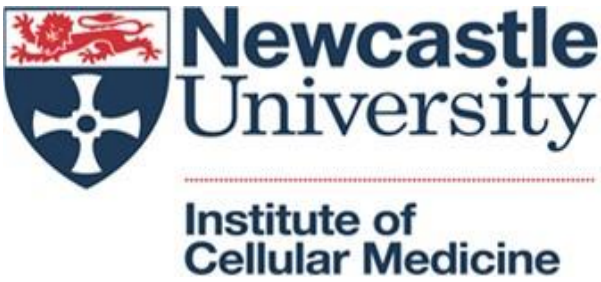

The Burden of Vulnerable Coronary Plaque Following Acute Coronary Syndrome in Older Patients: Evaluation Utilising Advanced Intracoronary Imaging Techniques

Thesis submitted for the degree of Doctor of Philosophy

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Abstract

Objectives

The burden of non-ST elevation acute coronary syndrome (NSTEACS) in older (≥75 years) patients is rising. However, there are few studies to date on the pattern of coronary disease in this cohort. Using intracoronary imaging, I aimed to evaluate the vulnerable plaque burden among older patients presenting with NSTEACS, establish its association with patient and lesion phenotypes, and explore determinants of adverse outcomes.

Methods

Prior to percutaneous coronary intervention (PCI), 3-vessel intracoronary imaging was performed with virtual histology intravascular ultrasound (VH IVUS) and optical coherence tomography (OCT). Angiographic, VH IVUS and OCT images were analysed offline and blinded to patient data. Major adverse cardiovascular events (MACE) at one year were defined as death, ACS, stroke, repeat unplanned revascularisation, and bleeding.

Results

Recruitment of older patients was successful, with 69.8% of approached patients recruited (91 patients, mean age 80.8 years, 63.7% male), and successful imaging performed in >70% of anatomically suitable vessels. There was a high success rate of PCI overall (90.4%).

With increasing age, %atheroma volume (<79 years: 42.7% vs. 79-82 years: 43.4% vs. >82 years: 50.0%, p<0.001) and burden of thin-cap fibroatheroma (TCFA) (5.7% vs. 9.3% vs. 14.1%, p<0.001) increased. Men had a higher burden of atheroma on all modalities but plaque composition did not differ between the sexes. Calcification on VH IVUS increased with frailty (robust: 13.7% vs. pre-frail: 13.0% vs. frail: 17.7%, p=0.018). Vulnerable plaque features on OCT such as rupture, microchannels and TCFA clustered together, suggesting they form part of the same pathophysiological process.

Calcification was initially associated with a reduction in the %stenosis of a lesion, mediated by a high rate of positive remodeling that slowed with severe calcification (R=0.363, p<0.001). Moderately calcified lesions had a higher residual %stenosis post-PCI (23.1% vs. none: 14.2% vs. severe: 19.0%, p=0.014) and were associated with higher MACE at 1 year (low: 9.5% vs. moderate: 31.6% vs. high 12.0%, p=0.044), driven by ACS. Previously identified vulnerable TCFA did not predict MACE at 1 year in this cohort (p=0.291).

Conclusions

Even in high-risk older patients, PCI after NSTEACS is successful and associated with a low rate of MACE at 1 year. At no age does the accumulation of coronary plaque plateau but frailty, not age, was associated with increased calcification. Calcium is not an inert plaque component, but actively shapes vessel remodeling. Moderate calcification had the highest risk for adverse outcomes at 1 year due to recurrent ACS, suggesting that these patients may derive greater benefit from an aggressive invasive strategy.

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Abbreviations

ACS	Acute Coronary Syndrome
ACUITY	Acute Catheterisation and Urgent Intervention Triage strategY [study]
ADAPT-DES	Assessment of Dual Anti-Platelet Therapy with Drug Eluting Stents [study]
ATHEROREMO-IVUS	European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound [study]
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCF	Congestive Cardiac Failure
ChC	Cholesterol Crystal
CI	Confidence Interval
CIA	Calcium Interface Area
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CTO	Chronic Total Occlusion
Cx	Circumflex (artery)
DC	Dense Calcium
DES	Drug Eluting Stent
EEM	External Elastic Membrane
EEP	Eagle Eye Platinum
FA	Fibroatheroma
FD-OCT	Frequency Domain Optical Coherence Tomography
FF	Fibro-Fatty
FFR	Fractional Flow Reserve
GRACE	Global Registry of Acute Coronary Events
HR	Hazard Ratio
hsCRP	Highly Sensitive C-Reactive Protein
IB-IVUS	Integrated Backscatter-Intravascular Ultrasound
ICON1	Improve Cardiovascular Outcomes in high-risk older patieNts with acute coronary syndrome [study]
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending (artery)
LAPS	Liverpool Active Plaque Score
LMS	Left Main Stem
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MLA	Minimum Lumen Area
MLD	Minimum Lumen Diameter

MRI	Magnetic Resonance Imaging
NC	Necrotic Core
NIRS	Near-Infrared Spectroscopy
NPV	Negative Predictive Value
NSTEACS	Non-ST Elevation Acute Coronary Syndrome
NSTEMI	Non-St Elevation Myocardial Infarction
OCT	Optical Coherence Tomography
OCT-TCFA	Optical Coherence Tomography Derived Thin-Cap Fibroatheroma
OR	Odds Ratio
PAV	Percent Atheroma Volume
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Substilisin/Kexin type 9
PIT	Pathological Intimal Thickening
PLATO	PLATelet inhibition and patient Outcomes [study]
PPV	Positive Predictive Value
PREDICT	Increasing The Participation Of The Elderly In Clinical Trials
PROSPECT	Providing Regional Observations to Study Predictors of Events in the Coronary Tree [study]
PSS	Plaque Structural Stress
PVD	Peripheral Vascular Disease
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
RCT	Randomised Controlled Trial
RD	Reference Diameter
RI	Remodeling Index
RSS	Residual SYNTAX Score
SD	Standard Deviation
SRI	SYNTAX Revascularisation Index
STEMI	ST Elevation Myocardial Infarction
SYNTAX	SYNergy between PCI with TAXus and cardiac surgery [study]
TCFA	Thin-Cap Fibroatheroma
TD-OCT	Time Domain Optical Coherence Tomography
UA	Unstable Angina
VH-IVUS	Virtual Histology Intravascular Ultrasound
VH-TCFA	VH IVUS-Defined Thin-Cap Fibroatheroma
VIVA	Virtual histology In Vulnerable Atherosclerosis [study]

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CHAPTER 1: INTRODUCTION

1.1 Acute Coronary Syndrome In Older Patients

Ischaemic heart disease (IHD) is a disease of ageing. In 2013-2014, almost half of all myocardial infarctions (MI) occurred among patients aged over 70 years in the UK[1]. Moreover, older patients presenting with acute coronary syndrome (ACS) are at higher risk of poor outcomes even after adjustment for confounding factors such as co-morbidities[2]. However, the rate of invasive angiography in patients with non-ST elevation ACS (NSTEACS) declines with age[3]. This has led to a treatment paradox, whereby high-risk older patients who are more likely to benefit from invasive treatment following ACS are less likely to receive it.

1.1.1 The Epidemiology of ACS In Older Patients

Table 1.1 illustrates the under-representation of older patients in international ACS registries for which data on older patients has been published. In the Global Registry of Acute Coronary Events (GRACE), the median age of patients was 65 years, and 24% were over the age of 75 years[4]. However, almost half of those with NSTEACS in GRACE were over the age of 70 years, reflecting the later age of presentation of NSTEACS versus ST elevation MI (STEMI). In a large Canadian registry, the proportion of women presenting with NSTEACS increased with age (23.1% of those ≤64 years vs. 46.0% of those ≥75 years, $p<0.001$)[5]. The proportion of patients with ACS with previous angina (41.8% of those ≤64 years vs. 65.6% of those ≥75 years, $p<0.001$), MI (25.2% vs. 41.7%, $p<0.001$), heart failure (5.0% vs. 17.9%, $p<0.001$), and cerebrovascular disease (4.1% vs. 12.1%, $p<0.001$) also increased with age[5]. The presence of such co-morbidities can influence the diagnosis, treatment and prognosis of ACS and, as such, requires accurate documenting to allow correction for confounding factors.

Registry	Recruiting Years	Country	Sample	Oldest cohort	% in Oldest cohort	% angiography in oldest cohort	In-hospital mortality in oldest cohort
Canadian ACS Registry[5]	1999-2001	Canada	4,627	>75	25.3%	OR 0.79*	5.5%
EuroHeart Survey ACS[6]	2000-2001	International	10,253	≥75	25%	38.5%	9.7%
CRUSADE[7]	2001-2003	USA	56,963	>65	58.4%	63.3%	7.1%
GRACE[3, 4]	2001-2007	International	31,982	>75	24%	41%	4.5%
SPACE[8]	2005-2007	Saudi Arabia	5,055	>70	16%	54%	7%
PL-ACS[9]	2003-2009	Poland	78,422	>80	17.5%	24%	5% (I), 14% (C)
MINAP[10]	2006-2010	England and Wales	155,818	≥85	12.9%	14%	40.8% (I), 66.2% (C)†

Table 1.1 Under-representation of older patients in registries of NSTEACS

Older patients are under-represented in the largest international registries of NSTEACS and several group patients >75 years in the "oldest" cohort within the registry. In addition, there is a low uptake of invasive management for older patients in these registries despite the fact that this has been demonstrated to be a superior treatment option vs. conservative management.

*every decade increase in age resulted in a decrease in coronary angiography
(I) invasive treatment, (C) conservative management
†all-cause mortality during mean follow up of 2.29 years

Schoenenberger et al enrolled a large, prospective cohort of 13,662 patients with ACS aged ≥70 years and stratified them by year of presentation (2001-4, 2005-8, 2009-12)[11]. Over the observed 12 year period, mean age increased (78.6 vs. 79.3 vs. 79.6 years, p<0.001), incidence of STEMI decreased (53.6% vs. 49.7% vs. 48.1%, p<0.001) and the prevalence of dementia increased (3.9% vs. 4.1% vs. 5.2%, p<0.001)[11]. In-hospital adverse outcomes decreased over time (14.4% vs. 11.5% vs. 11.3%, p<0.001), but not in the oldest (nonagenarian) sub-group[11].

1.1.2 Age Predicts Adverse Outcomes Following ACS

Older patients presenting with ACS are at high risk of poor short and long term outcomes. Each 10-year increase in age confers a 70-75% increase in in-hospital mortality in patients presenting with ACS (**Table 1.1, Figure 1.1**)[2, 12]. In the GRACE registry, when comparing the youngest (<45 years) with the oldest (≥85 years) age groups, cardiogenic shock was nearly 6 times more common and the rate of major bleeding was nearly tripled[12]. Predictors of peri-procedural mortality following percutaneous coronary intervention (PCI) in ACS in patients ≥75 years include presentation with haemodynamic instability, chronic renal failure, prior stroke and left main stem (LMS) disease and patients ≥75 years are more likely to suffer a non-fatal stroke, major bleeding or renal failure requiring dialysis following PCI for ACS[13].

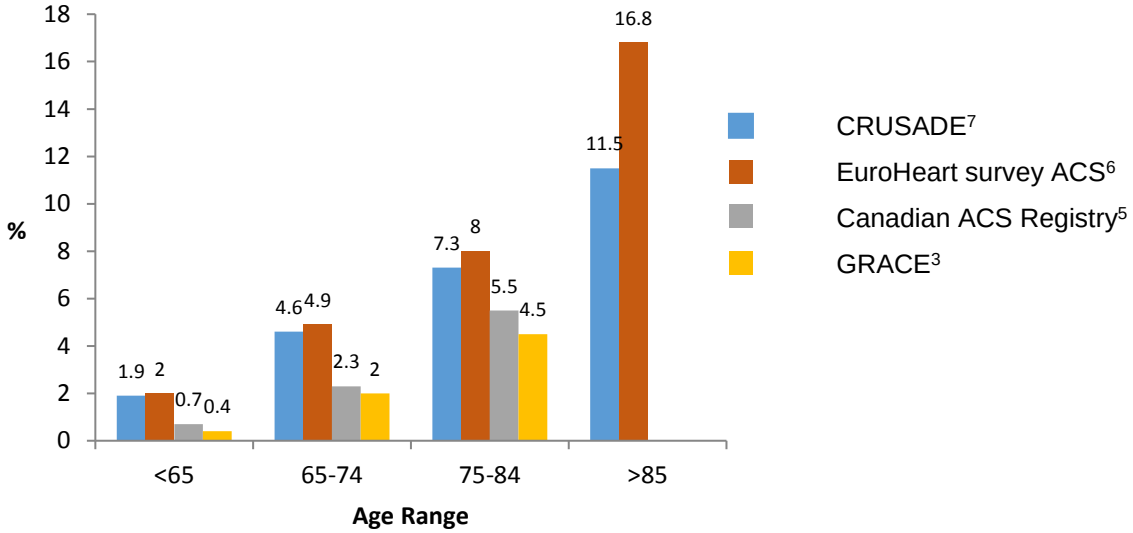


Figure 1.1 In-hospital mortality by age in ACS registries

In-hospital mortality increased with age in all 4 large international ACS registries (the Canadian ACS and GRACE registries have not published data for patients >85 years).

The increased risk persists after hospital discharge. In a prospective cohort study that enrolled 7,217 patients undergoing PCI in Rotterdam, after adjusting for confounding factors, all-cause mortality was significantly higher in octogenarians at 30 days, 1 year and four years[14]. However, the proportion of cardiac deaths declined over time and this reduction was more pronounced in octogenarians (although the difference in the proportion of non-cardiac deaths at 4 years between younger patients and octogenarians did not reach statistical significance: 57.5 vs. 72.2%, p=0.090)[14]. There was no difference in the incidence of MI following PCI in younger patients and octogenarians (9.7 vs. 14.0 per 1,000 person-years at four years), but a lower rate of target vessel revascularisation in the octogenarian cohort (25.0 vs. 37.7 per 1,000 person-years at four years)[14].

1.1.3 Frailty And The Vulnerable Patient

Frailty, a vulnerability to physiological stressors due to a decline in reserve and resilience with age, is emerging as an important concept in identifying older people at risk of adverse outcomes such as functional decline, institutionalisation and death. It has been defined by a consensus group as “a medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death”[15]. Although it is related to the ageing process, the concept of frailty may help to explain the variance in functional decline with

chronological ageing, and could predict an individual's vulnerability to adverse events in older age. A better understanding of the mechanisms underlying frailty may pave the way to identifying potential targets for its prevention and/or treatment.

There is currently no universally accepted definition or measurement tool for frailty, leading to difficulty in comparing studies of frailty. De Vries et al proposed that, as frailty is a multi-dimensional concept, a measurement tool should incorporate physical (e.g. nutrition, physical activity, mobility and strength), psychological (e.g. cognition and mood) and social (e.g. availability of support) components[16].

Fried et al were the first to develop an objective frailty scoring system, using data obtained from the Cardiovascular Health Study, a prospective observational cohort study of 5,317 participants aged ≥65 years from 4 communities in the USA[17]. **Table 1.2** outlines the Fried Frailty Criteria. Overall, 6.9% of the original study population were categorised as frail at baseline, and the prevalence of frailty increased with age and female gender[17]. Over a 7 year follow-up period, 43% of those originally categorised as frail had died, compared to 23% of those in the pre-frail group and 12% of the robust group ($p<0.0001$)[17]. Frailty, as measured by the Fried criteria, was also associated with hospitalisation, falls, and worsening mobility[17]. In addition, those who were pre-frail at baseline were more than twice as likely to become frail over 3 years, compared to those who were robust at baseline[17].

Frailty Characteristic	Cardiovascular Health Study Measure
Nutritional status	Weight loss >10 lbs unintentionally in the preceding year
Strength	Grip strength, the lowest 20% scoring positive (by gender and body mass index)
Endurance/Energy	Self-reported exhaustion
Mobility	Walking time over 15 feet, the lowest 20% scoring positive
Physical activity	Kcals/week, lowest 20% scoring positive

Table 1.2 Fried frailty criteria

Frail: ≥3 criteria present, pre-frail: 1-2 criteria present, robust: 0 criteria present

Gharacholou et al enrolled 545 patients aged ≥65 years undergoing PCI, of which 65.3% was an urgent or emergency procedure[18]. The mean age of participants was 74.8 ± 6.4 years and 18.6% were frail, 47.4% pre-frail, and 20.6% were robust according to the Fried frailty criteria[18]. Frailty was associated with increasing age,

female sex and increasing co-morbidity but there were no differences between frailty groups in the short-term (30-day) outcome rate[18]. Singh et al showed, in the same population, that the addition of frailty, quality of life and a co-morbidity index to a conventional cardiovascular risk score (the Mayo Clinic Risk Score: presence of cardiogenic shock, LMS disease, severe renal disease, urgent or emergency procedure, congestive heart failure, angiographic evidence of thrombus, multi-vessel disease or older age[19]) improved the risk prediction for older patients undergoing PCI (C-statistic improved from 0.628 with the risk score alone to 0.724, p=0.007)[20].

White et al measured self-reported Fried Frailty Score in 4,996 patients with NSTEACS aged ≥65 years[21]. The majority of the cohort were robust (72.3%), with 23.0% pre-frail and 4.7% frail. Increasing frailty was associated with older age, previous cardiovascular co-morbidities and GRACE risk score (all p<0.001) but the percentage of patients undergoing angiography did not differ (robust: 39.5% vs. pre-frail: 36.8% vs. frail: 41.8%, p=0.177)[21]. Frail patients experienced a higher likelihood of the composite endpoint of cardiovascular death, MI, or stroke compared with robust patients (39.7% vs. 23.1%; hazard ratio [HR]: 1.76; 95% confidence interval [CI]: 1.36–2.28; p<0.001). In addition, after adjustment for baseline characteristics and GRACE score, frailty remained independently associated with the composite endpoint[21].

1.1.4 The Treatment Paradox

Despite being a high-risk group, data from multiple global registries have consistently shown that older patients are much less likely to undergo invasive revascularisation following ACS (**Table 1.1**). In an analysis of three international registries (GRACE, and 2 Canadian registries: ACS I and ACS II), the rate of angiography following ACS decreased with age: 86.3% in patients ≤65 years, 80.3% in those 65-74 years, and 56.9% in patients ≥75 years (p<0.001)[3]. In addition, older patients waited longer for angiography following ACS (≤65 years: 3 days, interquartile range (IQR) 2-5; 65-74 years: 4 days, IQR 2-6; ≥75 years: 4 days, IQR 4-7; p<0.001)[3]. Physician-reported reasons given in the Canadian ACS II registry for not following an early invasive strategy included presence of significant co-morbidities (15.7% of those ≥75 years vs. 2.4% of those ≤65 years, p<0.001), patient or family refusal (10.2% vs. 5.2%, p=0.01), and bleeding or safety concerns (8.5% vs. 0%, p<0.001)[3]. Although rates of PCI in older patients have increased over time (**Figure 1.2**), they are still well below the rates seen in younger patients[11].

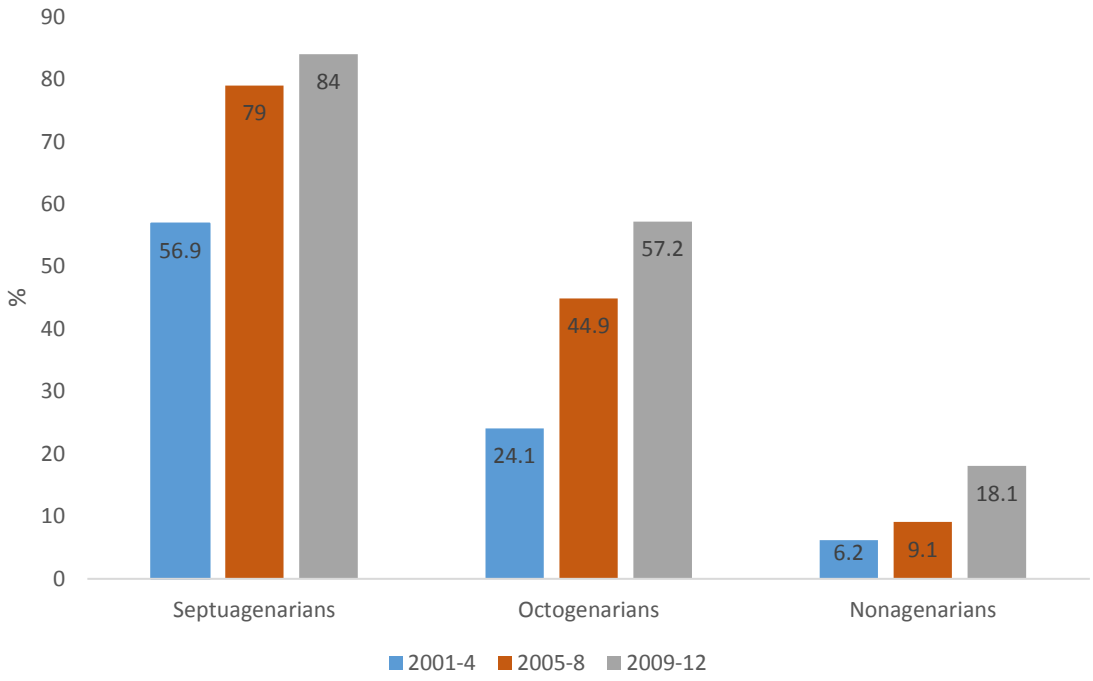


Figure 1.2 Temporal trends in the use of PCI in older patients with ACS

The use of PCI decreases as the age of patients increases although, overall, the use of PCI has increased for all ages, p<0.001 across time points in each age group[11]

Although the use of an invasive strategy offers the greatest relative benefit to younger patients, it offers the greatest absolute benefit to those over 75 years; within each age group, the 1-year mortality rate was significantly lower in those who underwent PCI compared to those who didn't (≤65 years: 1.6% vs. 4.9%; 65-74 years: 4.9% vs. 10.5%; ≥75 years: 11.6% vs. 21.8%; p<0.001)[3]. In an analysis of the Polish Registry of Acute Coronary Syndromes of 13,707 patients aged ≥80 years enrolled from 2003-2009, invasively managed patients had a higher rate of major bleeding but lower rates of MI, and in-hospital, 30-day, 6-month, 1-year and 2-year mortality compared to propensity score-matched patients that were managed conservatively. The rate of stroke was not significantly different between the two groups. Over the course of the study, the rate of PCI for NSTEACS in older patients did increase from 7.3% in 2003 to 37.3% in 2009[9].

Savonitto et al randomised 313 patients (mean age 82 years) with NSTEACS to either early (<72 hours) angiography or an initial conservative strategy, where angiography was only allowed in the case of ischaemia refractory to medical therapy, reinfarction, ischaemic heart failure or ventricular arrhythmia[22]. There was a significant reduction in in-hospital recurrent ischaemia (0.6% in the early angiography group vs. 9.4% in the initial conservative management group, p=0.0004). However, at 1 year, only patients with an elevated baseline troponin had a significant reduction in the primary composite

end-point (all-cause mortality, MI, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding) when managed with early angiography (22.1% vs. 40%, p=0.03)[22]. Likewise, the recent "After 80" study conducted in Norway, (n=457), showed a benefit with an invasive strategy compared with conservative treatment in patients presenting with NSTEACS in terms of reduction in the composite end point of death, MI, need for urgent revascularisation and stroke (41% vs. 61%, p=0.0001). However, this study excluded high-risk frail patients and had a high non-recruitment rate of eligible patients (89%) due to short life expectancy, ongoing or recent bleeding, unable to comply with protocol, clinically unstable including ongoing ischaemia, refusal to participate, 'logistical and other reasons'[23].

Finally, a meta-analysis of 6 randomised controlled trials (RCT) compared a routine invasive strategy to selective invasive strategy for 1887 patients ≥75 years of age with NSTEACS. A routine invasive strategy was superior for the composite end-point of death or MI (odds ratio [OR] 0.65; 95% CI 0.51-0.83), but this was primarily driven by the reduced risk of MI (OR 0.51; 95% CI 0.40-0.66) with no difference between the groups in all-cause mortality (OR 0.85; 95% CI 0.63-1.20) or cardiovascular death (OR 0.84; 95% CI 0.61-1.15)[24].

1.1.5 Coronary Intervention In The Older Patient With ACS

1.1.5.1 Vascular Access

Age is a powerful predictor of peri-procedural bleeding complications following PCI and it is known that radial artery access reduces the risk of bleeding complications compared to femoral artery access[25]. In addition, transfemoral access in older patients can be complicated by calcified and atherosclerotic peripheral arteries, thus increasing the risk of vascular injury. Moreover, older patients are less likely to be able to tolerate prolonged bed rest after a femoral approach procedure due to issues such as prostate problems or arthritis. However, older patients are less likely to undergo PCI via transradial access. In the UK, analysis of the British Cardiovascular Intervention Society Database demonstrated a lower rate of radial access with increasing age (p<0.0001)[26]. In this cohort, utilisation of transradial access was also associated with decreased 30-day mortality in all age groups[26].

1.1.5.2 Coronary Anatomy

Older patients with acute coronary syndrome have been shown to have more complex disease than younger patients, with one study demonstrating a higher rate of multi-vessel disease in octogenarians compared to patients <65 years (79% vs. 40%, p<0.05)[27]. In a study of older patients (≥65 years), multi-vessel or LMS disease was more common in frail patients compared to pre-frail or robust patients (74% vs. 68% vs. 60%, p=0.019), even after adjusting for age and sex (p=0.005)[18]. Because of this increased complexity of coronary disease, procedural success is lower in older patients (9.4% vs. 4.0%, p<0.001)[14].

In addition, the coronary vessels of older patients are frequently calcified (85% of lesions in one series of nonagenarians undergoing PCI). **Figure 1.3** shows a typical appearance of the coronary arteries of an older patient presenting with ACS. In an angiographic sub-study of patient-level pooled analysis of 2 large-scale, prospective, randomised trials consisting of 6,855 patients with ACS (Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY] and Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction) demonstrated an increase in target lesion calcium with increasing age[28]. In turn, moderate or severe target lesion calcification was a significant predictor of non-coronary artery bypass graft (CABG) related major bleeding (HR 1.24, 95% CI 1.02-1.52, p=0.03)[28]. There is little data available on the use of calcium debulking techniques such as rotational atherectomy in older patients but, in one registry of 218 patients, age >70 years was not a predictor of all-cause mortality after rotablation (p=0.615)[29].

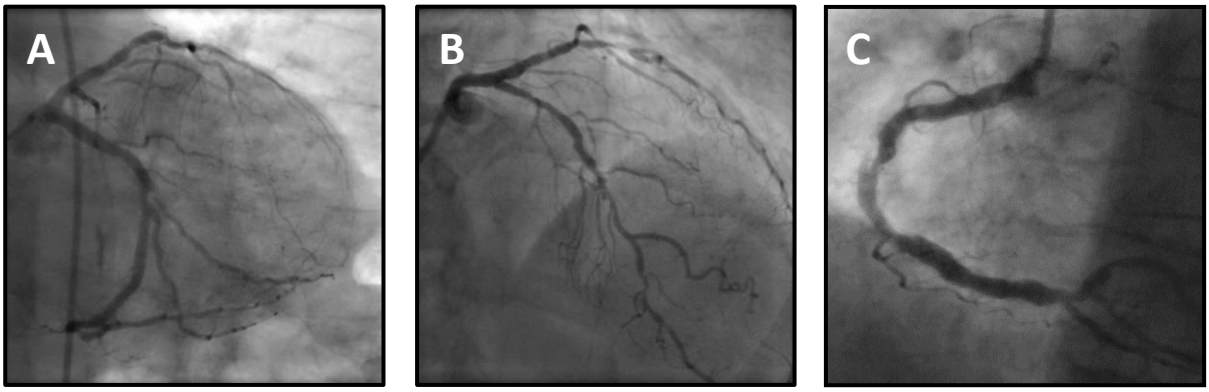


Figure 1.3 Examples of the pattern of coronary artery disease in older patients with ACS

Panel A: 77 year old male who presented with a non-ST elevation MI (NSTEMI). Angiography of his left coronary system showed multi-vessel disease and he received one stent to his left anterior descending (LAD) artery.

Panel B: 85 year old female who presented with an NSTEMI. She had diffuse disease of her LAD and circumflex (Cx) arteries, both of which were stented.

Panel C: 82 year old male with heavy calcification of his right coronary artery (RCA). PCI was attempted but unsuccessful.

A single-centre retrospective study of 158 patients with ACS categorised participants as elderly (≥75 years, n=65) or non-elderly (<75 years, n=93) and performed pre-intervention grayscale intravascular ultrasound (IVUS) in culprit arteries[30]. There were no differences between groups in the Synergy between PCI with Taxus and cardiac surgery (SYNTAX) score (10.8 ± 7.6 vs. 9.4 ± 5.4, p=0.500) or quantitative coronary angiography (QCA) measurements such as % diameter stenosis (73.1 ± 12.2 vs. 76.5 ± 10.0, p=0.15)[30]. On IVUS, elderly patients had a higher remodeling index (RI, 1.15 ± 0.14 vs. 1.12 ± 0.14, p=0.05) and a trend towards a higher incidence of calcification (85% vs. 72%, p=0.06) and attenuated plaque (63% vs. 47%, p=0.07) on qualitative assessment[30]. These findings correlate with a previous IVUS study that demonstrated that octogenarians had a greater calcium arc (199 ± 91º vs. 115 ± 71º, p<0.0001) and calcium length (5.5 ± 2.9 vs. 3.5 ± 2.8mm, p=0.006) than patients <65 years at the ACS culprit lesion site[27]. However, plaque burden and maximum stenosis were not significantly different between the two age groups.

1.1.5.3 Percutaneous Coronary Intervention Strategy

In an effort to reduce peri-procedural complications in older patients with ACS, it has been suggested that an incomplete revascularisation strategy may be preferable in this high-risk cohort with multi-vessel disease and complex co-morbidities. A prospective, single centre study followed 502 patients ≥75 years of age who presented with ACS

and multi-vessel disease and who underwent either complete or incomplete revascularisation[31]. There was no difference in major adverse cardiovascular events (MACE: cardiac death, non-fatal acute MI, target lesion/target vessel revascularisation and cerebral artery events) between the two groups after a median follow-up of 36 months (20.4% in the incomplete revascularisation group vs. 14.9% in the complete revascularisation group, p=0.141)[31]. However, there was a higher mortality rate in the incomplete revascularisation group both in-hospital (2.9% vs. 1.3%, p<0.0001) and at follow-up (13.6% vs. 7.7%, p=0.05)[31]. This may be due to the fact the incomplete revascularisation group had a higher incidence of multi-vessel disease and a higher SYNTAX score, and patients in the complete revascularisation group that had failed PCI (n=21) were transferred into the incomplete revascularisation cohort.

In a multi-centre RCT, 800 patients ≥80 years with NSTEACS and stable angina were randomised to receive either second-generation everolimus-eluting drug eluting stents (DES) or bare metal stents[32]. The incidence of MI (8.7% vs. 4.3%, p=0.014) and target vessel revascularisation (7.0% vs. 2.0%, p=0.0009) in the first year of follow-up were higher in the bare metal stent group, but there was no difference in mortality (7.2% vs. 8.5%, p=0.51) or major haemorrhage (1.7% vs. 2.3%, p=0.61) between the groups[32].

1.1.5.4 Coronary Artery Bypass Grafting

There are few studies examining the role of CABG in older patients with ACS. In a non-randomised prospective study of 249 patients aged ≥80 years with LMS disease (65.1% presented with ACS), patients who underwent CABG were more likely to have MACE (defined as cardiac death, MI, repeat revascularisation, and stroke/transient ischaemic attack) at 30 days than those who underwent PCI (27.6% vs. 18.3%)[33]. However, after a mean follow up of 23±16 months, the MACE-free survival rates between the groups were similar (56.7% in the PCI group and 64.8% in the CABG group, p=0.33). In a retrospective study of 10,141 older ACS patients with multi-vessel disease (mean age 87.2 years), higher mortality was noted in the early months after CABG compared to PCI (OR 1.48, 95% CI 1.34-1.64, p<0.01), but CABG provided significantly lower mortality (OR 0.60, 95% CI 0.53-0.69, p<0.05) and freedom from the composite outcome of death, repeat revascularisation, stroke and MI at 3 years (OR 0.83, 95% CI 0.76-0.91, p<0.01)[34]. However, both of these studies were conducted in the early 2000s in North America, before widespread use of DES and contemporary pharmacotherapy, so their results may not be applicable in the modern era of PCI.

1.1.6 Representation Of Older Patients In Cardiovascular Research

Despite this well documented increase in risk, older patients are significantly under-represented in cardiovascular clinical trials. In the Canadian ACS II registry, 9.6% of patients ≥75 years did not undergo angiography following ACS because their physician felt it was not supported by trial evidence[3]. A systematic review of RCTs in ACS showed that 55.2% of studies between 1996 and 2000 did not enrol any patients over the age of 75 years, and 31.9% actively excluded patients in this age group[35]. Although enrolment of older patients (≥75 years) has increased through the decades, only 10.3% of patients fell into this age category in the RCTs published between 1996 and 2000[35]. However, previous cohort studies of older patients have shown good recruitment rates (72% of eligible participants were recruited to the Newcastle 85+ study) and a willingness among this age group to actively participate in medical research[36].

Of the 44 previously published RCTs in ACS in 2014, 10 studies (22.7%) had upper age limits (4 RCTs excluded patients >75 years, 4 excluded >80 years, 1 excluded >85 years and 1 excluded >90 years) and the average age of participants across all RCTs was 62.0±6.8 years. Two RCTs (4.5%) specifically recruited older patients[32, 37]. Of the 70 published prospective observational studies, 11 (15.7%) had upper age limits (1 study excluded >55 years, 3 excluded >75 years, 5 excluded >80 years and 2 excluded >85 years) and the average age of participants was 61.3±5.9 years. Six prospective observational studies did not define whether there were any exclusion criteria related to age. Two observational studies (2.9%) specifically recruited older patients[38, 39]. However, at least in RCTs, the percentage of trials actively excluding older patients does seem to be falling, from 31.9% in 1996-2001[35] to 22.7% in 2014.

In addition, older participants in clinical trials may not be representative of the elderly population presenting with ACS. Kandzari et al analysed data from a multicentre registry of 55,172 patients with ACS, comparing those who were simultaneously enrolled in a clinical trial to those who were not, and showed that 24.1% of patients enrolled in trials were ≥75 years compared to 35.7% of those who were not ($p<0.0001$)[40]. Comparison of the patients in this community registry with those in the Virtual Coordinating Center for Global Collaborative Cardiovascular Research clinical trials group revealed that those patients in clinical trials are younger, more likely to be male, are less likely to have cardiac risk factors (including hypertension, hyperlipidaemia, diabetes and smoking), and less likely to have co-morbidities such as

heart failure, stroke and previous MI[41]. These differences are more pronounced with increasing age[41]. These factors make it more difficult to extrapolate evidence from clinical trials to the treatment of older patients in daily clinical practice.

Recently, the PREDICT (Increasing the PaRticipation of the ElDerly In Clinical Trials) Consortium, a group funded by the European Union to study and help boost the number of elderly people taking part in research, has compiled a charter for the rights of older patients in clinical trials (**Table 1.3**)[42]. The Consortium aims to narrow the gap between populations recruited to clinical trials and real clinical practice. Guidelines published by the European Forum for Good Clinical Practice Geriatric Working Party suggest that research in older people should actively recruit patients over 75 years with no upper age limit, should recruit a majority of women, and should justify exclusion of co-morbidities in order to accurately reflect the population studied[43].

Older people have the right to access evidence-based treatments
Promote the inclusion of older people in clinical trials and prevent discrimination
Clinical trials should be made as practicable as possible for older people
Clinical trials in older people should be safe
Outcome measures should be relevant for older people
The values of older people participating in clinical trials should be respected

Table 1.3 The PREDICT charter

1.1.7 Conclusion

As our population ages, the burden of ACS in complex older patients (and especially NSTEACS) is on the rise. Currently, older patients with ACS are at higher risk of adverse outcomes but are far less likely to receive contemporary invasive management. There is a dearth of good quality RCTs comparing contemporary treatments in older patients, and the benefits of incomplete versus complete revascularisation, use of pharmacotherapy, and CABG are unclear. Accurate risk stratification in the older age groups, taking into account frailty status, may aid individualised decision making with respect to identifying which patients will benefit most from invasive revascularisation, but more research is needed in this field.

1.2 The Role Of Virtual Histology Intravascular Ultrasound In ACS

In recent years, novel intravascular imaging modalities have been developed to aid identification of high risk atherosclerotic plaques that are prone to causing adverse cardiovascular events. Radiofrequency data analysis of IVUS images is one such technique that has been validated both in vivo and ex vivo; the most widely used version is the virtual histology (VH) IVUS (Volcano Corporation, San Diego, CA)[44]. VH IVUS utilizes spectral pattern analysis techniques to differentiate plaque components and potentially identify high-risk vulnerable lesions.

1.2.1 Plaque Characterisation on Grayscale and VH IVUS

Grayscale IVUS uses high frequency (20-45MHz) ultrasound to visualize the components of the vessel wall by measuring the amplitude of the reflected ultrasound wave. This allows both quantitative measurements of lumen and vessel dimensions, as well as qualitative characterization of intra-arterial pathology. However, the sensitivity of echolucent plaque on IVUS to identify lipid pools present on histology was only 67% in one study[45]. Atherosclerotic plaques are also seldom made up of just one tissue type. They are a heterogenous mix of calcium, necrotic tissue, and fibrous tissue, and grayscale IVUS is unable to accurately distinguish between small areas of adjacent tissue components[46].

Whereas only the amplitude of the reflected ultrasound wave is used to construct the grayscale IVUS picture, VH IVUS utilizes spectral pattern analysis of the frequency and amplitude of the reflected wave to generate a more accurate representation of the tissue subtypes present (**Figure 1.4**)[47]. The VH IVUS algorithm was generated in vitro by analysing multiple spectral parameters to discriminate between fibrous tissue (green), fibro-fatty tissue (FF, light green), dense calcium (DC, white) and necrotic core (NC, red) (**Figure 1.5**)[47]. While the original VH IVUS development and validation utilised a 30MHz rotating transducer, VH IVUS is now performed with either a 20MHz synthetic aperture array transducer or a 45MHz rotating transducer[44, 48].

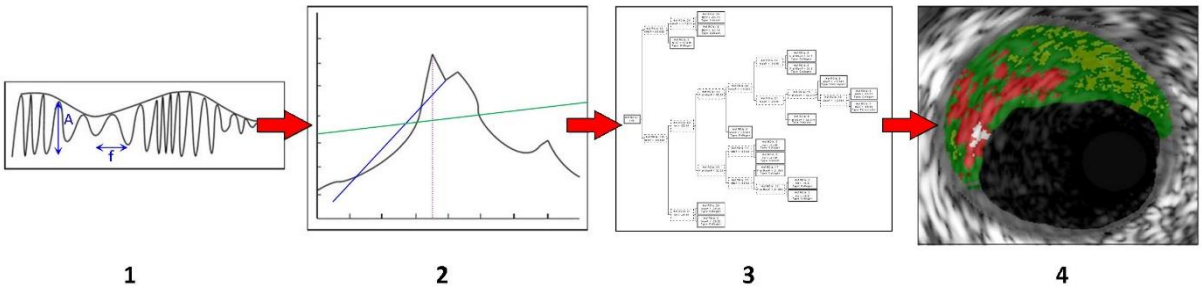


Figure 1.4 Schematic diagram of VH IVUS radiofrequency spectral pattern analysis

VH IVUS uses both the amplitude (A) and the frequency (f) of the reflected ultrasound wave to generate a tissue map (1). The data derived from the analysis of the power spectrum (2) is then fed into a statistical classifier (3) to generate plaque component classifications for the regions being analysed and, ultimately, the full IVUS image (4) (fibrous tissue: dark green, fibro-fatty: light green, necrotic core: red, dense calcium: white).

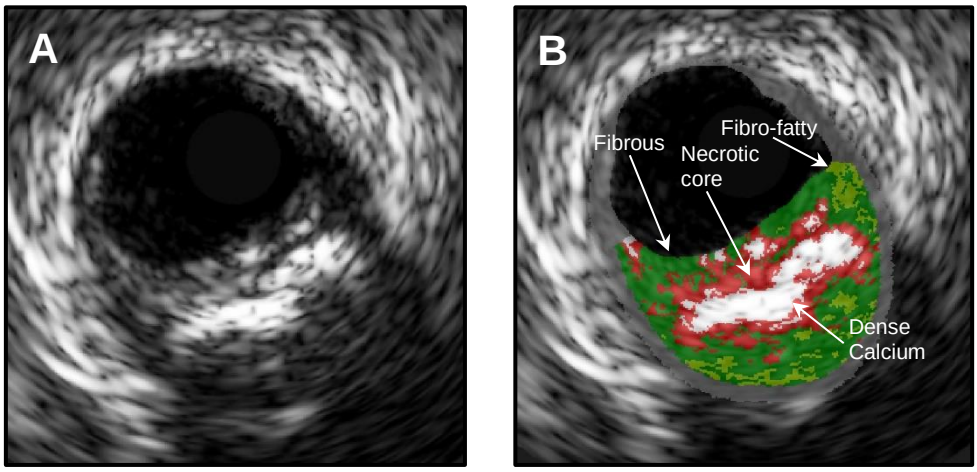


Figure 1.5 The appearance of plaque components on VH IVUS

Panel A: grayscale IVUS image of an eccentric and mildly calcified plaque

Panel B: the same plaque with VH IVUS plaque components overlaid

1.2.1.1 Accuracy Of VH IVUS In Identifying Plaque Components

An ex vivo validation study conducted by the patent holder, Volcano Corp., reported excellent accuracy between VH IVUS and histology in 184 plaques from 51 coronary arteries (fibrous: accuracy 93.5%, sensitivity 95.7%, specificity 90.9%; FF: accuracy 94.1%, sensitivity 72.3%, specificity 97.9%; NC: accuracy 95.8%, sensitivity 91.7%, specificity 96.6%; DC: accuracy 96.7%, sensitivity 86.5%, specificity 98.9%)[44]. In contrast, in vivo validation of VH IVUS against directional coronary atherectomy in 307 image pairs from 30 patients yielded slightly lower predictive accuracies (fibrous: 87.1%, FF: 87.1%, DC: 96.5%, NC: 88.3%), as directional coronary atherectomy can only sample the superficial part of the plaque and extracted tissue may reverse in the nosecone[49]. In a porcine model of atherosclerosis, there was no correlation between

VH IVUS and histology in the measurement of absolute or relative NC area, and the authors questioned the ability of VH IVUS to accurately identify this important plaque component[50]. However, this study was limited by the iatrogenic nature of the induced atherosclerosis, the small sample size, and the use of an animal model rather than human. More recently a study in human coronary arteries showed that VH IVUS had a high sensitivity (94%) for detecting NC when compared to histology, but low specificity (53%) and low positive predictive value (PPV, 48%)[51]. However, this study was limited by the small sample size (9 vessels from explanted hearts, with an average segment length of 35mm) and the very low plaque burden in those vessels[51]. The significant limitations of these validation studies mean that care must be taken when directly comparing plaque components seen on VH IVUS to histology or other intravascular imaging modalities.

1.2.1.2 Validation Of Lesion Classification

Virmani et al[9] have suggested a modification to the American Heart Association classification of atherosclerotic plaques[10,] taking into account stable and vulnerable lesion sub-types. Histological studies have shown that the plaque type most commonly associated with ACS and sudden death is the inflamed thin-cap fibroatheroma (TCFA, **Figure 1.6**), which consists of a large lipid core with a thin, inflamed fibrous cap infiltrated with macrophages[52].

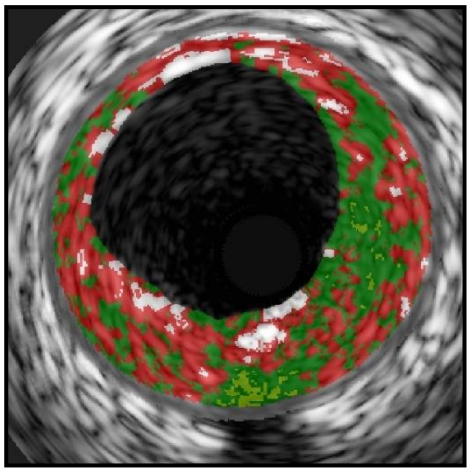


Figure 1.6 A representative image of VH-TCFA

A non-obstructive coronary plaque with >10% NC and NC in contact with the lumen for >36^{o}

Garcia-Garcia et al proposed standards for VH IVUS lesion classification based on histological classification (**Figure 1.7**)[53]. The definition of VH IVUS-derived TCFA (VH-TCFA) was first validated in a rabbit model of atherosclerosis and was shown to have a high sensitivity, specificity and positive predictive value (88%, 96%, and 87% respectively for non-calcified TCFA)[54]. Although this was an animal model, a previous study of 15 patients undergoing carotid endarterectomy showed that the accuracy of VH IVUS in identifying lesion type compared favourably to histology, with 99.4% accuracy for TCFA, 96.1% for calcified TCFA, 85.9% for fibroatheroma (FA), 72.4% for calcified FA, 85.5% for fibrocalcific plaque, and 83.4% in pathological intimal thickening (PIT)[55]. These findings were corroborated in a study of 8 ex vivo human coronary arteries which demonstrated VH IVUS to have a diagnostic accuracy of 82% in identifying TCFA[56]. However, these validation studies of the identification of TCFA by VH IVUS remain limited by their small size and use of animal models.

