. R. & Sniderman, A. D. Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurement. *J. Clin. Lipidol.* **5**, 264–272 (2011).

138. Ramjee, V., Sperling, L. S. & Jacobson, T. A. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. *J. Am. Coll. Cardiol.* **58**, 457–463 (2011).

139. Rabar, S., Harker, M., O'Flynn, N. & Wierzbicki, A. S. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ* **349**, (2014).

140. Brunzell, J. D. *et al.* Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care* **31**, 811–822 (2008).

141. Ridker, P. M. *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).

142. Sattar, N. *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet (London, England)* **375**, 735–742 (2010).

143. Thakker, D., Nair, S., Pagada, A., Jamdade, V. & Malik, A. Statin use and the risk of developing diabetes: a network meta-analysis. *Pharmacoepidemiol. Drug Saf.* **25**, 1131–1149 (2016).

144. Crandall, J. P. *et al.* Statin use and risk of developing diabetes: Results from the

diabetes prevention program. *BMJ Open Diabetes Res. Care* **5**, (2017).

145. Salem, A. M. *et al.* Achievement of the ESC recommendations for secondary prevention of cardiovascular risk factors in high-risk patients with type 2 diabetes: A real-world national cohort analysis. *Int. J. Cardiol.* (2023) doi:10.1016/J.IJCARD.2023.02.004.

146. Shin, D., Bohra, C. & Kongpakpaisarn, K. Abstract 181: Application of the 2018 Cholesterol Guideline for Secondary Prevention in Very High-risk Patients with Atherosclerotic Cardiovascular Disease in the United States. *Circ. Cardiovasc. Qual. Outcomes* **12**, (2019).

147. Cannon, C. P. *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.* **372**, 2387–2397 (2015).

148. Sabatine, M. S. *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N. Engl. J. Med.* **376**, 1713–1722 (2017).

149. Fonarow, G. C. *et al.* Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients With Atherosclerotic Cardiovascular Disease. *JAMA Cardiol.* **2**, 1069–1078 (2017).

150. Mach, F. *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur. Heart J.* **41**, 111–188 (2020).

151. 1 Recommendations | Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia | Guidance | NICE.

152. Pinkosky, S. L. *et al.* Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat. Commun. 2016 71* **7**, 1–13 (2016).

153. Ballantyne, C. M. *et al.* Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled

study. *Atherosclerosis* **277**, 195–203 (2018).

154. Nissen, S. E. *et al.* Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *https://doi.org/10.1056/NEJMoa2215024* (2023) doi:10.1056/NEJMOA2215024.

155. 1 Recommendations | Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia | Guidance | NICE.

156. Nordestgaard, B. G. & Varbo, A. Triglycerides and cardiovascular disease. *Lancet* **384**, 626–635 (2014).

157. Pradhan, A. Das *et al.* Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *https://doi.org/10.1056/NEJMoa2210645* (2022) doi:10.1056/NEJMOA2210645.

158. Nicholls, S. J. *et al.* Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA* **324**, 2268–2280 (2020).

159. Final draft guidance | Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides | Guidance | NICE.

160. Bhatt, D. L. *et al.* Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **380**, 11–22 (2019).

161. 1 Recommendations | Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides | Guidance | NICE.

162. Sposito, A. C., Berwanger, O., De Carvalho, L. S. F. & Saraiva, J. F. K. Correction: GLP-1RAs in type 2 diabetes: Mechanisms that underlie cardiovascular effects and overview of cardiovascular outcome data (Cardiovascular Diabetology (2018) 17 (157) DOI: 10.1186/s12933-018-0800-2). *Cardiovascular Diabetology* vol. 18 1–3 (2019).

163. Meier, J. J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes

mellitus. *Nat. Rev. Endocrinol.* **8**, 728–742 (2012).

164. Marso, S. P. *et al.* Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).

165. Marso, S. P. *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **375**, 1834–1844 (2016).

166. Hernandez, A. F. *et al.* Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* **392**, 1519–1529 (2018).

167. Yandrapalli, S. & Aronow, W. S. Cardiovascular benefits of the newer medications for treating type 2 diabetes mellitus. *Journal of Thoracic Disease* vol. 9 2124–2134 (2017).

168. Liu, H., Dear, A. E., Knudsen, L. B. & Simpson, R. W. A long-acting glucagon-like peptide-1 analogue attenuates induction of plasminogen activator inhibitor type-1 and vascular adhesion molecules. *J. Endocrinol.* **201**, 59–66 (2009).

169. Drucker, D. J. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metabolism* vol. 27 740–756 (2018).

170. Hernandez, A. F. *et al.* Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* **392**, 1519–1529 (2018).

171. Bain, S. C. *et al.* Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial. *Diabetes, Obes. Metab.* **21**, 499–508 (2019).

172. Nordisk, N., Bagsvaerd, D.-M. & Hospi, S. J. Liraglutide and cardiovascular outcomes in type 2 diabetes. *Drug and Therapeutics Bulletin* vol. 54 101 (2016).

173. Eliaschewitz, F. G. *et al.* Semaglutide and Cardiovascular Outcomes in Patients with

Type 2 Diabetes. (2016) doi:10.1056/NEJMoa1607141.

174. Gerstein, H. C. *et al.* Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* **394**, 121–130 (2019).

175. Task, A. *et al.* 2019 ESC Guidelines on diabetes , pre-diabetes , and cardiovascular diseases developed in collaboration with the EASD diseases of the European Society of Cardiology (ESC) and the. 255–323 (2020) doi:10.1093/eurheartj/ehz486.

176. Sarafidis, P. *et al.* SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol. Dial. Transplant.* **34**, 208–230 (2019).

177. Brownlee, M. Biochemistry and molecular cell biology of diabetic complications. *Nature* vol. 414 813–820 (2001).

178. Cernea, S. & Dobreanu, M. Diabetes and beta cell function: From mechanisms to evaluation and clinical implications. *Biochemia Medica* vol. 23 266–280 (2013).

179. Pussinen, P. J. *et al.* Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. *Arterioscler. Thromb. Vasc. Biol.* **27**, 1433–1439 (2007).

180. Severino, P. *et al.* Myocardial ischemia and diabetes mellitus: Role of oxidative stress in the connection between cardiac metabolism and coronary blood flow. *Journal of Diabetes Research* vol. 2019 (2019).

181. Hviid, A. V. R. & Sørensen, C. M. Glucagon-like peptide-1 receptors in the kidney: Impact on renal autoregulation. *American Journal of Physiology - Renal Physiology* vol. 312 F443–F454 (2020).

182. Avgerinos, I. *et al.* Glucagon-like peptide-1 receptor agonists and microvascular

outcomes in type 2 diabetes: A systematic review and meta-analysis. *Diabetes, Obes. Metab.* **21**, 188–193 (2019).

183. Saraheimo, M., Teppo, A. M., Forsblom, C., Fagerudd, J. & Groop, P. H. Diabetic nephropathy is associated with low-grade inflammation in Type 1 diabetic patients. *Diabetologia* **46**, 1402–1407 (2003).

184. Stehouwer, C. D. A. *et al.* Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: Progressive, interrelated, and independently associated with risk of death. *Diabetes* **51**, 1157–1165 (2002).

185. Yin, W. *et al.* Protein kinase C and protein kinase A are involved in the protection of recombinant human glucagon-like peptide-1 on glomeruli and tubules in diabetic rats. *J. Diabetes Investig.* **10**, 613–625 (2019).

186. Hendarto, H. *et al.* GLP-1 analog liraglutide protects against oxidative stress and albuminuria in streptozotocin-induced diabetic rats via protein kinase A-mediated inhibition of renal NAD(P)H oxidases. *Metabolism.* **61**, 1422–1434 (2012).