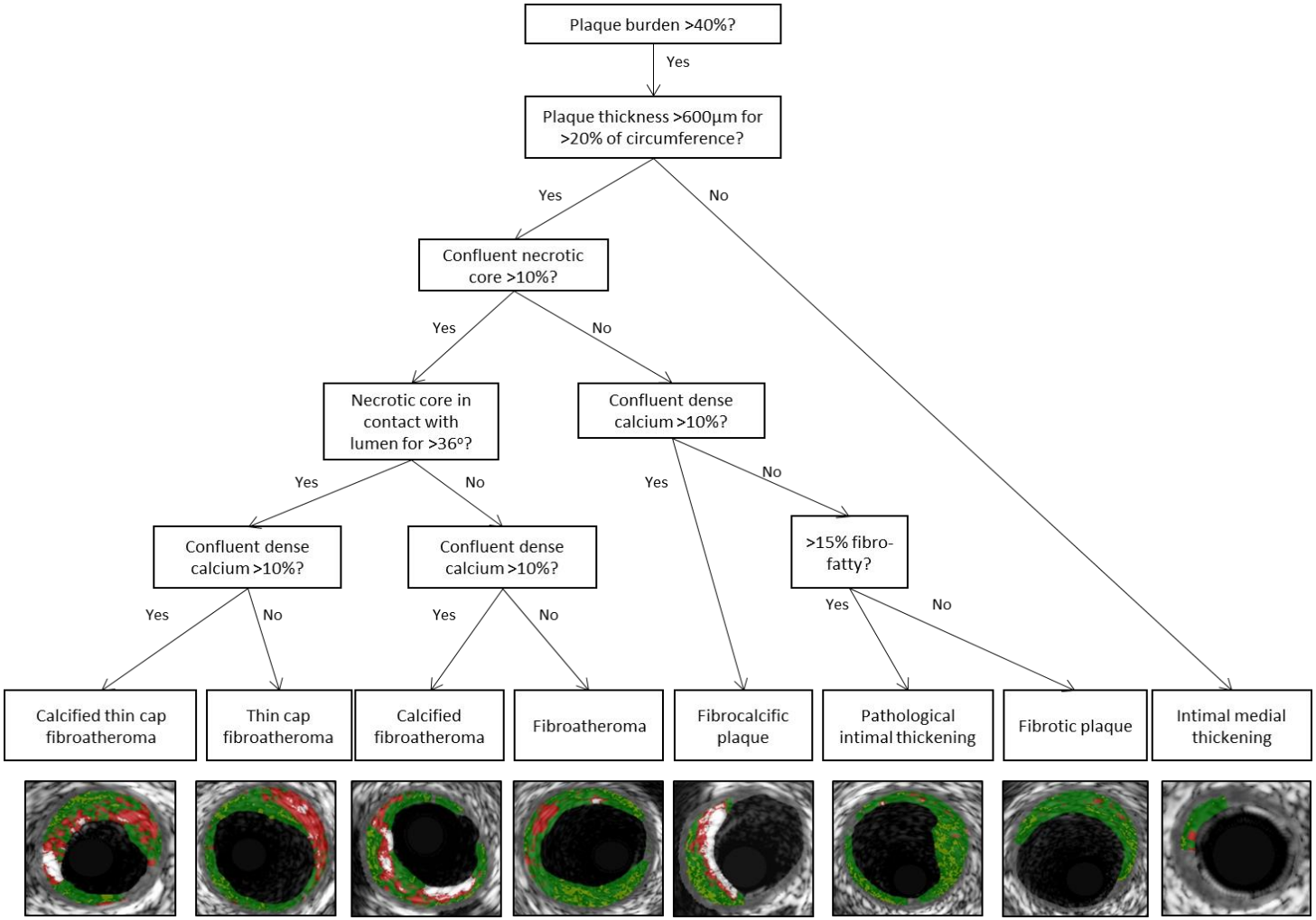


Figure 1.7 Decision tree for lesion classification on VH IVUS

A plaque becomes a lesion when the plaque burden is >40% for 3 consecutive images, and lesions separated longitudinally by >5mm of artery with a plaque burden <40% should be considered separate lesions. Where different plaque subtypes co-exist within a lesion, the lesion should be classified according to the highest risk subtype i.e. thin capped fibroatheroma> fibroatheroma> pathological intimal thickening> fibrotic plaque> intimal medial thickening.

1.2.2 VH IVUS Characterisation Of Patients With ACS

A study of 40 patients (32.5% with stable angina, 67.5% with ACS) demonstrated that patients with plaque rupture had a higher average cross sectional area of NC (0.30 vs. 0.22mm^2, p=0.02), DC (0.09 vs. 0.04mm^2, p=0.01) and FF tissue (0.58 vs. 0.34mm^2, p=0.03), and a lower cross sectional area of fibrous tissue (1.94 vs. 1.00mm^2, p<0.01)[57]. The site of plaque rupture was also shown to have a higher proportion of NC than the site of minimum lumen area (MLA, 16.7 vs. 11.8%, p=0.03)[57]. Hong et al demonstrated that patients with ACS had a higher proportion of NC (21.3 vs. 15.5%) and a lower proportion of fibrous tissue (55.5 vs. 62.3%) compared to those with stable angina[58]. The pattern of calcification may also be implicated in plaque vulnerability, with spotty calcification potentially increasing the likelihood of plaque rupture due to biomechanical stress. In a series of 225 patients with ACS, an NC/DC ratio ≥2 had a sensitivity of 50%, specificity of 76%, and a PPV of 91% for high-risk NSTEACS (p=0.010).

The CULPLAC trial enrolled 189 patients (70% with ACS, mean age 62.5 years) and demonstrated that VH-TCFA were more frequent in the culprit lesions of patients who presented with ACS (55.1% vs. 36.6% in non-culprit lesions in ACS patients vs. 14.4% in stable lesions, p=0.007)[59]. However, there were no differences in proportions of the four tissue components between culprit and non-culprit plaques, suggesting that it may be the lesion phenotype rather than the proportion of “adverse” tissue present that is responsible for plaque instability.

In a study of 172 patients with STEMI, VH-TCFA were identified in 37.8% of culprit lesions after thrombus aspiration, and plaque rupture was more commonly seen in VH-TCFA than non VH-TCFA (53.8% vs. 34.5%, p=0.009)[60]. However, this study was limited because residual thrombus is mis-classified as fibrous or FF tissue in the VH IVUS algorithm[61], and this may have led to an underestimation of the incidence of VH-TCFA. VH-TCFA were more commonly located proximal to the MLA and the site of maximum NC[59, 62], raising the prospect that they may not be covered by culprit lesion stenting. In one study of patients with STEMI, 50% of culprit VH-TCFA were not fully covered by the stent despite optimal angiographic placement, and this was more common at the proximal than the distal stent edge[63].

In a study of 105 patients (70 ACS and 35 stable angina), four IVUS and VH IVUS factors were found to be associated with an ACS culprit lesion phenotype: NC/DC ratio, MLA <4mm^2, remodelling index >1.05, and the presence of VH-TCFA[64]. These factors were subsequently utilised to construct the Liverpool Active Plaque Score (LAPS), where a score of >6 predicted an active plaque phenotype with a sensitivity of 75% and specificity of 91% in an independent validation cohort[64].

1.2.2.1 Serial VH IVUS Studies

It is recognized that atherosclerotic lesions are dynamic and can evolve from one sub-type to another. In a study of stable angina patients, Kubo et al utilised VH IVUS to assess the progression of plaques over 12 months in 99 patients[65]. Fifteen out of 20 VH-TCFA found at baseline had healed into different plaque types at 12 months (13 FA and 2 fibrotic plaques) and 12 new VH-TCFA had formed (6 from PIT and 6 from FA). VH-TCFA that had not healed were more likely to be located in the proximal segment of the vessel (distance from ostium to lesion was 16mm vs. 31mm for healed VH-TCFA, p=0.013). Calcified FA were the only lesion type to remain unchanged over 12 months. In a study combining VH IVUS with optical coherence tomography (OCT), evaluating plaque at bifurcation lesions at baseline and 6 months in 24 patients (80% with stable coronary disease), most high-risk plaques (81%) remained unchanged[66].

In a study of 63 patients with STEMI, 99 non-culprit lesions were evaluated by VH IVUS at baseline and 13 months. An increase in the proportion of NC (14% to 18%, p<0.0001) and DC (6% to 10%, p<0.0001) at follow-up was demonstrated[67]. Furthermore, 9/41 VH-TCFA had healed into either FA or fibrotic plaques at 13 month follow-up, but 18/41 FA and 3/16 PIT had transformed into VH-TCFA[67]. In a comparison of 26 patients with STEMI and 11 patients with chronic total occlusions (CTO, imaged proximal to the obstruction), the non-culprit lesions were more likely to be dynamic in the STEMI patients, with plaque composition changing significantly at 6 month follow-up compared to no significant change in the patients with CTO[68]. In addition, there was a trend in STEMI patients for lesions to progress to a more advanced plaque type (67% vs. 11%, p=0.089)[68].

Although these studies are limited by the small sample sizes, the results suggest that the development of vulnerable non-culprit plaques is, in part, determined by the underlying environment and presence of ACS-causing plaque elsewhere in the

coronary vasculature. Further research is required into the factors leading to this increase in plaque vulnerability after ACS.

1.2.2.2 The Role Of VH IVUS In Predicting Adverse Outcomes After ACS

To date, three studies have prospectively evaluated the association between VH IVUS-defined plaque classification and adverse outcomes in patients with ACS: the Providing Regional Observations to Study Predictors of Events in the Coronary Tree study (PROSPECT)[69], the VH IVUS in Vulnerable Atherosclerosis study (VIVA)[70], and the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound study (ATHEROREMO-IVUS)[71].

PROSPECT Study

In this multi-centre study, 697 patients (median age 58.1 years) with ACS (30.3% STEMI, 65.6% non-STEMI, 4.2% unstable angina [UA]) underwent three vessel VH IVUS (623 patients had successful VH IVUS image acquisition) and were followed up for a median of 3.4 years[69]. Of 2811 lesions identified, 596 were VH-TCFA in 313 patients. On multivariate analysis, predictors of non-culprit lesion-related MACE (death from cardiac causes, cardiac arrest, MI, or rehospitalisation due to unstable or progressive angina) were plaque burden ≥70% (HR 5.03, 95% CI 2.51-10.11, p<0.001), MLA ≤4.0 mm^2 (HR 3.21, 95% CI 1.61-6.42, p=0.001) or presence of VH-TCFA (HR 3.35, 95% CI 1.77-6.36, p<0.001). In addition, other predictors of MACE included median DC area ≥0.2mm^2 (HR 2.01, p=0.02) and median NC area ≥0.4mm^2 (HR 2.06, p=0.02)[69].

VIVA Study

In the VIVA single centre study, patients with stable angina (n=100) and ACS (n=70) underwent three-vessel VH IVUS pre-intervention, and post-intervention in the culprit artery[70]. Baseline demographics were not reported. After a 3-year follow-up, 18 MACE (death, MI, and unplanned revascularisation) occurred in 16 patients. On univariate analysis, non-culprit lesion factors associated with non-restenotic MACE (MACE excluding events related to in-stent restenosis) were VH-TCFA (HR 7.53, 95% CI 1.12-50.55, p=0.038), plaque burden >70% (HR 8.13, 95% CI 1.63-40.56, p=0.011) and RI (HR 2686, 95% CI 1.94-3.72x10^6, p=0.032).

Limitations of PROSPECT and VIVA

These studies confirmed that non-culprit lesions responsible for future MACE are characterized by the presence of VH-TCFA. However, the application of VH IVUS to interrogate non-culprit lesions for potential intervention is subject to a number of major limitations. First, while TCFA were commonly identified in non-culprit lesions (22.0% in PROSPECT, 60.2% in VIVA), the absolute event rates per individual VH-TCFA were low (4.9% in PROSPECT, 2.9% in VIVA). The differences in MACE were strongly driven by rehospitalisation and revascularisation, which may have been driven by physician bias rather than death or MI. In addition, in PROSPECT, a significant number of non-culprit lesions associated with recurrent events were not imaged on VH IVUS (51.9%). This was likely due to the fact that only the proximal 6-8 cm of the major three epicardial arteries were evaluated as the type of VH IVUS catheters used precluded navigation to the distal parts of the coronary arteries. Finally, non-culprit lesion-related adverse events were also associated with non-TCFA lesions at baseline (49.0% in PROSPECT, 38.5% in VIVA) and these were not imaged with VH IVUS when the patient re-presented with an adverse cardiovascular event. It is possible that many initially 'benign' plaques had progressed to TCFA, resulting in subsequent events.

ATHEROREMO-IVUS Study

ATHEROREMO-IVUS was a single centre cohort study that enrolled 581 patients (mean age 61.6 ± 11.3 years, 75.6% male) with either stable angina (43.7%) or ACS (54.7%)[71]. It aimed to answer some of the limitations of VH IVUS raised after publication of PROSPECT and VIVA. Following diagnostic coronary angiography, VH IVUS imaging was performed in one non-culprit vessel only (as 3 vessel VH IVUS is time consuming and impractical in the clinical setting) and the primary endpoints were death, ACS, or unplanned coronary revascularisation at 1-year follow-up[72]. The secondary endpoint was defined as a composite of death or ACS at one year, as the events in VIVA and PROSPECT were primarily driven by revascularisation and rehospitalisation respectively.

Of the 724 lesions identified, 271 (37.4%) were classified as VH-TCFA and these were independently associated with MACE (HR 1.96, 95% CI 1.08-3.53, p=0.026). There was no association between the presence of VH-TCFA and either C-reactive protein or circulating cytokines in patients with ACS[73, 74]. As in PROSPECT, a combination of the presence of TCFA, plaque burden ≥70% and MLA ≤4mm^2 increased the risk of

MACE significantly (HR 3.70, 95% CI 1.72-7.95, p<0.001)[71]. In addition, ATHEROREMO-IVUS was the first study to show that VH-TCFA in non-culprit vessels are associated with the secondary endpoint of death or ACS at 1 year (HR 2.56, 95% CI 1.18-5.54, p=0.017)[71]. VH-TCFA with a plaque burden ≥70% were also associated with a higher MACE rate both at early (<6 months) and late (>6 months) follow-up, whereas smaller VH-TCFA were only associated with late adverse events[71].

1.2.3 Comparison of VH IVUS With Other Imaging Modalities

Several other intracoronary imaging modalities are currently available and their physical properties are compared in **Table 1.4**.

	IVUS	OCT	Near infrared spectroscopy
Energy source	Ultrasound	Infrared	Near infrared
Wavelength (μm)	35-80	1.3	0.8-2.5
Penetration (mm)	10	1-2.5	1-2
Resolution (μm)	100-200	20-40	NA
Pullback speed (mm/s)	0.5-1	10-40	0.5

Table 1.4 Comparison of the different modalities of intravascular imaging

IVUS has a greater penetration than OCT or near-infrared spectroscopy (NIRS) and can therefore evaluate deep plaque structures, but has a poorer resolution than OCT and cannot image the thin fibrous cap of a TCFA. OCT has a faster imaging speed than either IVUS or NIRS.

1.2.3.1 Other Radiofrequency Analysis IVUS Algorithms

Two other technologies utilize radiofrequency ultrasound data to generate colour IVUS images: integrated backscatter-IVUS (IB-IVUS, Terumo, Tokyo, Japan) and iMap (Boston Scientific, MA, USA). IB-IVUS uses just one radiofrequency parameter to define tissue types, making it easier to provide feedback for misclassifications, but rendering it essentially a colour representation of the grayscale intensities within the IVUS image[75]. IB-IVUS was marginally more accurate than an older version of the VH IVUS algorithm in an ex vivo study against histology in identifying all 4 plaque components (IB-IVUS: κ=0.83, 95% CI 0.75-0.91, VH IVUS: κ=0.73, 95% CI 0.63-0.83)[76]. However, formalin-fixed tissue was imaged in the study, which is known to alter spectral properties of IVUS backscatter[77, 78].

iMap is the most complex of the three radiofrequency analysis technologies. It measures 40 different spectral parameters and compares how close the radiofrequency signal is to a database previously obtained from histological analysis,

giving a "confidence level" for identifying each tissue type[79]. iMap had only a moderate agreement with IB-IVUS in identifying fibrous (R^2=0.522, p<0.001) and calcific (R^2=0.560, p<0.001) plaque, with no agreement for the areas of lipid pool (R^2=0.071, p=0.149)[80].

1.2.3.2 Optical Coherence Tomography

OCT provides complementary information to VH IVUS. It has a superior resolution (10-40μm) but poorer penetration (2.5mm) (**Table 1.4**), and is therefore unable to quantify plaque burden (one of the main predictors of adverse events after ACS), deep lipid pools, necrotic regions or large calcium deposits[81].

Table 1.5 shows the studies that have evaluated VH IVUS as a diagnostic test for individual plaque subtypes against the "gold-standard" of OCT. However, using OCT as the gold-standard for identification of both FA and TCFA is flawed due to the limitations in penetration, and both studies used a wider definition of a VH IVUS-defined TCFA[82] than subsequently proposed by Garcia-Garcia[53]. Fujii et al assessed the combined accuracy of OCT and grayscale IVUS against histology in identifying TCFA in an ex vivo study of 165 arteries from 60 patients who had died from non-cardiac causes[83]. Of 685 imaged plaques, 8% met the IVUS criteria for TCFA, 4% met the OCT criteria, and only 2% met both. Respectively, the sensitivity, specificity, PPV, negative predictive value (NPV) and accuracy of the combined OCT and IVUS criteria were 92%, 99%, 69%, 99%, and 99%[83].

Study	Plaque Subtype	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Sawada et al, 2008[84]	TCFA	78%	63%	46%	88%	67%
Kubo et al, 2011[85]	TCFA	89%	86%	59%	97%	86%
Kashiwagi et al, 2014[86]	FA	71%	45%	56%	63%	58%

Table 1.5 Summary of studies comparing OCT and VH IVUS identification of TCFA/FA

Studies comparing the accuracy of VH IVUS against OCT for the identification of TCFA have been mixed. VH IVUS tends to "over-diagnose" TCFA when compared to OCT.

Combining the criteria for VH-defined FA and fibrous cap <85μm for three frames on OCT improved diagnostic accuracy to 89% for histologically-proven TCFA[87]. False

positive TCFA on VH IVUS were most commonly caused by heavy calcification, and false negatives on OCT were caused by under-estimation of the lipid pool and over-estimation of the fibrous cap thickness[87]. High negative predictive values[84, 85, 88] for VH IVUS may mean that it is used as a "rule-out" test for TCFA in the future, with OCT providing confirmation of the presence of a TCFA. A combination catheter that automatically co-registers OCT and IVUS data has been proposed[89] and could potentially be the key to accurately identifying TCFA.

1.2.3.3 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) provides information about the lipid composition of a plaque, but cannot measure the thickness of the overlying fibrous tissue. A comparison of NIRS and VH IVUS in 31 stable and unstable patients demonstrated that the agreement between NC on VH IVUS and a high probability of lipid pool on NIRS was only 14.2%[90]. This was confirmed in a subsequent study, demonstrating that the relationship between VH IVUS-derived NC and NIRS-derived lipid core burden index was not significant (r_S=0.16, p=0.11)[91]. A key reason for this observation could be that the NC classification by VH IVUS is specific to late NC with micro-calcifications[44, 47], whereas NIRS detects the chemical signature of lipids, which can be present at both early and late stages of plaque progression. However, NIRS is not affected by the presence of calcium and may provide more accurate information regarding the lipid content in highly calcified plaques than VH IVUS, as there is an overlap in the VH IVUS classification of NC and DC[44, 79].

1.2.3.4 Computed Tomography

Non-invasive imaging appears promising for identifying vulnerable coronary plaques without the risk of minimally-invasive imaging. Obaid et al imaged 108 plaques from 57 patients with ACS and stable angina with both computed tomography (CT) and VH IVUS to determine attenuation ranges for individual plaque components[56]. These plaque maps were then validated in a separate cohort of 47 patients, and showed good correlation between CT and VH IVUS (NC: r=0.41, p=0.002; fibrous plaque: r=0.54, p<0.001; DC: r=0.59, p<0.001)[72]. However, the spatial resolution precluded direct identification of TCFA. Joshi et al performed VH IVUS and positron-emission tomography-CT on 40 patients with stable angina[92]. High ^{18}F-sodium fluoride uptake on positron-emission tomography-CT (postulated to be a marker of plaque activity) correlated with VH IVUS features such as microcalcification (73 vs. 21%, p=0.002) and

higher mean NC burden (24.6 vs. 18.0, p=0.001), which may be markers of plaque vulnerability[92]. There was also a non-significant trend towards a higher incidence of VH-TCFA in ^{18}F-sodium fluoride positive plaques (47 vs. 16%, p=0.068)[92]. However, no VH IVUS data were reported from the MI sub-group of this study, and there was no correlation with adverse outcomes. Further studies are necessary before this non-invasive technique supplants minimally-invasive coronary imaging for the identification of vulnerable plaques.

1.2.4 Limitations of VH IVUS

The main technical limitation of VH IVUS is that it lacks the resolution to accurately identify a TCFA cap thickness of <65µm. Furthermore, VH IVUS lacks an algorithm for identifying thrombus, which may be misidentified as fibrous plaque unless care is taken to exclude it from the analysis[61]. The presence of thrombus at the site of TCFA might therefore appear as a thick-cap FA. It can also be difficult to analyse radiofrequency data in the acoustic shadow behind superficial calcium. More than 80% of regions of interest in this acoustic shadow had a radiofrequency signal greater than the background noise, but the accuracy of the VH plaque component classification within these regions requires further research[93]. It is unclear whether these signals are reflections from the ultrasound wave passing through “cracks” in the calcium (or around the edges) or just secondary echoes against the calcium itself. Use of a novel masking algorithm to prevent misclassification of the shadow behind the calcium improved the correlation between VH IVUS and quantitative computed tomography angiography in one study[94].

VH IVUS also has significant limitations that currently prevent it from being utilised routinely in clinical practice. Three-vessel VH IVUS imaging is time consuming and does carry a small but measurable risk of adverse events for the patient (1.6% of patients in PROSPECT had complications attributable to IVUS imaging), although the results from ATHEROREMO-IVUS suggest that imaging of one non-culprit vessel may be enough to predict adverse outcomes. Analysis of VH IVUS images currently requires manual verification of the lumen and vessel contours for each frame, which limits the application of VH IVUS in determining the individual patient’s treatment at the time of angioplasty. Finally, there are no studies to show that utilising VH IVUS to alter patient management can improve clinical outcomes, and such studies may require such large patient numbers and extended follow up as to be prohibitive. In the absence

of such studies, invasive imaging studies utilising technology such as VH IVUS may be better targeted at evaluating the effect of novel therapies on “soft” end points such as plaque composition or phenotype[49].

1.2.5 Conclusion

Despite its limitations, VH IVUS is a useful tool in identifying high risk plaque features and vulnerable lesions in patients with ACS in a research setting. The advent of combination imaging catheters and higher resolution IVUS may improve its predictive capabilities, especially in identifying the thin fibrous cap characteristic of TCFA[95]. Measurement of plaque components is relatively simple, objective and accurate, but does not perform as well in identifying patients at risk of adverse outcomes as conventional grayscale IVUS measurements. In contrast, lesion-level based analysis correlates better with adverse cardiovascular outcomes, but lesion classification is more subjective, requires time and experienced operators. In addition, focusing on local detection of vulnerable plaque does not address the systemic nature of atherosclerosis. The evidence is mounting that VH-TCFA adversely affect patient outcomes and this may lead to more aggressive therapy for these vulnerable plaques. However, despite the technology being available for over a decade, evidence for the use of VH IVUS in modifying patient outcomes is lacking, and this requires further evaluation in future studies.

1.3 Optical Coherence Tomography In ACS

OCT is an intravascular imaging modality that uses the reflection of near-infrared light to generate an image. OCT was first described over two decades ago when it was used to image the peri-papillary area of the human retina in vitro[96]. Eleven years later, OCT was used to image atherosclerotic plaques in human coronary arteries[97]. The image resolution achievable with OCT (axial: 10μm, lateral: 20-40μm) far surpasses that of IVUS (100-200μm). Histological studies have demonstrated that certain adverse plaque phenotypes are associated with the onset of an ACS[95]. With its excellent spatial resolution, OCT is ideally placed to identify vulnerable plaque that could result in ACS.

1.3.1 OCT Technology

To generate an image, a low coherence, near infrared (wavelength of 1.3μm) light source is directed at the tissue (**Figure 1.8**). The light beam is split into two arms, a sample arm and a reference arm, by an interferometer. The reference arm is directed to a mirror, which reflects the light directly back to the interferometer. The light of the sample arm is absorbed, refracted, or reflected from the sample tissue, scattering the light at large angles from its surface and sub-surface. Reflected light travels back to the interferometer and interacts with the reference arm light. The interaction between these two light waves determines the OCT image, depending on whether there is constructive or destructive interference between the waves[96]. Because red blood cells strongly scatter the light waves and hence attenuate the image, OCT requires a bloodless field. The OCT catheter is connected to a rotary junction, which utilises a motor to rotate the optical fibre in the catheter and couples light from this rotating fibre to light from the reference arm. The rotary junction is mounted to an automated pullback device, thus scanning the artery in a helical fashion.

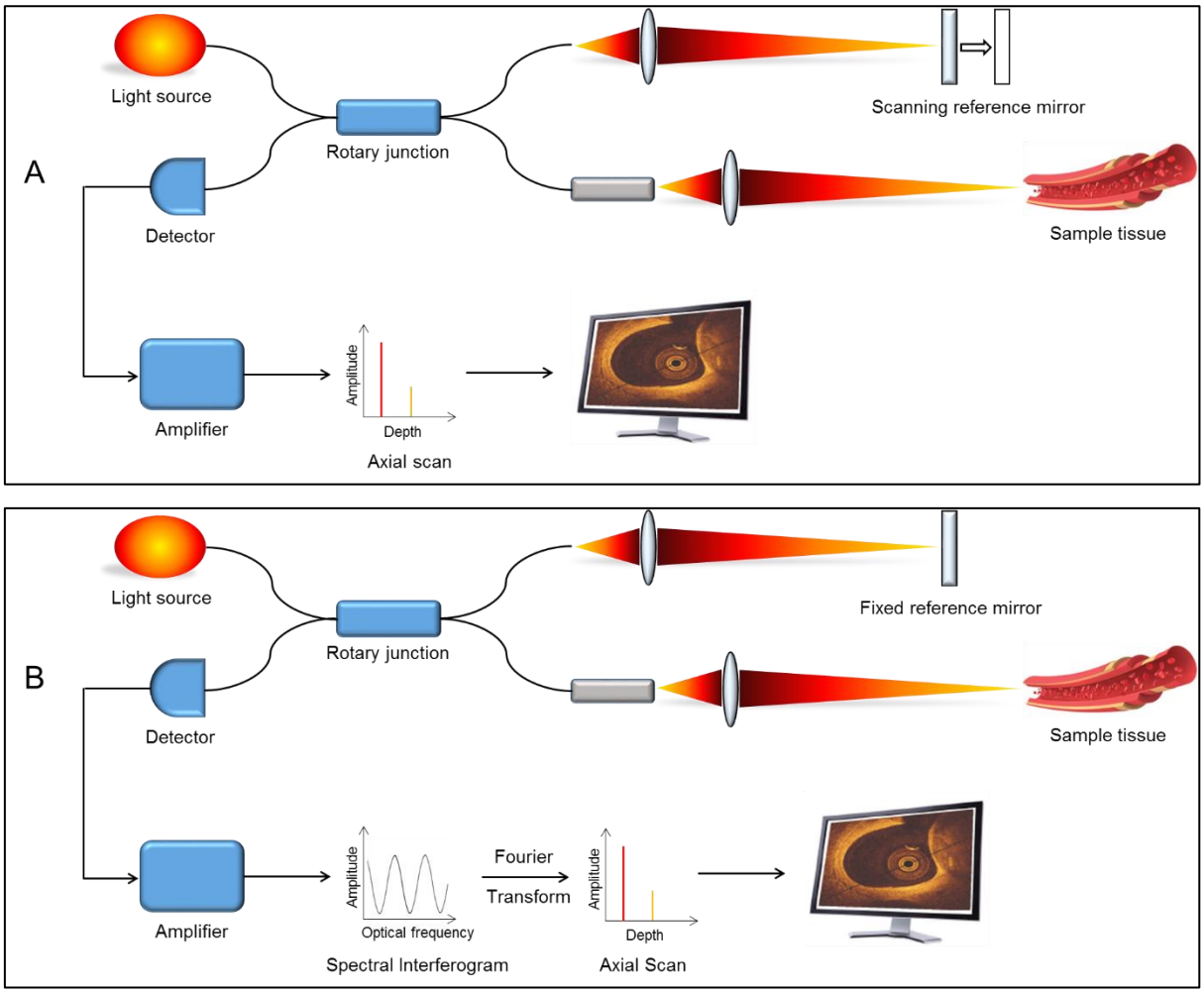


Figure 1.8 Diagrammatic representation of OCT technologies

Panel A: Time domain OCT

Panel B: Frequency domain OCT

There are two types of OCT systems: time domain (TD, **Figure 1.8A**) and frequency domain (FD, **Figure 1.8B**). The first generation TD-OCT system required sequential measurement of optical echoes from different depths by moving the reference mirror[98]. This initially required the use of a balloon to occlude coronary blood flow, and the slow pullback speed of 1-5mm/s led to image acquisition times of 3-45 seconds[98]. Subsequently, a blood-free imaging field was obtained by controlled intracoronary infusion of iso-osmolar contrast, negating the need for an occlusive balloon[99]. This reduced the procedure time, although the length of the analysed segments of artery were shorter[99]. Second generation FD-OCT systems employ a light source that is rapidly swept in time across wavelengths from 1.25-1.35μm, allowing simultaneous recording of reflections from different depths without movement of the reference mirror[100]. Depth profiles are then reconstructed by Fourier transformation. This speeds up image acquisition 10-fold, with achievable pullback speeds of up to 40mm/s and

imaging runs of up to 150mm in length with a 3-5 second flush of saline or contrast, without the need for prolonged vessel occlusion[100].

1.3.1.1 OCT Image Features

The normal coronary artery is seen as a three layered structure on OCT (**Figure 1.9A**)[101]. The internal elastic lamina appears as a signal-rich 20μm thick band that lies inside the dark band of the media and the further signal-rich band of the external elastic lamina[101]. An atherosclerotic lesion is seen on OCT as a mass lesion within the arterial wall, with focal intimal thickening or loss of the normal vessel architecture[102]. Fibrous plaque produces a relatively homogenous and highly backscattering signal[102] (**Figure 1.9B**). Calcified plaques appear as a signal-poor area with sharply delineated borders (**Figure 1.9C**). However, this only applies to larger regions of calcification; smaller areas and microcalcifications have yet to be validated against histology[102]. Necrotic core (and the broader histopathological category of a lipid pool) is seen as a signal-poor region with poorly defined borders and fast OCT signal drop-off (**Figure 1.9D**)[102]. Because light does not penetrate through these areas, OCT cannot be used to measure the depth or volume of lipid pools.

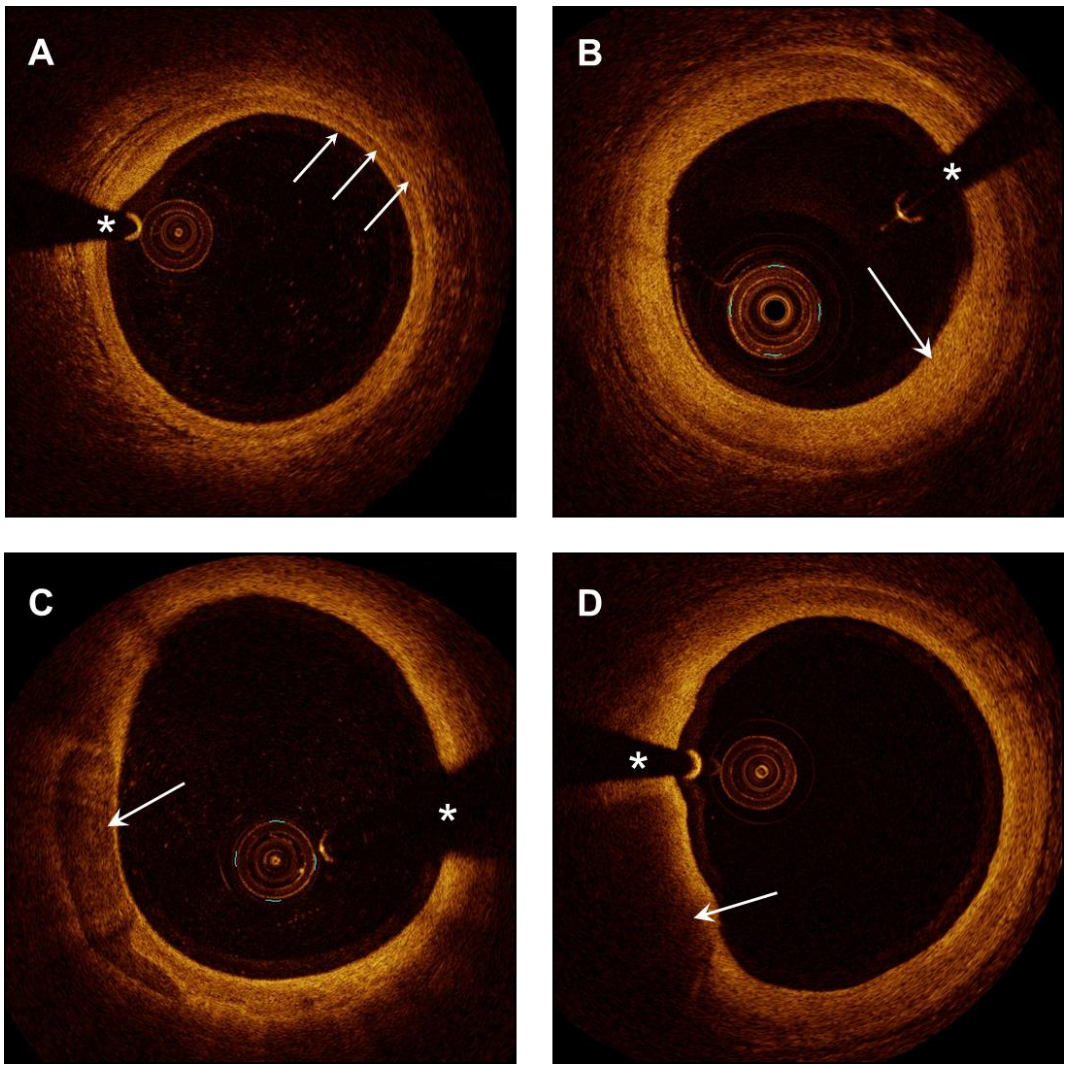


Figure 1.9 OCT image examples of plaque composition

A) Composition of the normal coronary artery, with white arrows depicting the internal elastic lamina, media and external elastic lamina

B) Concentric fibrous plaque

C) Calcified plaque

D) Necrotic core

* Guidewire artefact

Macrophage accumulations can sometimes be seen at the border of the fibrous cap and necrotic core and can appear as punctate signal-rich spots that exceed the background noise of the image[102]. Cholesterol crystals (ChC) are linear regions of high intensity, often associated with a lipid pool (**Figure 1.10C**)[102]. OCT can differentiate between white and red thrombus (**Figure 1.11**) due to the high proportion of red blood cells in red thrombi, which causes greater attenuation of the OCT signal and a lower half-width (the distance from peak signal intensity to its half-intensity). Kume et al demonstrated that a cut off of 250μm in the half-width could accurately discriminate between white and red thrombus with a sensitivity of 90% and a specificity of 88%[103].

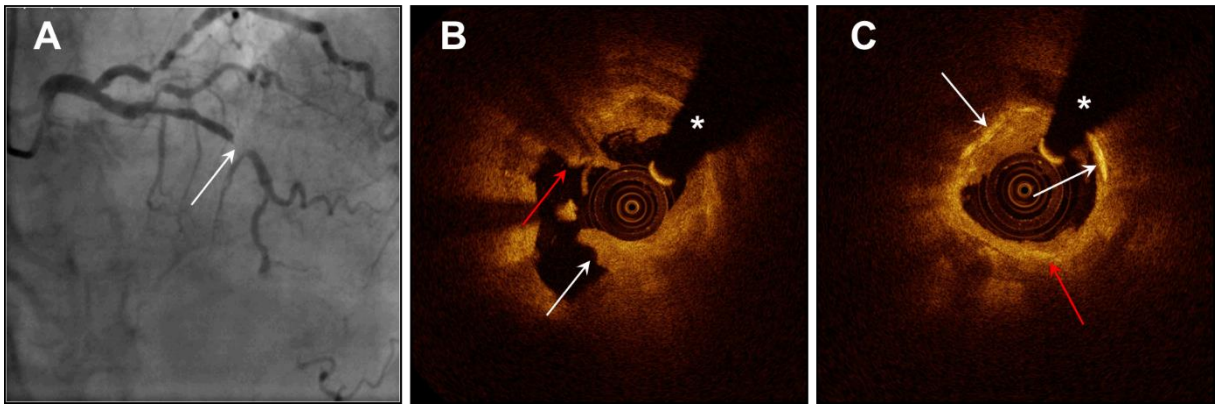


Figure 1.10 Cholesterol crystals on OCT

Images from an 80 year old female patient, with hypertension and hypercholesterolaemia, who presented with a NSTEMI.

A) Angiogram demonstrating a tight stenosis with thrombus in the mid-LAD artery (white arrow)

B) OCT image of red (red arrow) and white (white arrow) thrombus in the culprit lesion

C) OCT image of cholesterol crystals (white arrows) and macrophage accumulation (red arrow)

* Guidewire artefact

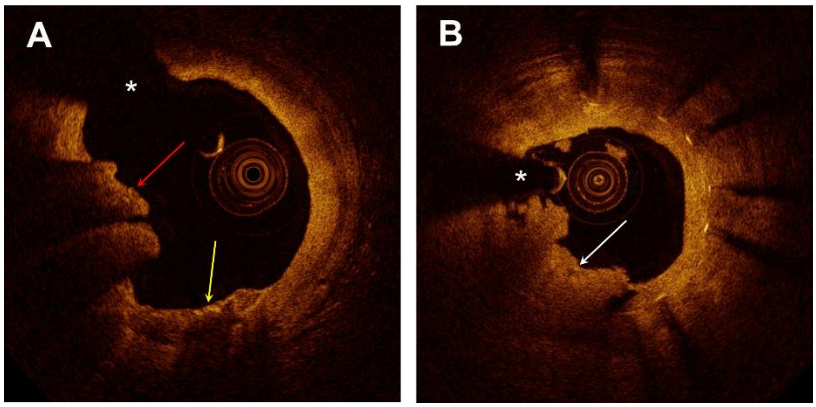


Figure 1.11 Red and white thrombus on OCT

A) Red thrombus (red arrow) with high attenuation, associated with a calcified plaque (yellow arrow)

B) Stent thrombosis with homogenous, low attenuation white thrombus (white arrow)

* Guidewire artefact

1.3.1.2 Histological Validation Of OCT

OCT was first validated for plaque characterisation in vitro in 2002[104]. Agreement between the histopathological and OCT findings were high (κ=0.83-0.84), and inter-observer and intra-observer reliability were good (κ=0.88 and κ=0.91, respectively)[104]. Intimal thickness measured by OCT also correlated well with histology (r=0.98, p<0.001)[105]. However, there were a number of false negative diagnoses of lipid pools, which could be attributed to the limited penetration of OCT, leading to deep lipid pools being misinterpreted as fibrous plaques[104].

In addition, OCT images are prone to artefacts; 30.9% of images contained artefact in one study, although this improved with operator experience[106]. Seam line artefacts cause apparent breaks in the lumen contour on the cross-sectional image (6.0% of images), decentration artefacts are caused by eccentric positioning of the imaging catheter within the artery and lead to image attenuation in remote structures (30.9%), calibre artefacts are caused by an arterial diameter greater than the penetration limit of the OCT and are a particular problem in vein grafts and in the LMS[107] (15.0%), and flow artefacts are caused by failure to clear blood from either the vessel or imaging catheter by flushing (19.6%)[106].

1.3.2 OCT And Vulnerable Plaque

1.3.2.1 Definition Of Thin-Cap Fibroatheroma

Given the high image resolution with OCT, it is well placed to identify these high-risk plaques in vivo (**Figure 1.12**). However, there is still debate over the exact definition of a TCFA on OCT (OCT-TCFA), as histological specimens of TCFA differ from OCT images (likely due to shrinkage of pathological specimens). Using a cut-off of 70μm (as the axial resolution of OCT is >10μm), only 67% of ruptured plaques in one study of 72 patients with ACS were defined as having a thin fibrous cap[108]. Therefore, the fibrous cap of a TCFA may be thicker in vivo than on histology. There is a higher proportion of lipid-rich plaque on OCT in patients with ACS compared to stable angina[109], and some studies have used an additional parameter to define a TCFA: that the arc of the lipid pool should subtend an angle >90^{o}[102]. However, there is no consensus on the exact cut-off value for the fibrous cap or arc of lipid pool for the identification of an OCT-TCFA, only that the definition of an OCT-TCFA should reflect the histological definition of a TCFA[102].

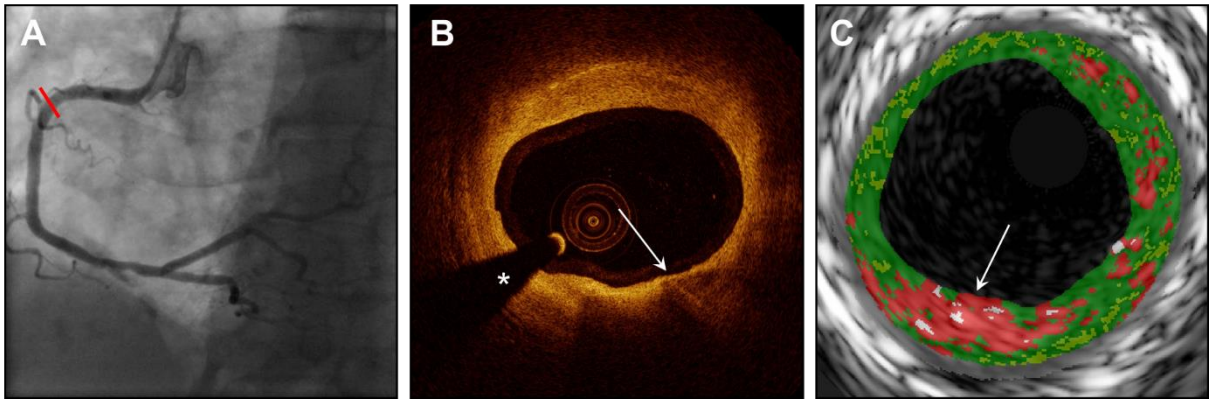


Figure 1.12 Thin-cap fibroatheroma on multi-modality imaging

Images from an 83 year old male ex-smoker, who presented with a NSTEMI. He underwent PCI to a culprit lesion in the LAD artery, but intravascular imaging of the RCA revealed a non-obstructive VH-TCFA in the non-culprit artery.

A) Angiogram with a non-obstructive lesion in the RCA (red bar)

B) OCT image of the thin-cap fibroatheroma (white arrow)

C) VH-IVUS image of the thin-cap fibroatheroma (white arrow)

* Guidewire artefact

1.3.2.2 Thin-Cap Fibroatheroma in ACS

OCT-TCFA are more common in patients with an acute or unstable clinical presentation than in stable angina. A comparison of 26 STEMI patients with 16 stable angina patients demonstrated that STEMI patients had a higher proportion of OCT-TCFA in the culprit lesion (85% vs. 13%, p<0.001) and a thinner fibrous cap (57±12 vs. 180±65µm, p<0.001)[110]. Patients with STEMI also had a higher prevalence of OCT-TCFA compared to patients with NSTEACS (78% vs. 49%, p=0.008)[111]. Similar results have been demonstrated in patients with UA compared to patients with stable angina (incidence of OCT-TCFA 81% vs. 47%, p=0.002; fibrous cap thickness of 56±20 µm vs. 75±30 µm, p<0.001)[112]. Patients with ACS also have a higher proportion of OCT-TCFA, and thinner fibrous caps, in non-culprit lesions[110, 113]. In a single-centre study of 150 lesions on OCT (73 ACS culprit lesions, 32 ACS non-culprit lesions and 45 stable angina culprit lesions), there was a higher incidence of OCT-TCFA (67% vs. 41% vs. 20%, p<0.01) and a thinner fibrous cap (60 vs. 82 vs. 114µm, p<0.001) in the ACS culprit lesions compared to the other two groups[114].

In patients with ACS, OCT-TCFA are more commonly found in the proximal segments of the culprit vessel[115, 116]. OCT has been utilised to confirm findings from histological studies that plaque rupture of TCFA occurs more often away from the site of MLA in

patients with STEMI and NSTEMI (mean distance of site of rupture from MLA = 2.34±2.31mm)[117].

1.3.2.3 Effects Of Therapy On TCFA

Methods to stabilise these vulnerable TCFA have been assessed using serial OCT studies. Patients taking statin therapy had an increased cap thickness of OCT-TCFA compared to patients not taking statins (an increase of 192±41μm vs. 25±8μm, p<0.001) at 9 months post-ACS[118]. In a prospective study of 42 patients with stable angina, statin therapy resulted in an increase in fibrous cap thickness when compared to dietary modification alone (+52±32μm vs. 2±22μm, p<0.001)[119]. Another study enrolled 30 patients (56.6% with ACS) with untreated dyslipidaemia and OCT-TCFA on baseline imaging and randomised them to either statin therapy alone or statin + eicosapentaenoic acid[120]. Despite similar levels of low density lipoprotein at follow up, those who received eicosapentaenoic acid had a greater increase in fibrous cap thickness (54.8±27.9μm vs. 23.5±11.6μm, p<0.0001)[120]. However, it remains to be seen whether stabilising these plaques actually improves clinical outcomes.

1.3.2.4 Plaque Rupture

Plaque rupture on OCT is associated with adverse outcomes in ACS[121, 122]. Ruptured plaques with thrombus have thinner fibrous caps than those without thrombus (57±17μm vs. 96±48μm, p=0.0076)[123]. Intracoronary thrombus is well visualised by OCT and is almost universally seen in STEMI[110]. However, care must be taken with interpretation of these results, as overlying thrombus may interfere with OCT characterisation of the lesion, and performing thrombus aspiration prior to OCT imaging may alter the underlying plaque anatomy.

Patients with ACS caused by ruptured culprit plaques are more likely to have non-culprit plaques with a higher lipid index (mean lipid arc multiplied by lipid length measured in the longitudinal view: 1196.9±700.5 vs. 747.7±377.3, p=0.001), higher incidence of OCT-TCFA (52.9% vs. 19.0%, p=0.029), and thinner fibrous caps (107.0±56.5mm vs. 137.3±69.8mm, p=0.035) on OCT than those with non-ruptured culprit plaques[124]. In addition, plaque ruptures in patients with ACS differ from those seen in patients with asymptomatic coronary artery disease with a greater lipid arc (171±71^{o} vs. 133±71^{o}, p=0.037), higher incidence of thrombus (78% vs. 9%, p<0.001) and a smaller minimum lumen area of the culprit lesion (1.79±0.92mm vs.

2.75±0.99mm, p<0.001), suggesting that the morphology of the plaque rupture may influence whether it heals asymptomatically or causes an adverse cardiovascular event[125].

Patients with ruptured culprit plaques were also more likely to have secondary, non-culprit plaques ruptures (35.3% vs. 4.8%, p=0.016)[124]. This suggests that these patients have increased pan-coronary vulnerability and may be at higher risk of future adverse events. In a study of 261 patients (41% with ACS), 20% had multiple plaque ruptures in non-culprit lesions[126]. The presence of OCT-TCFA, microchannels, and macrophage accumulations were independent predictors of multiple plaque ruptures[126].

1.3.2.5 Plaque Erosion

Contrary to plaque rupture, plaque erosion is characterised by luminal thrombus and absence of the endothelium, without evidence of fibrous cap disruption[95]. In one histological study, erosions were responsible for over 40% of thrombotic sudden cardiac deaths and were more prevalent in women[127]. Although OCT does not have the resolution necessary to identify the absence of the endothelium, OCT-identified plaque erosion has been defined as the presence of thrombus and an irregular luminal surface in the absence of cap rupture[102]. In a cohort of patients with STEMI (n=30), plaque erosions were more often seen by OCT than by IVUS or angioscopy (23% vs. 3% vs. 0%, p=0.003)[88]. In a previous study, OCT was performed in 126 patients with ACS and demonstrated plaque rupture in 43.7%, erosions in 31% and calcified nodules in 7.9%[128]. Plaque erosions were more commonly observed in younger patients (53.8±13.1 years vs. 60.6±11.5 years, p=0.005), and were more commonly associated with NSTEMI than STEMI (61.5% of patients with NSTEMI had a plaque erosion vs. 29.1% of STEMI patients, p=0.008). Patients with plaque erosion had a less severe diameter culprit stenosis than those with plaque rupture (55.4±14.7% vs. 68.8±12.9%, p<0.001)[128]. Plaque erosion on OCT was associated with a higher level of serum myeloperoxidase, a haemoprotein released on neutrophil activation, than plaque rupture (2500ng/ml vs. 707ng/ml, p=0.001)[129].

Prati et al performed OCT after thrombus aspiration in patients with STEMI and followed up 31 patients with plaque erosion for one year[130]. Twelve patients were managed with thombus aspiration only, and 19 had thrombus aspiration plus

angioplasty. There were no significant differences in outcomes (death, MI, and target vessel revascularisation) between the groups[130]. Although this study raised the possibility of using OCT to influence the management of patients with ACS, this study is limited in that it consisted of too small a sample size to draw definitive conclusions, and treatment was not randomised (patients managed conservatively were younger and had fewer cardiac risk factors).