187. Ye, Y., Zhong, X., Li, N. & Pan, T. Protective effects of liraglutide on glomerular podocytes in obese mice by inhibiting the inflammatory factor TNF-α-mediated NF-κB and MAPK pathway. *Obes. Res. Clin. Pract.* **13**, 385–390 (2019).

188. Wang, X. *et al.* An experimental study of exenatide effects on reninjury in diabetic rats. *Acta Cir. Bras.* **34**, (2019).

189. Courrèges, J. P. *et al.* Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes. *Diabet. Med.* **25**, 1129–1131 (2008).

190. A prospective randomized control study on effect of liraglutide on cardiovascular outcomes in type II diabetes mellitus | Request PDF.

https://www.researchgate.net/publication/337831585_A_prospective_randomized_control_study_on_effect_of_liraglutide_on_cardiovascular_outcomes_in_type_II_diabetes_mellitus.

191. Anholm, C. *et al.* Liraglutide in combination with metformin may improve the atherogenic lipid profile and decrease C-reactive protein level in statin treated obese patients with coronary artery disease and newly diagnosed type 2 diabetes: A randomized trial. *Atherosclerosis* **288**, 60–66 (2019).

192. Li, H. *et al.* A Randomized Study to Compare the Effects of Once-Weekly Dulaglutide Injection and Once-Daily Glimepiride on Glucose Fluctuation of Type 2 Diabetes Mellitus Patients: A 26-Week Follow-Up. *J. Diabetes Res.* **2019**, (2019).

193. Wang, J. *et al.* The Effects of Once-Weekly Dulaglutide and Insulin Glargine on Glucose Fluctuation in Poorly Oral-Antidiabetic Controlled Patients with Type 2 Diabetes Mellitus. *Biomed Res. Int.* **2019**, 2682657 (2019).

194. von Scholten, B. J. *et al.* Effects of liraglutide on cardiovascular risk biomarkers in patients with type 2 diabetes and albuminuria: A sub-analysis of a randomized, placebo-controlled, double-blind, crossover trial. *Diabetes. Obes. Metab.* **19**, 901–905 (2017).

195. Yao, M. Y., Li, L. Q., Ma, J. X., Xue, P. & Li, Y. K. Use of flash glucose-sensing technology in patients with type 2 diabetes treated with liraglutide combined with CSII: a pilot study. *Brazilian J. Med. Biol. Res. = Rev. Bras. Pesqui. medicas e Biol.* **53**, (2019).

196. Lambadiari, V. *et al.* Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes. *Cardiovasc. Diabetol.* **17**, (2018).

197. Motoyama, S. *et al.* Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J. Am. Coll. Cardiol.* **66**, 337–346 (2015).

198. Motoyama, S. *et al.* Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. *Circ. J.* **71**, 363–366 (2007).

199. Ozaki, Y. *et al.* Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy. *Eur. Heart J.* **32**, 2814–2823 (2011).

200. Otsuka, K. *et al.* Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc. Imaging* **6**, 448–457 (2013).

201. Ferencik, M. *et al.* Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. *JAMA Cardiol.* **3**, 144–152 (2018).

202. Leipsic, J. *et al.* SCCT guidelines for the interpretation and reporting of coronary CT angiography: A report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J. Cardiovasc. Comput. Tomogr.* **8**, 342–358 (2014).

203. Cury, R. C. *et al.* CAD-RADS^{TM} 2.0 - 2022 Coronary Artery Disease-Reporting and Data System: An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the No. *J. Cardiovasc. Comput. Tomogr.* **16**, 536–557 (2022).

204. Lyons, R. A. *et al.* The SAIL databank: linking multiple health and social care datasets. *BMC Med. Inform. Decis. Mak.* **9**, (2009).

205. Zinman, B. *et al.* Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG

OUTCOME™). *Cardiovasc. Diabetol.* **13**, (2014).