1.3.2.6 Calcified Nodules

Plaques with superficial calcified nodules are also considered prone to rupture[131, 132]. The pattern of plaque calcification on OCT was evaluated in 187 patients with acute MI, unstable and stable angina. Patients with acute MI and UA had less overall calcium (measured by arc, area, and length, $p<0.001$ for all measurements) than those with stable angina, but were more likely to have spotty calcium deposits closer to the surface of the plaque[133]. The incidence of calcified nodules in ACS in one study was 8%, but was more common with increasing age[128]. However, the accuracy of OCT in identifying smaller areas of calcification has also yet to be validated against histology[102].

1.3.2.7 Macrophage Infiltration

The resolution of OCT may allow identification of macrophages within an atherosclerotic plaque. In ACS patients, a higher prevalence of macrophage infiltration in non-culprit plaques was seen compared with non-ACS patients (82.4% vs. 37.9%, $p=0.001$)[113]. A study of diabetic patients also found those with poorly controlled diabetes (glycated haemoglobin ≥8%) had greater macrophage infiltration than non-diabetics or well-controlled diabetics (37.9% vs. 11.0%, $p=0.037$)[134]. Plaques that exhibited an increase in luminal stenosis over time were more likely to have higher numbers of macrophages (OR 9.6, $p=0.001$), TCFA (OR 20, $p<0.001$), intimal laceration (OR 10.2, $p<0.001$), and/or microchannels (OR 20, $p<0.001$)[135].

1.3.2.8 Microchannel Formation

Plaque neovascularisation and microchannel formation (**Figure 1.13**) are known to be markers of plaque vulnerability and rupture, as well as intraplaque haemorrhage, which can contribute to plaque progression[136]. Patients with microchannels in the culprit lesion were more likely to have presented with unstable than stable angina (83% vs.

17%), have a thinner fibrous cap (60µm vs. 100µm, p=0.001), and had a trend towards a higher incidence of plaque rupture (50% vs. 28%, p=0.11)[137]. In addition, in patients with early coronary artery disease (diameter stenosis <30%) patients with microchannels were more likely to have underlying coronary endothelial dysfunction as measured by the coronary artery diameter change in response to acetylcholine (−15.9±15.9% vs. −6.4±13.5%, p<0.01)[138].

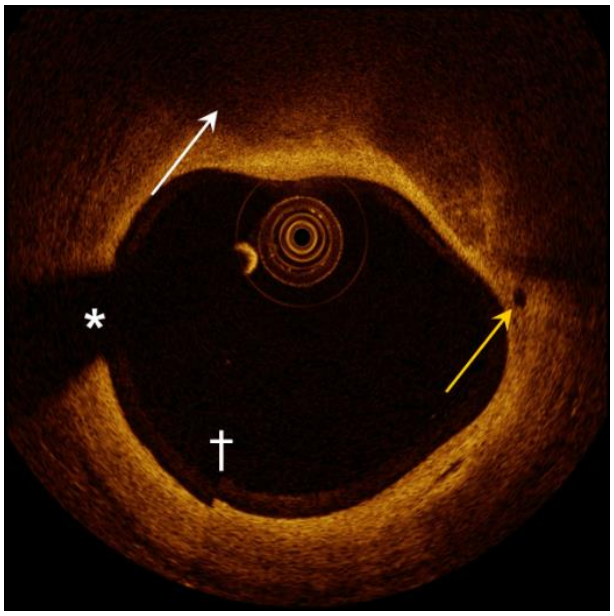


Figure 1.13 Microchannel

OCT image showing a microchannel (yellow arrow) associated with a non-obstructive lesion with a large necrotic core (white arrow)

* Guidewire artefact

† Seam line artefact

1.3.2.9 Cholesterol Crystals

In a study of 101 patients with stable coronary artery disease, 38.6% had ChC in the culprit lesion[139]. Patients with ChC were older (69.5 ± 8.0 vs. 65.3 ± 10.7 years, p=0.04) and had a higher glycated haemoglobin (7.0 ± 1.4 vs. 6.4 ± 1.2%, p=0.04) than those without. In addition, those with ChC had a higher frequency of spotty calcification (58.9 vs. 25.8%, p<0.001), microchannels (69.2 vs. 38.7%, p=0.003), and lipid-rich plaques (53.8 vs. 29.0%, p=0.01). Dai et al performed balloon-occlusion OCT in culprit lesions of 206 patients with STEMI (28.6%) or NSTEACS (71.4%) and demonstrated a ChC prevalence of 39.3%[140]. Patients with ChC were more likely to have presented with a STEMI (37.0% vs. 23.2%, p=0.032) and have a greater % diameter stenosis in the culprit lesion (68.1 ± 18.3% vs. 61.0 ± 19.1%, p=0.015)[140]. Lipid index

(3826.1 ± 2111.4 vs. 2855.0 ± 1753.0, p=0.001), macrophage accumulation (77.8% vs. 40.0%, p<0.001), microchannels (67.9% vs. 24.8%, p<0.001), plaque rupture (58.0% vs. 36.0%, p=0.001), and spotty calcification (35.8% vs. 10.4%, p<0.001) were all more common in those with ChC, but the prevalence of OCT-TCFA did not differ between groups (56.8% vs. 47.2%, p=0.179)[140]. However, it is unclear by what mechanism ChC potentially increase plaque vulnerability.

1.3.3 Comparison With Other Intravascular Imaging Modalities

1.3.3.1 Fractional Flow Reserve

Although OCT is a structural imaging technique, there have been attempts to correlate it with functional measures of stenosis severity, such as fractional flow reserve (FFR). **Table 1.6** summarises the studies that have correlated MLA (measured by OCT) and FFR and demonstrates a wide range of cut-offs for OCT-MLA in diagnosing functionally significant lesions. In a study of 106 patients with stable angina, an FFR <0.8 was associated with a smaller MLA (1.3 ± 0.5 vs. 2.9 ± 1.1mm^2, p<0.001), greater area stenosis (80.0 ± 11.4 vs. 63.6 ± 9.2%, p<0.001), greater lipid arc (145.1 ± 63.0 vs. 120.7 ± 48.9, p=0.047), and the presence of macrophage accumulations (45.0 vs 22.9%, p=0.016) and ChC (17.5 vs. 2.9%, p=0.011)[141]. However, it was not associated with the presence of OCT-TCFA (10.0 vs. 11.4%, p=1.000) or microchannels (27.5 vs. 22.9%, p=0.586)[141]. The ILUMIEN 1 study was designed to ascertain whether a combined OCT and FFR device aided peri-procedural decision making, and demonstrated over two thirds of physician decisions were influenced by either pre or post PCI OCT/FFR evaluation and there were low rates of post procedure MACE[142]. The COMBINE study aims to determine whether the addition of OCT evaluation to FFR measurement of intermediate lesions in patients with diabetes better predicts MACE[143].

Study	Size of Study	Type of OCT	FFR	MLA Cut-Off	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
Burzotta et al (2018)[144]	N=40	FD-OCT	<0.80	<2.5mm^2	Not reported	Not reported	64%	93%
Usui et al (2018)[145]	N=186	FD-OCT	<0.75	<1.39mm^2	54.4%	80.5%	69.0%	68.9%
Zafar et al (2013)[146]	N=41	FD-OCT	<0.80	<1.62mm^2	89%	91%	97%	70%
Reith et al (2013)[147]	N=62	FD-OCT	<0.80	<1.59mm^2	80.6%	74.2%	75.8%	79.3%
Pyxaras et al (2013)[148]	N=55	FD-OCT	<0.80	<2.88mm^2	Not reported	Not reported	73%	71%
Pawlowski et al (2013)[149]	N=48	Non-occlusive TD-OCT	<0.80	<2.05mm^2	Not reported	Not reported	75%	90%
Gonzalo et al (2012)[150]	N=61	FD-OCT	<0.80	<1.95mm^2	66%	80%	83%	63%
Shiono et al (2012)[151]	N=62	Occlusive TD-OCT	<0.75	<1.91mm^2	80.6%	92.3%	93.5%	77.4%

Table 1.6 Summary of studies comparing OCT and FFR in intermediate coronary lesions

There is a wide variation in values of MLA on OCT in functionally significant intermediate stenoses. Unlike on IVUS, there is no consensus on a value of MLA on OCT that would be considered flow-limiting.

1.3.3.2 Near-Infrared Spectroscopy

NIRS can only quantify the lipid content of the plaque, but the signal can pass through calcium and accurately quantify lipid behind this[90]. NIRS provides only compositional information regarding the plaque, but does not require a bloodless field[152] and can help discriminate between calcium and necrotic core, which can often be misinterpreted on OCT[153]. A comparison of a hybrid NIRS-IVUS catheter with OCT demonstrated that plaque burden, positive remodelling and lipid index measured by the hybrid catheter were associated with OCT-TCFA[154]. A hybrid NIRS-OCT catheter is in development and a proof-of-concept demonstration has been published, successfully imaging a 3cm section of one human coronary artery ex vivo to provide simultaneous structural and compositional information[155].

1.3.3.3 3-Dimensional Reconstruction

As the technology of OCT becomes more refined, and image acquisition faster, it has become possible to perform 3D reconstructions of the coronary anatomy by fusing X-ray and OCT data[156, 157]. This allows assessment of local haemodynamic flow patterns and hence the effects of endothelial shear stress on the risk of plaque progression and rupture[158]. Three-dimensional IVUS studies have demonstrated that localised

elevation of shear stress is correlated with the plaque rupture site in patients with ACS (κ=0.79)[159]. However, this has not yet been studied using OCT.

1.3.3.4 Computed Tomography

Several studies have attempted to correlate vulnerable lesions seen on invasive imaging such as OCT with markers on non-invasive imaging such as CT. Nakazato et al demonstrated, in a study of 68 coronary plaques in 45 patients, that OCT-TCFA with macrophage infiltration were associated with a higher prevalence of positive remodelling (71% vs. 11%, p<0.001) and low attenuation plaque (59% vs. 11%, p<0.001) on CT versus those without[160]. A study of 102 patients (24 with UA, 78 with stable angina) demonstrated that plaques exhibiting both positive remodelling and low attenuation on CT had significantly thinner fibrous caps (76 ± 24 vs. 192 ± 49μm, p<0.001) and had a higher prevalence of OCT-TCFA (38% vs. 0%, p<0.001)[161]. The diagnostic accuracy of these two CT characteristics in identifying OCT-TCFA was 78%[161]. Low attenuation plaque and napkin ring sign on CT were associated with OCT-TCFA on multi-variate analysis in a more recent study of 28 symptomatic patients[162]. Thus, CT may prove a viable adjunct in the identification of vulnerable lesions in patients for whom invasive intra-coronary imaging may hold higher risk.

1.3.4 Limitations Of OCT

A major limitation of OCT is its requirement for a blood-free field, necessitating flushing with either saline or contrast during image acquisition. Any contamination with blood during pullback results in loss of image data due to backscattering. Differentiation of calcium and lipid pool is more challenging than with IVUS, as both give low attenuation signals[163]. Moreover, the limited ranging depth of OCT (5-6mm) means that imaging of the LMS and vein grafts is limited[107], and calculation of plaque volume may be inaccurate[101]. Poor penetration of light through lipid-rich tissue also limits its use in quantifying certain plaque components. Imaging artefacts plague up to a third of OCT images and thrombus obscures the morphology of the underlying lesion. Plaque analysis of OCT images for features of vulnerability is currently done on a frame-by-frame basis and is therefore time consuming and not feasible in real time in the catheter laboratory, although automated processes for luminal border detection and plaque composition appear promising[164].

1.3.5 Conclusion

The detailed spatial resolution provided by OCT has allowed detailed in vivo correlation of those histopathological features thought to underlie plaque vulnerability. This has led to greater insight into the prevalence of vulnerable plaques in patients presenting with acute coronary syndrome, particularly in non-culprit vessels. Although there is lack of clinical data to guide the management of vulnerable lesions, a greater understanding of their natural history and temporal response to pharmacological or invasive interventions may help to deepen the understanding of ACS pathophysiology.

CHAPTER 2: HYPOTHESES AND AIMS

2.1 Hypotheses

I propose that the composition of coronary atherosclerotic plaque in older patients with NSTEACS differs to that found in previous studies in younger patients. I hypothesise that previously identified patient-level risk factors (age, sex, and frailty) are associated with different patterns of vulnerable plaque, and that certain plaque phenotypes observed on intravascular imaging are associated with a higher rate of adverse outcomes in this cohort. This will not only further our understanding of the pathophysiology of advanced and unstable coronary disease, but could lead to more individualised management of these high risk patients.

2.2 Aims

1. To evaluate the vulnerable plaque burden among high-risk older patients presenting with NSTEACS and determine its association with previously identified patient-level risk factors: age, sex and frailty.

2. To determine the association of previously identified vulnerable plaque phenotypes both with each other and with patient characteristics:
   a) Angiographic lesion calcification
   b) Culprit vs. non culprit lesions
   c) Dense calcium
   d) VH-TCFA
   e) Liverpool Active Plaque Score
   f) Plaque rupture
   g) Macrophage accumulation
   h) Microchannels
   i) Cholesterol crystals
   j) OCT-TCFA

3. To identify the lesion-related factors that put this cohort at higher risk of adverse outcomes at one year following an invasive treatment strategy for NSTEACS.

CHAPTER 3: METHODS

3.1 Author Statement

The subject of this thesis is data obtained from patients recruited to the invasive imaging sub-study of the Study to Improve Cardiovascular Outcomes in High Risk PatieNts (the ICON1 Study), a multi-centre prospective observational study of older patients with ACS[165]. A number of members of the research team were involved in the running of this study, but the author was personally responsible for the following:

- Ethics and Trust Research and Development study protocol amendments
- Provision of recruitment updates to the NIHR portfolio database
- Patient screening at Freeman Hospital, Newcastle Upon Tyne
- Patient consent and recruitment to the main study at both sites
- Collection of demographic data for the screening log
- Collection of blood samples at time of angiography
- Extraction of peripheral blood mononuclear cells for telomere analysis
- Support for the treating interventional cardiologist during invasive coronary imaging acquisition
- Obtaining anonymised imaging data on CD/DVD for offline analysis
- Collecting the clinical information from patients at baseline on standardised case report forms, including demographics, frailty scoring, quality of life indices, functional status, and cognitive function
- Performing non-invasive measures of vascular function such as echocardiography, ankle-brachial index, vascular stiffness, carotid intima media thickness, and endothelial function
- Writing standard operating protocols for the analysis of angiographic and VH IVUS data
- Offline analysis of angiographic data, and training members of the core lab in performing these analyses
- Offline analysis of all VH IVUS data
- Offline analysis of all OCT data
- Collecting the clinical information from patients, GPs and electronic health records at 1 year follow up on standardised case report forms
- Entering data into study databases
- All statistical analysis

3.2 Ethical Approval

The ICON1 study is registered on the UK Clinical Research Network portfolio (ID number 12742) and with clinicaltrials.gov (ID number NCT01933581). It was granted ethical approval by the North East Research Ethics Committee, Sunderland (ID number 12/NE/0160) on 25 May 2012 and was monitored by this Committee. Approval for the research to be carried out at the Newcastle Upon Tyne NHS Foundation Trust was granted by the Research and Development department at the Royal Victoria Infirmary. The study was performed in accordance with guidelines on Good Clinical Practice.

3.3 Patient Screening And Recruitment

The prospective observational ICON1 study recruited patients referred to the two tertiary cardiac centres in the North East of England: The Freeman Hospital in Newcastle upon Tyne, UK and The James Cook University Hospital in Middlesbrough, UK. In Freeman Hospital, approximately 3,000 PCI procedures are carried out every year and, in the James Cook University Hospital, approximately 1,750 PCI procedures are performed every year. All patients aged ≥75 years on the urgent/ACS PCI cardiac catheter laboratory list were screened by the study team.

3.3.1 Inclusion And Exclusion Criteria

The inclusion and exclusion criteria are detailed in **Table 3.1**. Patients with cardiac arrest and cardiogenic shock were excluded because it would not have been possible to obtain valid consent in these urgent cases. Ventricular arrhythmias and significant valvular disease were excluded as they may have been the primary cause for admission rather than NSTEACS. Patients with a life expectancy of <1 year were not included as it would preclude measurement of adverse outcomes, and patients with active infection were excluded as measurement of inflammatory markers would be confounded. Previous CABG was an exclusion criterion until a protocol amendment was approved by the ethics committee to include these patients on 18 October 2013. However, these patients were not included in the invasive imaging sub-study as OCT imaging would not have been possible in vein grafts due to the limitations in penetration of the technology, and it was felt that atheroma in CABG grafts may have a different pattern to native vessels.

Inclusion Criteria	Exclusion Criteria
≥ 75 years of age	Cardiac arrest at presentation or during admission
Initial presentation with NSTEACS (UA, NSTEMI)	Cardiogenic shock at presentation or during admission
Planned for angiography ± PCI	Ventricular arrhythmia at presentation or during admission
	Moderate or severe valvular disease
	Malignancy with <1 year expected survival
	Active infection during admission
	Previous CABG

Table 3.1 Inclusion and exclusion criteria for the ICON1 study

3.3.2 Consent And Information

Potential participants were approached on their arrival to the ward and the study explained in detail. They were given an opportunity to ask questions, and were given a written information sheet before the researcher returned to answer any further questions and to obtain informed consent. In patients with visual impairment, the researchers read the information sheet and consent form to the patient. Patients who were unable to consent, e.g. due to lack of capacity, were not recruited. The date of birth and gender of every patient who was screened for potential participation in the study was entered into a password protected screening log. Baseline demographic data for patients entered in the screening log was collected retrospectively from the local British Cardiovascular Intervention Society database, to which all patients undergoing angiography with a view to PCI consent to have data stored for audit purposes.

3.3.3 Study Protocol

The study flow chart is displayed in **Figure 3.1**. Participation in the study did not alter the contemporary treatment of NSTEACS (PCI, CABG or medical therapy) offered by the treating interventional cardiologist[166]. Each patient was assigned an anonymised study ID number and data was collected on standardised case report forms by members of the research team (**Appendix A**).

In total, the ICON1 study aimed to recruit 300 patients, with 100 patients undergoing invasive coronary imaging with VH-IVUS alone, and 30 patients undergoing both VH IVUS and OCT imaging.

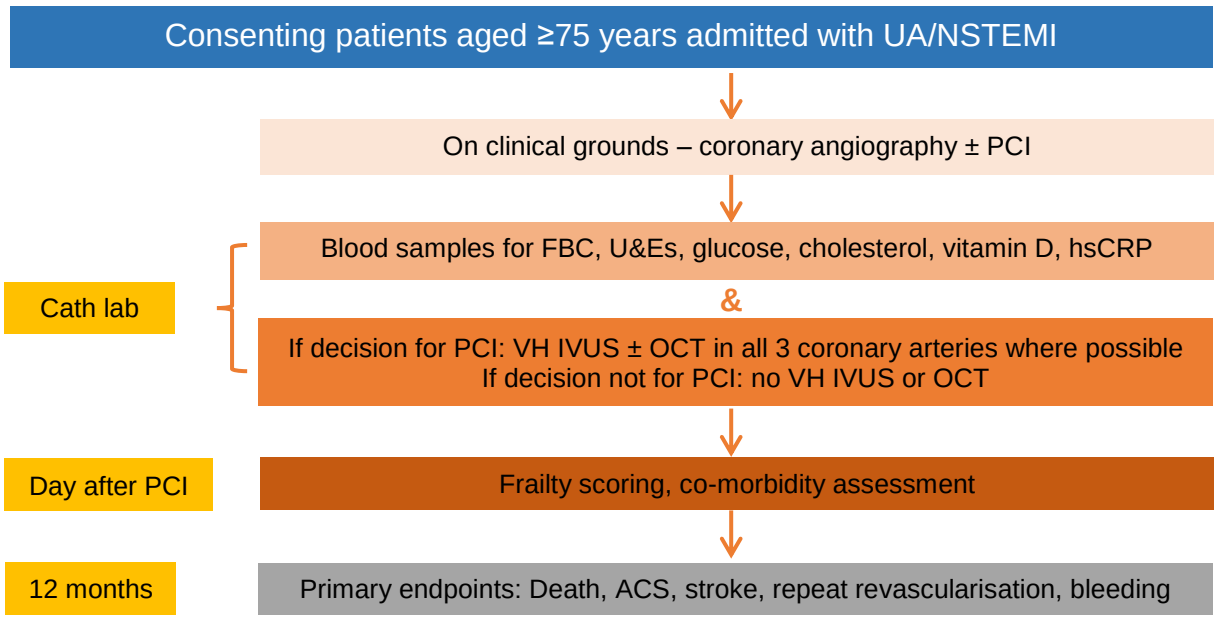


Figure 3.1 Flow diagram of the invasive imaging sub-study protocol

3.4 Quantitative Coronary Angiography

Angiography was performed according to local practice at 15 frames/second. Each angiogram was anonymised and transferred to optical disc for offline analysis by the ICON1 angiographic core lab. Readers were blinded to patient demographics. All readers were trained in QCA analysis by an experienced interventional cardiologist and followed the ICON1 QCA Standard Operating Protocol (**Appendix B**). Each angiogram was analysed by 2 readers and, in the case of any major discrepancies, a third reader adjudicated.

To gain an overview of the burden of coronary artery disease, the SYNTAX score[167] and BCIS Jeopardy Score (a semi-quantative assessment of the amount of myocardium at risk from coronary stenoses)[168] were calculated. All culprit lesions and all lesions that were subsequently intervened on were analysed (irrespective of % stenosis). Other lesions were analysed if the diameter stenosis was >40% in a vessel >1.5mm in diameter. Lesions were considered separately if they were >3 vessel reference diameters apart.

Specific lesion location, calcification score and lesion complexity were recorded. In addition, measurements of lesion length, minimum lumen diameter (MLD), MLA, maximum diameter and area % stenosis, and vessel reference diameter (RD) were

made using the Medis software, QAngioXA version 7.3. Finally, post-PCI lesion characteristics and any post-intervention complications were recorded. Residual SYNTAX Score (RSS) and SYNTAX Revascularisation Index (SRI:$\frac{baseline\ SYNTAX\ score - RSS}{baseline\ SYNTAX\ score}\ x\ 100$) were calculated[169, 170].

A PCI procedure was considered a complete success if the post-procedure residual diameter stenosis was <30% with TIMI grade 3 flow. A procedure was classified as a partial success if there was either a ≥30% residual stenosis by QCA or if TIMI grade 2 flow was attained. A procedure was classified a failure if there was a persistent total occlusion, if the lesion could not be crossed, or if there was persistent abrupt closure.

3.5 Invasive Coronary Imaging

This PhD project utilised patient data from the invasive imaging sub-study of ICON1, recruited between 31 October 2012 and 26 August 2015. It was expected that not all patients enrolled in ICON1 would be eligible for invasive imaging thus it was anticipated that, for every patient undergoing invasive imaging, 2 patients would be entered into the non-invasive sub-study. We aimed to image 100 patients with VH IVUS, of which 30 patients would be imaged with both VH IVUS and OCT.

3.5.1 Virtual Histology Intravascular Ultrasound

3.5.1.1 Acquisition

Following diagnostic angiography and decision to proceed to PCI, a 20MHz, phased-array Volcano Eagle Eye Platinum™ (EEP) catheter (**Figure 3.2A**) was mounted on an R-100 pullback device (**Figure 3.2B**) and connected to either an integrated S5i system or mobile S5 tower. Image acquisition was performed at a pullback speed of 0.5mm/s and was ECG gated to ensure only one frame was acquired per cardiac cycle. The maximum length of all three coronary arteries was imaged, where feasible[53]. The data was anonymised, then transferred to a DVD for offline data analysis. The treating interventional cardiologist was blinded to this data.

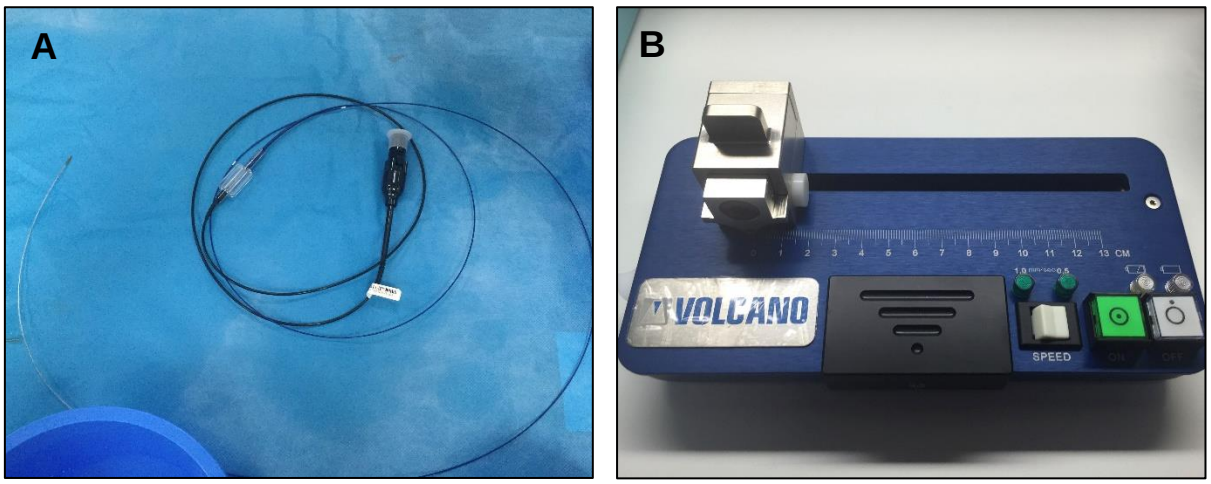


Figure 3.2 Eagle Eye Platinum catheter (A) and R-100 pullback device (B)

3.5.1.2 Analysis

VH IVUS intracoronary imaging analysis was performed using the Medis QIvus software, versions 2.2 and 3.0, which calculates the MLD and MLD, %stenosis, and absolute volume and percentage of each plaque component (fibrous, FF, NC and DC) after the reader had manually drawn the contours of the lumen and external elastic membrane in each frame (**Appendix C**). Percent atheroma volume was calculated as the proportion of the vessel wall occupied by plaque, as previously described[171]. RI was calculated by dividing the external elastic membrane (EEM) area at the site of maximal plaque burden by the EEM area at the reference site (the site of smallest plaque burden 10mm proximal to the target site but distal to any side branches)[172].

A manual frame-by-frame analysis was then performed to classify the lesion sub-type present according to definitions from a previously published consensus document (**Figure 1.7**)[53]. The percentage of frames containing each lesion sub-type, rather than number of separate lesions, was calculated, as the high plaque burden in this cohort led to relatively low prevalence of separate lesions when classified as per the consensus document (lesions separated longitudinally by >5mm of artery with a plaque burden of <40% should be considered separate lesions[53], but few of the ICON1 cohort of patients had long enough segments of "normal" coronary artery without atherosclerosis). The LAPS (= –2.149 + (0.68×$\frac{NC}{DC}$) + (3.39 if MLA <4) + (5.1 if RI@MLA >1.05) + (3.7 if TCFA present))[64] was also calculated.

3.5.2 Optical Coherence Tomography

3.5.2.1 Acquisition

OCT images were obtained using a Dragonfly catheter (St Jude Medical, Minnesota, USA) connected to the Ilumien™ PCI Optimization System. Immediately prior to image acquisition, a short flush of iso-osmolar contrast was administered to ensure the guide catheter was well engaged with the coronary artery and the catheter was clear of blood. The system was calibrated and the OCT pullback initiated with a flush of iso-osmolar contrast (10ml in the right coronary artery, 15ml in the left coronary artery). OCT images were obtained in 54mm segments at a pullback rate of 20mm/s in all three coronary arteries where feasible. Data was transferred anonymously to a DVD for offline analysis and the operator was blinded to this data during the procedure.

3.5.2.2 Analysis

OCT data was analysed using the Medis QIvus software, version 2.2. Contours were drawn around the lumen to generate data on the MLA and MLD. The whole vessel was then analysed frame-by-frame to identify lesion sub-types. An atherosclerotic lesion was defined on OCT as a mass lesion within the arterial wall, with focal intimal thickening or loss of the normal vessel architecture[102]. The number of frames containing significant lipid or calcium accumulations were recorded for each vessel, as were the presence or absence of other pathologies such as plaque rupture, thrombus, OCT-TCFA, microchannels, macrophage accumulations and ChC.

3.6 Frailty Assessment

The day following PCI, frailty was assessed by the Fried Frailty Criteria (**Table 1.2, Appendix B**)[17]. Nutritional status, endurance and physical activity were assessed by asking the patient pre-specified questions. Strength was assessed by grip dynamometer in the dominant hand (average of 3 readings), and mobility was assessed by timing the patient walking over 4.5m (15 feet). The patient was categorised as frail if 3 or more criteria were present, pre-frail if 1 or 2 criteria were present, and robust if no criteria were present.

3.7 Biomarker Analysis

Full blood count, renal function, blood glucose, cholesterol and troponin levels were measured in all patients as part of routine normal care and were recorded in the case report form. At the time of coronary angiography, before administration of any heparin, 30ml of blood was collected from the arterial sheath. Highly sensitive C-reactive protein (hsCRP) and vitamin D were analysed in real time. Vitamin D was stratified into deficient (<25nmol/L), insufficient (25-49nmol/L) and sufficient (≥50nmol/L) categories according to the local laboratory reference values.

3.8 Outcomes

Patients were followed up in the research clinic at 1 year from the recruitment date and data was collected on standardised case report forms (**Appendix D**). If this was not possible, the patient was contacted by telephone and primary outcome measures recorded from this. If the patient was unwilling or unable to be contacted directly, the patient's General Practitioner was contacted and a list of all medical consultations from the date of recruitment was obtained.

Primary outcome measures were defined as death, ACS, stroke, repeat unplanned revascularisation, and Bleeding Academic Research Consortium (BARC) defined bleeding (grade 2 and above)[173]. Time to first primary endpoint was recorded.

3.9 Statistical Analysis

The sample size was calculated to provide adequate power to detect whether the presence of TCFA are associated with a composite of the 1-year primary outcomes in this population. This required several assumptions taken from previous studies: a 27.9% rate of adverse outcomes in patients ≥75 years following interventional treatment for ACS[22], a 20% incidence of TCFA in patients ≥65 years[174], and a HR of 3.35 for a TCFA to cause an adverse event in patients of all ages[69]. Using the method described by Kelsey et al, a sample size of 97 patients is required to provide 80% power with a 95% two-sided confidence level[175].

Normality of the distribution of continuous variables was checked with the Shapiro-Wilk test. Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed or median and IQR if not normally distributed. Discrete variables are expressed as numbers and percentages

Results of patient-level, vessel-level and lesion-level data are presented. Where both independent and dependent variables were measured at the same level, they were analysed using unpaired Student's t-test or ANOVA test if continuous and normally distributed, Mann-Whitney U test or Kruskal-Wallis test if continuous but not normally distributed, Pearson's Chi Square test or Fisher's Exact Test (if any cell count was <5) if categorical.

Where the independent variable was measured at a patient-level but the dependent variable was measured at a vessel or lesion-level, a linear mixed-effects model was used, nesting lesions or vessels within patient identifiers. This model handles correlated data and unequal variances, and also allows an unequal number of measurement repetitions between subjects (as patients had differing numbers of vessels imaged by VH IVUS and OCT). It also estimates fixed (i.e. affects the population mean) and random (i.e. associated with the sampling procedure) effects and thus adjusts for the covariance structure of the data.

Predictors of plaque phenotypes were investigated by performing multiple regression analyses (for continuous dependent variables e.g. %NC) or multivariate logistic regression (for categorical dependent variables e.g. presence of VH-TCFA). Covariates for the multivariate analyses were chosen by purposeful selection, with any independent variable having a significant univariate test (with a p value cut-off point of 0.25) entered into an automated stepwise regression analysis with the non-candidate inclusion level set to 0.15. This is a method which has been shown to result in a more accurate model when risk factor modelling rather than just predicting events, as it identifies and retains confounders at a greater rate than other automated selection algorithms[176].

The Statistical Package for Social Sciences version 21.0 (SPSS Inc, Chicago, IL) and Stata version 14.0 (StataCorp LLC, College Station, Tx) were used for analyses.

CHAPTER 4: RESULTS – Demographics, Feasibility and Reproducibility

The data presented here is a sub-study of a larger prospective observational study of older patients with ACS. I evaluate the recruitment of older patients to this invasive imaging sub-study and quantify the challenges of three-vessel intravascular imaging in this complex cohort.

4.1 Recruitment

Recruitment is summarised in **Figure 4.1**. Of the 629 patients initially screened for participation in ICON1, 457 (72.7%) were eligible and approached to take part in the study. The average age of those screened was 81.2 ± 4.8 years and 43.6% were female. Of those approached, 319 (69.8%) consented to participation. Following coronary angiography, 20 (6.3%) of these patients were excluded from the study due to a non-NSTEACS final diagnosis, and one patient withdrew their consent.

In total, 99/298 (33.2%) underwent invasive imaging. Five of these patients were recruited after August 2015 and two patients were <75 years, so are therefore not included in this work. In addition, there were 8 patients that underwent VH IVUS evaluation with the Volcano Revolution® catheter as the EEP catheters were not available; these patients are also not included in the VH IVUS analysis (although 7 did have OCT imaging alone), as previous validation studies have shown that the EEP phased-array catheter demonstrates systematically higher volumetric measurements and therefore cannot be directly compared with the 45MHz rotational imaging catheter[177].

This leaves a final total of 91 patients recruited over 34 months from November 2012 to August 2015, 84 with VH IVUS imaging, 26 with OCT imaging, and 19 with both.

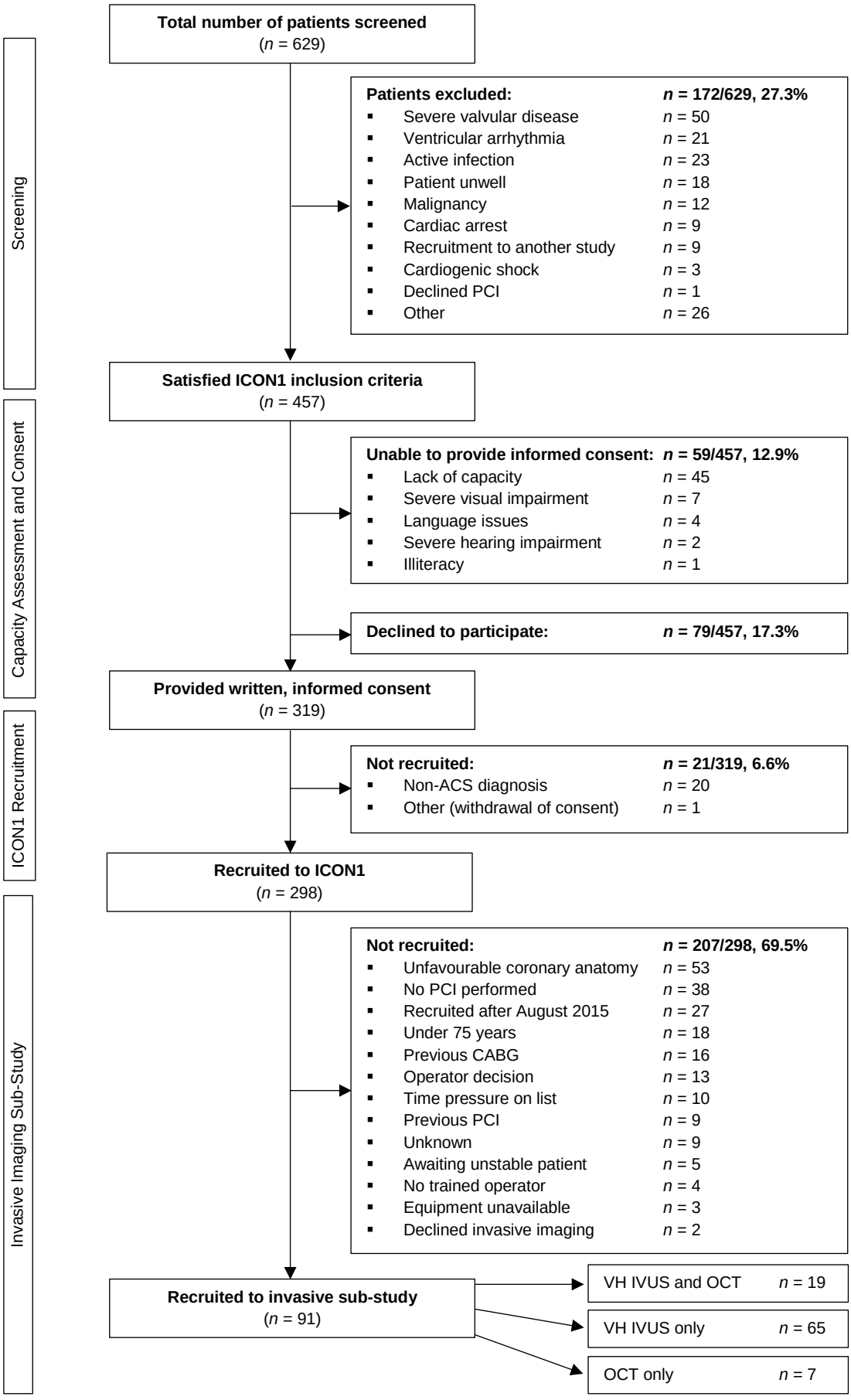


Figure 4.1 CONSORT flow diagram of study recruitment

Table 4.1 details the baseline characteristics of patients in the eligible and recruited populations to August 2015 (both to the main ICON1 study and to the invasive imaging sub-study). The ICON1 study cohort was slightly younger than the eligible population and had fewer females. This is because female patients were more likely to decline to participate than male (25.6% vs. 10.0% of eligible patients approached, p<0.001), and those who were unable to consent were older than those able to consent (83.0 ± 4.7 vs. 81.0 ± 4.7 years, p=0.002). The cardiovascular risk factor profile was similar other than family history of IHD. The invasive imaging sub-study cohort did not differ significantly from the ICON1 population other than lower incidences of hypertension, hyperlipidaemia and renal disease. This may reflect a higher incidence of unfavourable coronary anatomy for imaging in these conditions.

	Eligible patients (A) N=411	ICON1 study (B) N=258	Invasive sub-study (C) N=91	P value A vs B	P value B vs C
Age (years ± SD)	81.5 ± 4.4	81.1 ± 4.1	80.9 ± 3.8	***0.020**	0.693
Male, n (%)	213 (51.8)	152 (58.9)	58 (63.7)	***<0.001**	0.245
Presentation:					
• **NSTEMI**, n (%)	314 (76.4)	213 (82.6)	74 (81.3)	***<0.001**	0.699
• **Unstable angina**, n (%)	60 (14.6)	45 (17.4)	17 (18.7)		
• **Other**, n (%)	37 (9)	0	0		
Hypertension, n (%)	307 (74.7)	196 (76.0)	60 (65.9)	0.441	***0.005**
Diabetes, n (%)	103 (25.1)	63 (24.4)	18 (19.8)	0.696	0.200
Smoking status:					
• **Current smoker**, n (%)	31 (7.5)	18 (7.0)	8 (8.8)	0.793	0.348
• **Ex-smoker**, n (%)	215 (52.3)	134 (51.9)	42 (46.2)		
• **Never smoked**, n (%)	165 (40.1)	106 (41.1)	41 (45.1)		
Hyperlipidaemia, n (%)	234 (56.9)	155 (60.1)	45 (49.5)	0.095	***0.010**
Family history of IHD, n (%)	110 (26.9)	81 (31.6)	28 (31.5)	***0.005**	0.964
Renal disease, n (%)	92 (22.4)	56 (21.7)	13 (14.3)	0.668	***0.033**
Peripheral vascular disease, n (%)	39 (9.5)	25 (9.7)	6 (6.6)	0.857	0.215
Cerebrovascular disease, n (%)	55 (13.4)	42 (16.3)	12 (13.2)	***0.025**	0.321

Table 4.1 Baseline characteristics by eligibility and recruitment status

4.2 Baseline Demographics

Tables 4.2 and **4.3** demonstrate that there were few differences between the age groups in terms of patient demographics and baseline blood results. GRACE score and creatinine clearance both include age as one of their variables and therefore it was expected that there would be significant differences between the age groups. There was a non-significant trend towards higher frailty with increasing age, and older patients were more likely to have had a previous MI or PCI, and therefore a higher incidence of congestive cardiac failure (CCF). Body mass index (BMI) was lowest in the middle age group. Older patients were more likely to have a lower haemoglobin, in keeping with the known age-related decline in erythropoiesis[178].

Table 4.4 demonstrates that baseline demographics did not differ significantly between the sexes other than a higher number of male ex-smokers, and a higher incidence of previous stroke or transient ischaemic attack in males. In keeping with previous large studies of age related changes in peripheral blood counts, female patients had lower haemoglobin levels but higher platelet counts (**Table 4.5**)[178]. Female patients had a higher total cholesterol level, again in keeping with the known increase in cholesterol in post-menopausal women[179], and this may also reflect the higher rate of statin prescription pre-PCI in male patients (96.6% vs. 87.9% in this cohort). Vitamin D was lower in women than men, in line with a large meta-analysis of studies on vitamin D and cardiovascular disease in Europe and the USA[180].

Unsurprisingly, frailty was associated with increasing age (**Table 4.6**). Frailty was also significantly associated with GRACE risk score, in keeping with previous results from the Trilogy ACS trial[21]. Frail patients had a higher rate of diabetes, atrial fibrillation, angina and cerebrovascular disease, these conditions are likely the cause of the higher frailty rather than an effect. Other conditions that could be expected to cause increased frailty include chronic obstructive pulmonary disease (COPD), CCF, peripheral vascular disease (PVD) and anaemia, but these were present in very low numbers in this cohort, likely due to selection bias prior to referral for PCI. There were no significant differences in baseline blood tests when stratified by frailty (**Table 4.7**).