206. Neal, B. *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med.* **377**, 644–657 (2017).

207. Diabetes in Wales | Diabetes UK. https://www.diabetes.org.uk/in_your_area/wales/diabetes-in-wales.

208. Fewer people in Wales dying from heart disease – new report | GOV.WALES. https://gov.wales/fewer-people-wales-dying-heart-disease-new-report-0.

209. Catapano, A. L. *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur. Heart J.* **37**, 2999-3058l (2016).

210. Harris, D. E. *et al.* Achievement of European guideline-recommended lipid levels post-percutaneous coronary intervention: A population-level observational cohort study. *Eur. J. Prev. Cardiol.* **28**, 854–861 (2021).

211. Catapano Al Fau - Graham, I. *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Hear. J.* **14;37(39):**, (2016).

212. Cholesterol Treatment Trialists', C. *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet (London, England)* **376**, 1670–1681 (2010).

213. Fulcher J Fau - O'Connell, R. *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* **385(9976):**, (2015).

214. Casula, M. *et al.* Prognostic impact of achieving LDL cholesterol guidelines-recommended target in secondary prevention: A real-world study. *Eur. Heart J.* **42**, 2551 (2021).

215. Casula, M. *et al.* Reaching the LDL-cholesterol target recommended by the guidelines: Be ambitious to get the maximum benefit. *Circulation* **144**, (2021).

216. Morieri, M. L., Avogaro, A. & Fadini, G. P. Cholesterol lowering therapies and achievement of targets for primary and secondary cardiovascular prevention in type 2 diabetes: unmet needs in a large population of outpatients at specialist clinics. doi:10.1186/s12933-020-01164-8.

217. Sudevan, R. *et al.* Compliance of secondary prevention strategies in coronary artery disease patients with and without diabetes mellitus - A cross-sectional analytical survey from Kerala, India. *Indian J. Endocrinol. Metab.* **25**, 129–135 (2021).

218. Pagidipati, N. J. *et al.* Secondary Prevention of Cardiovascular Disease in Patients With Type 2 Diabetes Mellitus. *Circulation* **136**, 1193–1203 (2017).

219. Murphy, C. *et al.* Statin use in adults at high risk of cardiovascular disease mortality: Cross-sectional analysis of baseline data from The Irish Longitudinal Study on Ageing (TILDA). *BMJ Open* **5**, e008017 (2015).

220. Odesjo, H. *et al.* Better adherence to lipid lowering guidelines in secondary prevention may result in substantial reduction in cardiovascular events. *Eur. Heart J.* **40**, 868 (2019).

221. Helin-Salmivaara, A. *et al.* Long-term persistence with statin therapy: a nationwide register study in Finland. *Clin. Ther.* **30 Pt 2**, 2228–2240 (2008).

222. Matthews, A. *et al.* Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ* **353**, (2016).

223. Vikman, S. *et al.* Underuse of evidence-based treatment modalities in diabetic patients with non-ST elevation acute coronary syndrome. A prospective nation wide study on acute coronary syndrome (FINACS). *Diabetes Res. Clin. Pract.* **61**, 39–48 (2003).

224. Grundy, S. M. Can Statins Cause Chronic Low-Grade Myopathy? *Ann. Intern. Med.* **137**, 617–618 (2002).

225. Joy, T. R. & Hegele, R. A. Narrative Review: Statin-Related Myopathy. *Ann. Intern.*

Med. **150**, 858–868 (2009).

226. Cai, T. *et al.* Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* **374**, n1537 (2021).

227. Wood, F. A. *et al.* N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. *N. Engl. J. Med.* **383**, 2182–2184 (2020).

228. Allahyari, A. *et al.* Low-density lipoprotein-cholesterol target attainment according to the 2011 and 2016 ESC/EAS dyslipidaemia guidelines in patients with a recent myocardial infarction: Nationwide cohort study, 2013-17. *Eur. Hear. J. - Qual. Care Clin. Outcomes* **7**, 59–67 (2021).

229. Davies, M. J. *et al.* Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **45**, 2753–2786 (2022).

230. Rydén, L. *et al.* ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* **34**, 3035–3087 (2013).

231. Hwang, J. K. *et al.* Glycemic Control Status After Percutaneous Coronary Intervention and Long-Term Clinical Outcomes in Patients With Type 2 Diabetes Mellitus. *Circ. Cardiovasc. Interv.* **10**, e004157 (2017).

232. Bae, J. *et al.* Long-term effects of the mean hemoglobin A1c levels after percutaneous coronary intervention in patients with diabetes. *Korean J Intern Med* **36**, 1365–1376 (2021).

233. Sharma, P. K. *et al.* Association of Glycemic Control With Mortality in Patients With Diabetes Mellitus Undergoing Percutaneous Coronary Intervention. *Circ. Cardiovasc. Interv.* **7**, 503–509 (2014).

234. Wiviott, S. D. *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes.

N. Engl. J. Med. **380**, 347–357 (2018).

235. Steiner, S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *Zeitschrift fur Gefassmedizin* vol. 13 17–18 (2016).

236. Bang, C., Mortensen, M. B., Lauridsen, K. G. & Bruun, J. M. Trends in antidiabetic drug utilization and expenditure in Denmark: A 22-year nationwide study. *Diabetes. Obes. Metab.* **22**, 167–172 (2020).

237. Association, A. D. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2018. *Diabetes Care* **41**, S73–S85 (2018).

238. Schernthaner, G. *et al.* CARMELINA: An important piece of the DPP-4 inhibitor CVOT puzzle. *Diabetes Res. Clin. Pract.* **153**, 30–40 (2019).

239. Schernthaner, G. *et al.* Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. *Cardiovasc. Diabetol. 2020 191* **19**, 1–17 (2020).

240. Morieri, M. L., Lamacchia, O., Manzato, E., Giaccari, A. & Avogardo, A. Physicians' misperceived cardiovascular risk and therapeutic inertia as determinants of low LDL-cholesterol targets achievement in diabetes. *Cardiovasc. Diabetol.* **21**, 57 (2022).

241. Hopstock, L. A. *et al.* Secondary prevention of cardiovascular disease needs improvement in men and women, with and without diabetes: The Tromso Study 2015-16. *Nor. Epidemiol.* **28**, 19 (2019).

242. Yamada-Harada, M. *et al.* Relationship Between Number of Multiple Risk Factors and Coronary Artery Disease Risk With and Without Diabetes Mellitus. *J. Clin. Endocrinol. Metab.* **104**, 5084–5090 (2019).

243. Bohn, B. *et al.* Achievement of treatment goals for secondary prevention of myocardial infarction or stroke in 29,325 patients with type 2 diabetes: a German/Austrian DPV-multicenter analysis. *Cardiovasc. Diabetol.* **15**, 72 (2016).

244. Gikas A Fau - Sotiropoulos, A. *et al.* Current status in achievement of glycaemic, lipid and blood pressure goals in type 2 diabetic patients with coronary artery disease. *Hell. J Cardiol* **50(6):552**-, (2009).

245. Cacoub, P. P. *et al.* Effects of adherence to guidelines for the control of major cardiovascular risk factors on outcomes in the REduction of Atherothrombosis for Continued Health (REACH) Registry Europe. *Heart* **97**, 660–667 (2011).

246. Hopstock, L. A. *et al.* Treatment target achievement after myocardial infarction and ischaemic stroke: cardiovascular risk factors, medication use, and lifestyle: the Tromsø Study 2015–16. *Eur. J. Prev. Cardiol.* **29**, 362–370 (2022).