	Total N=91	<79 years N=30	79-82 years N=33	>82 years N=28	P value
Male, n (%)	58 (63.7)	19 (63.3)	22 (66.7)	17 (60.7)	0.889
Frailty:					
• **Robust**	25 (27.5)	13 (43.3)	9 (27.3)	3 (10.7)	0.076
• **Pre-frail**	51 (56.0)	14 (46.7)	19 (57.6)	18 (64.3)	
• **Frail**	15 (16.5)	3 (10.0)	5 (15.2)	7 (25.0)	
NSTEMI, n (%)	74 (81.3)	22 (73.3)	26 (78.8)	26 (92.9)	0.146
Unstable angina, n (%)	17 (18.7)	8 (26.7)	7 (21.2)	2 (7.1)	
GRACE score, ± SD	129.4 ± 17.2	118.0 ± 14.2	129.9 ± 15.2	141.5 ± 13.8	***<0.001**
BMI (IQR)	26.6 (24.0, 28.8)	27.9 (25.2, 32.3)	24.9 (23.5, 27.3)	26.1 (22.0, 28.1)	***0.005**
Hypertension, n (%)	60 (65.9)	20 (66.7)	19 (57.6)	21 (75.0)	0.357
Diabetes, n (%)	18 (19.8)	5 (16.7)	7 (21.2)	6 (21.4)	0.872
Smoking status:					
• **Current smoker**, n (%)	8 (8.8)	4 (13.3)	3 (9.1)	1 (3.6)	0.671
• **Ex-smoker**, n (%)	42 (46.2)	14 (46.7)	16 (48.5)	42 (42.9)	
• **Never smoked**, n (%)	41 (45.1)	12 (40.0)	14 (42.4)	15 (53.6)	
Hyperlipidaemia, n (%)	45 (49.5)	12 (40.0)	18 (54.5)	15 (53.6)	0.448
Family history of IHD, n (%)	28 (31.5)	12 (42.9)	9 (27.3)	7 (25.0)	0.287
Renal disease, n (%)	13 (14.3)	2 (6.7)	5 (15.2)	6 (21.4)	0.271
Previous MI, n (%)	18 (19.8)	7 (23.3)	2 (6.1)	9 (32.1)	***0.033**
Previous angina, n (%)	26 (28.6)	9 (30.0)	5 (15.2)	12 (42.9)	0.057
Previous PCI, n (%)	11 (12.1)	3 (10.0)	1 (3.0)	7 (25.0)	***0.029**
Atrial fibrillation, n (%)	13 (14.3)	3 (10.0)	6 (18.2)	4 (14.3)	0.651
PVD, n (%)	6 (6.6)	2 (6.7)	2 (6.1)	2 (7.1)	0.986
Cerebrovascular disease, n (%)	12 (13.2)	3 (10.0)	3 (9.1)	6 (21.4)	0.300
COPD, n (%)	13 (14.3)	3 (10.0)	6 (18.2)	4 (14.3)	0.651
CCF, n (%)	5 (5.5)	0	0	5 (17.9)	***0.003**
Anaemia, n (%)	3 (3.3)	0	1 (3.0)	2 (7.1)	0.312

Table 4.2 Baseline demographics and past medical history by age

	Total N=91	<79 years N=30	79-82 years N=33	>82 years N=28	P value
Haemoglobin (g/dL ± SD)	13.4 ± 1.8	14.1 ± 1.3	13.5 ± 1.3	12.6 ± 2.4	***0.004**
White cell count ($x10^9$ ± SD)	8.4 ± 2.1	8.1 ± 1.8	8.4 ± 2.1	8.9 ± 2.3	0.338
Platelets ($x10^9$ ± SD)	242 ± 83	233 ± 53	260 ± 95	230 ± 91	0.283
Creatinine clearance (ml/min ± SD)	58.5 ± 20.5	70.3 ± 22.7	56.4 ± 19.0	48.3 ± 12.6	***<0.001**
Glucose, mmol/L (IQR)	6.2 (5.3, 7.1)	5.9 (5.75, 7.0)	6.2 (5.1, 7.5)	6.3 (5.3, 7.5)	0.956
Cholesterol (mmol/L ± SD)	4.22 ± 0.99	4.43 ± 1.10	4.28 ± 0.96	3.91 ± 0.84	0.210
Peak troponin, ng/L (IQR)	150 (44, 504)	335 (32, 894)	88 (15, 246)	194 (29, 428)	0.707
Vitamin D, nmol/L (IQR)	39 (24, 53)	40 (23, 65)	28 (21, 46)	40 (30, 63)	0.570
hsCRP, mg/L (IQR)	4.8 (1.7, 15.1)	3.5 (1.2, 8.5)	9.2 (3.5, 21.9)	4.2 (1.3, 14.9)	0.098

Table 4.3 Routine baseline blood tests by age

	Total N=91	Male N=58	Female N=33	P value
Age (years ± SD)	80.8 ± 3.9	80.7 ± 3.8	81.1 ± 4.0	0.578
Frailty: • **Robust** • **Pre-frail** • **Frail**	 25 (27.5) 51 (56.0) 15 (16.5)	 14 (24.1) 36 (62.1) 8 (13.8)	 11 (33.3) 15 (45.5) 7 (21.2)	0.303
NSTEMI, n (%)	74 (81.3)	48 (82.8)	26 (78.8)	0.640
Unstable angina, n (%)	17 (18.7)	10 (17.2)	7 (21.2)	
GRACE score, ± SD	129.4 ± 17.2	128.5 ± 15.6	131.0 ± 19.8	0.531
BMI (IQR)	26.6 (24.0, 28.8)	26.7 (24.0, 28.7)	26.6 (23.6, 30.2)	0.650
Hypertension, n (%)	60 (65.9)	37 (63.8)	23 (69.7)	0.568
Diabetes, n (%)	18 (19.8)	12 (20.7)	6 (18.2)	0.773
Smoking status: • **Current smoker**, n (%) • **Ex-smoker**, n (%) • **Never smoked**, n (%)	 8 (8.8) 42 (46.2) 41 (45.1)	 3 (5.2) 32 (55.2) 23 (39.7)	 5 (15.2) 10 (30.3) 18 (54.5)	***0.044**
Hyperlipidaemia, n (%)	45 (49.5)	27 (46.6)	18 (54.5)	0.463
Family history of IHD, n (%)	28 (31.5)	14 (24.6)	14 (43.8)	0.061
Renal disease, n (%)	13 (14.3)	7 (12.1)	6 (18.2)	0.535
Previous MI, n (%)	18 (19.8)	12 (20.7)	6 (18.2)	0.773
Previous angina, n (%)	26 (28.6)	17 (29.3)	9 (27.3)	0.836
Previous PCI, n (%)	11 (12.1)	7 (12.1)	4 (12.1)	1.000
Atrial fibrillation, n (%)	13 (14.3)	11 (19.0)	2 (6.1)	0.123
PVD, n (%)	6 (6.6)	6 (10.3)	0	0.083
Cerebrovascular disease, n (%)	12 (13.2)	11 (19.0)	1 (3.0)	***0.050**
COPD, n (%)	13 (14.3)	7 (12.1)	6 (18.2)	0.535
CCF, n (%)	5 (5.5)	3 (5.2)	2 (6.1)	1.000
Anaemia, n (%)	3 (3.3)	2 (3.4)	1 (3.0)	1.000

Table 4.4 Baseline demographics and past medical history by sex

	Total N=91	Male N=58	Female N=33	P value
Haemoglobin (g/dL ± SD)	13.4 ± 1.8	14.0 ± 1.4	12.5 ± 2.1	***<0.001**
White cell count ($x10^9$ ± SD)	8.4 ± 2.1	8.3 ± 1.8	8.6 ± 2.5	0.586
Platelets ($x10^9$ ± SD)	242 ± 83	218 ± 59	287 ± 100	***<0.001**
Creatinine clearance (ml/min ± SD)	58.5 ± 20.5	60.9 ± 19.5	54.2 ± 21.9	0.137
Glucose, mmol/L (IQR)	6.2 (5.3, 7.1)	6.2 (5.1, 7.0)	6.4 (5.8, 7.5)	0.435
Cholesterol (mmol/L ± SD)	4.2 ± 1.0	4.0 ± 0.8	4.6 ± 1.1	***0.015**
Peak troponin, ng/L (IQR)	150 (44, 504)	189 (44, 708)	116 (40, 364)	0.583
Vitamin D, nmol/L (IQR)	39 (24, 53)	41 (28, 64)	29 (13, 40)	***0.002**
hsCRP, mg/L (IQR)	4.8 (1.7, 15.1)	5.2 (2.2, 15.3)	4.5 (1.5, 14.9)	0.492

Table 4.5 Routine baseline blood tests by sex

	Total N=91	Robust N=25	Pre-frail N=51	Frail N=15	P value
Age (years ± SD)	80.8 ± 3.9	79.1 ± 2.9	81.2 ± 4.0	82.6 ± 3.8	***0.011**
Male, n (%)	58 (63.7)	14 (56.0)	36 (70.6)	8 (53.3)	0.303
NSTEMI, n (%)	74 (81.3)	23 (92.0)	39 (76.5)	12 (80.0)	0.261
Unstable angina, n (%)	17 (18.7)	2 (8.0)	12 (23.5)	3 (20.0)	
GRACE score, ± SD	129.4 ± 17.2	124.2 ± 14.4	128.8 ± 16.9	140.6 ± 18.5	***0.014**
BMI (IQR)	26.6 (24.0, 28.8)	27.3 (24.2, 27.3)	25.7 (23.8, 29.4)	26.6 (23.1, 28.2)	0.327
Hypertension, n (%)	60 (65.9)	16 (64.0)	32 (62.7)	12 (80.0)	0.451
Diabetes, n (%)	18 (19.8)	2 (8.0)	10 (19.6)	6 (40.0)	***0.049**
Smoking Status:					0.452
• **Current smoker**, n (%)	41 (45.1)	2 (8.0)	3 (5.9)	3 (20.0)	
• **Ex-smoker**, n (%)	42 (46.2)	10 (40.0)	25 (49.0)	7 (46.7)	
• **Never smoked**, n (%)	8 (8.8)	13 (52.0)	23 (45.1)	5 (33.3)	
Hyperlipidaemia, n (%)	45 (49.5)	11 (44.0)	27 (52.9)	7 (46.7)	0.744
Family history of IHD, n (%)	28 (31.5)	10 (43.5)	11 (21.6)	7 (46.7)	0.065
Renal disease, n (%)	13 (14.3)	3 (12.0)	7 (13.7)	3 (20.0)	0.771
Previous MI, n (%)	18 (19.8)	6 (24.0)	8 (15.7)	4 (26.7)	0.531
Previous angina, n (%)	26 (28.6)	3 (12.0)	17 (33.3)	6 (40.0)	0.087
Previous PCI, n (%)	11 (12.1)	3 (12.0)	5 (9.8)	3 (20.0)	0.567
Atrial fibrillation, n (%)	13 (14.3)	2 (8.0)	6 (11.8)	5 (33.3)	0.063
PVD, n (%)	6 (6.6)	0	4 (7.8)	2 (13.3)	0.223
Cerebrovascular disease, n (%)	12 (13.2)	0	8 (15.7)	4 (26.7)	***0.040**
COPD, n (%)	13 (14.3)	2 (8.0)	8 (15.7)	3 (20.0)	0.525
CCF, n (%)	5 (5.5)	1 (4.0)	3 (5.9)	1 (6.7)	0.922
Anaemia, n (%)	3 (3.3)	0	2 (3.9)	1 (6.7)	0.485

Table 4.6 Baseline demographics and past medical history by frailty

	Total N=91	Robust N=25	Pre-frail N=51	Frail N=15	P value
Haemoglobin (g/dL ± SD)	13.4 ± 1.8	13.7 ± 1.2	13.5 ± 2.1	12.7 ± 1.5	0.190
White cell count ($x10^9$ ± SD)	8.4 ± 2.1	7.9 ± 2.1	8.7 ± 2.1	8.2 ± 2.0	0.271
Platelets ($x10^9$ ± SD)	242 ± 83	251 ± 94	245 ± 83	217 ± 59	0.411
Creatinine clearance (ml/min ± SD)	58.5 ± 20.5	60.2 ± 17.4	59.6 ± 22.9	51.9 ± 16.3	0.397
Glucose, mmol/L (IQR)	6.2 (5.3, 7.1)	6.9 (5.8, 7.5)	5.9 (5.3, 6.9)	6.4 (4.9, 11.2)	0.284
Cholesterol (mmol/L ± SD)	4.2 ± 1.0	4.6 ± 1.1	4.1 ± 0.9	4.3 ± 1.1	0.274
Peak troponin, ng/L (IQR)	150 (44, 504)	152 (36, 426)	197 (49, 696)	85 (32, 172)	0.251
Vitamin D, nmol/L (IQR)	39 (24, 53)	35 (24, 58)	35 (23, 52)	40 (22, 50)	0.868
hsCRP, mg/L (IQR)	4.8 (1.7, 15.1)	4.0 (1.7, 17.6)	5.4 (2.4, 15.8)	6.7 (1.1, 11.6)	0.666

Table 4.7 Routine baseline blood tests by frailty

4.3 Safety and Feasibility of Three Vessel Intravascular Imaging

VH IVUS and OCT intravascular imaging in this cohort was safe, with no complications attributable to VH IVUS imaging. There was only one complication of imaging during the study, and this occurred during OCT imaging. Ventricular fibrillation was induced by contrast flushing of the LAD artery in a patient with a CTO of the RCA and was successfully treated with defibrillation with no sequelae for the patient.

The feasibility of VH IVUS and OCT imaging in an older cohort is shown in **Table 4.8**. Overall, there was a high success rate, with successful imaging performed in 80.6% of anatomically suitable vessels with VH IVUS and 74.7% with OCT. The success rate was similar between the LAD and RCA but the success rate in the Cx artery was slightly lower, due to the higher number of non-dominant or tortuous vessels in this group.

The definition of unsuitable coronary anatomy included CTO, tortuous vessels or heavy calcification, which would preclude the imaging catheter being delivered into the artery (as determined by the operator). It also included previous stenting, which would prevent VH IVUS or OCT analysis behind the stent struts. Failure to cross the lesion with the imaging catheter and unsuitable anatomy for intravascular imaging defined by the operator was more common with the VH IVUS EEP catheter, as the transducer has a 3.5F external diameter, compared to 2.7F for the Dragonfly OCT catheter.

Only one set of OCT acquisitions was affected by a technical problem; the optical lens of the imaging catheter was damaged when introducing it into the guide catheter. “Sufficient quality for analysis” was defined as acquisition of >70% of the region of interest and satisfactory blood clearing with visibility of >3 quadrants in >70% of the pullback length. Three VH IVUS pullbacks were unable to be analysed, as the imaging catheter “stuck” in tortuous and calcified vessels, leading to non-continuous automated pullback, and 6 arteries imaged by OCT had insufficient blood clearing.

Prolonged catheterisation time was defined as premature termination of the 3-vessel imaging procedure due to patient discomfort . This was a particular concern prior to the commencement of the study, due to the nature of the patient cohort, but occurred in a very small number of patients. It was marginally more common in the OCT imaging sub-study (6.7 vs. 5.5%), as this imaging modality tended to be

performed second. Cath lab time constraints included premature termination of the 3-vessel imaging procedure due to arrival of an unscheduled emergency or if the imaging had a detrimental effect of the timely running of the list and was unavoidable, as all cases were scheduled on “urgent” lists rather than in a dedicated research lab.

	LAD		Cx		RCA	
	VH IVUS	**OCT**	**VH IVUS**	**OCT**	**VH IVUS**	**OCT**
Number of vessels	84	27	84	27	84	27
Unsuitable coronary artery anatomy (%)	4 (4.8)	0	14 (16.7)	2 (7.4)	18 (21.4)	4 (14.8)
Number of vessels available for imaging	80	27	70	25	66	23
Successful imaging (%)	67 (83.8)	20 (74.1)	53 (75.7)	18 (72.0)	54 (81.8)	18 (78.3)
Unsuccessful imaging:						
• Failure to cross lesion (%)	4 (5.0)	0	5 (7.1)	2 (8.0)	0	0
• Technical problem (%)	0	1 (3.7)	0	1 (4.0)	0	1 (4.3)
• Insufficient quality for analysis (%)	1 (1.3)	2 (7.4)	0	2 (8.0)	2 (3.0)	2 (8.7)
• Prolonged catheterisation time (%)	5 (6.4)	3 (11.1)	5 (7.1)	2 (8.0)	2 (3.0)	0
• Cath lab time constraints (%)	3 (3.8)	0	7 (10.0)	0	8 (12.1)	2 (8.7)
• Complication (%)	0	1 (3.7)	0	0	0	0

Table 4.8 Feasibility of VH IVUS and OCT imaging

Because of the reasons for unsuccessful imaging of an artery outlined in **Table 4.8**, <30% of patients underwent 3 vessel imaging using either VH IVUS or OCT (**Table 4.9**). However, >75% of patients had at least 2 epicardial vessels imaged by either technology. OCT image runs were shorter than VH IVUS acquisitions as the automatic pullback device had a 56mm limit; two imaging runs were done in some patients but this required more time and contrast injection.

	VH IVUS N=84	**OCT N=26**
Number of epicardial arteries imaged:		
• **Three** (%)	25 (29.8)	7 (26.9)
• **Two** (%)	40 (47.6)	14 (53.8)
• **One** (%)	19 (22.6)	5 (19.2)
Culprit vessel length imaged (mm ± SD)	47.5 ± 27.4	33.9 ± 18.0
Non-culprit vessel length imaged (mm ± SD)	71.9 ± 37.2	53.9 ± 24.5
Total length imaged per patient (mm ± SD)	105.2 ± 54.5	75.3 ± 31.1
• **LMS** (mm ± SD)	9.4 ± 7.1	7.2 ± 4.8
• **LAD** (mm ± SD)	46.1 ± 24.0	34.0 ± 14.6
• **Cx** (mm ± SD)	41.7 ± 17.9	32.6 ± 14.0
• **RCA** (mm ± SD)	58.4 ± 25.8	39.1 ± 17.9

Table 4.9 Imaged coronary arteries available for analysis

There was a small increase in contrast volume (**Figure 4.2A**) and procedure duration (**Figure 4.2B**) for patients undergoing PCI with invasive imaging compared to those undergoing PCI alone, but no difference in radiation dose (**Figure 4.2C**). Median contrast volume increased by 40ml with the addition of invasive imaging, and median procedure duration increased by 15 mins. The increase in contrast use persisted even when patients undergoing only VH IVUS were analysed (i.e. disregarding patients who underwent OCT imaging, during which contrast is administered). This increase in contrast use can be explained by the need for additional angiography of non-target vessels when positioning guide catheters for invasive imaging, or at the end of imaging when demonstrating that there were no adverse sequelae following removal of the imaging catheter. Although the increase in time and contrast used are small, this has implications for valid patient consent in future studies utilising multi-vessel invasive imaging.

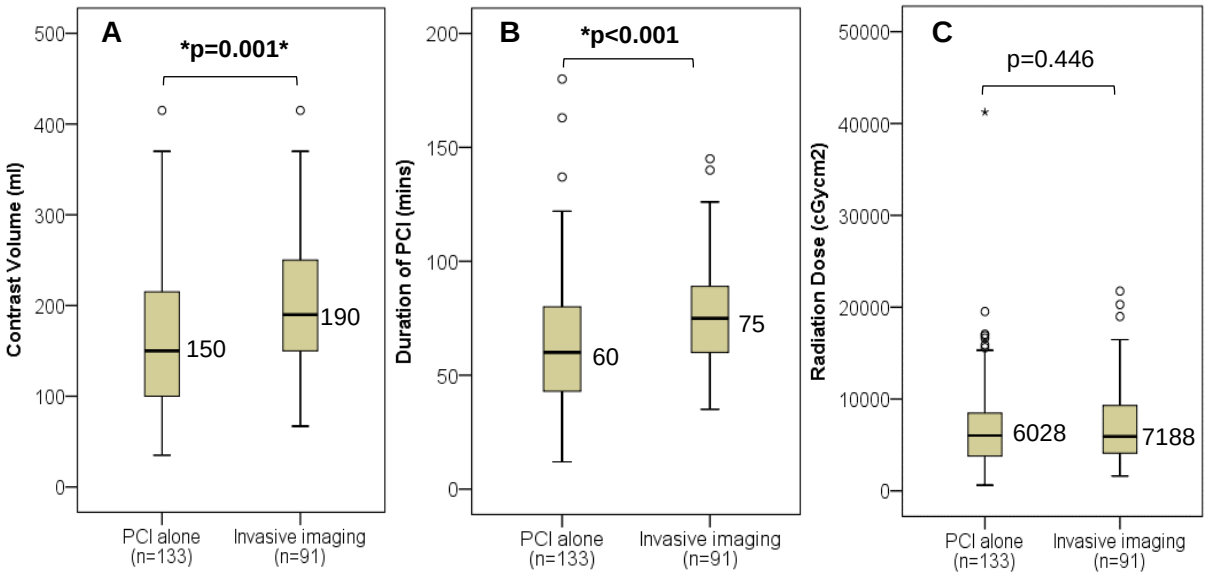


Figure 4.2 Procedure characteristics for patients undergoing PCI + invasive imaging vs. PCI alone

Patients in the invasive imaging sub-study had a longer procedure duration and increase in the volume of radio-opaque contrast, but no difference in the radiation dose, in comparison to patients in the ICON1 study undergoing PCI but no invasive imaging. Data presented as median (central line), interquartile range (upper and lower box limits) and range (error bars). PCI alone n = 133; PCI + imaging n = 91.

4.4 Reproducibility of Measurements

Following training in the use of the analytical software (QAngio and QIvus) by Medis Product Support Specialists, I analysed 15 patients' data (angiographic, VH IVUS and OCT) which was then checked by the study's Chief Investigator for accuracy. After this learning phase was approved, the official analysis was then commenced. A random sample of 8 lesions/arteries was re-analysed for each imaging modality several months later to provide data on intra-observer variability.

4.4.1 Quantitative Coronary Angiography

Figure 4.3 details the intra-observer variability on selected measurements on QCA. All show a very strong correlation between measurements, as denoted by the intraclass correlation coefficients (r).

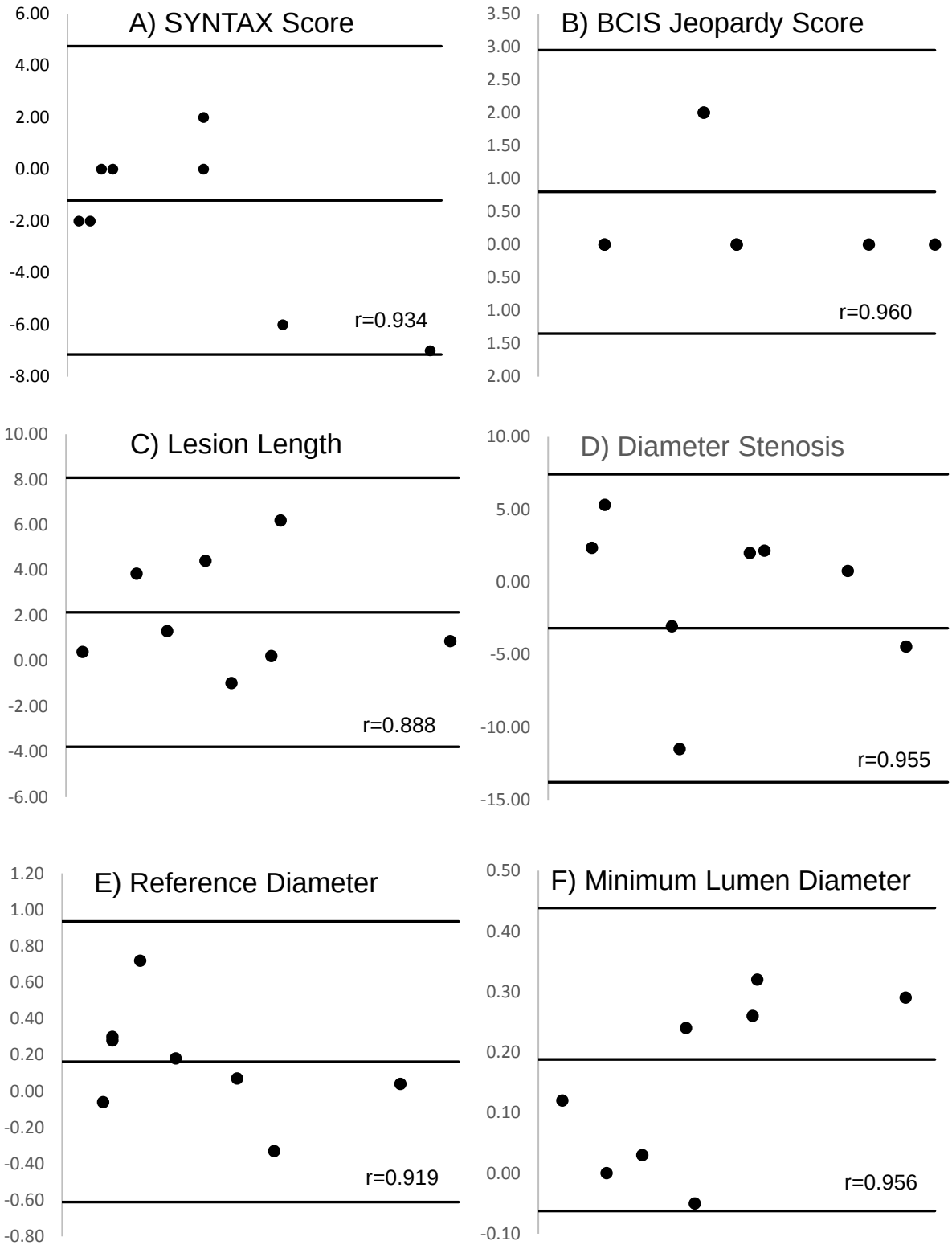


Figure 4.3 Intra-observer variability in measurements on QCA

4.4.2 VH IVUS

In total, 636 frames from 8 patients were analysed twice to provide data on area and volumetric measurements (**Figure 4.4**), plaque composition (**Figure 4.5**) and lesion classification (**Figure 4.6**). Again, there was excellent reproducibility.

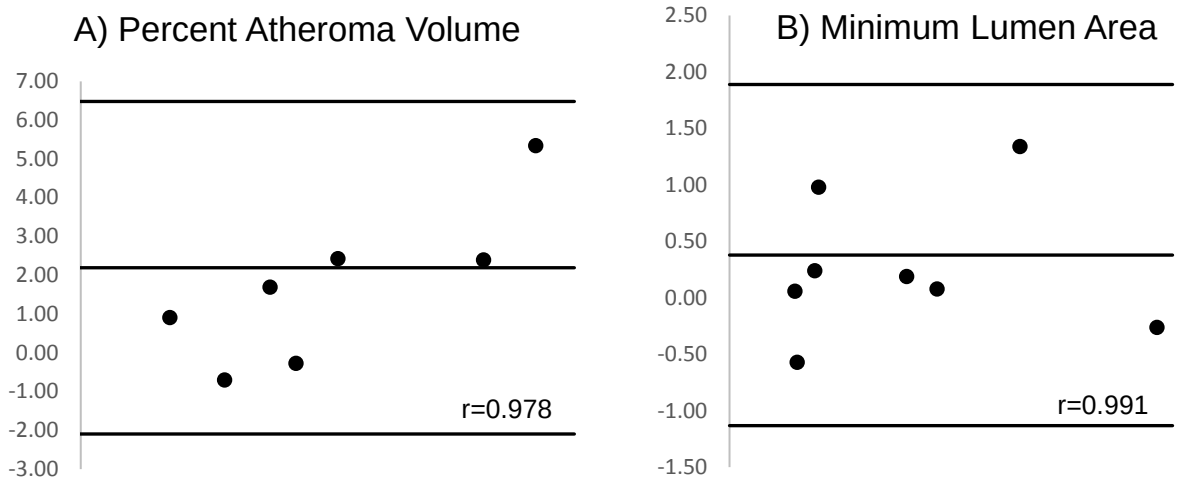


Figure 4.4 Intra-observer variability in grayscale IVUS measurements

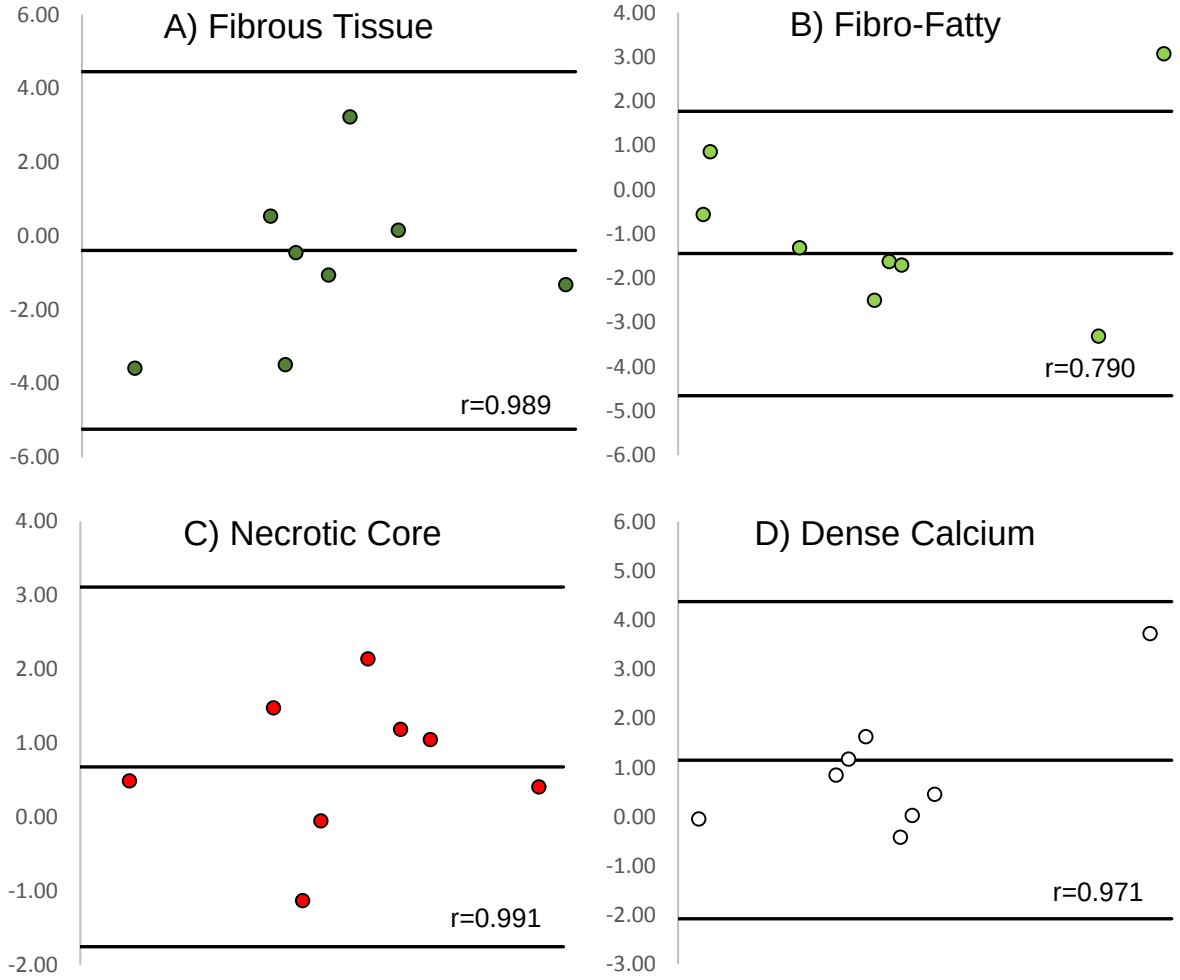


Figure 4.5 Intra-observer variability in VH IVUS plaque composition

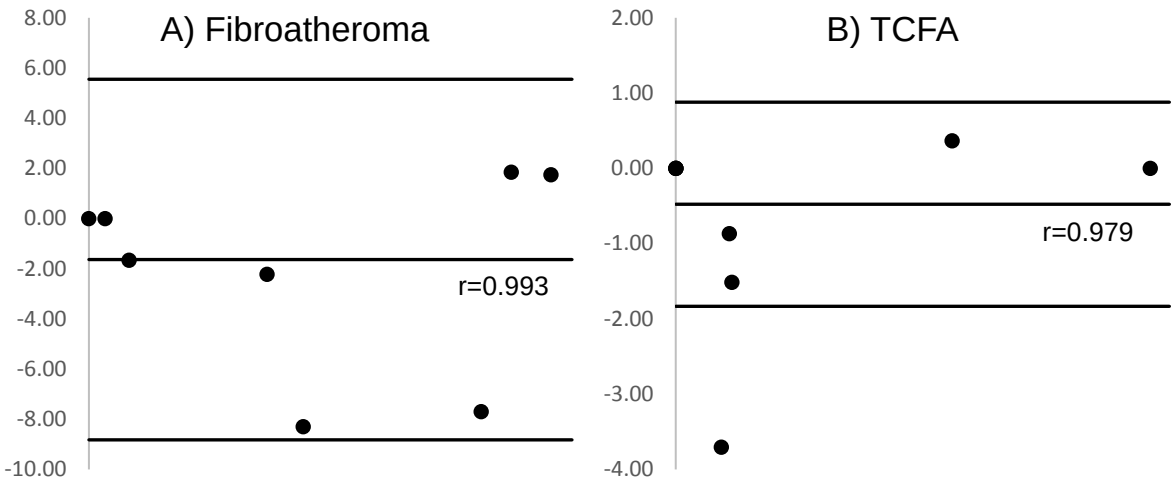


Figure 4.6 Intra-observer variability in VH IVUS lesion classification

The outlier in **Figure 4.6B** represents an artery with very little plaque (measurements of 2/54 and 0/54 frames with VH-TCFA), therefore the absolute agreement between measurements remains good.

4.4.3 OCT

There was very little intra-observer variability in OCT measurements (**Figure 4.7**).

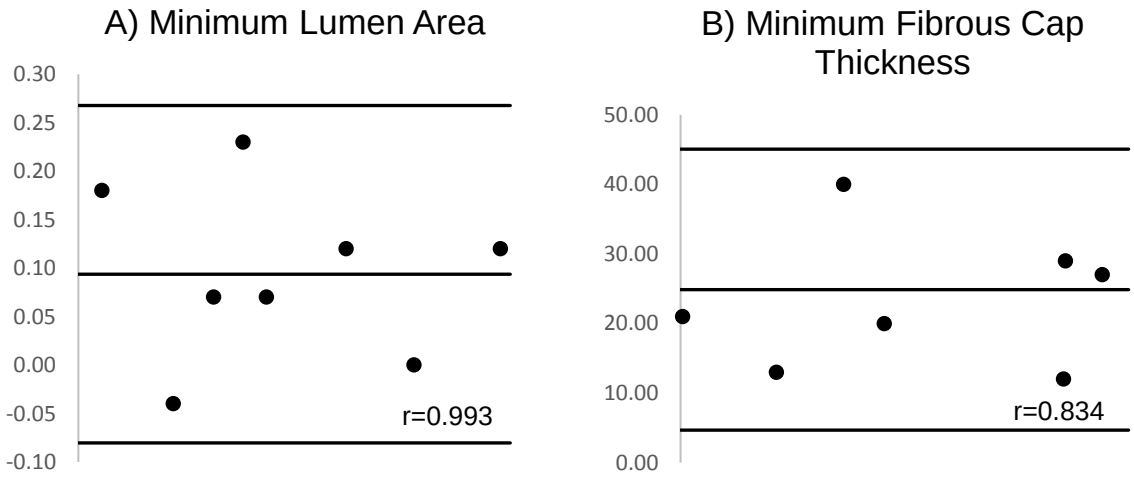


Figure 4.7 Intra-observer variability in OCT measurements

4.5 Discussion

4.5.1 Feasibility of Recruiting Older Patients with ACS to Research Studies

Historically, the recruitment of older patients to clinical research has represented a significant challenge. In this study, we have demonstrated that the majority of patients meeting the inclusion criteria (69.8%) were recruited to participate in the ICON1 study, with a low rate of patients declining to participate (17.3%). Those who declined were more likely to be female, and those unable to consent were older than those who could.

Despite a recent focus on the importance of recruiting older people to cardiovascular research, the majority of RCTs and observational studies fail to recruit older patients with ACS, and a significant minority actively exclude them. This leads to the continuing paucity of data in this age group. A systematic review of RCTs in ACS showed that, although enrolment of older patients has increased through the decades, only 10.3% of patients fell into this age category in the RCTs published between 1996 and 2000[35]. In one meta-analysis of trials in heart failure, the use of arbitrary age cut-offs was more common in European studies than those conducted in the USA[181]. Of the 44 published RCTs in ACS in 2014, 10 studies (22.7%) had upper age limits (4 RCTs excluded patients >75 years, 4 excluded >80 years, 1 excluded >85 years and 1 excluded >90 years) and the average age of participants across all RCTs was 62.0 ± 6.8 years. Only two RCTs (4.5%) specifically recruited older patients[32, 37]. Of the 70 published prospective observational studies, 11 (15.7%) had upper age limits (1 study excluded >55 years, 3 excluded >75 years, 5 excluded >80 years and 2 excluded >85 years) and the average age of participants was 61.3 ± 5.9 years. Six prospective observational studies did not define whether there were any exclusion criteria related to age. Two observational studies (2.9%) specifically recruited older patients[38, 39]. However, at least in RCTs, the percentage of trials actively excluding older patients does seem to be falling, from 31.9% in 1996-2001[35] to 22.7% in 2014.

Recruiting older patients to this cardiovascular research study has been a very positive experience. The recruitment rate of 69.8% compares favourably to that of the Newcastle 85+ study (71.7%)[36], which recruited from a similar geographic population, but recruited in the community and did not involve patients undergoing invasive investigations. Patients who were approached to participate in this study were

generally enthusiastic about taking part in research, citing their wish to “give something back” and to improve the treatment of patients presenting in the future.

Several cardiovascular studies have exclusively recruited older patients, with mixed success. The Italian Elderly ACS study recruited a population comparable to ICON1, patients with NSTEACS, aged ≥75 years[22]. Initially planning to recruit 504 patients, the trial design was amended due to a slower-than-expected recruitment rate and recruited 313 patients in total. The investigators attributed slow recruitment to a number of factors, including difficulty in obtaining informed consent and significant co-morbidity burden, making many patients ineligible for recruitment due to exclusion criteria. More recently, the After Eighty study patients recruited aged ≥75 years, and also evaluated conservative versus invasive management of NSTEACS[23]. Out of 4,187 patients in this age group with NSTEACS, 1,973 patients met the inclusion criteria but only 457 (23.2%) were recruited. The authors credit the low recruitment rate to logistical reasons (1011 patients, mainly due to lack of funding in community hospitals for 24/7 recruitment) and refusal to participate (402 patients, 20.4%).

A previous cardiovascular RCT in patients aged 70-82 years found that the most common reason for taking part in research was self-interest (52.9%) such as for “health checks” or “peace of mind”, followed by a sense of altruism (39.6%) to “help research” or “help others”[182]. Several patients mentioned the importance of as few clinic visits as possible after the initial recruitment in hospital, citing a lack of transport and unwillingness to “bother” family members. Five patients cited distance from the research venue as a reason for declining, and previous research has demonstrated an inverse correlation between distance from the older patient’s residence to the research venue and their likelihood of participation in a clinical trial[183].

Several patients expressed anxiety regarding the PCI procedure and felt unable to consider any additional procedures at that time. Care was taken by the researchers not to overwhelm the patient and to provide them with adequate time to assimilate the information given, often with multiple conversations with them and their family. Older patients who agree to participate in research often take more time to make the decision[184] and patients who feel they have sufficient time to consider the information are more likely to consent[185]. This is time-consuming for the research team and

requires dedicated researchers who are able to develop a rapport with the patient and their family.

Guidance on ethical research for and with older people has stipulated that studies recruiting older people should aim to recruit a majority of women in order to reflect the general population[43]. However, women approached for participation were much more likely to decline than men. There was an anxiety among older patients, not just about research, but about the wider experience of having PCI that prevented them from agreeing to take part in the study. The research team therefore had to be knowledgeable not just about the study, but about the whole in-patient journey. In addition, 3 female patients declined to participate in ICON1 because of concerns that taking part in research would affect their ability to care for their spouse. Although a greater proportion of men than women over the age of 75 years are unpaid carers, this figure may be skewed as more women in this age group are likely to be widowed[186]. Indeed, two female patients screened for inclusion declined because of a recent bereavement. Therefore it is important for researchers to be sensitive to these issues when approaching older patients for participation in studies.

Patients approached for participation in ICON1 who were unable to provide informed consent were, on average, older than those who could. The most common reason for being unable to consent was a lack of capacity due to cognitive impairment (70%). Around 10% of the population over 85 have dementia[187]; all research involving older patients should take due consideration of mental capacity and the process of informed consent. However, it is still possible to recruit patients without mental capacity whilst still protecting them from coercion, allowing them to take part and benefit from the advances brought about by such research. In the UK, specific Research Ethics Committees consider the involvement of patients without capacity on an individual study basis[188]. Other reasons for being unable to consent included hearing or visual impairment. The patient information sheet was written in plain English in a large font size to facilitate reading, and researchers often took time to read it aloud to patients with visual impairment.

Therefore, if older patients are willing to participate, is the poor recruitment rate the fault of the study investigators? In a study of patients with breast cancer eligible to participate in research, 51% of patients <65 years of age were offered the chance to

participate, compared with 35% of those ≥65 years (p=0.006)[189]. Age was not a predictor of consenting to participate in a study once it was offered (56% of younger patients vs. 50% of older, p=0.67)[189]. The most common reasons given by physicians for not offering a trial to older patients were that they believed treatment was too toxic for the patient (33%), the best treatment was not available in the trials (27%), the physician was unaware that the patient was eligible (21%), and the physician thought that the patient was not eligible (18%)[189]. A further study of patients with breast cancer demonstrated that physicians cited age as a factor in deciding not to discuss a trial in 17% of patients ≥65 years vs. 3% of younger patients (p=0.04) and, if a trial was discussed, cited age as a factor in not enrolling the patient in 11% of older vs. 3% of younger patients (p=0.04)[190]. A change in attitudes towards older patients in research is required if we are to see substantial improvements in their recruitment rates.

Recently, the PREDICT Consortium, a group funded by the European Union to study and help boost the number of elderly people taking part in research, has compiled a charter for the rights of older patients in clinical trials, aiming to narrow the gap between populations recruited to clinical trials and real clinical practice[42]. Guidelines published by the Geriatric Working Party of the European Forum for Good Clinical Practice suggest that research in older people should: 1) actively recruit patients over 75 years with no upper age limit, 2) recruit a majority of women, and 3) justify exclusion co-morbidities in order to accurately reflect the population studied[43].

The recruitment rate of older patients to studies in ACS remains low even in the contemporary era, resulting in a paucity of data in this high-risk cohort. However, the contribution of older patients must not be ignored, particularly in the setting of an ever-ageing population, in whom cardiovascular disease burden is high. The recruitment of older patients to the present study was robust, comparing favourably to previous longitudinal studies within this age group. Although enrolling older people to research remains challenging and requires significant adaptation from the inception of study design, this cohort is generally enthusiastic to participate. By taking the time to build a rapport with the potential participant, identifying any consent issues, involving relatives in the decision making process, and minimising the burden of the study on the participant, researchers can ensure this valuable cohort of patients can contribute to our understanding and management of cardiovascular disease in our ageing population.

4.5.2 Three Vessel Invasive Coronary Imaging In Older Patients with ACS

This is the first study of multi-modality invasive coronary imaging in a “real world” older population with few exclusion criteria, and demonstrated an excellent rate of successful imaging. In this study, >75% of patients underwent invasive imaging in at least 2 coronary vessels. This is a slightly lower success rate than a similarly-sized prospective cohort study utilising 3 vessel EEP VH IVUS and OCT imaging in young patients (n=103, mean age 58.2 ± 10.5 years) with STEMI, who were successful in imaging >90% of arteries, with no IVUS complications and <2% OCT complications[191]. However, as well as recruiting younger and less complex patients than ICON1, that study recruited at 5 separate hospitals in Switzerland, The Netherlands and Denmark so each site did not have the same pressures to recruit large numbers as in ICON1. Interestingly, this European study also demonstrated that 3 vessel multi-modality intra-coronary imaging was associated with an increased use of contrast agent (268.3 ± 109.8 vs. 197.9 ± 88.8ml in the PCI alone cohort)[191].

The number and length of arteries imaged by VH IVUS was also lower than in the PROSPECT (total length imaged per patient ≥65 years = 165.9mm)[69, 174] or VIVA (181.7mm)[70] studies, but these studies again recruited a much less complex patient cohort. In addition, the PROSPECT investigators explicitly excluded patients requiring 3 vessel PCI, patients with LMS lesions, patients receiving unsuccessful PCI, and patients with marked calcification or tortuosity of their coronary vessels. Previous studies have demonstrated that vulnerable coronary lesions are more likely to be found in proximal vessels[192, 193], therefore it may not be necessary to focus on longer pullbacks when performing intracoronary imaging in more complex patient groups such as this, but instead concentrate on good quality acquisitions.

There was one complication due to invasive imaging during this study: ventricular fibrillation following contrast flush prior to OCT image acquisition. This is a recognised complication of OCT imaging, occurring in 1.1% of patients in a large registry[194]. In general, these additional imaging procedures are safe; in a prospective, single-centre study, 1142 OCT and 2476 IVUS imaging procedures were carried out with no difference in the complication rate between imaging modalities (IVUS: 0.48% vs. OCT: 0.61%, p=0.6)[195].

The reproducibility of measurements for all three modalities presented here was excellent. Variability in the measurement of VH IVUS parameters has been of particular concern previously, due to the derived nature of many of the plaque composition values (**Figure 1.4**). Differences in the definition of the lumen or vessel contour, difficulty in distinguishing between the plaque margins and artefact or thrombus, and differences in segment length analysed (e.g. due to incorrect identification of proximal or distal landmarks, or repeated frames due to a "stuck" catheter in heavy calcification), can all contribute to a wide variation in the final calculation of plaque composition. A validation study of VH IVUS measurements in patients with ACS demonstrated that there was differences in the repeatability coefficient of up to 14% in vessel area and 31% for lumen area[196]. The intra-class correlation co-efficients reported here for VH IVUS plaque components are in keeping with those reported by previous validation studies, with all co-efficients >0.95 with the exception of fibro-fatty tissue, probably due to the difficulties in tracing the lumen border around soft plaque or thrombus[196, 197].

Although intracoronary invasive imaging in older patients with ACS has its challenges due mainly to their complex coronary anatomy, it is feasible, safe and yields reproducible results in this "real world" population.

CHAPTER 5: RESULTS – The Pattern of Coronary Plaque Burden on Multi-Modality Invasive Imaging in Older Patients with Acute Coronary Syndrome

This high-risk, older patient cohort underwent rigorous examination of their coronary vasculature on three intravascular imaging modalities: invasive angiography, VH IVUS and OCT. Results from these modalities are stratified by both patient-level factors (age, sex and frailty) and vessel or lesion-related factors to attempt to gain a better understanding of the pattern of coronary artery disease in older patients with ACS.

5.1 Quantitative Coronary Angiography

5.1.1 Age

In total, 217 lesions in 91 patients were identified on QCA (<79 years n=60, 79-82 years n=85, >82 years n=72).

Table 5.1 demonstrates that, overall, the complexity of coronary disease was higher than in previous studies of patients with NSTEACS. The overall median SYNTAX score was higher than in the sub-analysis of patients with NSTEACS in the ACUITY study (13 vs. 9)[198], but did not increase with age in our cohort. Older patients did not have a higher rate of multi-vessel disease but were more likely to undergo multi-vessel PCI, suggesting that they were more likely to have their complex coronary disease treated with a single procedure. This is in keeping with a previous study, which demonstrated that octogenarians were more likely to undergo multi-vessel PCI than younger patients (35 vs. 27%, p=0.004)[14]. However, this did not increase the procedure duration, contrast volume used or radiation dose.

There were high rates (>90%) of radial artery access for all age groups, higher than the national average of 80.5%[199], in contrast to previous UK data demonstrating lower rates of radial access with increasing age[26]. Many older patients were still waiting longer than the 72 hour target for PCI, with a median time from presentation to procedure of 5 days[199].

	Total N=91	<79 years N=30	79-82 years N=33	>82 years N=28	P value
Time from presentation to angiography, days (IQR)	5 (3, 6)	3 (3, 5)	5 (4, 7)	5 (3, 6)	0.381
Radial arterial access, n (%)	85 (93.4)	27 (90.0)	32 (97.0)	26 (92.9)	0.533
Culprit artery: • **LMS**, n (%) • **LAD**, n (%) • **Cx**, n (%) • **RCA**, n (%)	 3 (3.3) 46 (51.1) 16 (17.8) 25 (27.8)	 0 13 (43.3) 7 (23.3) 10 (33.3)	 0 17 (53.1) 5 (15.6) 10 (31.3)	 3 (10.7) 16 (57.1) 4 (14.3) 5 (17.9)	0.148
Number of diseased vessels, (IQR)	2 (1, 3)	2 (1, 2)	2 (1, 3)	2 (2, 3)	0.507
Number of lesions, (IQR)	3 (1, 3)	2 (1, 3)	3 (1, 4)	3 (2, 3)	0.222
SYNTAX score, (IQR)	13 (7, 19)	9 (6, 16)	13 (7, 22)	16 (11, 24)	0.193
BCIS Jeopardy Score, (IQR)	6 (4, 7)	6 (3, 6)	6 (4, 6)	6 (4, 10)	0.391
Multi-vessel PCI (%)	27 (29.7)	3 (10.0)	13 (39.4)	11 (39.3)	***0.016**
Number of stents (IQR)	1 (1, 3)	1 (1, 3)	2 (1, 2)	2 (1, 3)	0.304
Contrast volume (ml ± SD)	196.1 ± 68.9	212.7 ± 63.2	181.7 ± 77.0	195.4 ± 62.7	0.205
Radiation dose, cGycm^2 (IQR)	6098 (4033, 10957)	6223 (4650, 11105)	5393 (3303, 11264)	5932 (4970, 10253)	0.419
Procedure duration (mins ± SD)	75.5 ± 23.4	75.1 ± 23.1	71.8 ± 22.1	80.5 ± 25.3	0.381
SYNTAX Revascularisation Index, (IQR)	75.0 (33.3, 100)	62.5 (33.3, 100)	69.3 (28.6, 100)	82.4 (55.0, 100)	0.350

Table 5.1 Angiographic characteristics by age

Figure 5.1 demonstrates no difference in QCA measurements between age groups either before or after PCI. Although the post-PCI % diameter stenosis is greater than that seen in studies of ACS such as the study of PLATelet inhibition and patient Outcomes (PLATO: which had a 6% residual diameter stenosis in almost 2000 patients with an average age of 61 years[200]), the post-PCI MLD and MLA are very similar.

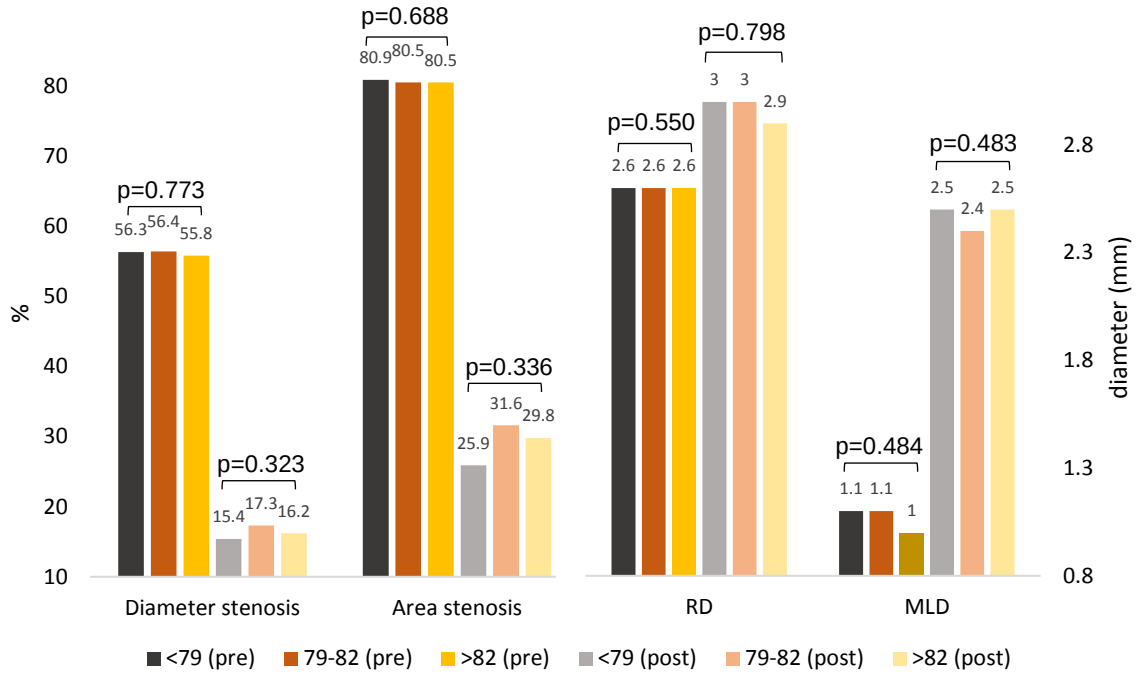


Figure 5.1 Median pre and post-PCI QCA measurements by age

There was a trend towards older patients having fewer CTO lesions (p=0.077) but otherwise there were no differences in calcification score or complexity of lesion between age groups (**Table 5.2**). There was a higher complexity of lesions overall compared to the younger patients in the PLATO study (type A: 9.3%, type B1: 54.0%, type B2: 32.1%, type C: 4.6%)[200] which, in part, is reflective of the higher overall level of calcification. There were no procedure failures in the whole cohort, and a high rate of complete angiographic success across all groups, which is comparable to previous studies of PCI in ACS[200].