247. Tran, J. N. *et al.* Impact of the 2013 cholesterol guideline on patterns of lipid-lowering treatment in patients with atherosclerotic cardiovascular disease or diabetes after 1 year. *J. Manag. Care Spec. Pharm.* **22**, 901–908 (2016).

248. Gulati, M. *et al.* 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **78**, e187–e285 (2021).

249. Hoffmann, U. *et al.* Noninvasive Assessment of Plaque Morphology and Composition in Culprit and Stable Lesions in Acute Coronary Syndrome and Stable Lesions in Stable Angina by Multidetector Computed Tomography. *J. Am. Coll. Cardiol.* **47**, 1655–1662 (2006).

250. Schuijf, J. D. *et al.* Differences in plaque composition and distribution in stable coronary artery disease versus acute coronary syndromes; non-invasive evaluation with multi-slice computed tomography. *Acute Card. Care* **9**, 48–53 (2007).

251. Maroules, C. D. *et al.* Coronary artery disease reporting and data system (CAD-RADS TM): Inter-observer agreement for assessment categories and modifiers. *J.*

Cardiovasc. Comput. Tomogr. **12**, 125–130 (2018).

252. Voros, S. *et al.* Prospective Validation of Standardized, 3-Dimensional, Quantitative Coronary Computed Tomographic Plaque Measurements Using Radiofrequency Backscatter Intravascular Ultrasound as Reference Standard in Intermediate Coronary Arterial Lesions: Results From the ATLANTA (Assessment of Tissue Characteristics, Lesion Morphology, and Hemodynamics by Angiography With Fractional Flow Reserve, Intravascular Ultrasound and Virtual Histology, and Noninvasive Computed Tomography in Atherosclerotic Plaques) I. *JACC Cardiovasc. Interv.* **4**, 198–208 (2011).

253. De Knegt, M. C. *et al.* Relationship between patient presentation and morphology of coronary atherosclerosis by quantitative multidetector computed tomography. *Eur. Heart J. Cardiovasc. Imaging* **20**, 1221–1230 (2019).

254. Hell, M. M. *et al.* Quantitative global plaque characteristics from coronary computed tomography angiography for the prediction of future cardiac mortality during long-term follow-up. *Eur. Hear. journal. Cardiovasc. Imaging* **18**, 1331–1339 (2017).

255. Chang, H. J. *et al.* Coronary Atherosclerotic Precursors of Acute Coronary Syndromes. *J. Am. Coll. Cardiol.* **71**, 2511–2522 (2018).

256. Liu, T. *et al.* Quantitative coronary plaque analysis predicts high-risk plaque morphology on coronary computed tomography angiography: results from the ROMICAT II trial. *Int. J. Cardiovasc. Imaging* **34**, 311–319 (2018).

257. Williams, M. C. *et al.* Coronary Artery Plaque Characteristics Associated With Adverse Outcomes in the SCOT-HEART Study. *J. Am. Coll. Cardiol.* **73**, 291–301 (2019).

258. Puchner, S. B. *et al.* High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain:

Results from the ROMICAT-II trial. *J. Am. Coll. Cardiol.* **64**, 684–692 (2014).

259. Park, H. B. *et al.* Atherosclerotic Plaque Characteristics by CT Angiography Identify Coronary Lesions That Cause Ischemia: a Direct Comparison to Fractional Flow Reserve. *JACC. Cardiovasc. Imaging* **8**, 1 (2015).

260. Cury, R. C. *et al.* CAD-RADSTM Coronary Artery Disease – Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NA. *J. Cardiovasc. Comput. Tomogr.* **10**, 269–281 (2016).

261. Shaw, L. J. *et al.* Society of Cardiovascular Computed Tomography / North American Society of Cardiovascular Imaging – Expert Consensus Document on Coronary CT Imaging of Atherosclerotic Plaque. *J. Cardiovasc. Comput. Tomogr.* **15**, 93–109 (2021).

262. Kubo, T. *et al.* The Dynamic Nature of Coronary Artery Lesion Morphology Assessed by Serial Virtual Histology Intravascular Ultrasound Tissue Characterization. *J. Am. Coll. Cardiol.* **55**, 1590–1597 (2010).

263. Arbab-Zadeh, A. & Fuster, V. The myth of the 'vulnerable plaque': transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J. Am. Coll. Cardiol.* **65**, 846–855 (2015).

264. Xu, P. *et al.* Radiomics: The Next Frontier of Cardiac Computed Tomography. *Circ. Cardiovasc. Imaging* **14**, E011747 (2021).

265. Kolossváry, M. *et al.* Radiomics versus visual and histogram-based assessment to identify atheromatous lesions at coronary CT angiography: An ex vivo study. *Radiology* **293**, 89–96 (2019).

266. Cardiovascular disease in Europe–epidemiological update 2015. Eur - Google Search.

https://www.google.com/search?client=safari&rls=en&q=Cardiovascular+disease+in+Europe–epidemiological+update+2015.+Eur&ie=UTF-8&oe=UTF-8.

267. Hecht, H. S. *et al.* 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J. Cardiovasc. Comput. Tomogr.* **11**, 74–84 (2017).

268. Cho, I. *et al.* Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur. Heart J.* **39**, 934–941 (2018).

269. Fulcher, J. *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet (London, England)* **385**, 1397–1405 (2015).

270. Yusuf, P. S. *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)* **364**, 937–952 (2004).

271. Williams, M. C. *et al.* Coronary CT angiography-guided management of patients with stable chest pain: 10-year outcomes from the SCOT-HEART randomised controlled trial in Scotland. *Lancet* **405**, 329–337 (2025).

272. Blankstein, R. *et al.* Perceived Usefulness of Cardiac Computed Tomography as Assessed by Referring Physicians and Its Effect on Patient Management. *Am. J. Cardiol.* **105**, 1246–1253 (2010).

273. Naue, V. M. *et al.* Changes in Medical Management after Coronary CT Angiography. *Arq. Bras. Cardiol.* **105**, 410 (2015).

274. Cheezum, M. K. *et al.* Changes in preventive medical therapies and CV risk factors after CT angiography. *JACC. Cardiovasc. Imaging* **6**, 574–581 (2013).

275. Laimoud, M., Faris, F., Elghawaby, H. & Garg, A. Coronary Atherosclerotic Plaque Vulnerability Rather than Stenosis Predisposes to Non-ST Elevation Acute Coronary Syndromes. *Cardiol. Res. Pract.* **2019**, 2642740 (2019).

276. Park, S. J. *et al.* Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial. *Lancet* **403**, 1753–1765 (2024).

277. Recommendations | Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis | Guidance | NICE. https://www.nice.org.uk/guidance/cg95/chapter/recommendations.

278. Naghavi, M. *et al.* From Vulnerable Plaque to Vulnerable Patient: A Call for New Definitions and Risk Assessment Strategies: Part II. *Circulation* **108**, 1772–1778 (2003).

279. De Korte, C. L., Pasterkamp, G., Van Der Steen, A. F. W., Woutman, H. A. & Bom, N. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. *Circulation* **102**, 617–623 (2000).

280. Wang, J. C., Normand, S. L. T., Mauri, L. & Kuntz, R. E. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* **110**, 278–284 (2004).

281. Bergström, G. *et al.* Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. *Circulation* **144**, 916 (2021).

282. Deng, W. *et al.* Characteristics of coronary artery atherosclerotic plaques in chronic kidney disease: evaluation with coronary CT angiography. *Clin. Radiol.* **74**, 731.e1-731.e9 (2019).

283. Zhang, J. *et al.* Coronary Plaque Characteristics Assessed by 256-Slice Coronary CT

Angiography and Association with High-Sensitivity C-Reactive Protein in Symptomatic Patients with Type 2 Diabetes. *J. Diabetes Res.* **2016**, 4365156 (2016).