	Total N=91	<79 years N=30	79-82 years N=33	>82 years N=28	P value
CTO, n (%)	17 (8.1)	7 (12.1)	8 (9.5)	2 (2.9)	0.077
Calcification:					
• **None**, n (%)	64 (31.1)	18 (32.1)	27 (32.5)	19 (28.4)	
• **Mild**, n (%)	60 (29.1)	19 (33.9)	21 (25.3)	20 (29.9)	0.577
• **Moderate**, n (%)	32 (15.5)	7 (12.5)	14 (16.9)	11 (16.4)	
• **Severe**, n (%)	50 (24.3)	12 (21.4)	21 (25.3)	17 (25.4)	
Lesion complexity:					
• **Type A**, n (%)	13 (6.3)	5 (8.6)	2 (2.4)	6 (8.8)	
• **Type B1**, n (%)	51 (24.5)	17 (29.3)	19 (23.2)	15 (22.1)	0.683
• **Type B2**, n (%)	93 (44.7)	21 (36.2)	41 (50.0)	31 (45.6)	
• **Type C**, n (%)	51 (24.5)	15 (25.9)	20 (24.4)	16 (23.5)	
Procedure performed, n (%)	136 (62.7)	37 (61.7)	52 (61.2)	47 (65.3)	0.659
Procedure success, n (%)	123 (90.4)	35 (94.6)	44 (84.6)	44 (93.6)	0.987

Table 5.2 Lesion characteristics by age

5.1.2 Sex

Of the 217 lesions, 148 were identified in men and 69 in women.

Women were less likely than men to have multi-vessel disease, had fewer lesions, and less extensive disease on the SYNTAX and BCIS jeopardy scores (**Table 5.3**). Consequently, fewer stents were implanted in women and they had a lower procedural radiation dose (although the lower contrast volume and procedure duration in women did not reach statistical significance). Similar results were demonstrated in a sub-analysis of the PROSPECT data (lower incidence of non-culprit lesions in women compared to men: 2.38 ± 1.84 vs. 2.72 ± 2.03, p=0.05[201]), and in a large registry (>100,000 patients) of Swedish ACS patients (lower incidence of 3 vessel/LMS disease in women: 20.9 vs. 30.4%, p<0.001[202]). Thus the sex differences in the extent of coronary disease persist despite increasing age.

	Total N=91	**Male** N=58	**Female** N=33	**P value**
Time from presentation to angiography, days (IQR)	5 (3, 6)	5 (3, 6)	5 (4,7)	0.248
Radial arterial access, n (%)	85 (93.4)	56 (96.6)	29 (87.9)	0.185
Culprit artery:				
• **LMS**, n (%)	3 (3.3)	2 (3.4)	1 (3.1)	
• **LAD**, n (%)	46 (51.1)	25 (43.1)	21 (65.6)	0.159
• **Cx**, n (%)	16 (17.8)	11 (19.0)	5 (15.6)	
• **RCA**, n (%)	25 (27.8)	20 (34.5)	5 (15.6)	
Number of diseased vessels, (IQR)	2 (1, 3)	2 (2, 3)	1 (1, 2)	***0.003**
Number of lesions, (IQR)	3 (1, 3)	3 (2, 3)	2 (1, 3)	***0.045**
SYNTAX score, (IQR)	13 (7, 19)	13 (9, 23)	9 (5, 17)	***0.037**
BCIS Jeopardy Score, (IQR)	6 (4, 7)	6 (4, 8)	6 (2, 6)	***0.041**
Multi-vessel PCI (%)	27 (29.7)	21 (36.2)	6 (18.2)	0.070
Number of stents (IQR)	1 (1, 3)	2 (2, 3)	2 (1, 3)	***0.047**
Contrast volume (ml ± SD)	196.1 ± 68.9	201.9 ± 73.7	185.6 ± 59.1	0.285
Radiation dose, cGycm^2 (IQR)	6098 (4033, 10957)	7275 (4927, 10997)	4917 (3155, 6370)	***<0.001**
Procedure duration (mins ± SD)	75.5 ± 23.4	77.8 ± 26.2	71.6 ± 17.0	0.188
SYNTAX Revascularisation Index, (IQR)	75.0 (33.3, 100)	69.3 (33.3, 100)	77.1 (38.1, 100)	0.614

Table 5.3 Angiographic characteristics by sex

When analysed at a lesion level, male and female patients had similar measurements on QCA both pre and post-PCI (**Figure 5.2**). This differs from the PROSPECT sub-analysis, which demonstrated that women have a smaller RD pre-PCI (2.2 vs. 2.3mm, p=0.01) but a similar diameter stenosis in non-culprit lesions[201]. However, there were no differences in pre-PCI measurements in culprit arteries in the PROSPECT study so,

overall, there may be no sex differences in lesion measurements. In contrast to PROSPECT, we demonstrated no difference in post-PCI measurements. This suggests that there may be a tendency to undersize stents in women, leading to the increase in culprit lesion-related worsening angina seen at follow up in PROSPECT[201].

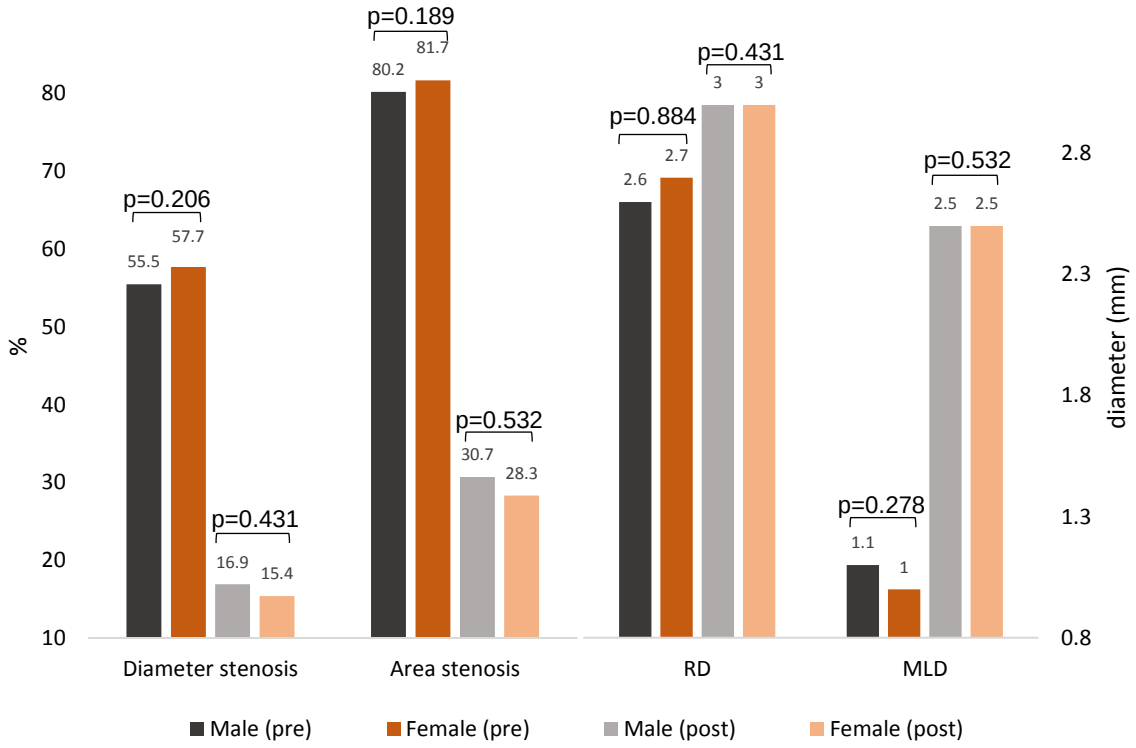


Figure 5.2 Median pre and post PCI QCA measurements by sex

The lesion complexity was similar between the sexes, and the procedure success remained high in both groups (**Table 5.4**). There was a non-significant trend towards less calcification in male patients. However, in the Assessment of Dual Anti-Platelet Therapy with Drug Eluting Stents (ADAPT-DES) study, angiographic calcification was more common in women vs. men in the younger cohort, but this relationship was not present in the ≥65 years cohort, suggesting that age may attenuate this relationship[203].

	Total N=91	Male N=58	Female N=33	P value
CTO, n (%)	17 (8.1)	10 (7.0)	7 (10.4)	0.505
Calcification:				
• **None**, n (%)	64 (31.1)	53 (37.9)	11 (16.7)	
• **Mild**, n (%)	60 (29.1)	35 (25.0)	25 (37.9)	0.080
• **Moderate**, n (%)	32 (15.5)	24 (17.1)	8 (12.1)	
• **Severe**, n (%)	50 (24.3)	28 (20.0)	22 (33.3)	
Lesion complexity:				
• **Type A**, n (%)	13 (6.3)	6 (4.2)	7 (10.8)	
• **Type B1**, n (%)	51 (24.5)	39 (27.3)	12 (18.5)	0.440
• **Type B2**, n (%)	93 (44.7)	60 (42.0)	33 (50.8)	
• **Type C**, n (%)	51 (24.5)	38 (26.6)	13 (20.0)	
Procedure performed, n (%)	136 (62.7)	96 (64.9)	40 (58.0)	0.394
Procedure success, n (%)	123 (90.4)	86 (89.6)	37 (92.5)	0.600

Table 5.4 Lesion characteristics on QCA by sex

5.1.3 Frailty

Of the 217 lesions, 67 were found in robust patients, 114 in pre-frail patients and 36 in the frail group.

Femoral access was more common in frail patients (**Table 5.5**). All bar one (frail) patient had an attempt at radial access before conversion to femoral; the right radial artery was impalpable in the remaining patient and left radial access was not attempted before femoral puncture. Radial access failures were all due to failed radial artery punctures except in one frail patient, where the operator was unable to access the aortic root due a subclavian loop.

In the ICON1 invasive imaging cohort, there were no differences in the extent of coronary disease or rate of multi-vessel PCI with frailty, in keeping with a previous study that demonstrated a higher rate of PCI to the LMS but no difference in number of coronary arteries treated[18].

	Total N=91	Robust N=25	Pre-frail N=51	Frail N=15	P value
Time from presentation to angiography, days (IQR)	5 (3, 6)	5 (4, 7)	5 (3, 6)	4 (3, 8)	0.989
Radial arterial access, n (%)	85 (93.4)	24 (96.0)	50 (98.0)	11 (73.3)	***0.006**
Culprit artery:					
• **LMS**, n (%)	3 (3.3)	1 (4.0)	2 (4.0)	0	
• **LAD**, n (%)	46 (51.1)	11 (44.0)	26 (52.0)	9 (60.0)	0.686
• **Cx**, n (%)	16 (17.8)	4 (16.0)	11 (22.0)	1 (6.7)	
• **RCA**, n (%)	25 (27.8)	9 (36.0)	11 (22.0)	5 (33.3)	
Number of diseased vessels, (IQR)	2 (1, 3)	2 (1, 2)	2 (1, 3)	2 (1, 3)	0.691
Number of lesions, (IQR)	3 (1, 3)	3 (2, 4)	2 (1, 3)	3 (1, 3)	0.419
SYNTAX score, (IQR)	13 (7, 19)	14 (7, 24)	12 (7, 21)	13 (10, 15)	0.737
BCIS Jeopardy Score, (IQR)	6 (4, 7)	6 (4, 6)	6 (4, 8)	6 (4, 9)	0.825
Multi-vessel PCI (%)	27 (29.7)	8 (32.0)	16 (31.4)	3 (20.0)	0.702
Number of stents (IQR)	1 (1, 3)	2 (1, 3)	1 (1, 2)	1 (1, 3)	0.372
Contrast volume (ml ± SD)	196.1 ± 68.9	194.4 ± 75.7	196.8 ± 66.0	196.7 ± 71.9	0.989
Radiation dose, cGycm^2 (IQR)	6098 (4033, 10957)	6919 (3359, 9982)	5931 (4314, 9777)	6867 (3973, 10685)	0.962
Procedure duration (mins ± SD)	75.5 ± 23.4	77.4 ± 25.3	73.0 ± 21.4	80.6 ± 27.1	0.513
SYNTAX Revascularisation Index, (IQR)	75.0 (33.3, 100)	79.2 (26.6, 100)	69.3 (33.3, 100)	75.5 (53.8, 100)	0.662

Table 5.5 Angiographic characteristics by frailty

Figure 5.3 demonstrates that pre-frail patients had a smaller pre-PCI reference diameter than robust or pre-frail patients, with no differences post-PCI.

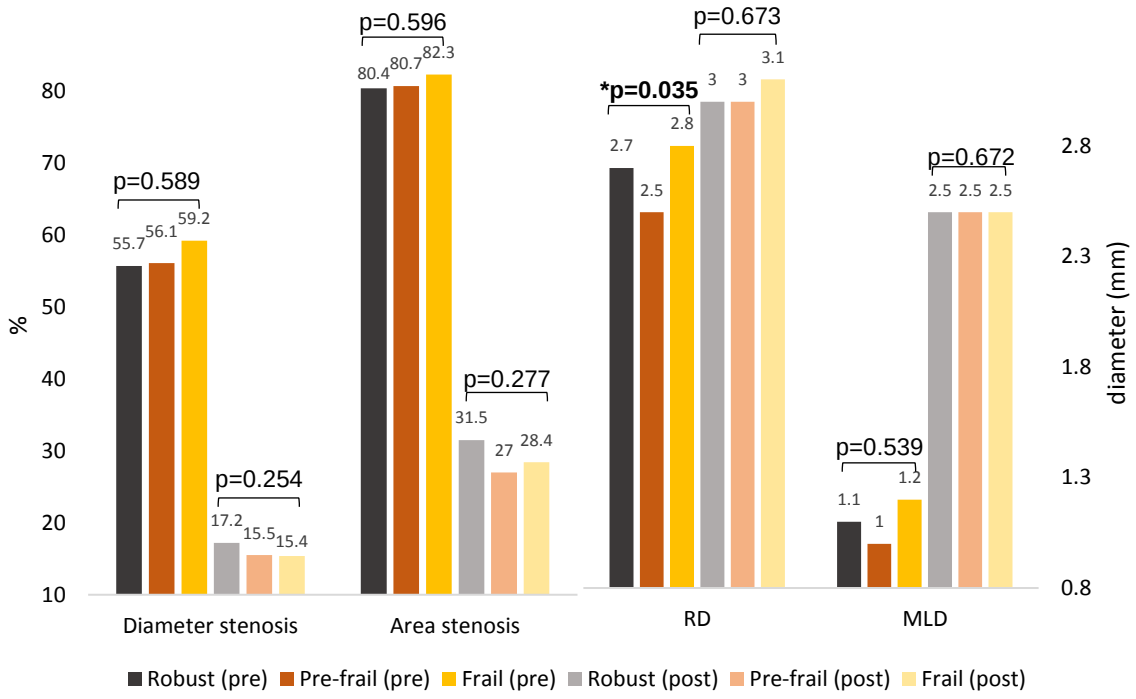


Figure 5.3 Median pre and post PCI QCA measurements by frailty

There were no differences in angiographic calcification between frailty groups (**Table 5.6**), in contrast to the results seen when calcification was measured by VH IVUS (**Figure 5.8**). However, angiographic calcification is a subjective observation rather than an objective measurement and may also reflect adventitial rather than just intimal calcification.

	Total N=91	Robust N=25	Pre-frail N=51	Frail N=15	P value
CTO, n (%)	17 (8.1)	7 (10.8)	8 (7.3)	2 (5.6)	0.364
Calcification:					
• **None**, n (%)	64 (31.1)	12 (18.8)	45 (41.7)	7 (20.6)	
• **Mild**, n (%)	60 (29.1)	27 (42.2)	23 (21.3)	10 (29.4)	0.707
• **Moderate**, n (%)	32 (15.5)	11 (17.2)	14 (13.0)	7 (20.6)	
• **Severe**, n (%)	50 (24.3)	14 (21.9)	26 (24.1)	10 (29.4)	
Lesion Complexity:					
• **Type A**, n (%)	13 (6.3)	4 (6.3)	4 (3.7)	5 (14.3)	
• **Type B1**, n (%)	51 (24.5)	12 (18.8)	31 (28.4)	8 (22.9)	0.073
• **Type B2**, n (%)	93 (44.7)	27 (42.2)	51 (46.8)	15 (42.9)	
• **Type C**, n (%)	51 (24.5)	21 (32.8)	23 (21.1)	7 (20.0)	
Procedure performed, n (%)	136 (62.7)	42 (62.7)	72 (63.2)	22 (61.1)	0.920
Procedure success, n (%)	123 (90.4)	37 (88.1)	68 (94.4)	18 (81.8)	0.692

Table 5.6 Lesion characteristics on QCA by frailty

5.1.4 Key Findings From Angiographic Sub-Study

- Angiographic success of PCI is high in this older age group
- Older patients are not more likely to have multi-vessel disease, but are more likely to undergo multi-vessel PCI
- Women are likely to have less extensive coronary disease than men, in keeping with studies in younger patients
- Frail patients had a higher rate of femoral vs. radial artery access

5.2 Virtual Histology Intravascular Ultrasound

In total, 221 vessels were imaged in 84 patients with VH IVUS (20,078 frames).

5.2.1 Age

Overall, 74 vessels were imaged in patients aged <79 years (6161 frames), 76 in patients 79-82 years (7266 frames), and 71 in patients >82 years (6651 frames).

With increasing age, there was a significant increase in coronary plaque burden, as measured by the maximum vessel stenosis and the percent atheroma volume (PAV) (**Table 5.7**). This is consistent with previous studies demonstrating an increase of plaque burden with age[58, 204, 205]. The sub-analysis of the PROSPECT data by age also demonstrated similar results, whereby plaque volume in non-culprit segments was greater in the older age cohort (<65 years: 49.0% [46.5, 51.9], ≥65 years: 49.7% [47.2, 52.9], p=0.01)[174]. The results also demonstrate increasing LAPS with age, suggesting that older patients may have a higher burden of more active plaque.

	Total N=84	<79 years N=26	79-82 years N=31	>82 years N=27	P value
MLA (mm^2 ± SD)	5.2 ± 2.4	5.7 ± 2.5	5.2 ± 2.5	4.8 ± 2.1	0.174
MLD (mm ± SD)	2.5 ± 0.6	2.6 ± 0.6	2.5 ± 0.6	2.4 ± 0.5	0.167
Maximum stenosis (% ± SD)	67.2 ± 12.2	63.7 ± 13.0	66.6 ± 12.1	71.5 ± 10.4	***0.003**
Remodeling index (± SD)	1.04 ± 0.13	1.04 ± 0.12	1.02 ± 0.13	1.07 ± 0.15	0.137
Percent atheroma volume (± SD)	45.3 ± 10.9	42.7 ± 11.4	43.4 ± 10.9	50.0 ± 8.9	***<0.001**
Liverpool Active Plaque Score (± SD)	4.19 ± 3.57	3.32 ± 3.63	4.01 ± 3.24	5.24 ± 3.66	***0.015**

Table 5.7 Grayscale and VH IVUS parameters by age

Figure 5.4 illustrates the proportion of plaque components in each age group and demonstrates that there was no difference between the groups, in contrast to the PROSPECT sub-analysis, which demonstrated more DC and less fibrous tissue in the older age group[174]. However, this cohort had a much higher proportion of DC overall (over twice as much) due to selection bias in the PROSPECT study, and a much older and narrower age range such that differences in plaque composition due to age may not be as apparent. A further retrospective, single-centre study of 553 patients undergoing VH IVUS imaging demonstrated that elderly patients (>70 years) had greater %NC and %DC than non-elderly patients. However, when results were broken down by clinical presentation, this only held true for patients with stable angina; those with ACS had no difference in relative plaque components when stratified by age[58].

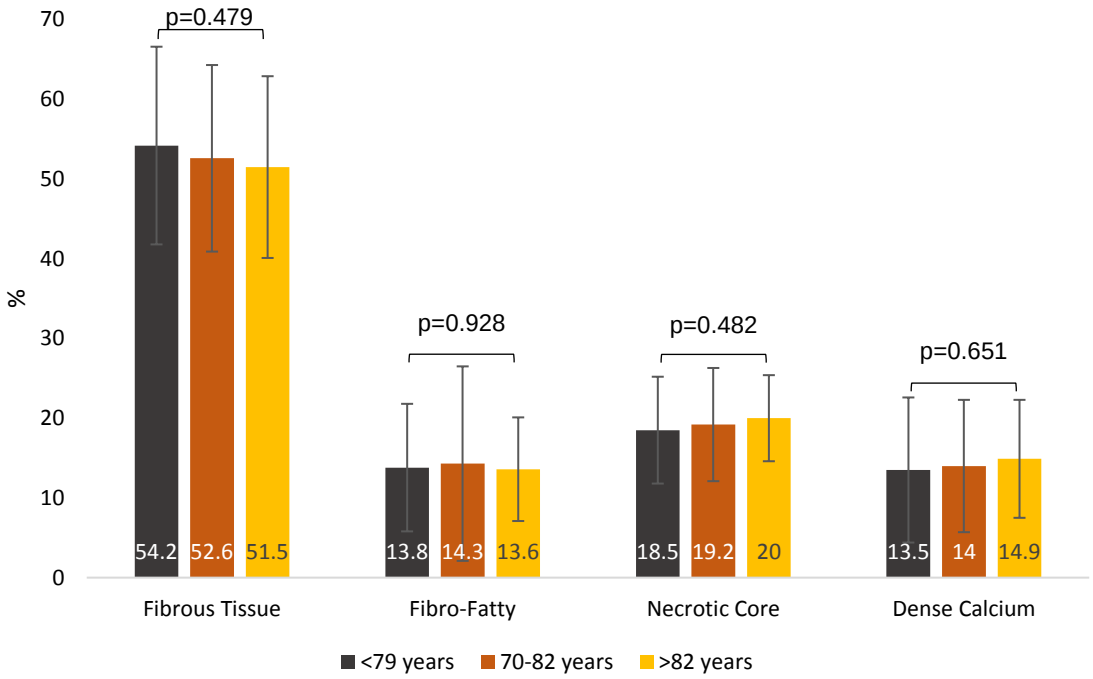


Figure 5.4 Proportion of plaque components by age

Figure 5.5 demonstrates that there was a greater burden of advanced and vulnerable lesions (FA and VH-TCFA) with age. Interestingly, the PROSPECT investigators demonstrated greater FA in the older cohort (42.5 vs. 35.8%, p=0.0007) but a trend towards fewer VH-TCFA (23.2 vs. 20.3%, p=0.08)[174]. This may reflect the fact that they only reported non-culprit lesions and there was a trend in our cohort for a greater burden of VH-TCFA in culprit arteries that may have biased our results.

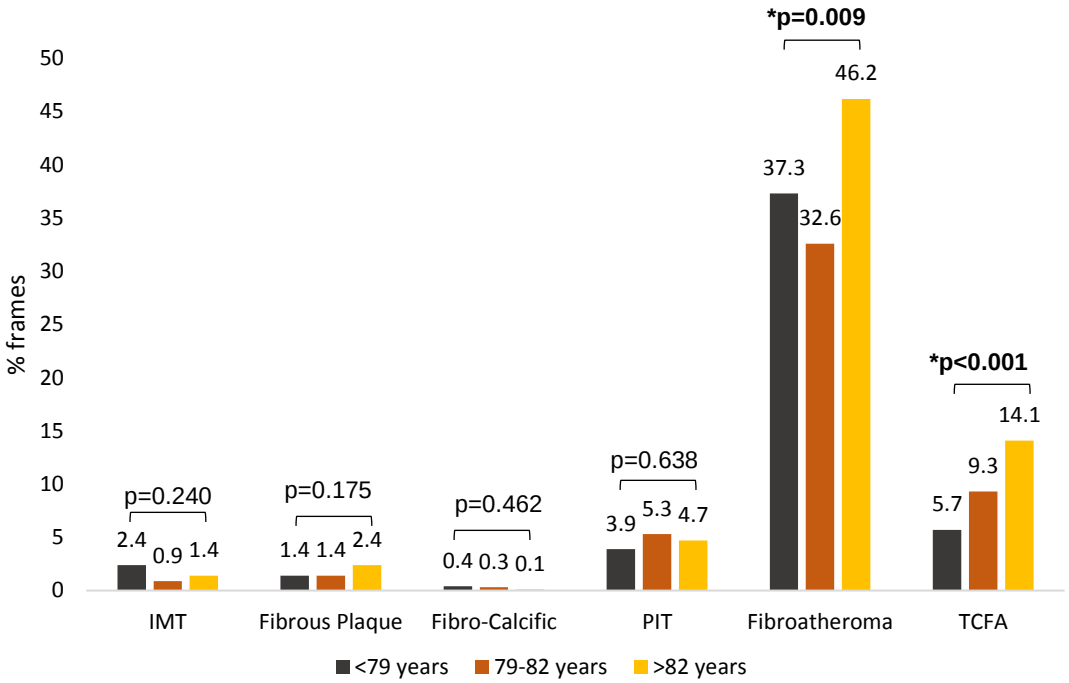


Figure 5.5 Lesion classification by age

5.2.2 Sex

Overall, 138 vessels were imaged in men (11841 frames) and 83 in women (8237 frames).

Male patients had a higher burden of atheroma, as measured by the PAV and maximum vessel stenosis, than female patients (**Table 5.8**). This concurs with a Swiss VH IVUS study of patients with ACS and stable angina, which demonstrated that men had a higher plaque burden than women in every age tertile (p<0.001)[205], and in a sub-analysis of the ADAPT-DES study[203]. The PROSPECT investigators also showed a non-significant trend towards greater plaque volume in older men (48.5 vs. 48.0, p=0.17)[174].

	Total N=84	Male N=55	Female N=29	P value
MLA (mm^2 ± SD)	5.2 ± 2.4	5.2 ± 2.5	5.3 ± 2.2	0.203
MLD (mm ± SD)	2.5 ± 0.6	2.5 ± 0.6	2.5 ± 0.5	0.298
Maximum stenosis (% ± SD)	67.2 ± 12.2	69.1 ± 11.5	64.3 ± 12.9	***0.011**
Remodeling index (± SD)	1.04 ± 0.13	1.05 ± 0.13	1.02 ± 0.14	0.147
Percent atheroma volume (± SD)	45.3 ± 10.9	47.6 ± 10.4	41.7 ± 10.8	***<0.001**
Liverpool Active Plaque Score (± SD)	4.19 ± 3.57	4.51 ± 3.73	3.66 ± 3.24	0.128

Table 5.8 Grayscale and VH IVUS parameters by sex

The proportion of plaque components between the sexes was similar (**Figure 5.6**). Previous studies have shown a blunting of sex differences in plaque composition with age. Although Shoenenberger et al demonstrated sex differences in plaque composition in younger patients, there were no differences between the sexes in the oldest age tertile[205]. An analysis of a registry of almost 1000 patients undergoing VH IVUS imaging also demonstrated attenuation of the sex differences in plaque components with increasing age[204], and this phenomenon was also seen in a registry of patients with STEMI[206]. In contrast, the PROSPECT investigators demonstrated that older female patients had a higher proportion of NC and DC (and concomitantly less FF tissue) than male patients, but their "older" female group was actually significantly older than the male group (73.7 [68.8, 77.3] vs. 70.4 [67.3, 74.5] years, p=0.001)[174] and this may be a confounding factor in their results.

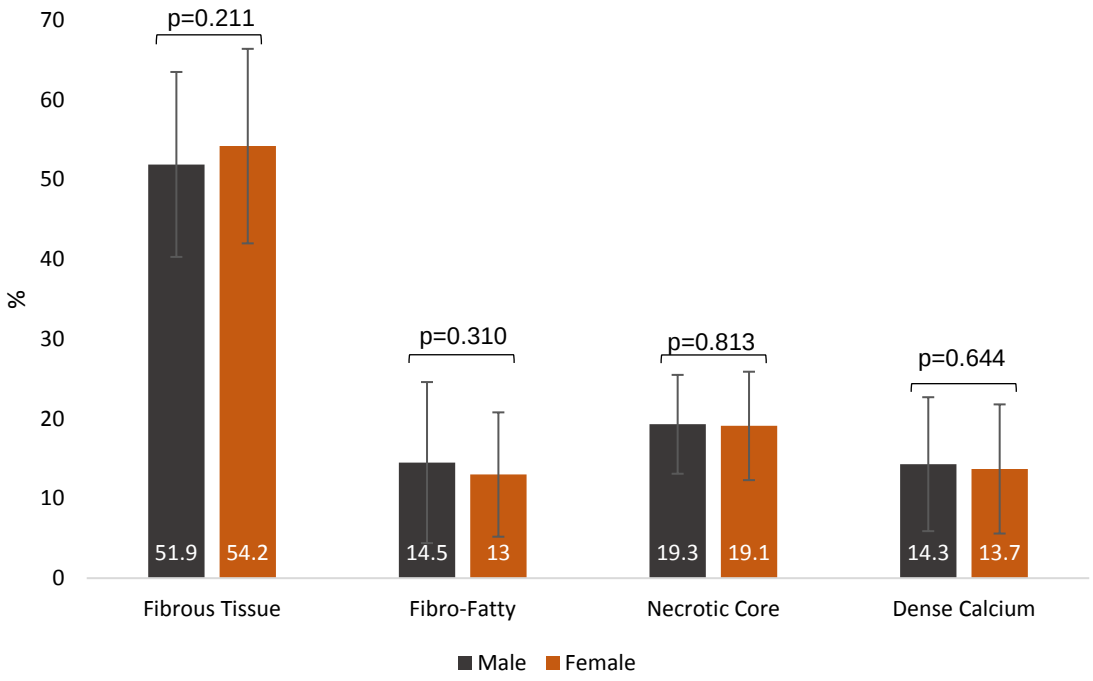


Figure 5.6 Proportion of plaque components by sex

There were no differences between the sexes in the vulnerability of the lesions (as measured by LAPS and %TCFA), although male patients had more FA present (**Figure 5.7**). This is probably a reflection of the higher plaque burden seen in men, whereby the increase in plaque is predominantly with thick capped FA. This was not seen in the PROSPECT sub-analysis, with no differences in the lesion phenotypes between the sexes[174].

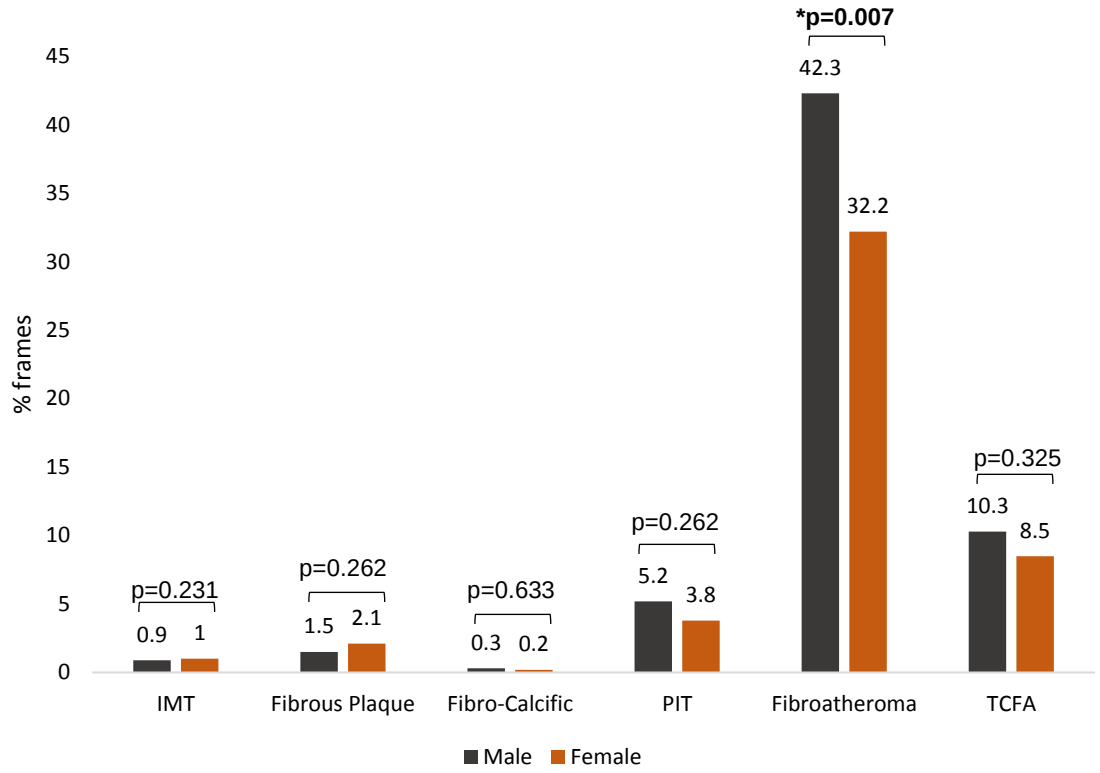


Figure 5.7 Lesion classification by sex

5.2.3 Frailty

Of the 221 vessels imaged, 65 were in robust patients (4865 frames), 112 in pre-frail (11413 frames) and 44 in the frail group (3800 frames).

Table 5.9 demonstrates a non-linear relationship between frailty and severity of stenosis, as measured by the MLA, MLD and maximum vessel stenosis. This is in keeping with the results seen in the QCA analysis, whereby pre-frail patients had a smaller reference diameter than robust or frail patients, although this was not seen when measured by the RI on IVUS, possibly because the site of tightest stenosis and highest remodeling was not always imaged due to failure to deliver the EEP catheter through the lesion.

	Total N=84	Robust N=24	Pre-frail N=45	Frail N=15	P value
MLA (mm^2 ± SD)	5.2 ± 2.4	5.7 ± 2.5	4.8 ± 2.2	5.7 ± 2.6	0.053
MLD (mm ± SD)	2.5 ± 0.6	2.6 ± 0.6	2.4 ± 0.5	2.6 ± 0.6	***0.039**
Maximum stenosis (% ± SD)	67.2 ± 12.2	63.8 ± 13.6	69.5 ± 10.9	66.1 ± 12.5	***0.025**
Remodeling index (± SD)	1.04 ± 0.13	1.05 ± 0.15	1.03 ± 0.13	1.07 ± 0.13	0.432
Percent atheroma volume (± SD)	45.3 ± 10.9	42.8 ± 11.5	46.7 ± 10.6	45.4 ± 10.6	0.139
Liverpool Active Plaque Score (± SD)	4.19 ± 3.57	3.41 ± 3.60	4.70 ± 3.60	3.94 ± 3.29	0.115

Table 5.9 Grayscale and VH IVUS parameters by frailty

This non-linear relationship may be related to the pattern of calcification (as discussed in **Section 6.3**), as frail patients had a higher proportion of dense calcium overall and proportionally less fibrous tissue (**Figure 5.8**), which may have affected how the vessel remodels with increasing calcification.

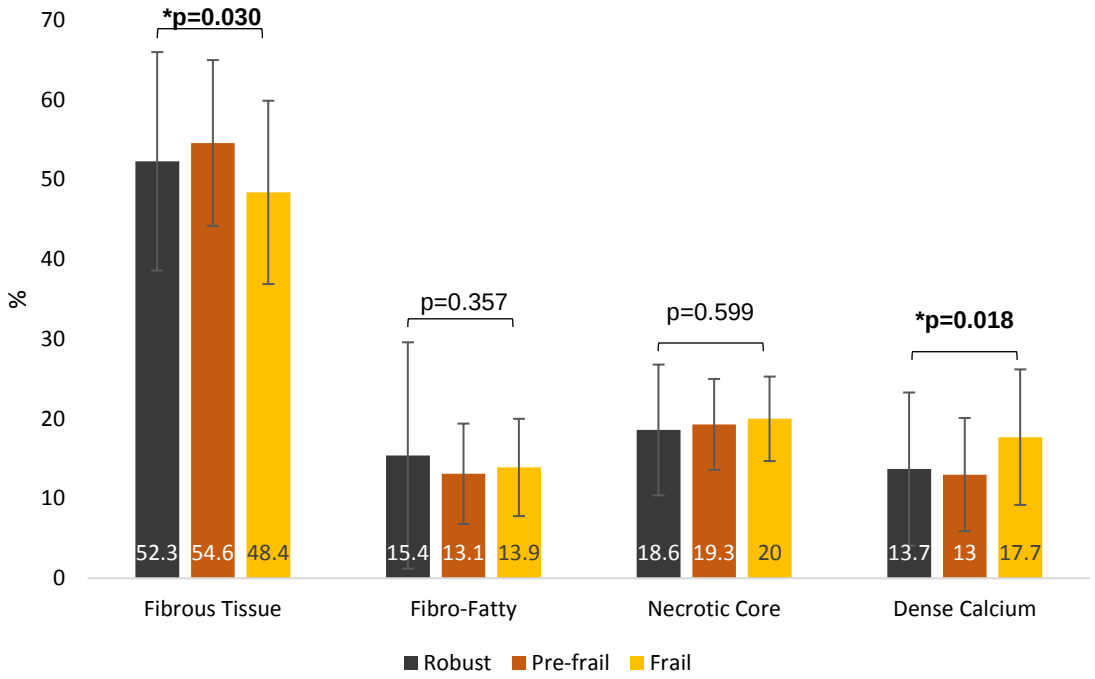


Figure 5.8 Proportion of plaque components by frailty

With the increasing proportion of calcium, frail patients had a higher proportion of fibro-calcific plaque present (**Figure 5.9**) but no evidence of more vulnerable lesions on VH IVUS.

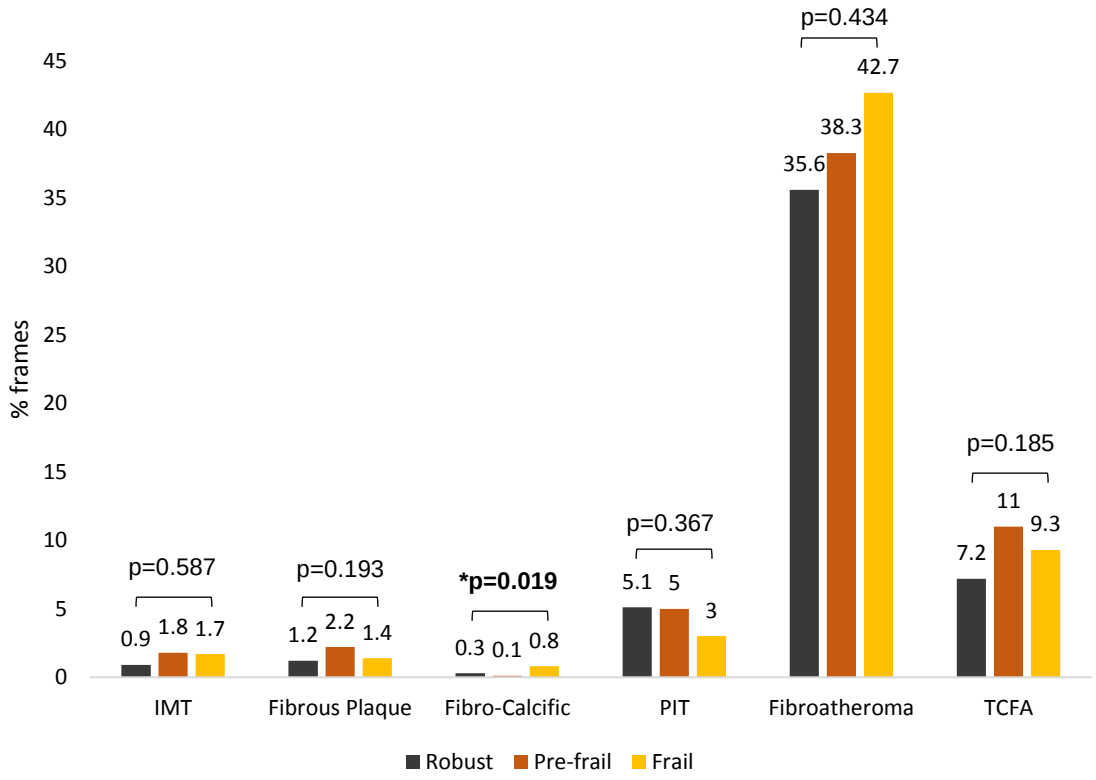


Figure 5.9 Lesion classification by frailty

5.2.4 Culprit vs. Non-Culprit Artery

As expected, culprit arteries had a greater degree of stenosis, higher plaque burden and a higher LAPS (**Table 5.10**). There were no differences in the proportions of plaque components between culprit and non-culprit arteries (FT: 51.4 ± 11.6% vs. 53.7 ± 11.9%, p=0.289; FF: 14.6 ± 10.3% vs. 13.4 ± 8.5%, p=0.336; NC: 19.3 ± 5.9% vs. 19.2 ± 6.8%, p=0.995; DC: 14.7 ± 8.7% vs. 13.7 ± 8.0%, p=0.494). Culprit arteries had a higher proportion of plaque categorised as FA (42.8 ± 23.1% vs. 35.3 ± 24.6%, p=0.034) but the proportions of TCFA were not statistically different (10.5 ± 11.5% vs. 9.0 ± 11.8%, p=0.145). These results are similar to those demonstrated by Schoenenberger et al, with a higher plaque burden in culprit arteries but no differences in plaque composition on VH IVUS[205].

	Total N=174	Culprit N=72	Non-culprit N=102	P value
MLA (mm^2 ± SD)	5.22 ± 2.37	4.82 ± 2.29	5.51 ± 2.40	***0.033**
MLD (mm ± SD)	2.52 ± 0.55	2.42 ± 0.53	2.59 ± 0.56	***0.032**
Maximum stenosis (% ± SD)	67.2 ± 12.2	71.2 ± 10.8	64.4 ± 12.5	***<0.001**
Remodeling index (± SD)	1.04 ± 0.13	1.07 ± 0.16	1.03 ± 0.11	0.137
Percent atheroma volume (± SD)	45.3 ± 10.9	48.5 ± 10.0	43.0 ± 11.0	***0.001**
Liverpool Active Plaque Score (± SD)	4.19 ± 3.57	4.92 ± 4.06	3.67 ± 3.09	***0.034**

Table 5.10 Grayscale and VH IVUS parameters by culprit vs. non-culprit vessel

5.2.5 VH-TCFA

Using the standard definition of VH-TCFA[53], there were 79 vessels with VH-TCFA present and 95 without. In the univariate analysis of baseline patient characteristics, presence of VH-TCFA was correlated ($p<0.25$) with age, frailty, NSTEMI, GRACE score, BMI, hyperlipidaemia, family history of IHD, cerebrovascular disease, platelets, cholesterol, troponin and vitamin D level. These variables were entered into a multivariate logistic regression analysis and increasing age, presentation with NSTEMI, and increasing vitamin D level were demonstrated to be independent predictors of the presence of VH-TCFA. **Table 5.11** shows the output from the regression analysis.

	Regression co-efficient	Standard error	P value	Odds ratio (95% CI)
Age	0.207	0.096	0.031	1.229 (1.019, 1.483)
NSTEMI	2.158	0.772	0.005	8.650 (1.903, 39.315)
Vitamin D	0.038	0.012	0.002	1.038 (1.014, 1.063)
Intercept	-22.961	7.822	0.003	

Table 5.11 Multiple regression analysis for VH-TCFA

Table 5.12 demonstrates the association of VH-TCFA with other vessel characteristics. VH-TCFA were more common in the RCA and were associated with maximum stenosis and PAV on IVUS, but were not co-located with OCT-TCFA.

	No VH-TCFA N=95	VH-TCFA N=79	P value
Angiography			
Vessel:			
• **LAD**, n (%)	39 (41.1)	28 (35.4)	*0.014
• **Cx**, n (%)	35 (36.8)	18 (22.8)	
• **RCA**, n (%)	21 (22.1)	33 (41.8)	
Culprit, n (%)	37 (38.9)	35 (44.3)	0.475
Calcification:			
• **None**, n (%)	16 (31.4)	16 (28.6)	0.542
• **Mild**, n (%)	12 (23.5)	15 (26.8)	
• **Moderate**, n (%)	11 (21.6)	7 (12.5)	
• **Severe**, n (%)	12 (23.5)	18 (32.1)	
Lesion complexity:			
• **Type A**, n (%)	6 (11.5)	2 (3.6)	0.076
• **Type B1**, n (%)	10 (19.2)	14 (25.5)	
• **Type B2**, n (%)	23 (44.2)	33 (60.0)	
• **Type C**, n (%)	13 (25.0)	6 (10.9)	
Procedure success, n (%)	36 (87.8)	43 (87.8)	0.626
VH IVUS			
MLA, mm^2 (IQR)	4.8 (3.4, 6.5)	4.6 (3.5, 6.5)	0.987
Maximum stenosis, % (IQR)	64.2 (53.3, 71.4)	72.5 (65.7, 80.2)	*<0.001
Remodeling index (IQR)	1.03 (0.95, 1.10)	1.02 (0.97, 1.13)	0.914
Percent atheroma volume (IQR)	41.3 (32.9, 49.9)	51.7 (45.5, 57.0)	*<0.001
OCT			
MLA, mm^2 (IQR)	3.2 (1.5, 5.6)	2.8 (1.9, 4.6)	0.988
Minimum fibrous cap, µm (IQR)	87 (58, 118)	79 (61, 115)	0.960
% fibroatheroma frames (IQR)	41.5 (16.6, 100)	29.1 (12.3, 75.2)	0.398
% fibrocalcific frames (IQR)	60.6 (32.9, 100)	70.2 (45.0, 96.7)	0.816
Rupture, n (%)	6 (28.6)	3 (18.8)	0.702
Macrophage, n (%)	12 (54.4)	7 (43.8)	0.511
Microchannel, n (%)	9 (40.9)	7 (43.8)	0.861
ChC, n (%)	6 (27.3)	5 (31.3)	1.000
OCT-TCFA, n (%)	6 (28.6)	4 (25.0)	0.809

Table 5.12 Association of VH-TCFA with other vessel characteristics

5.2.6 Liverpool Active Plaque Score

In the univariate analysis of baseline patient characteristics, LAPS was correlated ($p<0.25$) with age, sex, presentation with NSTEMI, white cell count, creatinine clearance and cholesterol level. These variables were entered into a multiple linear regression analysis and only increasing age and male sex were independent predictors of higher LAPS. **Table 5.13** shows the output from the regression analysis.

	Regression co-efficient	Standard error	P value
Age	0.305	0.095	0.002
Male	1.983	0.698	0.005
Intercept	-19.267	7.642	0.013

Table 5.13 Multiple regression analysis for LAPS

A LAPS >6 has been previously shown to correlate with an active plaque phenotype[64]. **Table 5.14** demonstrates the association between LAPS and other vessel characteristics (not including those that make up the score itself, i.e. MLA, RI and VH-TCFA). It was significantly associated with the culprit artery, maximum stenosis and PAV, and a thinner fibrous cap on OCT. There was also a non-significant association with the presence of OCT-TCFA (p=0.096).

	LAPS ≤6 N=115	LAPS >6 N=58	P value
Angiography			
Vessel: • **LAD**, n (%) • **Cx**, n (%) • **RCA**, n (%)	 46 (40.0) 35 (30.4) 34 (29.6)	 21 (36.2) 18 (31.0) 19 (32.8)	0.871
Culprit, n (%)	39 (33.9)	33 (56.9)	***0.004**
Calcification: • **None**, n (%) • **Mild**, n (%) • **Moderate**, n (%) • **Severe**, n (%)	 19 (30.2) 14 (22.2) 14 (22.2) 16 (25.4)	 13 (29.5) 13 (29.5) 4 (9.1) 14 (31.8)	0.309
Lesion complexity: • **Type A**, n (%) • **Type B1**, n (%) • **Type B2**, n (%) • **Type C**, n (%)	 6 (9.4) 14 (21.9) 32 (50.0) 12 (18.8)	 2 (4.7) 10 (23.3) 24 (55.8) 7 (16.3)	0.852
Procedure success, n (%)	46 (90.2)	33 (84.6)	0.522
VH IVUS			
Maximum stenosis, % (IQR)	65.4 (56.5, 72.8)	72.7 (66.3, 81.2)	***<0.001**
Percent atheroma volume (IQR)	42.3 (33.8, 50.8)	52.6 (46.2, 57.1)	***<0.001**
OCT			
MLA, mm^2 (IQR)	3.2 (2.1, 5.2)	2.4 (1.4, 3.9)	0.270
Minimum fibrous cap, µm (IQR)	94 (72, 140)	60 (56, 80)	***0.005**
% fibroatheroma frames (IQR)	32.6 (10.7, 100)	33.2 (22.1, 71.2)	0.902
% fibrocalcific frames (IQR)	58.3 (32.7, 100)	73.9 (44.5, 100)	0.768
Rupture, n (%)	4 (17.4)	5 (35.7)	0.255
Macrophage, n (%)	11 (45.8)	8 (57.1)	0.501
Microchannel, n (%)	8 (33.3)	8 (57.1)	0.152
ChC, n (%)	7 (29.2)	4 (28.6)	0.969
OCT-TCFA, n (%)	4 (17.4)	6 (42.9)	0.096

Table 5.14 Association of LAPS with other vessel characteristics

In a validation cohort, LAPS was demonstrated to have good diagnostic ability in discriminating between ACS and stable angina culprit lesions[64]. In this study, many had multi-vessel coronary disease, and we hypothesised that LAPS may be a useful diagnostic test to confirm the culprit artery if there was diagnostic uncertainty. It had a PPV of 56.9% (95% CI 43.2-69.8%), NPV of 66.1% (95% CI 56.7-69.8%), sensitivity of 43.8% (95% CI 34.0-58.0%), specificity of 75.3% (95% CI 65.7-83.3%) and an accuracy of 63%. The most discriminatory cut-off LAPS was >5.74 for predicting the culprit artery (similar to the LAPS of >6 for predicting an active plaque phenotype in the original study[64]). However, **Figure 5.10** displays the receiver operating characteristic curve for LAPS, demonstrating a poor diagnostic ability (area under the curve = 0.594) for culprit vs. non-culprit arteries in NSTEACS in older patients.

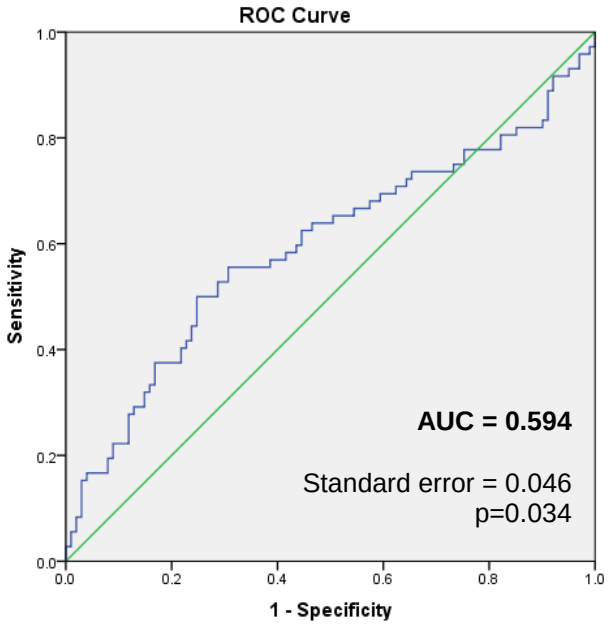


Figure 5.10 ROC curve for LAPS in predicting culprit artery

Although LAPS has previously been shown to have good discriminatory ability between plaques from patients with stable angina vs. ACS, results here demonstrate that it would be less useful as a tool to aid identification of the culprit lesion in patients presenting with NSTEACS and multiple coronary lesions.

5.2.7 Key Findings From VH IVUS Sub-Study

- Plaque burden, but not plaque composition, increases with age
- Men have a greater plaque burden than women, but there were no differences in plaque composition between the sexes
- Pre-frail patients have the greatest severity of stenosis on VH IVUS
- Calcification increases with increasing frailty

- VH-TCFA are associated with increasing plaque burden, but not with OCT-TCFA
- LAPS is a poor diagnostic test to discriminate between culprit and non-culprit arteries in this cohort

5.3 Optical Coherence Tomography

The sub-group of patients who underwent OCT imaging was small (n=26 with analysable data) and therefore these results should be treated as exploratory and hypothesis-generating only. In total, 65 vessels in 26 patients were imaged on OCT (9142 frames).

5.3.1 Age

32 vessels were imaged in patients <80 years (4429 frames) and 33 were imaged in patients ≥80 years (4713 frames).

Due to the smaller numbers in the OCT sub-analysis, the cohort was split into just 2 age categories. As in the VH IVUS cohort, there was no difference in MLA or MLD with age on OCT (**Table 5.15**). There was a non-significant trend towards a greater proportion of fibroatheroma and OCT-TCFA present with increasing age but no differences in the other potential markers of plaque vulnerability. This correlates with the results seen in the larger group who underwent VH IVUS imaging. Data from a large registry of patients with ACS showed a similar non-significant trend for younger (<50 years) patients to have a greater prevalence of OCT-TCFA (70 vs. 58%, p=0.06) but no difference in the rate of plaque rupture (70 vs. 64%, p=0.29)[207].

	Total N=26	<80 years N=12	≥80 years N=14	P value
MLA, mm^2 (IQR)	3.0 (1.7, 5.6)	3.0 (2.1, 5.7)	3.0 (1.5, 5.5)	0.449
MLD, mm (IQR)	1.9 (1.5, 2.7)	1.9 (1.6, 2.7)	2.0 (1.4, 3.4)	0.317
Minimum fibrous cap, µm (IQR)	83 (60, 116)	94 (72, 124)	71 (57, 98)	0.283
% fibroatheroma frames (IQR)	24.3 (14.4, 40.5)	20.3 (9.2, 31.1)	29.0 (19.2, 52.0)	0.066
% fibrocalcific frames (IQR)	37.3 (15.8, 57.3)	42.8 (18.4, 65.1)	32.3 (15.8, 56.8)	0.864
Rupture, n (%)	11 (22.0)	4 (16.0)	7 (28.0)	0.333
Macrophage, n (%)	30 (56.6)	15 (55.6)	15 (57.7)	0.875
Microchannel, n (%)	21 (39.6)	9 (33.3)	12 (46.1)	0.433
ChC, n (%)	13 (24.5)	4 (14.8)	9 (34.6)	0.102
OCT-TCFA, n (%)	14 (26.9)	3 (11.5)	11 (42.3)	0.060

Table 5.15 OCT parameters by age

5.3.2 Sex

38 vessels were imaged in men (5342 frames) and 54 in women (3800 frames).

There were no significant differences in OCT measurements or plaque characteristics when stratified by sex (**Table 5.16**). This is similar to results previously reported by Chia et al, who demonstrated no sex differences in incidence of lipid-rich plaque, OCT-TCFA, minimum fibrous cap or plaque rupture[208]. A study of patients with STEMI demonstrated no difference in the rate of plaque rupture between men and women[209].

	Total N=26	Male N=16	Female N=10	P value
MLA, mm^2 (IQR)	3.0 (1.7, 5.6)	2.8 (1.7, 5.6)	3.7 (2.2, 5.4)	0.838
MLD, mm (IQR)	1.9 (1.5, 2.7)	1.9 (1.5, 2.7)	2.2 (1.7, 2.6)	0.955
Minimum Fibrous Cap, µm (IQR)	83 (60, 116)	85.0 (60.0, 112.0)	81.0 (59.0, 112.0)	0.721
% fibroatheroma frames (IQR)	24.3 (14.4, 40.5)	27.0 (16.2, 40.3)	21.8 (14.4, 35.9)	0.809
% fibrocalcific frames (IQR)	37.3 (15.8, 57.3)	48.3 (24.6, 58.3)	30.9 (6.9, 41.7)	0.127
Rupture, n (%)	11 (22.0)	8 (26.7)	3 (15.0)	0.356
Macrophage, n (%)	30 (56.6)	18 (56.3)	12 (57.1)	0.949
Microchannel, n (%)	21 (39.6)	11 (34.4)	10 (47.6)	0.346
ChC, n (%)	13 (24.5)	8 (25.0)	5 (23.8)	0.922
OCT-TCFA, n (%)	14 (26.9)	9 (29.0)	5 (23.8)	0.651

Table 5.16 OCT parameters by sex

5.3.3 Frailty

Of the 65 vessels imaged, 16 were in robust patients (1693 frames), 35 in pre-frail (5515 frames) and 14 in the frail group (1934 frames).

Although not statistically significant, there were trends towards more calcium and a thicker fibrous cap in frail patients (**Table 5.17**). This suggests that frail patients may have more stable coronary plaque than robust patients (and, indeed, no OCT-TCFA were seen in the frail group).

	Total N=26	Robust N=7	Pre-frail N=14	Frail N=5	P value
MLA, mm^2 (IQR)	3.0 (1.7, 5.6)	4.1 (1.6, 5.6)	2.7 (1.4, 4.1)	3.7 (2.7, 6.9)	0.505
MLD, mm (IQR)	1.9 (1.5, 2.7)	2.3 (1.4, 2.7)	1.8 (1.4, 2.3)	2.2 (1.9, 3.0)	0.324
Minimum Fibrous Cap, µm (IQR)	83 (60, 116)	72 (58, 140)	82 (57, 98)	114 (84, 155)	0.055
% fibroatheroma frames (IQR)	24.3 (14.4, 40.5)	21.8 (14.8, 48.3)	27.0 (19.9, 41.6)	15.5 (7.6, 34.3)	0.521
% fibrocalcific frames (IQR)	37.3 (15.8, 57.3)	22.8 (2.2, 44.2)	42.2 (19.4, 58.9)	49.6 (31.3, 85.0)	0.101
Rupture, n (%)	11 (22.0)	4 (30.8)	6 (24.0)	1 (8.3)	0.187
Macrophage, n (%)	30 (56.6)	5 (35.7)	19 (70.4)	6 (50.0)	0.400
Microchannel, n (%)	21 (39.6)	5 (35.7)	13 (48.1)	3 (25.0)	0.814
ChC, n (%)	13 (24.5)	4 (28.6)	8 (29.6)	1 (8.3)	0.257
OCT-TCFA, n (%)	14 (26.9)	3 (23.1)	11 (40.7)	0	0.294

Table 5.17 OCT parameters by frailty

5.3.4 Plaque Rupture

There were 11 plaque ruptures seen in the OCT sub-study. In the univariate analysis of baseline patient characteristics, presence of plaque rupture on OCT was correlated ($p<0.25$) with male sex, NSTEMI, GRACE score, hypertension, diabetes, smoking status, family history of IHD, cerebrovascular disease, platelets, glucose and cholesterol. These variables were entered into a multivariate logistic regression analysis. However, no patient baseline characteristics were independently associated with plaque rupture. Age, diabetes, hypertension and hyperlipidaemia were independent predictors of plaque rupture in a previous meta-analysis of NSTEACS[210] but the ICON1 sample size is likely too small to demonstrate these associations due to the small regression coefficients reported.

Plaque rupture was more common in lesions with higher angiographic complexity but not necessarily more common in the culprit artery (**Table 5.18**). This confirms that patients with NSTEACS may have multiple asymptomatic plaque ruptures at the time of their coronary event. The MLA and MLD were smaller in the plaque rupture group (although this did not reach significance when measured on IVUS), suggesting that rupture occurs in more tightly stenosed vessels. There was also a greater degree of lipid present in vessels with plaque rupture, as well as a higher incidence of microchannels and ChC (but not VH-TCFA or OCT-TCFA).

	No Rupture N=39	Rupture N=11	P value
Angiography			
Vessel:			
• **LAD**, n (%)	12 (30.8)	4 (36.4)	1.000
• **Cx**, n (%)	13 (33.3)	3 (27.3)	
• **RCA**, n (%)	14 (35.9)	4 (36.4)	
Culprit, n (%)	14 (35.9)	7 (63.6)	0.166
Calcification:			
• **None**, n (%)	11 (40.7)	2 (22.2)	0.337
• **Mild**, n (%)	7 (25.9)	1 (11.1)	
• **Moderate**, n (%)	4 (14.8)	4 (44.4)	
• **Severe**, n (%)	5 (18.5)	2 (22.2)	
Lesion complexity:			
• **Type A**, n (%)	0	0	***0.036**
• **Type B1**, n (%)	11 (42.3)	1 (11.1)	
• **Type B2**, n (%)	13 (50.0)	4 (44.4)	
• **Type C**, n (%)	2 (7.7)	4 (44.4)	
Procedure success, n (%)	17 (85.0)	6 (75.0)	0.606
VH IVUS			
MLA, mm^2 (IQR)	4.4 (3.2, 6.0)	3.7 (2.5, 6.5)	0.519
Maximum stenosis, % ± SD	69.8 ± 9.5	73.6 ± 14.4	0.375
Remodeling index, ± SD	1.03 ± 0.18	1.03 ± 0.10	0.927
Percent atheroma volume (IQR)	50.3 (42.8, 57.2)	59.3 (50.3, 61.3)	0.116
% Fibrous tissue, ± SD	54.1 ± 10.3	52.3 ± 16.6	0.767
% Fibro-fatty tissue, ± SD	10.6 ± 4.4	11.6 ± 5.4	0.588
% Necrotic core, ± SD	21.4 ± 6.3	21.6 ± 10.2	0.957
% Dense calcium, ± SD	13.8 ± 6.7	14.5 ± 10.2	0.861
% frames VH-TCFA (IQR)	9.9 (0.7, 12.7)	6.0 (0.9, 20.3)	0.614
LAPS, ± SD	3.75 ± 3.61	5.95 ± 2.92	0.107
OCT			
MLA, mm^2 (IQR)	3.2 (2.2, 6.1)	1.5 (1.0, 3.3)	***0.006**
Minimum fibrous cap, µm (IQR)	92 (68, 123)	64 (53, 94)	0.106
% fibroatheroma frames (IQR)	17.0 (7.5, 28.0)	35.3 (27.7, 53.7)	***0.001**
% fibrocalcific frames (IQR)	39.7 (22.8, 68.8)	27.2 (9.6, 54.2)	0.292
Macrophage, n (%)	21 (53.8)	8 (72.7)	0.319
Microchannel, n (%)	12 (30.8)	7 (63.6)	***0.047**
ChC, n (%)	7 (17.9)	6 (54.5)	***0.023**
OCT-TCFA, n (%)	7 (17.9)	5 (45.5)	0.059

Table 5.18 Association of plaque rupture with other vessel characteristics

5.3.5 Macrophage Accumulation

There were 30 vessels with macrophage accumulations on OCT. In the univariate analysis of baseline characteristics, their presence was correlated ($p<0.25$) with frailty, BMI, hypertension, diabetes, previous MI, atrial fibrillation, and troponin. These variables were entered into a multivariate logistic regression analysis but no patient characteristics were independently associated with macrophage accumulations.

Table 5.19 demonstrates that macrophage accumulations were associated with a greater degree of stenosis and with greater %lipid on OCT (but not VH IVUS). There were non-significant trends towards the presence of other markers of plaque vulnerability but there was no association with culprit vs. non-culprit lesions.

	No Macrophage N=23	Macrophage N=30	P value
Angiography			
Vessel:			
• **LAD**, n (%)	7 (30.4)	11 (36.7)	0.883
• **Cx**, n (%)	8 (34.8)	9 (30.0)	
• **RCA**, n (%)	8 (34.8)	10 (33.3)	
Culprit, n (%)	9 (39.1)	13 (43.3)	0.758
Calcification:			
• **None**, n (%)	6 (37.5)	8 (36.4)	1.000
• **Mild**, n (%)	3 (18.8)	5 (22.7)	
• **Moderate**, n (%)	3 (18.8)	5 (22.7)	
• **Severe**, n (%)	4 (25.0)	4 (18.2)	
Lesion complexity:			
• **Type A**, n (%)	0	0	0.682
• **Type B1**, n (%)	4 (26.7)	9 (40.9)	
• **Type B2**, n (%)	8 (53.3)	9 (40.9)	
• **Type C**, n (%)	3 (20.0)	4 (18.2)	
Procedure success, n (%)	11 (84.6)	13 (81.3)	1.000
VH IVUS			
MLA, mm^2 (IQR)	5.3 (3.8, 6.5)	3.6 (2.8, 5.3)	***0.030**
Maximum stenosis, % ± SD	67.1 ± 11.0	74.0 ± 9.6	***0.045**
Remodeling index, ± SD	1.04 ± 0.11	1.03 ± 0.14	0.780
Percent atheroma volume (IQR)	50.5 (45.5, 56.9)	55.8 (42.4, 61.1)	0.246
% Fibrous tissue, ± SD	54.6 ± 12.0	52.6 ± 11.7	0.614
% Fibro-fatty tissue, ± SD	10.6 ± 4.3	11.3 ± 4.9	0.668
% Necrotic core, ± SD	21.1 ± 6.8	21.7 ± 7.7	0.820
% Dense calcium, ± SD	13.7 ± 7.0	14.5 ± 8.1	0.756
% frames VH-TCFA (IQR)	4.8 (0, 16.2)	8.3 (1.7, 12.6)	0.506
LAPS, ± SD	3.50 ± 3.33	5.05 ± 3.58	0.175
OCT			
MLA, mm^2 (IQR)	4.0 (2.6, 6.1)	2.5 (1.4, 3.4)	***0.021**
Minimum fibrous cap, µm (IQR)	98 (68, 137)	81 (57, 101)	***0.043**
% fibroatheroma frames (IQR)	10.7 (3.9, 44.2)	27.0 (19.9, 36.5)	***0.011**
% fibrocalcific frames (IQR)	76.2 (46.2, 86.7)	36.8 (15.1, 55.4)	0.524
Microchannel, n (%)	6 (26.1)	15 (50.0)	0.078
ChC, n (%)	3 (13.0)	10 (33.3)	0.089
OCT-TCFA, n (%)	4 (18.2)	10 (33.3)	0.224

Table 5.19 Association of macrophage accumulations with other vessel characteristics

5.3.6 Microchannel Formation

There were 21 vessels with macrophage accumulations seen in the OCT sub-study. In the univariate analysis of baseline patient characteristics, presence of microchannels on OCT was correlated ($p<0.25$) with NSTEMI, hypertension, platelets, and troponin. These variables were entered into a multivariate logistic regression analysis. Platelet count was the only variable independently associated with presence of microchannels. **Table 5.20** shows the output from the regression analysis.

	Regression co-efficient	Standard error	P value	Odds ratio (95% CI)
Platelet count	0.07	0.003	0.045	1.007 (1.00,1.014)
Intercept	-2.564	1.000	0.010	

Table 5.20 Multiple regression analysis for microchannels

Table 5.21 demonstrates that microchannels were associated with the burden of coronary disease on IVUS and OCT (maximum stenosis, PAV, and MLA/MLD on OCT), and negatively associated with % fibrous tissue on VH IVUS. They were also significantly associated with the burden of VH-TCFA and OCT-TCFA. Microchannels were also associated with other markers of plaque vulnerability on OCT such as macrophage accumulations and ChC.

	No Microchannel N=43	Microchannel N=21	P value
Angiography			
Vessel: • **LAD**, n (%) • **Cx**, n (%) • **RCA**, n (%)	 9 (28.1) 11 (34.4) 12 (37.5)	 9 (42.9) 6 (28.6) 6 (28.6)	0.538
Culprit, n (%)	12 (37.5)	10 (47.6)	0.465
Calcification: • **None**, n (%) • **Mild**, n (%) • **Moderate**, n (%) • **Severe**, n (%)	 8 (38.1) 7 (33.3) 3 (14.3) 3 (14.3)	 6 (35.3) 1 (5.9) 5 (29.4) 5 (29.4)	0.154
Lesion complexity: • **Type A**, n (%) • **Type B1**, n (%) • **Type B2**, n (%) • **Type C**, n (%)	 0 8 (40.0) 7 (35.0) 5 (25.0)	 0 5 (29.4) 10 (58.8) 2 (11.8)	0.393
Procedure success, n (%)	11 (78.6)	13 (86.7)	0.651
VH IVUS			
MLA, mm^2 (IQR)	4.7 (3.3, 5.6)	3.7 (2.8, 6.4)	0.569
Maximum stenosis, % ± SD	68.4 ± 11.7	73.5 ± 8.7	0.150
Remodeling index, ± SD	1.02 ± 0.10	1.06 ± 0.15	0.341
Percent atheroma volume (IQR)	50.8 (38.4, 56.0)	58.5 (47.7, 60.7)	***0.022**
% Fibrous tissue, ± SD	56.8 ± 11.3	49.2 ± 11.1	***0.046**
% Fibro-fatty tissue, ± SD	11.4 ± 3.7	10.3 ± 5.6	0.510
% Necrotic core, ± SD	19.4 ± 5.6	24.1 ± 8.3	***0.048**
% Dense calcium, ± SD	12.3 ± 6.5	16.4 ± 8.2	0.096
% frames VH-TCFA (IQR)	3.7 (0, 11.5)	10.0 (6.4, 25.2)	0.069
LAPS, ± SD	3.18 ± 3.26	5.78 ± 3.35	***0.022**
OCT			
MLA, mm^2 (IQR)	3.2 (2.1, 6.0)	2.4 (1.2, 4.0)	0.089
Minimum Fibrous Cap, µm (IQR)	93 (69, 133)	72 (58, 99)	0.118
% fibroatheroma frames (IQR)	17.0 (7.6, 30.0)	30.3 (19.5 (51.0)	***0.018**
% fibrocalcific frames (IQR)	34.5 (17.0, 56.1)	73.8 (44.6, 73.8)	0.585
ChC, n (%)	5 (15.6)	8 (38.1)	0.063
OCT-TCFA, n (%)	6 (18.8)	8 (40.0)	0.093

Table 5.21 Association of microchannels with other vessel characteristics

5.3.7 Cholesterol Crystals

There were 13 vessels with ChC in the OCT sub-study. In the univariate analysis of baseline patient characteristics, presence of ChC on OCT was correlated ($p<0.25$) with age, NSTEMI, BMI, hypertension, diabetes, family history of IHD, troponin and hsCRP. These variables were entered into a multivariate logistic regression analysis. However, no patient baseline characteristics were independently associated with presence of ChC.

Table 5.22 demonstrates that presence of ChC was associated with a greater degree of stenosis on both IVUS and OCT (consistent with results from Tian et al, who demonstrated the association of ChC with greater angiographic lesion severity[211]), as well as with a thinner fibrous cap and greater prevalence of OCT-TCFA (and a trend towards more VH-TCFA).

	No ChC N=40	ChC N=13	P value
Angiography			
Vessel: • **LAD**, n (%) • **Cx**, n (%) • **RCA**, n (%)	 13 (32.5) 15 (37.5) 12 (30.0)	 5 (38.5) 2 (15.4) 6 (46.2)	0.370
Culprit, n (%)	14 (35.0)	8 (61.5)	0.092
Calcification: • **None**, n (%) • **Mild**, n (%) • **Moderate**, n (%) • **Severe**, n (%)	 11 (40.7) 5 (18.5) 4 (14.8) 7 (25.9)	 3 (27.3) 3 (27.3) 4 (36.4) 1 (9.1)	0.398
Lesion complexity: • **Type A**, n (%) • **Type B1**, n (%) • **Type B2**, n (%) • **Type C**, n (%)	 0 10 (38.5) 12 (46.2) 4 (15.4)	 0 3 (27.3) 5 (45.5) 3 (27.3)	0.729
Procedure success, n (%)	16 (84.2)	8 (80.0)	1.000
VH IVUS			
MLA, mm^2 (IQR)	5.1 (3.4, 6.4)	3.3 (2.4, 5.3)	***0.045**
Maximum stenosis, % ± SD	67.5 ± 10.5	78.0 ± 7.4	***0.005**
Remodeling index, ± SD	1.05 ± 0.12	0.99 ± 0.13	0.172
Percent atheroma volume (IQR)	49.3 (41.6, 57.5)	55.8 (51.9, 61.2)	***0.049**
% Fibrous tissue, ± SD	54.3 ± 13.2	51.8 ± 7.3	0.562
% Fibro-fatty tissue, ± SD	10.8 ± 4.6	11.2 ± 4.7	0.826
% Necrotic core, ± SD	20.8 ± 8.0	22.9 ± 4.4	0.413
% Dense calcium, ± SD	14.1 ± 8.2	14.1 ± 5.6	0.993
% frames VH-TCFA (IQR)	4.8 (0, 11.4)	10.9 (8.0, 23.1)	0.088
LAPS, ± SD	4.15 ± 3.54	4.60 ± 3.56	0.723
OCT			
MLA, mm^2 (IQR)	3.2 (2.2, 6.0)	1.3 (0.9, 3.4)	***0.002**
Minimum Fibrous Cap, µm (IQR)	92 (67, 122)	64 (55, 97)	***0.037**
% fibroatheroma frames (IQR)	19.6 (7.6, 34.3)	30.3 (15.8, 66.7)	0.069
% fibrocalcific frames (IQR)	35.5 (15.8, 66.7)	44.6 (12.4, 56.8)	1.000
OCT-TCFA, n (%)	6 (15.4)	8 (61.5)	***0.001**

Table 5.22 Association of cholesterol crystals with other vessel characteristics

5.3.8 OCT-TCFA

There were 14 vessels with OCT-TCFA identified in the OCT sub-study. In the univariate analysis of baseline patient characteristics, presence of OCT-TCFA on OCT was correlated ($p<0.25$) with age, frailty, NSTEMI, BMI, hypertension, diabetes, family history of IHD, previous MI, atrial fibrillation, cerebrovascular disease, platelet count, glucose level, cholesterol level, peak troponin and hsCRP. These variables were entered into a multivariate logistic regression analysis. However, no patient baseline characteristics were independently associated with the presence of OCT-TCFA.

OCT-TCFA were evenly distributed between culprit and non-culprit vessels (**Table 5.23**). They were associated with higher degrees of stenosis within the vessel on both OCT and VH IVUS, and there was a trend towards less %DC in vessels with OCT-TCFA. Presence of OCT-TCFA was also significantly associated with plaque rupture ($p=0.020$), presence of thrombus ($p=0.005$), microchannel formation ($p=0.021$) and ChC ($p<0.001$).

	No OCT-TCFA N=38	OCT-TCFA N=14	P value
Angiography			
Vessel:			
• **LAD**, n (%)	13 (34.2)	4 (28.6)	0.732
• **Cx**, n (%)	11 (28.9)	6 (42.9)	
• **RCA**, n (%)	14 (36.8)	4 (28.6)	
Culprit, n (%)	14 (36.8)	7 (50.0)	0.391
Calcification:			
• **None**, n (%)	9 (34.6)	5 (45.5)	0.824
• **Mild**, n (%)	6 (23.1)	2 (18.2)	
• **Moderate**, n (%)	5 (19.2)	3 (27.3)	
• **Severe**, n (%)	6 (23.1)	1 (9.1)	
Lesion Complexity:			
• **Type A**, n (%)	0	0	0.498
• **Type B1**, n (%)	9 (36.0)	4 (36.4)	
• **Type B2**, n (%)	13 (52.0)	4 (36.4)	
• **Type C**, n (%)	3 (12.0)	3 (27.3)	
Procedure success, n (%)	15 (83.3)	8 (80.0)	1.000
VH IVUS			
MLA, mm^2 (IQR)	4.4 (3.4, 6.4)	2.8 (2.3, 5.5)	0.072
Maximum Stenosis, % ± SD	68.9 ± 9.3	75.8 ± 13.4	0.085
Remodeling Index, ± SD	1.01 ± 0.12	1.07 ± 0.10	0.242
Percent Atheroma Volume (IQR)	50.1 (43.9, 57.5)	55.1 (49.5, 61.6)	0.158
% Fibrous Tissue, ± SD	52.7 ± 12.2	56.2 ± 11.2	0.435
% Fibro-Fatty Tissue, ± SD	10.6 ± 4.3	11.6 ± 5.7	0.555
% Necrotic Core, ± SD	21.4 ± 7.0	21.6 ± 8.5	0.938
% Dense Calcium, ± SD	15.3 ± 7.9	10.5 ± 3.6	0.090
% frames VH-TCFA (IQR)	7.8 (0.5, 11.8)	9.7 (1.3, 24.8)	0.468
LAPS, ± SD	3.67 ± 3.58	5.97 ± 3.02	0.079
OCT			
MLA, mm^2 (IQR)	3.3 (2.1, 5.9)	1.6 (1.1, 3.1)	***0.029**
Minimum Fibrous Cap, µm (IQR)	97 (81, 140)	57 (51, 61)	***<0.001**
% fibroatheroma frames (IQR)	17.0 (7.5, 27.8)	36.7 (29.0, 54.3)	***<0.001**
% fibrocalcific frames (IQR)	38.0 (21.0, 70.0)	30.9 (8.9, 53.6)	0.327

Table 5.23 Association of OCT-TCFA with other vessel characteristics

5.3.9 Key Findings From OCT Sub-Study

- There was a trend for more OCT-TCFA with advancing age
- Markers of plaque vulnerability tend to cluster together, suggesting an element of pancoronary vulnerability in older patients with ACS

5.4 Discussion

5.4.1 Patient-Level Factors And Pattern Of Plaque Burden

It was the “English Hippocrates”, Thomas Sydenham, who declared that “a man is as old as his arteries”. This is the first prospective study utilising advanced intracoronary imaging techniques to explore the pattern of coronary artery disease in older patients presenting with NSTEACS. It has provided unique insights into the progression of advanced atherosclerosis, and revealed a population with high levels of so-called “vulnerable” plaque characteristics who could prove a valuable resource for future research studies. Overall, across all 3 imaging modalities, the study cohort had a higher plaque burden and greater levels of advanced and vulnerable plaque than other contemporary studies in patients with NSTEACS, but comparably excellent levels of procedural success, low complication rate and a lower than expected adverse event rate.

This ICON1 invasive imaging sub-study confirms multiple previous observational and randomised controlled studies that early invasive management is both feasible and safe in older patients with NSTEACS. The results presented here should reassure clinicians that, even in the presence of frailty, comorbidities and complex coronary disease, patients ≥75 years of age should be referred for PCI in the absence of any absolute contraindications. Indeed, the current UK guidelines state that all patients with ≥3% risk of mortality at 6 months after ACS should be referred for PCI within 72 hours[212]; all patients aged ≥75 years, regardless of any other clinical measurement, fall into this category on the most widely used risk score, GRACE 2.0. The European Society of Cardiology guidelines state that “elderly patients should be considered for an invasive strategy and, if appropriate, revascularisation after careful evaluation of risks and benefits”[213]. I would argue that this statement does not go far enough and that all patients with NSTEACS should be considered for an early invasive strategy, regardless of age. The recently commenced SENIOR-RITA trial will hopefully put this question of conservative vs. early invasive strategy to bed once and for all[214].

The data presented here corroborates the findings of previous studies in younger patients in demonstrating that ageing is associated with a higher plaque burden, greater severity of stenosis, and increasing incidence of advanced plaque sub-types

such as FA and TCFA. It would therefore appear that at no age does the acquisition of more atherosclerotic plaque plateau or cease.

Figure 5.1 demonstrates the commonly held theory of atherosclerotic plaque progression based on historical ex vivo histological studies, proposed by Stary et al[215]. The loop between types V and VI illustrates the repeated rupture and healing of atherosclerotic plaques, sometimes silently, leading to an increasing burden of complex plaque. These in vivo imaging results support this theory of plaque progression, as they clearly show increasing proportions of FA and TCFA, alongside high numbers of plaque rupture and thrombus in both culprit and non-culprit lesions (the OCT sub-study was underpowered to show any differences between age groups). Advanced plaque features suggestive of repeated rupture such as macrophage accumulations, microchannels and ChC clearly clustered together within lesions, suggesting that they may be part of the remodeling process in silently ruptured plaques.

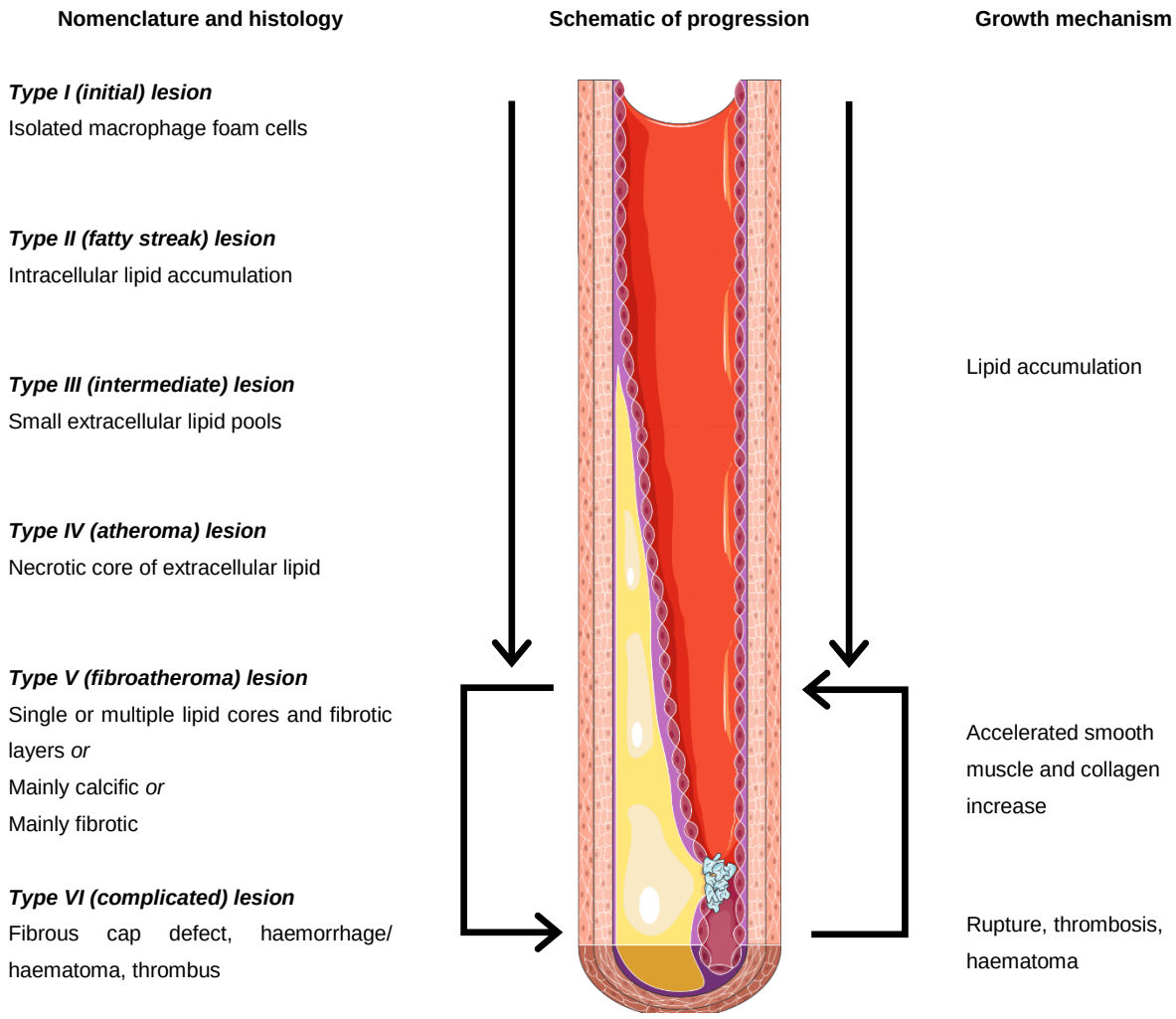


Figure 5.11 Atherosclerotic plaque progression with age

Flow diagram demonstrating progression of atherosclerosis with age[215]. From types I-IV, lipid accumulation is the main reason for plaque growth, facilitated by inflammatory insults to the endothelium, migration of monocytes into the intima, and transformation of those monocytes into macrophages. These macrophages then engulf lipid and form foam cells, eventually aggregating into fatty streaks and lipid pools. In more advanced lesions (types V and VI), incomplete clearance of apoptotic foam cells and migration of vascular smooth muscle cells into the intima forms necrotic cores with overlying fibrotic caps. Rupture or erosion of the cap can lead to thrombus and subsequent acute coronary syndrome, or healing with deposition of calcium within the plaque[216].

When the results were analysed by sex, they supported previous studies that suggested that the sex differences in plaque composition in younger age groups disappear in later life, but the plaque burden differential (men>women) persists. Men and women were evenly matched from the point of view of cardiovascular risk factors and GRACE risk score (**Table 4.6**), in contrast to previous studies that have demonstrated a worse cardiovascular risk profile in younger women[217]. It has been proposed that oestrogen has a cardio-protective effect in pre-menopausal women, stabilising and thickening the fibrous cap of coronary plaques[218] and potentially

interrupting the plaque rupture/healing loop. A sub-analysis of the PROSPECT data demonstrated that younger women had more fibrous tissue on VH IVUS (61.1 vs. 60.0%, p<0.05) and less FF (19.1 vs. 21.6%, p<0.05)[174]. All the women in this study had been post-menopausal for many years and none were taking hormone replacement therapy, thus lacked this protective effect. Women in the oldest age groups therefore "catch up" with men as they age from the point of view of plaque composition and fibrous cap thickness, but not plaque burden.

It is becoming increasingly apparent that biological age, i.e. frailty, is a better predictor of adverse outcomes after NSTEACS than chronological age[219]. Recently published results from the full ICON1 study cohort (n=279) demonstrate that frailty is associated with increased adverse outcomes at 1 year, driven by all-cause mortality, MI and repeat hospitalisation[220]. Although there were no differences in overall in-hospital or 30-day outcomes, frailty was associated with higher arterial complications following angiography ± PCI (robust: 0, pre-frail: 1.3%, frail: 5.2%, p=0.049)[220], concordant with the data presented here, demonstrating a higher rate of femoral access in frail patients (robust: 4.0%, pre-frail: 2.0%, frail: 26.7%, p=0.006). This may help to explain the higher rate of major bleeding post-ACS in frail patients in previous studies[18, 221] and would certainly increase the time-to-ambulation post-procedure, increasing the risk of adverse events. Yet again, this illustrates the treatment paradox for frail patients whereby the patients at highest risk of complications are undergoing angiography/PCI via the riskiest route. It is a clear indication that, if an invasive strategy is followed in frail patients, radial access must be treated as a priority.

Frailty (but not age alone) was also associated with increasing intimal calcification on VH IVUS imaging. This is the first study to show this association in patients with symptomatic cardiovascular disease and has wide ranging implications for both invasive treatment strategies in individual patients, and future research into vascular calcification, as previous studies demonstrating an increase in coronary calcium with age[174] have failed to take frailty into account. Two previous studies have utilised CT calcium scoring to explore if there is an association between frailty and vascular calcification. The first recruited 42 institutionalised patients and classified them by Fried frailty status, excluding pre-frail patients[222]. They demonstrated no differences between robust and frail patients in coronary artery calcium score. However, this was a small study in asymptomatic patients, and CT calcium score measurement does not

discriminate between intimal or adventitial calcification. Indeed, the angiographic results presented here did not show any difference in calcification between frailty groups, suggesting that it is only intimal calcification that is associated with frailty. The second, larger study utilising CT calcium scoring recruited 374 asymptomatic men and again classified them according to Fried frailty status, but combined the robust and pre-frail groups[223]. They demonstrated that frail patients had a 53% increased prevalence of coronary artery calcification, which remained significant even after adjustment for traditional cardiovascular risk factors (prevalence ratio 1.27, 95% CI 1.02-1.59, $p<0.05$)[223]. As these patients were asymptomatic, it may suggest that there is something about the frailty phenotype that is independently involved in causing coronary calcification, rather than the other way around.

It seems intuitive that an increasing burden of coronary artery disease causes frailty. However, neither the angiographic nor the VH IVUS results presented here have shown that plaque burden or disease extent increases with frailty. Thus, the association of coronary calcification with frailty is not necessarily due solely to increasing burden of disease. There are several other plausible explanations. Firstly, coronary calcification may be a marker of subclinical vascular disease elsewhere in the body, thus decreasing overall physiological reserve without necessarily having overt clinical events (e.g. stroke, intermittent claudication). Idoate et al demonstrated greater femoral artery calcification in frail vs. robust nonagenarians, which was associated with lower bone mineral density and leg muscle mass and could, in turn, be associated with sarcopenia[224]. Secondly, plaque rupture and healing is known to be a process associated with inflammation[225] and a state of chronic inflammation could lead to a systemic catabolic phenomenon leading to frailty. Our data did not show an association between frailty or calcification and hsCRP, but other inflammatory markers such as interleukin-6, myeloperoxidase and lipoprotein-associated phospholipase A_2 are worthy of investigation in future studies[226, 227]. Thirdly, frailty and coronary calcification may be mediated by a confounding factor such as vitamin D.

In practical terms, coronary calcification matters when planning PCI. It often requires specialised kit and advanced techniques such as high maximum inflation pressures, cutting and scoring balloons, laser, rotational atherectomy and, more recently, intravascular lithotripsy, not all of which are available at all centres by all operators[228]. Knowing the frailty status of a patient would go some way to stratifying their risk of

coronary calcification prior to the procedure, allowing scheduling of the individual patient on an appropriate procedure list. Angiographic results presented here demonstrated that moderately calcified lesions had the highest residual %diameter stenosis post-PCI, leaving them at risk of adverse outcomes such as MI and repeat revascularisation, so adequate lesion preparation is paramount[229].

Although age and male sex were associated with increased atherosclerotic plaque burden on multi-modality imaging it is frailty, not age alone, that predicts coronary arterial calcification and poor outcomes following PCI for NSTEACS.

5.4.2 Vulnerable Plaque In The Older Patient With ACS

Due to the high-risk nature of the patient cohort examined in this ICON1 sub-study, there was a high prevalence of vulnerable plaque sub-types identified on intracoronary imaging. On VH IVUS, 45.4% of vessels imaged had a VH-TCFA present (more than double the prevalence of 21.6% in the PROSPECT study[69]) and, on OCT, 26.9% of vessels imaged had an OCT-TCFA present. However, there was significant discordance between imaging modalities in the identification of TCFA, both when using the standard definition of VH-TCFA[53] or when measuring the overall burden of VH IVUS frames with VH-TCFA present.

Several studies have shown a poor correlation between OCT-TCFA and VH-TCFA[83, 86, 87]. As discussed previously, VH IVUS lacks the resolution to accurately identify the thin fibrous cap, and OCT lacks the penetration to accurately measure deep lipid pools. Increasing calcium (a particular issue in this cohort) may lead to false positives, as it is associated with increasing necrotic core, a key component in the decision tree for lesion classification. Microcalcifications can also lead to false positives on OCT[83]. Combining OCT and VH IVUS imaging is one method of improving diagnostic accuracy ex vivo[87] but there are no commercially available in vivo catheters capable of this at present[230]. Although there was no correlation between burden of VH-TCFA and OCT-TCFA, there was a non-significant trend towards higher LAPS in the presence of OCT-TCFA (p=0.079). Refining this type of VH IVUS score may circumvent the need for combined imaging catheters.

We found no association between the presence of TCFA on either imaging modality with markers of inflammation such as hsCRP. In previous studies, there has been

discord as to whether inflammatory markers such as hsCRP, interleukin-6 or pentraxin 3 are associated with TCFA on VH IVUS or OCT[115, 231-233]. However, our results have shown that vulnerable plaque features identified on OCT did seem to be co-localised: OCT-TCFA, plaque rupture, thrombus, microchannels and ChC were all significantly correlated with each other, even in non-culprit arteries. This higher pancoronary vulnerability in patients with ACS has been reported in several previous studies[124,234,140], suggesting that ACS is a syndrome of multi-focal instability throughout the coronary tree. Although one particular lesion is the culprit for an ACS event, the factors that have led to that lesion rupturing at that time are also responsible for the destabilisation of non-culprit lesions and subsequent progression of coronary atheroma.

Specifically, we have demonstrated a strong association between microchannels and atheroma burden, and platelet count was the only factor independently associated with presence of microchannels. This is consistent with previous studies showing a higher prevalence in lesions of greater angiographic severity[211] and an association with rapid angiographic progression of previously non-significant lesions, possibly by promoting inflammation and plaque haemorrahge/rupture[135].

Older patients with NSTEACS have a high prevalence of previously identified vulnerable plaque characteristics, and they may prove to be a valuable resource in future studies into potential plaque stabilisation therapies. However, the complexity of coronary disease in this population has exposed the limitations of current definitions of vulnerable plaque, in particular TCFA identification on VH IVUS, and further work is needed to refine this.

CHAPTER 6: RESULTS – Multi-Modality Assessment of Coronary Calcification

One of the striking features of the analysis of the pattern of plaque burden in older patients with ACS was the high burden of coronary calcification. This group of patients is therefore ideal to investigate the hypothesis that calcium plays an important role in the response to atheroma deposition in these patients.

6.1 Angiographic Calcification

In the univariate analysis of baseline patient characteristics, angiographic lesion calcification was correlated ($p<0.25$) with sex, frailty, NSTEMI, GRACE score, smoking status, family history of IHD, renal impairment, previous angina, CCF, and glucose level. These variables were entered into an ordinal logistic regression analysis and history of angina and being a current smoker (vs. never smoked) were demonstrated to be independent predictors of greater calcification (**Table 6.1).**

	Regression co-efficient	Standard error	P value	Odds ratio (95% CI)
No history of angina	-1.433	0.463	0.002	0.239 (0.096, 0.591)
Non smoker	-1.291	0.555	0.020	0.275 (0.093, 0.817)

Table 6.1 Multiple regression analysis for angiographic calcification

Figure 6.1 demonstrates the association between angiographic lesion calcification and QCA measurements. Actual MLD increases at a greater rate ($p<0.001$) than the derived RD ($p=0.003$), so %stenosis initially decreases. However, this reaches a limit when calcification is severe so % stenosis starts to increase again ($p=0.003$). These results are similar to those demonstrated by Genereux et al in the pooled analysis of two major ACS trials: pre-PCI RD increased as calcification of the target lesion increased. They demonstrated that % diameter stenosis was similar between the no/mild calcification and moderate calcification groups, but increased as calcification became severe[28].