284. Marassi, M. & Fadini, G. P. Real-world Evidence on Oral Semaglutide for the Management of Type 2 Diabetes. A Narrative Review for Clinical Practice. *Clin. Ther.* **47**, 102–110 (2025).

285. Petrie, J. R. The cardiovascular safety of incretin-based therapies: A review of the evidence. *Cardiovascular Diabetology* vol. 12 1–12 (2013).

286. Marso, S. P. *et al.* Diabetes mellitus is associated with plaque classified as thin cap fibroatheroma: An intravascular ultrasound study. *Diabetes Vasc. Dis. Res.* **7**, 14–19 (2010).

287. Halon, D. A. *et al.* Plaque Morphology as Predictor of Late Plaque Events in Patients With Asymptomatic Type 2 Diabetes A Long-Term Observational Study. (2018) doi:10.1016/j.jcmg.2018.02.025.

288. Gaspari, T., Welungoda, I., Widdop, R. E., Simpson, R. W. & Dear, A. E. The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE-/- mouse model. *Diabetes Vasc. Dis. Res.* **10**, 353–360 (2013).

289. Franklin, K. *et al.* Implications of diabetes in patients with acute coronary syndromes: The global registry of acute coronary events. *Arch. Intern. Med.* **164**, 1457–1463 (2004).

290. Pfeffer, M. A. *et al.* Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N. Engl. J. Med.* **373**, 2247–2257 (2015).

291. Husain, M. *et al.* Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* **381**, 841–851 (2019).

292. Cooke, C. E., Lee, H. Y., Tong, Y. P. & Haines, S. T. Persistence with injectable

antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr. Med. Res. Opin.* **26**, 231–238 (2010).

293. Lorber, D. GLP-1 receptor agonists: effects on cardiovascular risk reduction. *Cardiovasc. Ther.* **31**, 238–249 (2013).

294. Khan, M. S. *et al.* Glucagon-Like Peptide 1 Receptor Agonists and Heart Failure. *Circulation* **142**, 1205–1218 (2020).

295. Palmer, S. C. *et al.* Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* **372**, (2021).

296. Brock, C. *et al.* Liraglutide treatment reduced interleukin-6 in adults with type 1 diabetes but did not improve established autonomic or polyneuropathy. *Br. J. Clin. Pharmacol.* **85**, 2512 (2019).

297. Jensen, J. K. *et al.* Semaglutide reduces vascular inflammation investigated by PET in a rabbit model of advanced atherosclerosis. *Atherosclerosis* (2022) doi:10.1016/J.ATHEROSCLEROSIS.2022.03.032.

298. Jensen, J. K. *et al.* Effect of 26 Weeks of Liraglutide Treatment on Coronary Artery Inflammation in Type 2 Diabetes Quantified by [64Cu]Cu-DOTATATE PET/CT: Results from the LIRAFLAME Trial. *Front. Endocrinol. (Lausanne).* **12**, 1 (2021).

299. Hamal, S. *et al.* Effect of semaglutide on coronary atherosclerosis progression in patients with type II diabetes : rationale and design of the semaglutide treatment on coronary progressiontrial. 1–9 (2019) doi:10.1097/MCA.0000000000000830.

300. Ripa, R. S. *et al.* Effect of Liraglutide on Arterial Inflammation Assessed as [18 F]FDG Uptake in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial. *Circ. Cardiovasc. Imaging* **14**, 632–644 (2021).

301. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in

Diabetes-2021. *Diabetes Care* **44**, S111–S124 (2021).

302. Das, S. R. *et al.* 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes. *J. Am. Coll. Cardiol.* **76**, 1117 (2020).

303. Recommendations | Type 2 diabetes in adults: management | Guidance | NICE. https://www.nice.org.uk/guidance/ng28/chapter/Recommendations#first-line-drug-treatment.