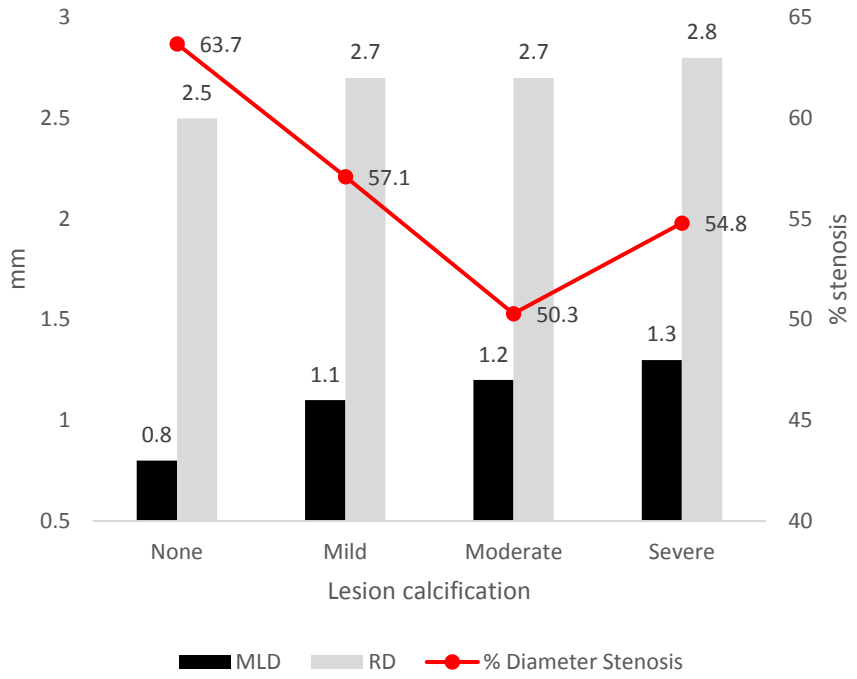


Figure 6.1 Pre-PCI QCA measurements by lesion calcification

There is a non-linear relationship between lesion calcification and severity of % stenosis. This is likely to be mediated by positive remodeling in the early stages of calcification.

The procedure success was similar between calcification groups (no calcification: 93.2%, mild: 91.7%, moderate: 82.4%, severe: 89.5%, p=0.624), but there was a significant difference in residual % diameter stenosis post-PCI (no calcification: 14.2%, mild: 17.0%, moderate: 23.1%, severe: 19.0%, p=0.014). This may suggest that moderately calcified lesions are stiffer and more resistant to stretching by PCI, or that heavily calcified lesions were more likely to be prepared better pre-stent e.g. by rotablation/laser/repeated balloon angioplasty.

6.2 VH IVUS Dense Calcium

Previous studies with VH IVUS have expressed concerns regarding the accuracy of measurement of NC in the presence of heavy calcification. **Figure 6.3** demonstrates that %DC was strongly correlated with %NC (r=0.725, p<0.001). This association was also present when correlating angiographic calcification and %NC (p=0.004). This illustrates a major limitation of VH IVUS in accurately assessing heavily calcified arteries, as large areas of calcified plaque are a barrier to IVUS assessment of deeper regions due to acoustic shadowing.

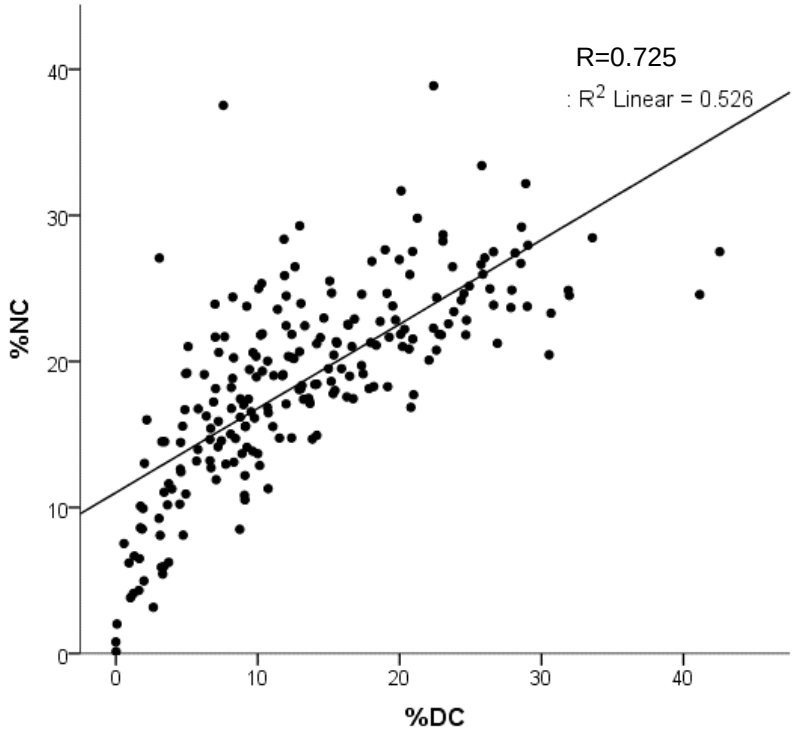


Figure 6.2 Association of %NC with %DC

There was a strong linear association of DC and NC on VH IVUS, leading to overestimation of %NC in the presence of high calcification.

In the univariate analysis of baseline patient characteristics, %DC was correlated ($p<0.25$) with frailty, GRACE score, family history of IHD, previous MI, atrial fibrillation, cerebrovascular disease, white cell count and vitamin D level. These variables were entered into a multiple linear regression analysis and increasing GRACE score, presence of atrial fibrillation, previous MI, and increasing vitamin D level were demonstrated to be independent predictors of higher %DC. **Table 6.2** shows the output from the regression analysis.

	Regression co-efficient	Standard error	P value
GRACE Score	0.113	0.037	0.003
Atrial fibrillation	4.417	1.649	0.008
Previous MI	5.494	1.547	0.001
Vitamin D	0.088	0.025	<0.001
Intercept	-7.037	4.966	0.159

Table 6.2 Multiple regression analysis for %DC

When analysed by vitamin D category, there was a clear association between increasing vitamin D and %DC with a concomitant drop in %fibrous tissue (**Figure 6.2**).

This association between increasing vitamin D and calcification held true even when discounting the 8 patients receiving vitamin D supplementation (p=0.005).

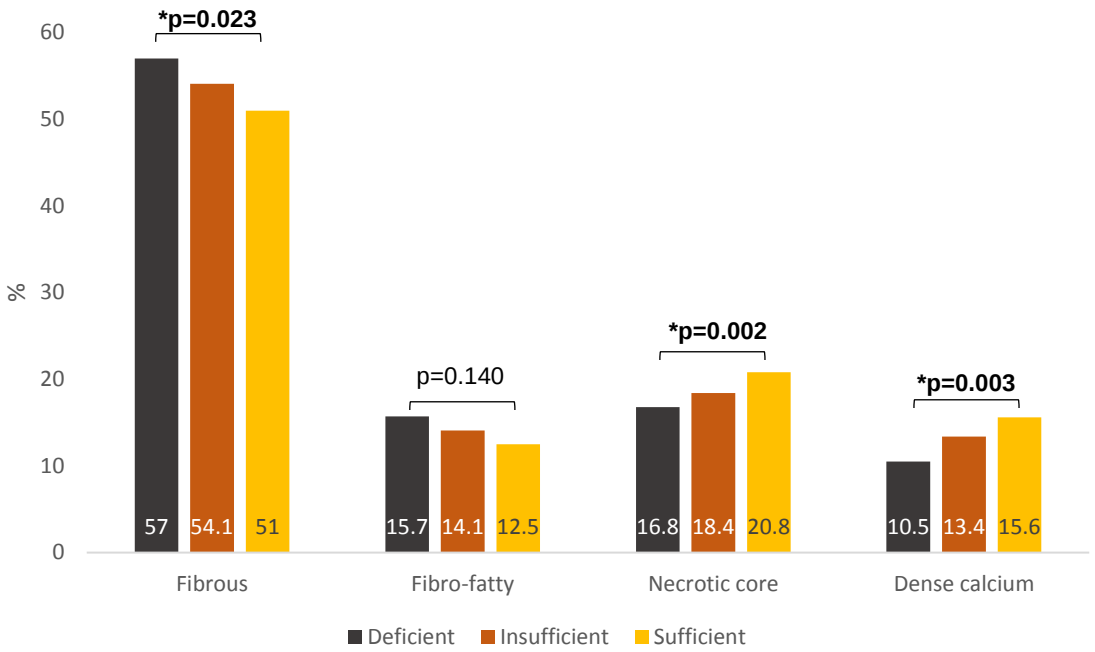


Figure 6.3 Proportion of plaque components by vitamin D status

Increasing vitamin D was associated with a decreasing proportion of fibrous tissue and an increasing proportion of NC and DC. Deficient n=25, insufficient n=38, sufficient n=28.

The imaged vessels were then split into 3 equal tertiles by %DC: low (<9.4%), intermediate (9.4-16.7%) and high (>16.7%) calcification. **Table 6.3** demonstrates that %DC was significantly associated with maximum stenosis, PAV and %VH-TCFA frames on IVUS, suggesting that calcification increases with overall burden, severity and complexity of atherosclerotic plaque. %DC on VH IVUS correlated well with angiographic calcification, although a proportion of vessels had significant amounts of calcium on VH IVUS but very little visible angiographically.

There were 7 vessels that required complex PCI techniques (rotablation or laser atherectomy) in this cohort. All were vessels in the high %DC tertile (mean %DC in vessels with no complex PCI: 12.9 ± 8.3% vs. complex PCI: 25.3 ± 3.7%, p=0.044).

	Low %DC	Intermediate %DC	High %DC	P value
Angiography				
Vessel:				
• **LAD**, n (%)	15 (25.9)	24 (41.4)	28 (48.3)	0.155
• **Cx**, n (%)	21 (36.2)	18 (31.0)	14 (24.1)	
• **RCA**, n (%)	22 (37.9)	16 (27.6)	16 (27.6)	
Culprit, n (%)	23 (39.7)	25 (43.1)	24 (41.4)	0.981
Calcification:				
• **None**, n (%)	16 (50.0)	10 (28.6)	6 (15.0)	***0.001**
• **Mild**, n (%)	12 (37.5)	8 (22.9)	7 (17.5)	
• **Moderate**, n (%)	2 (6.3)	7 (20.0)	9 (22.5)	
• **Severe**, n (%)	2 (6.3)	10 (28.6)	18 (45.1)	
Lesion complexity:				
• **Type A**, n (%)	5 (15.2)	1 (2.9)	2 (5.0)	0.090
• **Type B1**, n (%)	11 (33.3)	8 (23.5)	5 (12.5)	
• **Type B2**, n (%)	11 (33.3)	20 (58.8)	25 (62.5)	
• **Type C**, n (%)	6 (18.2)	5 (14.7)	8 (20.0)	
Procedure success, n (%)	23 (85.2)	29 (93.5)	27 (84.4)	0.515
VH IVUS				
MLA, mm^2 (IQR)	4.9 (2.7, 6.9)	5.1 (3.3, 6.4)	4.4 (3.4, 5.9)	0.488
Maximum stenosis, % (IQR)	66.0 (53.0, 72.9)	67.0 (60.3, 76.1)	71.1 (62.4, 78.4)	***0.036**
Remodeling index (IQR)	1.02 (0.93, 1.13)	1.04 (0.99, 1.11)	1.02 (0.95, 1.13)	0.507
Percent atheroma volume (IQR)	41.7 (31.7, 47.5)	45.7 (36.2, 53.2)	52.3 (41.9, 57.8)	***<0.001**
% frames VH-TCFA (IQR)	2.0 (0, 10.0)	5.1 (0.5, 16.2)	9.1 (4.2, 20.4)	***<0.001**
OCT				
MLA, mm^2 (IQR)	3.3 (1.7, 5.8)	2.8 (1.3, 4.0)	3.2 (2.2, 5.2)	0.526
Minimum fibrous cap, µm (IQR)	76 (57, 92)	72 (57, 112)	94 (61, 140)	0.339
% fibroatheroma frames (IQR)	39.7 (27.1, 100)	24.3 (7.5, 65.3)	60.9 (14.7, 100)	0.198
% fibrocalcific frames (IQR)	45.7 (12.6, 100)	55.9 (38.1, 90)	86.6 (61.5, 100)	0.095
Rupture, n (%)	3 (30.0)	2 (12.5)	4 (36.4)	0.347
Macrophage, n (%)	6 (60.0)	7 (41.2)	6 (54.5)	0.706
Microchannel, n (%)	4 (40.0)	5 (29.4)	7 (63.6)	0.216
ChC, n (%)	1 (10.0)	8 (47.1)	2 (18.2)	0.113
OCT-TCFA, n (%)	3 (30.0)	6 (37.5)	1 (9.1)	0.294

Table 6.3 Association of %DC with other vessel characteristics

The results from the angiographic sub-study suggested that there may be an association between calcification and vessel remodeling. Although there was no association of whole vessel %DC with RI, deeper analysis of the site of MLA in vessels with a stenosis ≥50% revealed a non-linear positive association between DC area and the RI (**Figure 6.3**). There was no relationship between %DC at the MLA and RI (R^2=0.028, p=0.141).

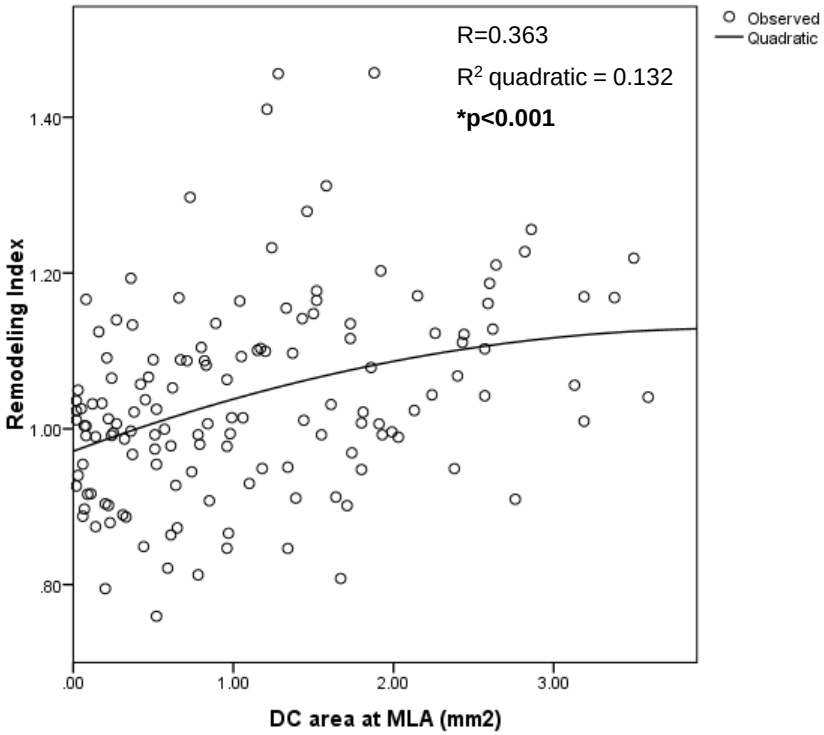


Figure 6.4 Association of DC area at MLA with remodeling index

Increasing DC area at the site of the MLA is associated with increasing RI in vessels with a maximum stenosis ≥50. The data was best fit by a quadratic curve, with severely calcified MLA sites more limited in their capacity to expansively remodel.

6.3 Discussion

6.3.1 Predictors Of Coronary Calcification

The older population studied in ICON1 has given us a unique opportunity to investigate the pathophysiology of coronary artery calcification. Although calcification measured on angiography and VH IVUS were broadly associated with each other, they differed in terms of patient-level predictive factors and this may be due to the fact that angiographic calcification is a subjective “eyeball” assessment whereas the VH IVUS algorithm is arguably a more objective measurement.

In terms of patient-level factors, previous angina or MI was a predictor of both angiographic and VH IVUS calcification, concurring with the pooled analysis of 2 large ACS studies, which demonstrated that previous IHD was associated with angiographic calcification (p=0.005)[28]. This lends further weight to the theory that calcification accumulates following coronary events due to plaque rupture and healing. There were no consistent cardiovascular risk factors that predicted coronary calcification, contradicting a large meta-analysis of >12,000 symptomatic patients (although not necessarily patients with ACS) that demonstrated that hypertension (OR 1.71, p<0.001) and diabetes (OR 1.34, p=0.03), but not smoking (OR 1.42, p=0.13) predicted the presence and extent of coronary calcification[235]. However, it may be that age and/or frailty attenuates these relationships such that they were not apparent in our smaller cohort size.

Interestingly, vitamin D level independently predicted calcification on VH IVUS in this study. Zitterman et al proposed a biphasic dose-response curve between vascular calcification and vitamin D, with both low and high levels associated with adverse effects (**Figure 6.5**)[236]. Physiological levels of vitamin D may inhibit calcification through modulating inflammatory cytokines, with vitamin D deficiency leading to pro-inflammatory activity that subsequently drives calcification, and hyper-vitaminosis D leading to increased free calcium and phosphate levels and vascular mineralisation. In contrast to this theory, the results presented here demonstrated a linear positive relationship between vitamin D and coronary calcification, although the majority of the patients were deficient/insufficient in vitamin D (69.2%), only 4 were supra-therapeutic (>100nmol/L) and results were not corrected for the time of year of vitamin D measurement.

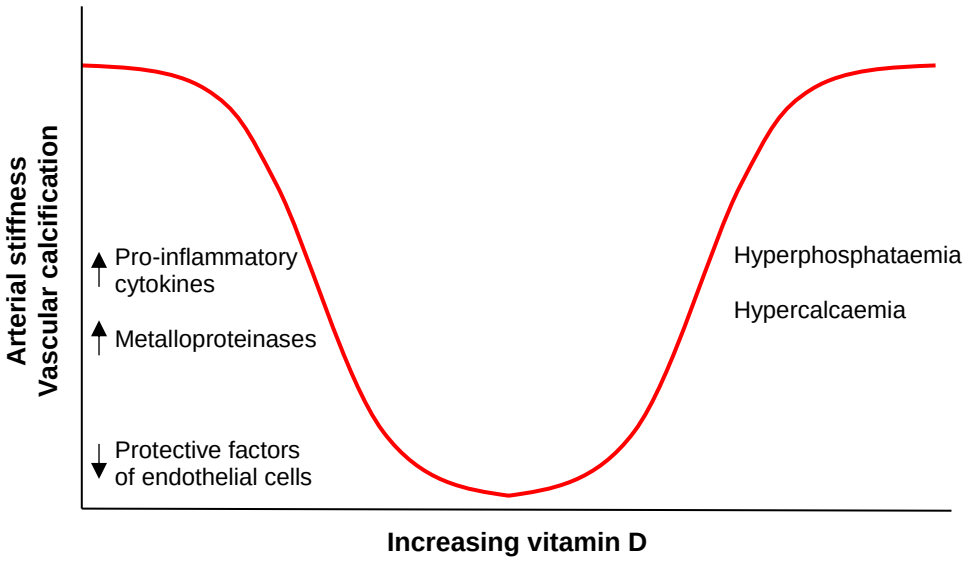


Figure 6.5 Biphasic dose response curve for adverse effects of vitamin D

Low vitamin D promotes arterial stiffness and calcification by increasing pro-inflammatory cytokines and metalloproteinases, whilst supra-therapeutic vitamin D has a direct effect on vascular calcification through hyperphosphataemia and hypercalcaemia. There may be an optimum level of vitamin D which has yet to be fully established.

A recent systematic review of 10 studies found insufficient evidence to support an association between vitamin D level and the presence or severity of coronary artery calcification on CT[237]. Since then, two prospective studies have shown no association between vitamin D and CT coronary calcification[238, 239], one study showed an inverse association in men only[240], and two showed an inverse association in the whole cohort[241, 242]. However, these studies are all limited by the fact that they are small and often conducted in asymptomatic individuals, so the results may not be applicable to a "real-world" population. In addition, they have all utilised CT calcium scoring rather than invasive imaging. One study has evaluated coronary artery calcification on grayscale and VH IVUS and fibroblast growth factor 23, a regulator of vitamin D metabolism; it was associated with a non-significant increase in volume of DC on VH IVUS (p=0.063), but the %DC was not reported and the study excluded patients with ACS[243].

It has been postulated that vitamin D metabolism could be the mechanism linking frailty and coronary calcification. However, there was no difference in baseline vitamin D between frailty groups, which contradicts a large meta-analysis of >17,000 patients that demonstrated a significant association between vitamin D and frailty (pooled OR = 1.25, 95% CI = 1.14–1.37)[244]. The 7 studies analysed all utilised different definitions of both frailty and vitamin D insufficiency, and a subsequent prospective

longitudinal study has demonstrated that cardiometabolic disease in older women attenuates the association between vitamin D and frailty[245].

The results presented here have demonstrated that the effects of previously demonstrated patient-related risk factors for coronary calcification may be attenuated in older patients, with calcification in this cohort more strongly associated with previous coronary events. The association between vitamin D metabolism and vascular calcification, if there is one, is complex and requires further investigation with large scale prospective clinical trials before widespread supplementation is advised for patients.

6.3.2 The Vascular Effects Of Coronary Calcification

By utilising multi-modality intracoronary imaging, it has been possible to investigate the effects of increasing calcification on the coronary vasculature. In this study, calcification was positively associated with plaque burden, vessel remodeling and VH-TCFA, consistent with A VH IVUS sub-study of a large registry of “all-comer” PCI patients demonstrating that %DC was positively associated with plaque burden and VH-TCFA[246]. A study utilising serial grayscale IVUS also demonstrated that coronary artery calcification was associated with increasing total atheroma burden, and that patients with more calcification were less likely to have a reduction in atheroma burden in response to medical therapies targeting cardiovascular risk factors[247]. This supports the conventional theory that atheromatous plaques calcify in response to a chronic rupture and healing process, and that this is the end-stage of plaque evolution.

On angiography, moderate calcification was associated with the lowest degree of stenosis pre-PCI, and analysis of the VH IVUS data demonstrated that calcification at the site of MLA increased the RI in a non-linear fashion. As plaque burden increased linearly with calcification, the lesion diameter stenosis initially decreased as the vessel remodeled quicker than plaque accumulated, then increased as the positive vessel remodeling slowed and the plaque continued to accumulate. Although the best-fit curve for the association of DC and RI was a quadratic curve, suggesting that very severe calcification leads to negative remodeling of the vessel at some point, the measurement of RI in the presence of large amounts of calcification may be inaccurate due to difficulty in determining the border of the vessel EEM in the acoustic shadow of the calcium (**Figure 6.6**). The QCA-measured RD also increased with increasing

calcification, but it should be remembered that RD is not a direct measure of arterial dimensions but is a computer estimate of the vessel diameter at the maximum stenosis site derived by an iterative linear regression technique, and therefore cannot be utilised to directly calculate vessel remodeling[248].

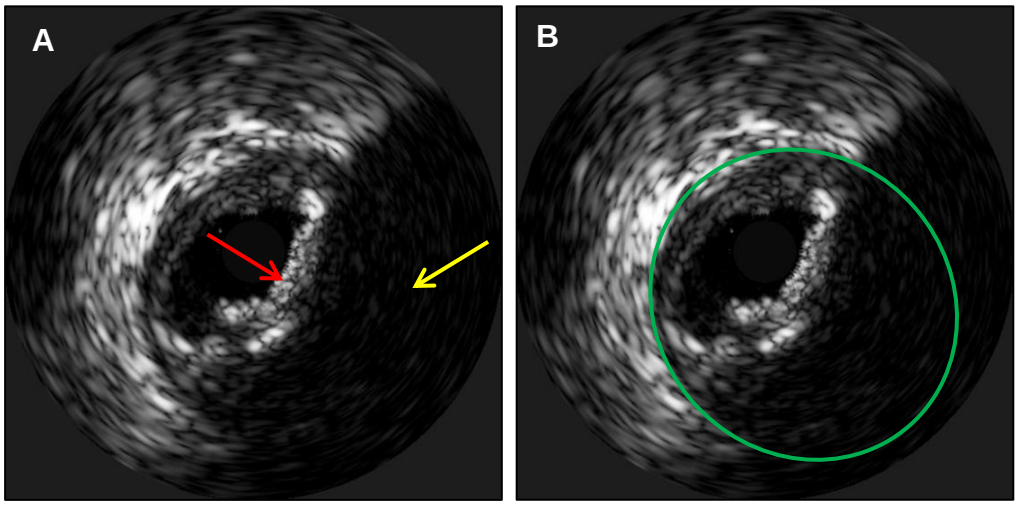


Figure 6.6 Acoustic shadow of calcium obscures the EEM border

In the presence of severe calcification, precise tracing of the EEM border of the vessel in the acoustic shadow of the calcium is often problematic and could lead to inaccuracies in the derivation of the RI. Panel A demonstrates a heavily calcified eccentric plaque (red arrow) with the acoustic shadow obscuring the EEM border (yellow arrow). Panel B demonstrates extrapolation of the circumference of the EEM (green line) as the cross section of the artery is roughly ovoid.

These findings are consistent with the few previous studies looking at coronary calcification and vessel remodeling. In a small study (n=15) of minimally calcified lesions, calcification was associated with plaque shrinkage and luminal enlargement during a 5 year follow up[249]. In an analysis of 138 patients with ACS (NSTEACS and STEMI), calcification on serial OCT and IVUS (baseline and 12 months) was associated with a reduction in the expansive remodeling capacity[250]. Glagov et al postulated that coronary arteries enlarge as atheromatous plaque develops as a mechanism to preserve lumen cross-sectional area in a study of 136 histological specimens of the LMS artery[251]. Our data has demonstrated that, as calcium accumulates and the artery becomes stiffer, its capacity to positively remodel decreases, EEM enlargement slows and the severity of stenosis increases.

In addition, previous research has demonstrated that arteries with positive remodeling are more likely to harbour adverse plaque characteristics such as plaque rupture and massive thrombus formation[122], OCT-TCFA and lipid-rich plaque[252, 253], VH-TCFA and

necrotic core[254, 255], and thinning of the fibrous cap of the plaque on OCT[253, 256]. A positive RI was also shown to be predictive of troponin positive ACS culprit lesions in a study of VH IVUS in 70 patients[257]. Deposition of significant amounts of calcium may help to stabilise these plaques despite increasing the overall plaque burden, potentially reducing the risk of adverse cardiovascular events.

It has been proposed that plaque vulnerability and risk of plaque rupture is modulated by accumulation of calcium in the vessel. A sub-analysis of VH IVUS data from the VIVA study in lesions with plaque burden ≥40%, plaque structural stress (PSS) was calculated using 3D reconstructions[258]. PSS increased with increasing calcification until it plateaued or even reduced with severe calcification[258]. It is postulated that PSS is highest at sites of interface between plaque components with different levels of stiffness i.e. calcified and non-calcified plaque[259]. As spotty calcium is deposited, the number of interfaces initially increases, increasing the PSS, but coalescence of areas of calcium in the latter stages of plaque formation leads to a decrease in the interface area and consequent stabilisation of the lesion (**Figure 6.7**)[259].

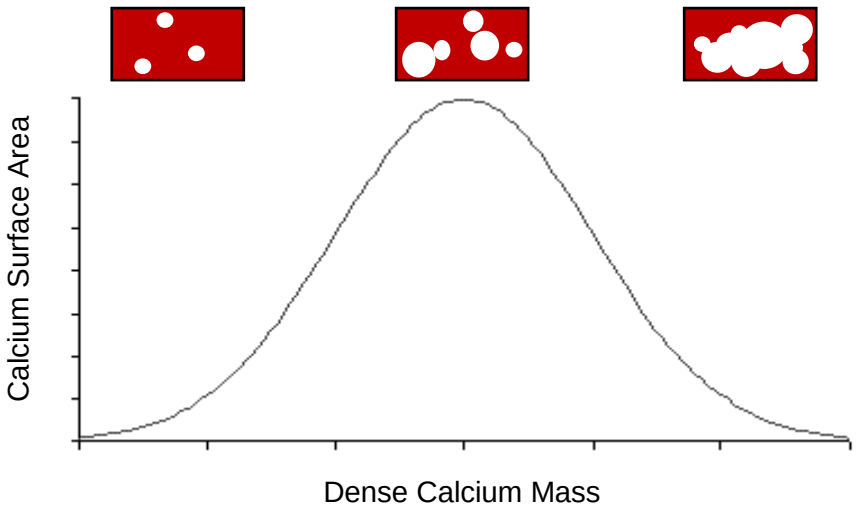


Figure 6.7 Relationship between calcium surface area and total mass

In the early stages of calcification, discrete depositions of calcium have an increasing surface area and therefore an increasingly adverse effect on plaque structural stress. As the calcium deposits coalesce, the surface/interface area decreases with a corresponding decrease in the propensity for the plaque to rupture. Adapted from Abedin et al[259]

Murray et al delved further into this relationship by looking for “blueprints” associated with plaque vulnerability and spotty calcification. They calculated a “calcified interface area” (CIA = $\frac{NC+DC}{DC}$) as a mathematical surrogate for the interface between DC and

NC, and demonstrated that ACS culprit lesions had a higher CIA at the MLA site than stable plaques (5.38 ± 2.72 vs. 3.58 ± 2.26, p=0.001)[257]. There was a trend towards a positive correlation between CIA and remodelling index (p=0.07) but only in stable plaques[257]. However, we have demonstrated a strong linear relationship between DC and NC that is, in part, artefactual due to acoustic shadowing behind heavy calcification. In the presence of significant calcium, relying on ratios of plaque components to identify spotty calcification is therefore too simplistic. Joshi et al defined microcalcifications on VH IVUS as “spotty calcification in the absence of acoustic shadowing on 3 consecutive frames” and demonstrated that they were associated with high risk plaques in patients with stable angina (73 vs. 21%, p=0.002). A consistent definition of “spotty calcification” is required if future studies are to unpick the relationship between the deposition of calcium and the vulnerability of the plaque to rupture and cause adverse events.

In addition to modulating lesion vulnerability, the pattern of plaque calcification has also been shown to influence the haemodynamic significance of the lesion. In a grayscale IVUS study of 70 coronary lesions in patients with stable angina and ACS, FFR was negatively correlated with the maximal thickness of calcification and calcification angle[260]. In addition, superficial calcification was associated with negative remodeling but deep calcification was associated with positive remodeling[260]. The relationship between the severity of coronary artery stenosis (measured by QCA) and haemodynamic significance (measured by FFR) is also influenced by the degree of coronary calcification, with no association between degree of stenosis and FFR in patients with heavy calcification[261]. It is clear that, not only is the amount of calcification important in predicting the haemodynamic significance of a lesion, but the geometry and location of the calcium plays an additional role, possibly by affecting arterial wall compliance.

Although analysis of this patient cohort has yielded significant results, caution must be used when interpreting VH IVUS measurements in the presence of high calcification. In particular, the potential for the misclassification of NC could be a factor in the association of %DC with VH-TCFA seen here, and therefore the over-reporting of VH-TCFA overall. A study utilising both NIRS and VH IVUS to characterise plaques demonstrated no correlation between %NC and lipid index by NIRS in calcified plaques (as NIRS assesses the chemical composition of plaque, measurement of lipid index is

not affected by calcification)[91]. Sales et al demonstrated that, when stent struts were used to simulate calcium, there was a linear increase in measured NC on VH IVUS[262]. This linear relationship suggests that it may be possible to mathematically correct for this overestimation. Masking algorithms have also been shown to improve the accuracy of VH IVUS classification behind calcified plaques[94].

These results demonstrate that the progressive deposition of calcium within coronary plaque results in dynamic positive remodeling of the vessel, initially preserving or even increasing the lumen size before increasing plaque burden subsequently encroaches on the lumen. Lesions with a moderate amount of calcium may be at highest risk of rupture and subsequent adverse events, as they have a high interface area between calcium and other plaque components, leading to an increase in shear stress at these sites.

CHAPTER 7: RESULTS – Primary Outcomes at One Year

The primary aim of the ICON1 study was to describe the patient-level predictors of adverse outcomes at one year following NSTEACS in older patients. This thesis focusses on investigating the coronary plaque phenotypes associated with adverse outcomes in this patient group.

7.1 Major Adverse Cardiovascular Events

In total, there were 19 MACE in 17 patients: 3 deaths, 5 ACS, 2 unplanned revascularisations (both had already re-presented with ACS: one received PCI to an acute stent thrombosis in culprit vessel, and one had a CABG for severe ISR in culprit and non-culprit vessels), 1 stroke and 8 bleeding events. All bar one of the bleeding events were BARC grade 2 (the other was grade 3). Median follow up time was 364 days (IQR 355 to 369 days) and there were no patients lost to follow up. Only 2 MACE occurred in the OCT sub-group therefore the association of adverse outcomes with plaque characteristics on OCT is not reported here due to lack of statistical power.

Figure 7.1 details the Kaplan-Meier curves for the association of MACE at 1 year with age (**Figure 7.1A**), sex (**Figure 7.1B**) and frailty (**Figure 7.1C**). There were no differences in survival between any of these patient-level factors in this cohort.

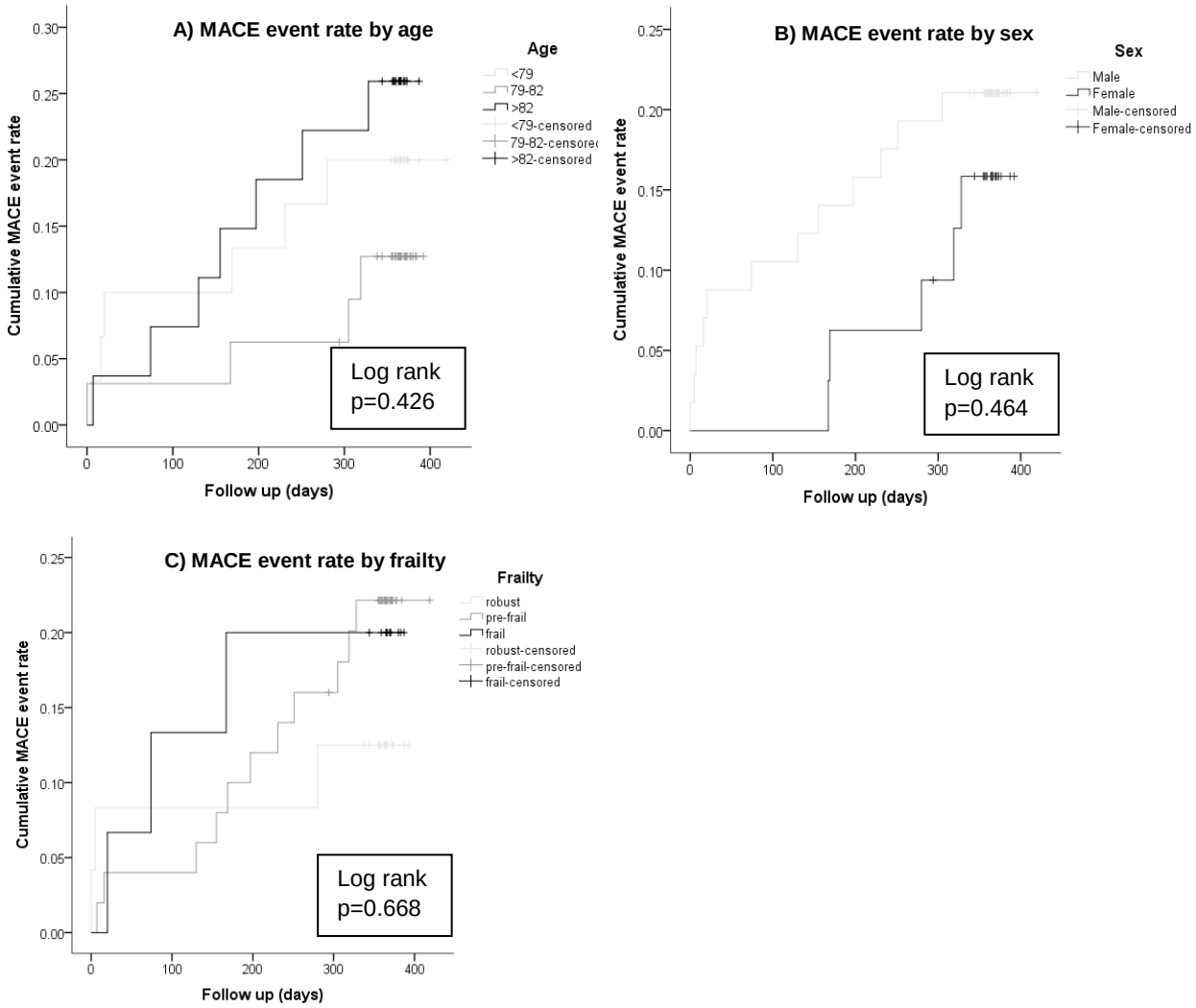


Figure 7.1 Kaplan-Meier curves of MACE by patient-level factors

Figure 7.2 displays the Kaplan-Meier curves for the association of MACE with angiographic and VH IVUS findings. There were no differences in adverse outcomes at one year between groups when classified by baseline SYNTAX score (**Figure 7.2A**), SYNTAX Revascularisation Index >70% (**Figure 7.2B**), overall %NC (**Figure 7.2C**), presence of VH-TCFA in a non-culprit vessel (**Figure 7.2E**), or presence of a high LAPS in a non-culprit vessel (**Figure 7.2F**). However, the intermediate %DC group was at significantly higher risk of MACE than either the low or high %DC groups (**Figure 7.2D**).

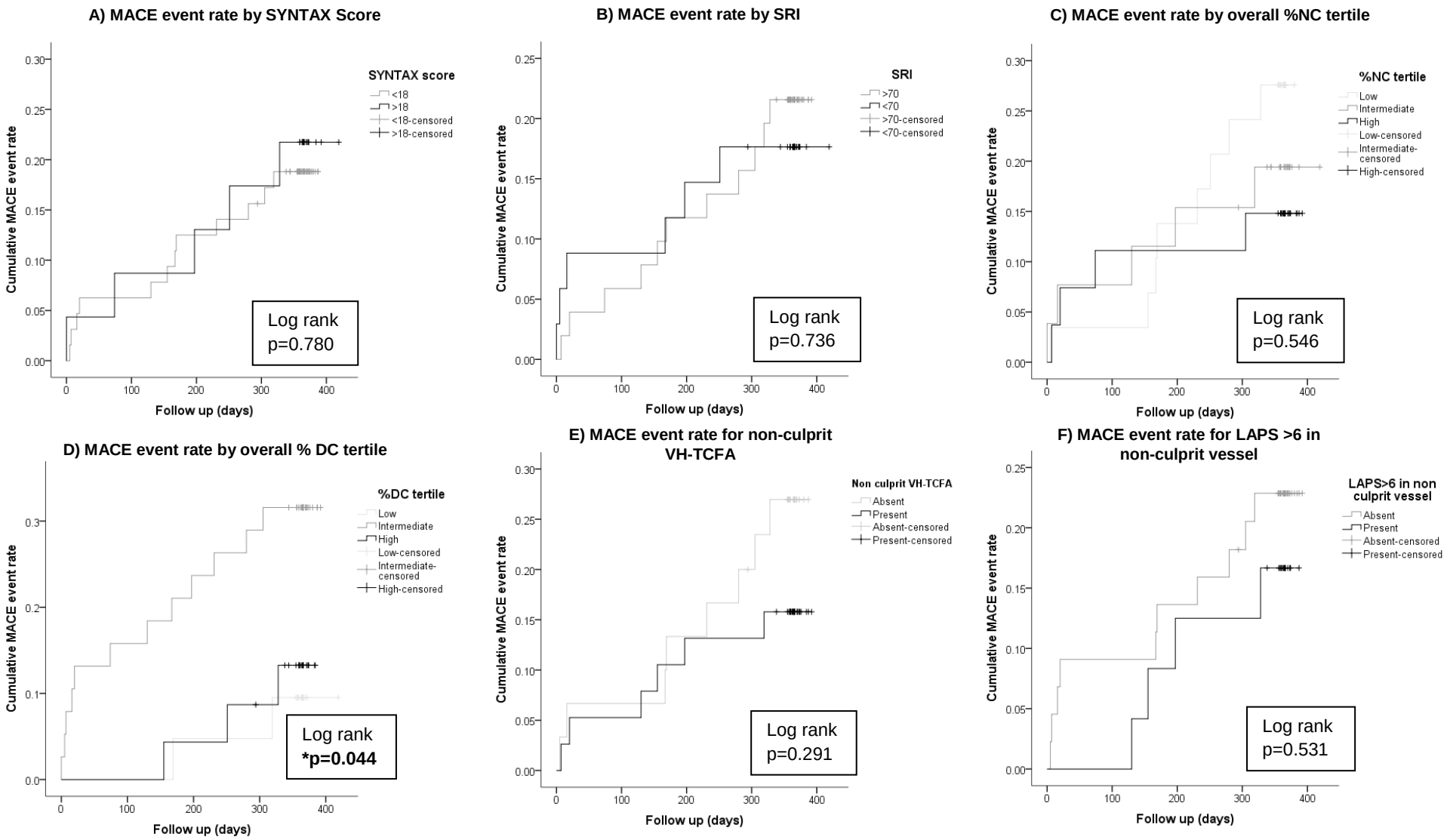


Figure 7.2 Kaplan-Meier curves of MACE by vessel-level factors

Table 7.1 summarises the clinical outcomes at 1 year when stratified by %DC and demonstrates that the increase in adverse outcomes in the intermediate calcification group was driven by rehospitalisation for ACS.

	Low N=21	Intermediate N=38	High N=25	P value
Composite MACE, n (%)	2 (9.5)	12 (31.6)	3 (12.0)	***0.044**
All-cause mortality, n (%)	0	2 (5.3)	1 (4.0)	0.523
ACS, n (%)	0	5 (13.2)	0	***0.043**
Stroke, n (%)	0	1 (2.6)	0	0.477
Bleeding, n (%)	2 (9.5)	4 (10.5)	2 (8.0)	0.879
Unplanned revascularisation, n (%)	0	2 (5.3)	0	0.269

Table 7.1 Clinical outcomes at 1 year by overall proportion of dense calcium

Results from the PROSPECT, VIVA and ATHEROREMO-IVUS studies consistently demonstrated that the combination of MLA ≤4mm^2 + plaque burden ≥70% + presence of VH-TCFA was associated with adverse outcomes[69-71]. However, when combining these variables in this cohort (**Figure 7.3**), there were no differences in outcomes at 1 year. This persisted even when only taking into account non-culprit lesions (log rank p=0.473), or non-culprit lesions that were not intervened on (log rank p=0.101), although there were only 4 non-culprit lesions (4.8%) that had this combination of plaque characteristics and did not undergo PCI (similar to the prevalence in PROSPECT of 25 lesions [4.2%][69]).

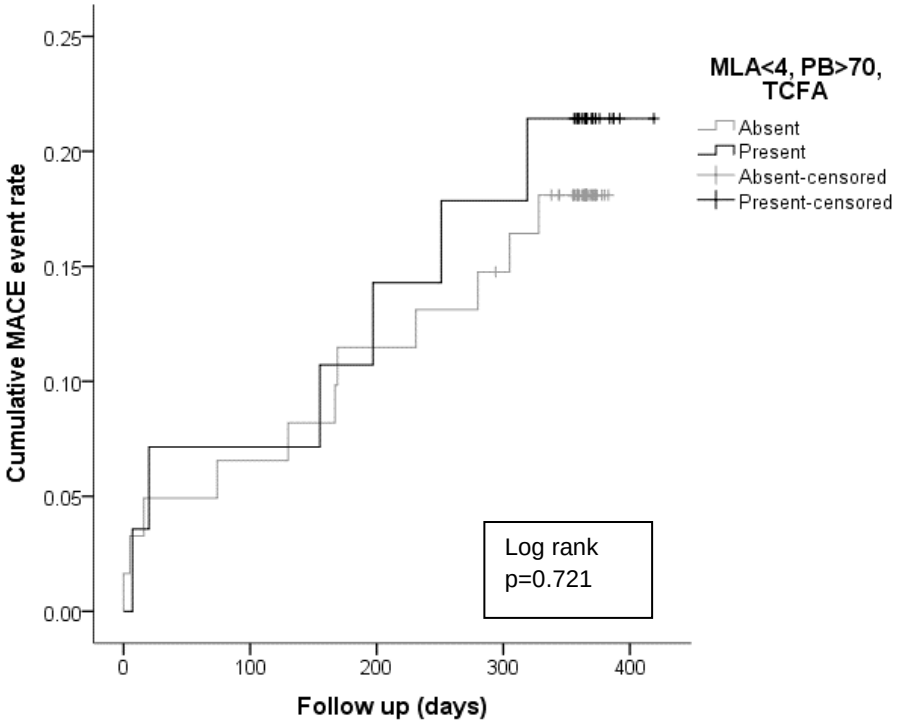


Figure 7.3 MACE event rate for all lesions with MLA ≤4mm^2 + plaque burden ≥70% + VH-TCFA

7.2 Discussion

There was a consistently low adverse event rate at one year in older patients undergoing PCI for NSTEACS. The lack of difference in MACE between patient-level factors such as age, sex and frailty (factors that have previously been shown to be associated with poorer prognosis post NSTEACS[14, 21, 202]) is likely to be due to patient selection bias in this small, and largely homogenous, cohort. Indeed, results from the full ICON1 patient cohort (both invasive and non-invasive sub-studies, n=279) demonstrated that increasing frailty was associated with MACE and greater unplanned hospitalisations at 1 year (although not in-hospital or at 30 days)[220].

Utilising angiography and radiofrequency intravascular ultrasonographic imaging, we have also shown that previously identified lesion-related risk factors such as SYNTAX score, SYNTAX revascularisation index, lipid burden and VH-TCFA are not associated with MACE at one year in this cohort. Moreover, a previously validated scoring system designed to identify "active" plaque, LAPS[64], was also not associated with adverse outcomes. However, moderate total vessel %DC was associated with higher MACE than either low or high calcification, adding weight to the theory that it is these

intermediate lesions that are highest risk. The event rate in this group was primarily driven by an excess of rehospitalisation for ACS.

There could be multiple mechanisms by which moderate calcification is associated with adverse events. Firstly, although procedural success was similar between VH IVUS calcification tertiles (**Table 6.3**), the angiographic sub-study results demonstrated that moderately calcified lesions had a higher residual % diameter stenosis post-PCI than none/mildly and severely calcified lesions. Thus moderate/intermediate calcified lesions may not be prepared adequately prior to stenting (perhaps due to the perceived risks of using complex interventions such as rotablation/laser in an older patient cohort), and therefore may be at higher risk of restenosis and subsequent coronary events. Indeed, in a large analysis of outcomes stratified by angiographic calcification, moderate calcification was significantly associated with definite stent thrombosis at 1 year (no/mild calcification: 1.7% vs. moderate: 2.9% vs. severe: 1.9%, p=0.01)[28]. As well as stent under-expansion, residual calcification following preparation of the lesion can be associated with structural damage during stent delivery, with stripping of the polymer from the drug eluting stent[263].

Secondly, the relationship between moderate calcification and high PSS has already been discussed here, and our results support the theory that high levels of calcification in the coronary tree could stabilise lesions and lower the risk of adverse events. Thirdly, a large retrospective study of patients with ACS demonstrated the association of coronary calcification and increased risk of major bleeding after PCI[264]. As well as calcification of the coronary arteries, it is expected that other peripheral arteries such as the femoral and radial arteries also undergo the same calcification, thus increasing the risk of bleeding from the access site[265]. In addition, the need for advanced PCI techniques such as rotablation in highly calcified lesion, and thus potentially more potent anti-thrombotic and anti-platelet regimens, further increases the risk of bleeding.

The results presented here contrast previous prospective studies utilising VH IVUS to predict adverse outcomes in patients with ACS, which demonstrated that the combination of small lumen area, large plaque burden and the presence of VH-TCFA was associated with adverse events at one year[69-71]. However, there were only 4 (4.8%) lesions with this combination in non-culprit arteries that did not receive PCI during the index admission. This may suggest that a policy of full revascularisation at

the time of PCI after NSTEACS negates the adverse effect of these previously identified vulnerable lesions, although a large RCT would be needed to test this hypothesis. Moreover, the pitfalls of TCFA identification on VH IVUS in a population with complex coronary disease have been discussed here previously and this lesion phenotype is simply not an accurate predictor of adverse outcomes in the real world.

In an older, real-world population with NSTEACS, it is moderate calcification that was associated with the highest risk of adverse outcomes at one year, rather than “vulnerable” TCFA that have been identified in previous prospective studies .

CHAPTER 8: FINAL SUMMARY AND CONCLUSIONS

8.1 Final Summary

The results presented in this thesis demonstrate for the first time that recruitment of older patients to a study of invasive coronary imaging is safe, feasible, and has a high yield of advanced plaque phenotypes to study the pathophysiology of coronary disease following NSTEACS. We performed a comprehensive assessment of the pattern and burden of coronary plaque in this cohort, and identified that moderate coronary calcification is associated with adverse outcomes.

8.1.1 Engaging Older Patients In Invasive Cardiovascular Research Is A Positive Experience

The recruitment rate reported in this study was high and compared favourably to previous observational studies in community populations in this age group[36]. Overall, 69.8% of patients consented after being approached and 33.2% of those were suitable for invasive imaging. 80.6% of anatomically suitable vessels were successfully imaged with VH IVUS and 74.7% with OCT. There was only one adverse event attributable to intracoronary imaging, concordant with the safety profile reported previously[194, 195].

Three-vessel intracoronary imaging in an older cohort does present challenges to the researcher due to issues in delivering the catheters through tortuous and calcified arteries, and the total length of coronary artery imaged here was lower than in previous 3-vessel intracoronary imaging studies (e.g. 105.2mm on VH IVUS vs. 165.9mm in the older cohort in PROSPECT[174]). However, the majority of proximal arteries were imaged and the results presented focus on overall burden of plaque phenotypes rather than presence or absence of one lesion sub-type. The population studied were a “real-world” population that are encountered every day in the coronary catheter laboratory, and exclusion co-morbidities were minimised to accurately reflect this.

This body of work endeavoured to adhere to the PREDICT charter for research in older patients, paving the way for more individualised clinical decision-making in this cohort. Older age should not preclude enrolment in future studies of coronary pathophysiology and, indeed, should be encouraged as this population is enthusiastic about participating in research and have a lot to offer in terms of progressing the understanding of advanced coronary atherosclerosis.

8.1.2 Increasing Burden Of Atheroma Is Associated With Age And Male Sex, But Frailty Is Associated With Changes In Plaque Composition

With increasing age, the angiographic severity and complexity of coronary disease did not change, but older patients were more likely to undergo multi-vessel PCI (<79 years: 10% vs. 79-82 years: 39.4% vs. >82 years: 39.3%, p=0.016). Overall PAV on IVUS increased with age (42.7 ± 11.4% vs. 43.4 ± 10.9% vs. 50.0 ± 8.9%, p<0.001) and there was an increasing burden of advanced lesion phenotypes such as VH-TCFA (5.7% vs. 9.3% vs. 14.1% p<0.001). Men had a higher burden of coronary disease than women when measured by number of lesions (3 [2,3] vs. 2 [1,3], p=0.045), SYNTAX score (13 [9,23] vs. 9 [5,17], p=0.037), and PAV (47.6 ± 10.4% vs. 41.7 ± 10.8%, p<0.001). This would suggest that at no age does the accumulation of coronary plaque cease to increase, with women lagging around 10 years behind men in the incidence of cardiac events[266].

It has been postulated that this consistent deposition of coronary plaque with ageing is regulated by a reduction in the repair mechanisms critical in maintaining arterial homeostasis in the face of cardiovascular risk factors. In an apolipoprotein-E deficient (hyperlipidaemic) mouse model, the capacity of bone marrow-derived progenitor cells to repair damaged arteries was reduced with ageing and atheroma deposition began with the loss of repair capacity rather than with onset of hyperlipidaemia[267, 268]. Senescent cells may also secrete cytokines, matrix metalloproteinases and other inflammatory biomarkers, which propagate the development of atherosclerosis[269]. Genetic factors that occur with ageing such as telomere shortening[270] or development of clonal haematopoiesis of intermediate potential[271] may contribute to the ongoing deposition of plaque via their association with inflammation and oxidative stress.

Interestingly, neither age nor sex were associated with a difference in the proportion of plaque components, but frail patients had a higher burden of calcified plaque on VH IVUS (robust: 13.7%, vs. pre-frail: 13.0% vs. frail: 17.7%, p=0.018). This is the first time that this association has been demonstrated on invasive imaging and risk-stratification by frailty may therefore aid decision-making prior to PCI. Frailty was not associated with an increase in plaque burden or disease severity, suggesting that the association of calcification with frailty is not necessarily mediated by increasing burden of disease, but could be related to external factors such as vitamin D metabolism or chronic systemic inflammation.

Adverse features on OCT such as plaque rupture, microchannels, cholesterol crystals and TCFA were clustered together in vessels, suggesting that these features develop in tandem and may be representative of increased overall coronary vulnerability. Indeed, 36.4% of plaque ruptures seen in this study were in non-culprit arteries. A recent study utilising NIRS and OCT demonstrated the association of inflammatory $CD14^{++}CD16^{+}$ monocytes, previously shown to be associated with acute MI, with fibrous cap thickness, OCT-TCFA and thrombus[272]. A French study demonstrated that, in the immediate aftermath of an acute MI, 10% of patients had evidence of two areas of myocardial necrosis (one in a region not attributable to the culprit lesion) on magnetic resonance imaging (MRI) and, in 3.8% of patients, this corresponded to a coronary vessel with normal flow[273]. Thus, pancoronary instability in NSTEACS may be related to a systemic inflammatory process and contribute to accelerated accumulation of coronary atheroma through repeated rupture and healing of plaques.

8.1.3 Moderate Coronary Calcification Is Associated With Positive Remodeling And Adverse Outcomes

The high burden of coronary calcification in our cohort provided an invaluable opportunity to investigate the causes and effects of this important plaque component. Calcification on angiography and VH IVUS was associated with previous coronary events such as angina and previous MI, and with PAV (low %DC: 41.7%, vs. intermediate %DC: 45.7%, vs. high %DC: 52.3%, $p<0.001$), which would suggest that calcification accumulates with repeated plaque rupture and healing. Calcification was also independently associated with vitamin D in a positive linear fashion (VH IVUS %DC: $\beta=0.088$, $p<0.001$), in contrast to previous theories suggesting a biphasic association between vascular calcium and vitamin D[236].

Increasing calcification was initially associated with a reduction in the %diameter stenosis on angiography ($p=0.003$), likely mediated by a high rate of positive remodeling that slowed with severe calcification ($R=0.363$, $p<0.001$). Thus, moderate levels of calcification at the MLA site were associated with the highest RI. Previous studies have demonstrated that these moderate levels of calcium are deposited in a “spotty” fashion, increasing the number of interfaces between calcium and soft plaque and subsequently increasing shear stress across the lesion[258]. As well as facilitating positive remodeling to preserve lumen area, this turbulent flow may increase the rate

of damage to the vessel wall and, with impaired repair mechanisms unable to keep up with this, lead to a greater burden of atheroma and high risk plaque.

Consistent with this theory, patients with moderate levels of overall coronary calcification had a higher MACE rate at 1 year (low: 9.5% vs. moderate: 31.6% vs. high 12.0%, p=0.044), driven by an excess of repeat hospitalisation for ACS. This may also be partly due to the fact that these moderately calcified lesions had a higher residual %diameter stenosis post-PCI (23.1% vs. no calcification: 14.2%, mild calcification: 17.0%, severe calcification: 19.0%, p=0.014), a risk factor for restenosis.

In a large registry of histological specimens, there was a clear relationship between plaque morphology and radiographic calcification (erosions: predominantly none, ruptures: predominantly speckled calcium, healed ruptures: predominantly blocks of diffuse calcification)[274]. However, there are no current consistent definitions of “spotty calcification” on in vivo coronary imaging. Utilisation of ratios of NC and DC on VH IVUS to derive a calcified interface area[257] is limited by the impact of heavy calcification on over-measurement of NC. Observation of calcification without acoustic shadow on IVUS[92] merits further investigation. OCT is probably best placed to identify small deposits of calcium within the vessel wall but could still be missed if located behind deep lipid pools. Frequency of spotty calcification on OCT (defined as length <4mm and arc <90^{o}) was not significantly different in one study of patients with STEMI vs. stable angina[275] but was higher in ruptured vs. non-ruptured culprit plaques in another study of patients with ACS[276]. To date, there have been no studies investigating spotty calcification on OCT with adverse patient outcomes after ACS, with previous research focussing on TCFA as the main vulnerable plaque phenotype, and we would argue that this is certainly warranted in light of the findings presented here.

8.1.4 Clinical Relevance

Due to the nature of the real-world population studied in this thesis, the results are applicable and very relevant to day-to-day practice in the coronary catheter laboratory. There is still a reluctance amongst interventionists to adopt an early invasive strategy in older patients with NSTEACS, possibly due to perceived risks or difficulty of the procedure in this groups. However, we have demonstrated a high angiographic success rate in the whole cohort (90.4%) and a low adverse event rate at 1 year (20.9%) confirming previous studies demonstrating that an early invasive strategy in

older patients with NSTEACS is not only safe but also potentially superior to conservative therapy[22-24]. This should serve to reassure operators that this group of high-risk patients really do have the most to gain from PCI following NSTEACS.

Frailty is known to be a risk factor for adverse outcomes following NSTEACS and this may be related to procedural and anatomical factors identified in this work. Femoral access was far more common in frail patients (robust: 4%, vs. pre-frail: 2% vs. frail: 26.7%, p=0.006) and is a well-recognised determinant of bleeding complications following PCI. Increasing frailty was also associated with increasing coronary calcification (robust: 13.7% vs. pre-frail: 13.0% vs. frail: 17.7%, p=0.018), another factor associated with adverse outcomes[264]. A simple frailty assessment of older patients prior to PCI would allow the operator to risk-stratify and plan in advance for the use of complex PCI techniques such as rotablation and laser atherectomy, as well as prioritising radial arterial access. Greater use of left radial access following failure of right radial puncture may reduce the procedural risk for these vulnerable patients.

The identification of moderate calcification as a predictor of poorer angiographic results post-PCI and adverse outcomes at 1 year is of high clinical importance. Whilst vessels with severe calcification were more likely to be prepared with advanced PCI techniques (all 7 vessels that underwent complex PCI were in the high %DC tertile), moderately calcified lesions were not and stents deployed in these lesions may have been less well expanded and therefore at risk of stent thrombosis and restenosis. The results presented here have demonstrated that the use of IVUS or OCT in this cohort is safe and feasible and therefore these technologies could be used pre and/or post-PCI to optimise results.

The majority of previous research into vulnerable plaque in ACS has focussed on therapies aimed at stabilising TCFA. However, there was discordance between OCT and VH IVUS in the identification of TCFA in this study, and they were not associated with adverse outcomes at 1 year, suggesting that it may not be clinically useful to attempt to identify these in the real world. Moderate spotty calcification may be the true vulnerable plaque phenotype in older patients with NSTEACS and future research needs to be directed at understanding the pathological mechanisms behind this.

8.2 Strengths and Limitations

The main strength of this study lies in the population recruited. It is the first study of invasive coronary imaging to exclusively recruit older patients with ACS and complex coronary disease, a group that have been excluded from previous similar studies. However, the extent to which the results of this study can be generalised to all older people with ACS is limited. The study was an observational cohort study rather than an RCT and the strategies employed to yield the high recruitment rate may therefore not be applicable to the latter. In addition, the population screened was relatively small, from a single geographical area, and the majority of study participants were male (63.7%) despite efforts to recruit more women. The prospective patients in ICON1 had already been selected by cardiologists at district general hospitals to be fit for referral for PCI, and we may therefore have been recruiting from a more robust and motivated pool of patients. Furthermore, the median delay of 5 days from index presentation to intravascular imaging may have had an impact on plaque composition, lesion characteristics, and patient outcome. However, we believe that the cohort studied here is representative of older patients receiving contemporary invasive treatment for of ACS in the United Kingdom.

Although a number of univariate analyses are presented here, the power calculation performed prior to the study commencement was to evaluate the association of TCFA with 1 year outcomes only. In addition, the actual adverse event rate of 20.9% is lower than the assumed rate of 28% and therefore is underpowered with respect to outcomes. The small number of adverse events also precluded multivariate regression analysis. Therefore, the results presented here should be viewed as exploratory findings only to provide a basis for further research. However, a strength of the statistical analysis is the use of a linear mixed-effects model to account for the covariance of the data, something that has not always been accounted for in previous studies utilising a mix of patient-level, vessel-level and lesion-level measurements.

A further limitation of the invasive imaging protocol was that the VH IVUS and OCT pullbacks in each coronary artery were not co-registered therefore may not represent the same stretch of artery. This was often due to the practical difficulties in delivering both imaging catheters to the same location in the artery, given their different size and deliverability. Thus, direct comparison of the VH IVUS and OCT results (e.g. for

identification of an individual TCFA) is not feasible and the results presented for each technology should be viewed as complementary rather than interchangeable. Even if the EEP catheter was successfully delivered through vessels with heavy calcification or tortuosity, it was prone to “jumping” or “sticking” within lesions and therefore some pullbacks required repeating or removal from the study due to poor quality.

In contrast to the PROSPECT and ATHEROREMO-IVUS studies, intravascular imaging in this study was performed in both culprit and non-culprit arteries prior to PCI. This has allowed a more complete study to be made of the intracoronary pathology of NSTEACS in older patients. Moreover, we have been able to correlate our intravascular findings with a comprehensive assessment of angiographic data for each patient. However, these analyses were done several days after the index event (median time to angiography from event was 5 days) and therefore we cannot say for certain that we have captured the true picture of plaque physiology at the time of acute coronary event. In addition, we only have data for all-cause mortality and therefore cannot comment specifically on cardiac death.

The limitations of VH IVUS and OCT in identifying the plaque components measured here are well described. VH IVUS lacks the resolution to identify the thin cap of a vulnerable plaque, and OCT lacks the penetration to quantify deep lipid. Confounding factors such as thrombus (common in the setting of NSTEACS) can make identification of the border of the lumen difficult on both technologies, and the acoustic shadow of calcium on VH IVUS can obscure the EEM border. Although the reported intra-observer variability in plaque component quantification was excellent (with <5% variability in fibrous tissue, NC and DC measurements), previous research has demonstrated that this may still represent large absolute measurement errors[196]. In addition, these limitations are compounded by the overall heavy burden of calcification in the arteries imaged, leading to overestimation of the NC component on VH IVUS and subsequent high false positive rate of diagnosis of VH-TCFA. However, the accuracy of calcium identification on VH IVUS is the highest of all four plaque components[44, 49] and therefore, despite all the limitations of the technology, the main results presented here remain robust.

8.3 Future Directions

Clinical application of intracoronary imaging techniques such as VH IVUS and OCT in identifying vulnerable plaque phenotypes at the time of PCI is currently limited by the time consuming manual frame-by-frame data interpretation. The current automated analysis systems only provide information on the area and percent of each plaque component, and only then once the lumen and vessel borders have been manually defined (the automated detection of the borders is inaccurate). Papaioannou et al devised a novel automated computational system in Java that calculated not only the area and percent of each plaque component, but also the number of solid segments of each component within the plaque and their relationship to the lumen border (**Figure 8.1**)[277]. Although they did not validate this system against conventional manual analysis, and excluded plaques with heavy calcification, it provides hope that automated detection of TCFA and spotty calcification may be possible in the future.

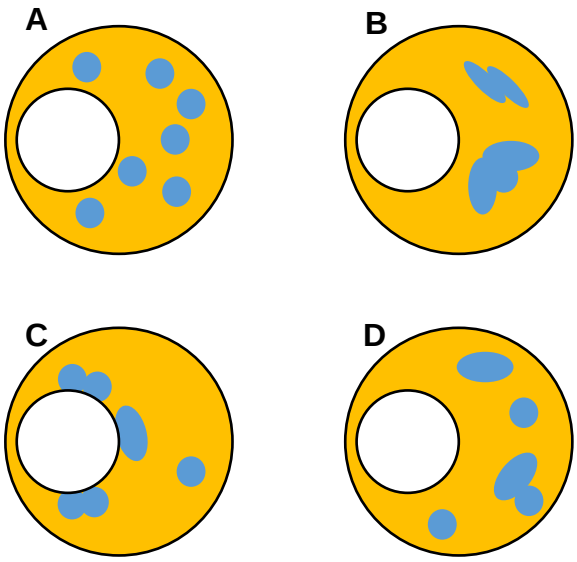


Figure 8.1 Varying features of a plaque component's distribution on VH IVUS

In plaques with the same area and % of a plaque component (e.g. DC or NC), there can be differing dispersities and relationships to the lumen border that may be quantifiable on automated analysis[277].

Panel A: Greater dispersity, with the plaque component scattered within the plaque at many discrete areas e.g. spotty calcification.

Panel B: Lesser dispersity, with the component concentrated in a few areas e.g. advanced calcification.

Panel C: Superficial plaque component, adjoined to the lumen border e.g. VH-TCFA.

Panel D: Deep plaque component, with none in contact with the lumen border.

This study confirms that moderate calcification is a high-risk plaque phenotype but previous VH IVUS studies looking for spotty calcification are flawed due to the

definitions used. A universal definition of this term is urgently called for, whether it is an objective automated measurement of the surface area of the calcium or a subjective observation of calcification without acoustic shadow. This would then allow correlation of this vulnerable plaque phenotype with markers of cellular senescence, inflammation or novel genetic regulators such as micro-RNAs, ultimately enabling development of prognostic markers or therapeutic targets. For example, proprotein convertase substilisin/kexin type 9 (PCSK9), a regulator of low-density lipoprotein receptors, has been shown to be associated with increased NC and DC, but not TCFA, independently of serum cholesterol level[278]. The advent of PCSK9 inhibitors opens the door for a longitudinal study of coronary calcification, PCSK9 levels and the effect of inhibition.

Non-invasive imaging technologies such as CT and MRI are becoming increasingly popular as research tools as they do not carry the same risk as invasive intracoronary imaging. When combined with positron-emission tomography, it is possible to simultaneously assess both plaque activity and morphology in coronary and carotid arteries[92, 279, 280]. This could prove to be valuable in assessing coronary vulnerability in patients currently perceived to be unsuitable for invasive angiography, a group who were not included in the current study.

Although our study did not directly compare early invasive to conservative management in older high-risk patients with NSTEACS, the results demonstrated that this strategy was safe, successful and led to a low rate of MACE in this cohort. The British Heart Foundation SENIOR-RITA trial aims to investigate whether invasive or conservative management is superior in older patients with NSTEACS, with particular focus not only on MACE but on frailty, cognition, quality of life and service utilisation[214]. Future cardiovascular research in older patients should be mindful of including outcome measures relevant to this population such as these.

8.4 Conclusions

This thesis has established that the recruitment of older patients to complex and invasive cardiovascular research is feasible, and that this group is an under-valued resource in the investigation of the pathophysiology of advanced coronary disease. Even in these high-risk patients, PCI after NSTEACS is safe, successful and associated with a low rate of MACE at 1 year, and it is hoped that this will encourage

cardiologists not to discriminate on age alone when deciding when to refer for PCI. At no age does the accumulation of coronary plaque plateau but it was frailty, not age alone, which was associated with increased intracoronary calcification. This calcium is not an inert plaque component, but actively shapes vessel remodeling and its subsequent vulnerability to coronary events. Moderate coronary calcification had the highest risk for adverse outcomes at 1 year, driven by recurrent ACS, suggesting that these patients may derive greater benefit from an aggressive invasive strategy at the outset.

APPENDICES

Appendix A – ICON1 Study Case Report Form

A Study to **I**mprove **C**ardiovascular **O**utcomes in High Risk Patie**N**ts with Acute Coronary Syndrome.

ICON 1 Study
Case Report Form

DOB	_____
Gender	Male □ Female □
Date of PCI	/ /
Time from presentation to PCI	_____
NSTEMI	Yes □ No □
UA	Yes □ No □
STEMI	Yes □ No □
Single Vessel-PCI	Yes □ No □
Multivessel PCI	Yes □ No □
LAD	Yes □ No □
RCA	Yes □ No □
CX	Yes □ No □
SVG	Yes □ No □
Culprit vessel	LAD □ Cx □ RCA □
No. of stents	_____
Arterial Access	_____
Guide catheter size	5F □ 6F □ 7F □ 8F □
Contrast volume	_____
Radiation dose	_____
Duration of PCI	_____
Complications during PCI procedure	Yes □ No □
Please specify:	_____
On admission to DGH:	
Heart rate	_____
Blood pressure	_____
Creatinine	_____
Killip class	_____
Any ST segment changes on ECG?	Yes □ No □
On a statin at admission to DGH?	Yes □ No □
List of medications on discharge:	
Aspirin	Yes □ No □
Clopidogrel	Yes □ No □
Statin	Yes □ No □
ACEI/ARB	Yes □ No □
Betablocker	Yes □ No □
Others (please specify)	_____
Height (cm)	_____
Weight (kg)	_____
BMI (kg/m2)	_____

Hypertension	Yes □ No □
Diabetes	Yes □ No □
Smoking current	Yes □ No □
Ex smoker	Yes □ No □
Hypercholesterolemia	Yes □ No □
Family history of IHD	Yes □ No □
Renal disease	Yes □ No □
Previous MI	Yes □ No □
Previous angina	Yes □ No □
Previous PCI	Yes □ No □
Previous CABG	Yes □ No □
Previous peripheral vascular disease	Yes □ No □
Previous TIA/Stroke	Yes □ No □
H/O arthritis	Yes □ No □
H/O COPD	Yes □ No □
H/O malignancy	Yes □ No □
H/O congestive heart failure	Yes □ No □
H/O dementia	Yes □ No □
H/O liver disease	Yes □ No □
H/O ulcer disease	Yes □ No □
H/O bleeding problems	Yes □ No □
H/O Anaemia	Yes □ No □
H/O any other co-morbid condition	Yes □ No □
Please specify	_____
	_____
Haemoglobin at time of PCI	_____
White cell count at time of PCI	_____
Platelet count at time of PCI	_____
Creatinine at time of PCI	_____
Glucose at time of PCI	_____
Cholesterol at time of PCI	_____
Peak troponin value during hospitalisation	_____

Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status	Yes or No
Nutritional Status	**Frailty cut point:** **Baseline:** Self-reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2	
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.	
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.	
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21	
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds	

Positive for frailty phenotype: ≥3 criteria present , **Intermediate or prefrail:** 1 or 2 criteria present, **Robust:** 0 criteria present

Rockwood Frailty Score

1	Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age	
2	Well – without active disease, but less fit than people in category 1.	
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4	
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.	
5	Mildly frail – with limited dependence on others for instrumental activities of daily living	
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living	
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.	

NYHA Symptom Class:

I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.	
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.	
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.	
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.	

The Canadian Cardiovascular Society Angina Grading Scale:

I	Angina only during strenuous or prolonged physical activity	
II	Slight limitation, with angina only during vigorous physical activity	
III	Symptoms with everyday living activities, i.e., moderate limitation	
IV	Inability to perform any activity without angina or angina **at rest**, i.e., severe limitation	

QOL Index (SF 36) Questionnaire

1- In general, would you say your health is:
□ 1. Excellent □ 2. Very good □ 3. Good □ 4. Fair □ 5. Poor

2- Compared to ONE YEAR AGO, how would you rate your health in general NOW?
□ 1. MUCH BETTER than one year ago.
□ 2. Somewhat BETTER now than one year ago.
□ 3. About the SAME as one year ago.
□ 4. Somewhat WORSE now than one year ago.
□ 5. MUCH WORSE now than one year ago.

3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	□	□	□
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	□	□	□
c) Lifting or carrying groceries?	□	□	□
d) Climbing **several flights** of stairs?	□	□	□
e) Climbing **one** flight of stairs?	□	□	□
f) Bending, kneeing or stooping?	□	□	□
g) Walking **more than a mile**?	□	□	□
h) Walking **several** blocks?	□	□	□
i) Walking **one** block?	□	□	□
j) Bathing or dressing yourself?	□	□	□

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Were limited in the **kind** of work or other activities?	□ 1. yes	□ 2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	□ 1. yes	□ 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Didn't do work or other activities as **carefully** as usual?	□ 1. yes	□ 2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1. Not at all □ 2. Slightly □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?
□ 1. None □ 2. Very mild □ 3. Mild □ 4. Moderate □ 5. Severe □ 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
□ 1. Not at all □ 2. A little bit □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks** …

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	□	□	□	□	□	□
b) Have you been a very nervous person?	□	□	□	□	□	□
c) Have you felt so down in the dumps that nothing could cheer you up?	□	□	□	□	□	□
d) Have you felt calm and peaceful?	□	□	□	□	□	□
e) Did you have a lot of energy?	□	□	□	□	□	□
f) Have you felt downhearted and blue?	□	□	□	□	□	□
g) Do you feel worn out?	□	□	□	□	□	□
h) Have you been a happy person?	□	□	□	□	□	□
i) Did you feel tired?	□	□	□	□	□	□

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1. All of the time
□ 2. Most of the time.
□ 3. Some of the time
□ 4. A little of the time.
□ 5. None of the time.

11. How TRUE or FALSE is **<u>each</u>** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	□	□	□	□	□
b) I am as healthy as anybody I know?	□	□	□	□	□
c) I expect my health to get worse?	□	□	□	□	□
d) My health is excellent?	□	□	□	□	□

EuroQol EQ-5D™

Please tick which statements best describe your own health state today.

1A. Mobility
I have no problems in walking about □
I have some problems in walking about □
I am confined to bed □

1B. Self-Care
I have no problems with self-care □
I have some problems washing or dressing myself □
I am unable to wash or dress myself □

1C. Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities □
I have some problems with performing my usual activities □
I am unable to perform my usual activities □

1D. Pain/Discomfort
I have no pain or discomfort □
I have moderate pain or discomfort □
I have extreme pain or discomfort □

1E. Anxiety/Depression
I am not anxious or depressed □
I am moderately anxious or depressed □
I am extremely anxious or depressed □

Frail Yes □ No □

Fried Frailty Score _____

Rockwood Frailty Score _____

Charlson Co-morbidity Index _____

Ankle Brachial Index _____

EndoPAT Score _____

Augmentation Index _____

CIMT _____

Echocardiogram and LV Function (Please tick)

Mild LV □

Moderate LV □

Severe LV □

Ejection Fraction (%) if known _____

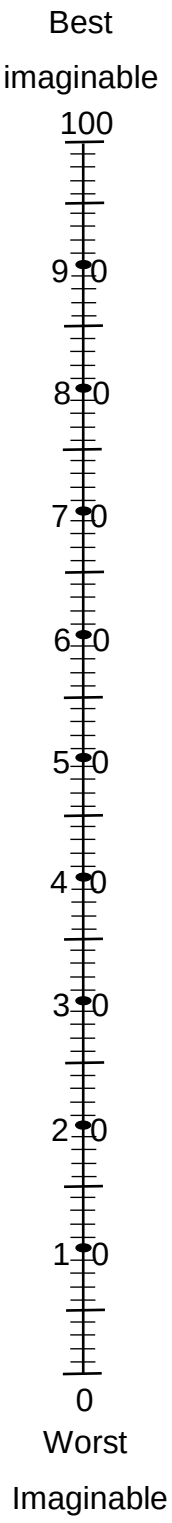
Significant valve disease Yes □ No □

Please specify _____

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

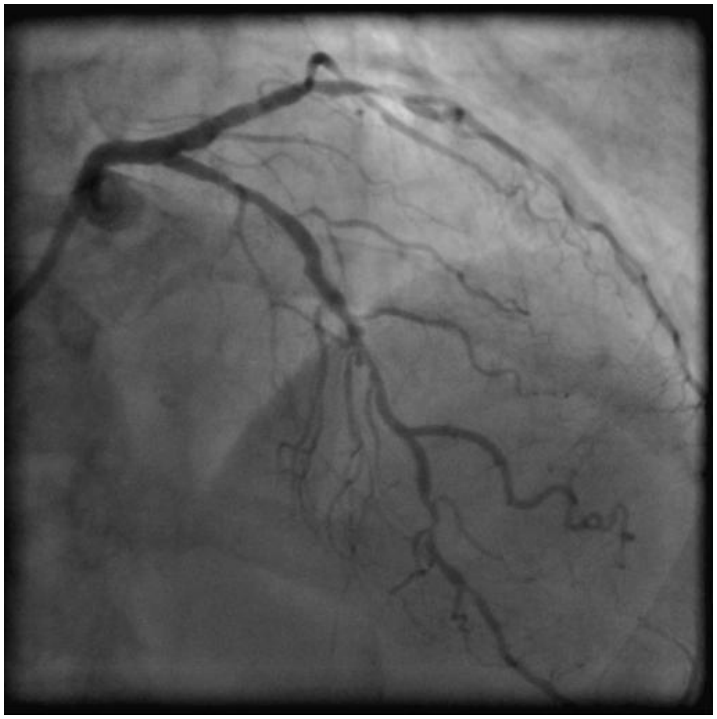
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state



ICON1 Study

Quantitative Coronary Angiography Standard Operating Protocol



ANGIOGRAPHIC CORE LAB DEFINITIONS

Cannot Assess (CNA): When film analysis cannot be performed due to a technical flaw in filming, procedure, or due to protocol violations, 'CNA' will be marked on the Case Report Form (CRF). When no data is available, a "-1" will be inserted on the data spreadsheet.

Does Not Apply (DNA): When analysis does not apply to a given situation, 'DNA' will be marked on the Case Report Form (CRF). When no data is available, a "-1" will be inserted on the data spreadsheet.

Patient ID Number: A numeric value that corresponds to the patient.

ASSESSMENT OF THE EPICARDIAL ARTERIES

Lesion identification: All culprit lesions and all lesions that are subsequently intervened on should be recorded (irrespective of % stenosis). Lesion characteristics are to be recorded if the diameter stenosis is >40% in a vessel >1.5mm in diameter. Lesions are considered separately if they are >3 vessel reference diameters apart.

Primary lesion location

The coronary anatomy is divided into the following segments.

1. *Proximal right coronary artery:* Extends from the ostium of the right coronary artery (RCA) to the first of the three longest acute marginal branches.

2. *Mid right coronary artery:* Extends from the origin of the first acute marginal branch to the origin of the third acute marginal branch.

3. *Distal right coronary artery:* Extends from the origin of the third acute marginal to the origin of the posterior descending artery.

4. *Right posterior descending artery:* In all but left dominant systems, this vessel runs in the posterior interventricular groove and supplies septal perforator branches.

5. *Left main stem:* Extends from the origin of the left coronary artery to the bifurcation into the left anterior descending (LAD) and circumflex (Cx) arteries.

6. *Proximal left anterior descending artery:* Extends from the bifurcation of the left main coronary artery to the origin of the first septal.

7. *Mid left anterior descending artery:* Extends from the origin of the first septal artery to the origin of the third septal artery.

8. *Apical left anterior descending artery:* Extends from the origin of the third septal artery to the apex of the left ventricle. If there is no third septal branch, then the third segment begins halfway between the proximal LAD and the apex of the left ventricle.

9. *First diagonal branch:* The first of the three longest branches from the LAD, which supplies the anterolateral wall of the left ventricle.

10. *Second diagonal branch:* The second of the three longest branches from the LAD which supplies the anterolateral wall of the left ventricle.

11. *Proximal circumflex artery:* Extends from the origin of the Cx off of the left main to the origin of the first marginal or obtuse marginal branch. When a second obtuse marginal is present and the first marginal is absent, the Cl - C2 transition is defined as halfway from the origin of the circumflex to the origin of the second obtuse marginal.

12. *Intermediate artery:* An artery whose origin bisects the origins of both the LAD and the Cx arteries. When an intermediate branch is present, the left main will be seen to trifurcate, and the intermediate artery is the middle artery at this point of trifurcation. When grouping with general culprit lesion location it is grouped with the Cx.

12a. *First obtuse marginal branch:* A large branching artery which dominates the lateral left ventricular wall.

12b. *Second obtuse marginal branch:* The second large branch from the Cx artery.

13. *Distal circumflex artery:* Extends from the origin of the second marginal or obtuse marginal to the termination of the Cx artery in large right dominant anatomy or to the origin of the Cx posterior branch in all other dominance.

14. *Left posterolateral branch:* In left or co-dominant systems this is the distal continuation of the Cx artery in the atrio-ventricular groove. It carries blood to the left posterior descending artery and circumflex inferior artery in left dominant systems and to just the circumflex inferior artery in balanced dominant systems.

16. *Right posterolateral branch:* This is the distal continuation of the RCA after the origin of the posterior descending artery. It often has an inverted U shape and the AV nodal branch originates from this artery.

Disease Extent

This variable refers to how many of the 3 major epicardial vessels have a narrowing of greater than 40%. Possible values are 1, 2, 3, and "-1" if none of the vessels meet the criteria or if analysis of one or more arteries is not possible.

Dominance

Describes how many of the three major branches supplying the inferior wall of the heart arise from the RCA and how many arise from the Cx.

Right dominant: This occurs when the descending and inferior both arise from the RCA (the posterior branch may also arise from the RCA).

Co-dominant: This occurs when only the descending branch arises from the RCA, while the inferior and posterior branches arise from the Cx.

Left dominant: This occurs when all three branches arise from the Cx.

Definitions of Segmental Coronary Anatomy

If a lesion occurs at a branch-point, then the lesion is said to be part of the proximal vessel adjacent to the branch-point.

If the lesion involves both parent vessel and a side branch at a branch-point (such as occurs with a trifurcation lesion or "Mercedes Benz" emblem lesion involving the LAD and the origin of a diagonal) then the larger parent vessel is defined as the culprit.

Only the branches> 1.5mm in diameter should be taken into account. To assess the diameter, the branch should be compared to the catheter size, given the fact that the French sizes correspond to millimeters as follows:

4 Fr = 1.3mm	8 Fr = 2.7mm
5 Fr = 1.7mm	9 Fr = 3.0mm
6 Fr = 2.0mm	10 Fr = 3.3mm
7 Fr = 2.3mm	

Projection Angles

RAO (Right Anterior Oblique) Caudal: The best overall view to assess the Cx, as it minimizes intra- and inter-arterial overlap. In this view, the system in question appears angiographically to the right of the spine with a slight inferior angulation (from below).

RAO Cranial: The best overall view to assess the LAD, as it minimizes intra- and inter-arterial overlap. In this view, the system in question appears angiographically to the right of the spine with a slight anterior angulation (from above).

RAO: In this view, the system in question appears angiographically to the right of the spine with little or no vertical angulation.

AP (Anterior-Posterior): In this view, the system in question angiographically overlaps or is in line with the spine.

LAO Caudal: Also called the spider view. In this view, the system in question appears angiographically to lie to the left of the spine with a slight inferior angulation (from below).

LAO Cranial: In this view, the system in question appears angiographically to lie to the left of the spine with a slight anterior angulation (from above).

LAO: The best overall view to assess the RCA. In this view, the system in question appears angiographically to the right of the spine with little or no vertical angulation.

QUANTITATIVE CORONARY ANGIOGRAPHY (QCA)

Analysis Software

Medis QAngioXA version 7.3.54.0

Performing QCA

1. Insert the QAngio dongle into a USB port on the computer.
2. Insert the CD with the patient's angiogram. The study will open automatically when the QAngioXA program is started.
3. Choose the image run with the appropriate projection for the lesion to be measured.
4. Ensure the ECG trace is visible by selecting the ECG curve icon.
5. Calibrate the software: Choose a frame where the catheter is fully opacified by contrast but where contrast has not yet entered the artery of interest. Select the catheter calibration icon and click two points within the catheter. Select the correct size of catheter (default is 6F). The coefficient of variation must be less than 8%. Click "Done".
6. Select a frame in end-diastole where the vessel is well opacified by contrast and the lesion of interest is at maximal stenosis.
7. Choose either the straight segment analysis or bifurcation segment analysis depending on the type of lesion (use the straight segment analysis setting if possible as it gives more consistent results). Click two points proximal and distal to the lesion to create an automatic pathline. Adjust this with secondary points if necessary. On the next "contours" stage, either automatically adjust the vessel contours by clicking and dragging support points, or manually delete and redraw.
8. On the next "markers" stage, adjust the reference vessel contours by using the "flagging" system to remove segments of vessel that have been contoured incorrectly. The results can then be displayed.

Definitions of Measurements

Minimum Lumen Diameter (MLD): The minimum diameter of the stenosis relative to the reference diameter.

Reference Diameter (RD): An interpolated reference diameter. The proximal and distal extremities of the lesion are identified by the software, a second degree polynomial function is applied to diameter measurements at 0.1mm intervals, and vessel tapering is taken into account. The reported vessel diameter is the RD on the diametric function curve at the point of the MLD.

% Diameter Stenosis: [1-(MLD/RD)]x100

% Area Stenosis: $[1-(MLD/RD)^2]x100$

Length: Starting and ending where the artery first and last tapers into the stenosis, respectively.

INFARCT-RELATED ARTERY MORPHOLOGY

Definitions of morphology

Eccentric: The plaque is twice as large on one side of the arterial border compared with the other. "Stenosis noted to have one of its lumen edges in the outer one-quarter of the apparent normal lumen."

Calcification: Densities noted within the apparent vascular wall at the site of the stenosis.

Mild: faint radio-opacities noted only during cardiac motion before contrast injection

Moderate: dense radio-opacities noted during cardiac motion before contrast injection

Severe: dense radio-opacities noted without cardiac motion before contrast injection, comprising both sides of the arterial lumen

Diffuse: Lesion is ≥20mm in length.

Bifurcation: Atherosclerotic plaque involves the origin of two separate arteries. It does not necessarily require two guidewires.

Ostial Lesion: Lesion beginning within 3-5 mm of the origin of a major epicardial artery.

Pulsatile Flow: Cessation of antegrade flow during systole or frank: flow reversal during systole.

Deceleration: Dye flow down the artery is slowed at any point during the course of flow.

Collateral Circulation

Assessed visually using the following grading system:

Grade 0: No collaterals present. Angiography fails to reveal evidence of collateral vessels.

Grade 1 (or partial): Minimal collaterals present. Evidence of minimal to partial filling of the recipient branch epicardial arteries/infarct region. It is not necessary for one to see the branches connect directly to the major epicardial artery.

Grade 2 *(or complete):* Well-developed collaterals. Evidence of collateral circulation with near complete to complete filling of the recipient major epicardial artery/infarct region.

Thrombus Grade

Assessed visually using the following grading system:

Grade 0: No cineangiographic characteristics of thrombus present.

Grade 1: Hazy, possible thrombus present. Angiography demonstrates characteristics such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus.

Grade 2: Thrombus present - small size: Definite thrombus with greatest dimensions less than or equal to 1/2 vessel diameter.

Grade 3: Thrombus present - moderate size: Definite thrombus but with greatest linear dimension greater than 1/2 but less than 2 vessel diameters.

Grade 4: Thrombus present -large size: As in grade 3 but with the largest dimension greater than or equal to 2 vessel diameters.

Grade 5: Recent total occlusion, can involve some collateralization but usually does not involve extensive collateralization, tends to have a "beak" shape and a hazy edge or appearance of distince thrombus.

Grade 6: Chronic total occlusion, usually involving *extensive* collateralization, tends to have distinct, blunt cutoff/edge and will generally clot up to the nearest proximal side branch.

Aneurysm

A localized arterial widening (dilatation) that usually manifests itself as a bulge. Its presence may lead to weakening of the wall and eventual rupture.

Grade 0: None - no ectasia present.

Grade 1: Ectasia - visual assessment of ectasia> 1 and < 1.5 times the normal artery diameter located anywhere in the culprit artery.

Grade 2: Aneurysm - visual assessment of an aneurysm> 1.5 times the normal artery diameter located anywhere in the culprit artery.

NOTE: An aneurysm can be further classified as either *saccular* (wider than it is long) *or fusiform* (elongated).

Ulceration

A lesion with a small crater consisting of a discrete lumen widening in the area of the stenosis that does not extend beyond the normal arterial lumen. Assessed visually:

Grade 0: No angiographic evidence of ulceration.

Grade 1: The lesion contains a neck with contrast material dissecting under the plaque either proximally or distally.
Grade 2: Distinct extravascular extravasation of contrast material with the appearance of a mushroom.

Lesion Complexity

Graded as A, Bl, B2, or C according to the Abrupt Vessel Closure-AHA Task Force Definition as modified by Ellis et al:
Type A: <10 mm, discrete, concentric, readily accessible, <45 degree angle smooth contour, little or no calcification, less than totally occluded, not ostial, no major side branch involvement, absence of thrombus.
Type B1: One of the following characteristics:
Type B2: Two or more of the following characteristics: 10-20 mm, eccentric, moderate tortuosity of proximal segment, irregular contour, presence of any thrombus grade moderate or heavy calcification, total occlusion <3 months old, ostial lesion or bifurcation lesion
Type C: ≥20 mm diffuse, excessive tortuosity of proximal segment, total occlusion> 3 months old and/or bridging collaterals, inability to protect major side branches, or degenerated vein graft with friable lesions.

Post -Intervention Complications

Dissection: An intraluminal filling defect or flap associated with a hazy, ground-glass appearance.

Type A: Radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast after dye has cleared.

Type B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye has cleared.

Type C: Contrast outside the coronary lumen, with persistence of contrast in the area after dye has cleared

Type D: Spiral luminal filling defects frequently with extensive contrast staining of the vessel

Type E: New persistent filling defects that may be caused by thrombus

Type F: These are non A - E dissection types that lead to impaired flow or total occlusion of the coronary artery

Perforation: Presence of extraluminal contrast that develops during the procedure.

Loss of side branch: Development of TIMI grade 0 or 1 flow in a side branch that was >1.5mm in diameter prior to the procedure and was initially patent with ≥TIMI grade 2 flow.

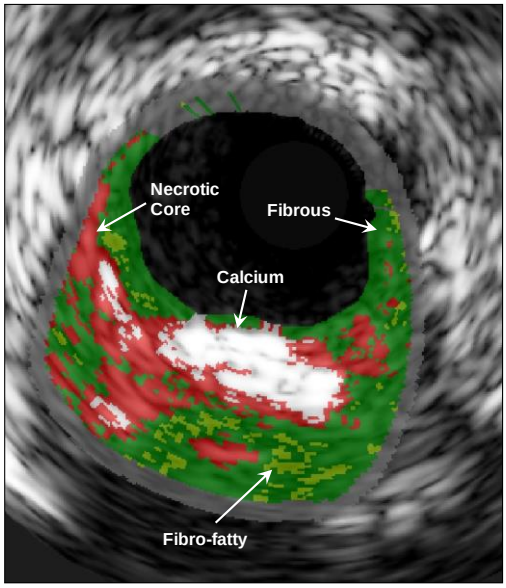
Distal embolisation: The appearance of an abrupt cutoff in the distal vessel following PCI.

No reflow: Markedly delayed flow down the artery with minimal residual stenosis.

Procedure Success: A procedure is considered a complete success if the post-procedure residual diameter stenosis is <30% with TIMI grade 3 flow. A procedure will be classified as a partial success if there is either a ≥30% residual stenosis by QCA *or* if TIMI Grade 2 Flow is attained (this includes TFG 2.5). A procedure will be classified a failure if there is a persistent total occlusion, if the lesion cannot be crossed, or if there is persistent abrupt closure.

ICON1 Study

Virtual Histology IVUS Analysis Standard Operating Protocol



Opening An IVUS Run

1. Ensure the dongle is plugged into a USB port before opening QIvus. The light will glow green on the end of the dongle when operational.

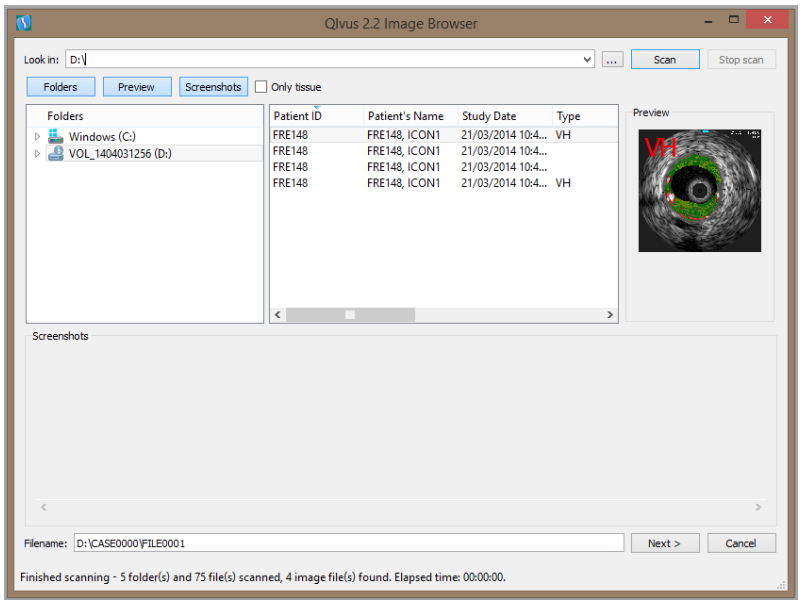
2. Open QIvus software. 

3. Insert DVD.

4. Click 

or select **File** > **Browse for Dicom...** or use the keyboard shortcut **Ctrl+O**.

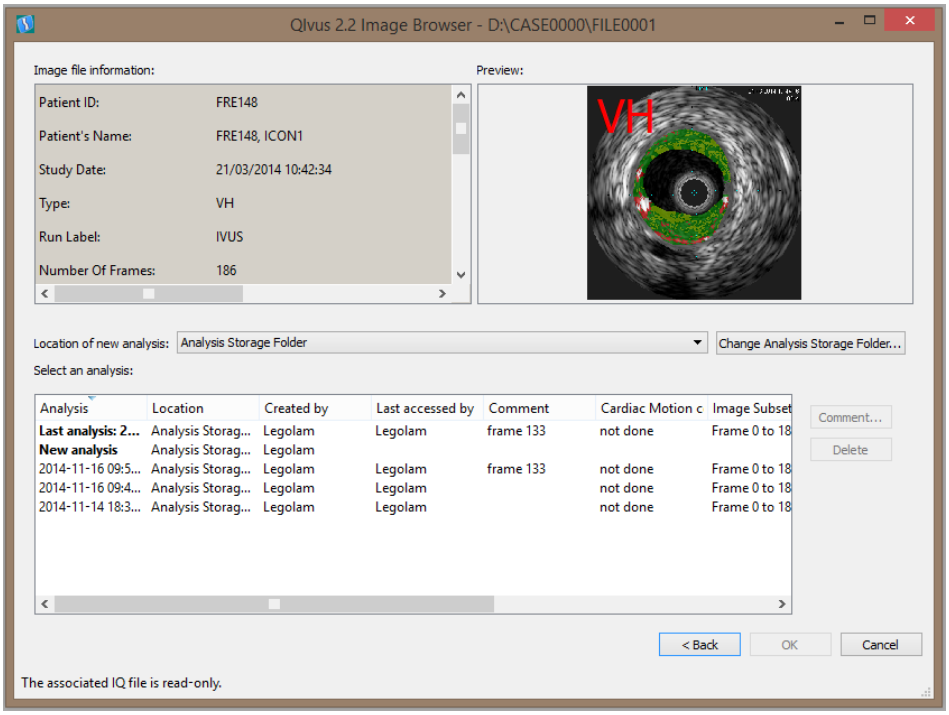
5. Select the directory in which the image run is located (in this case, the DVD drive). The software will automatically search for all files that QIvus can open (DICOM and AVI). Select the VH file and click **Next**.



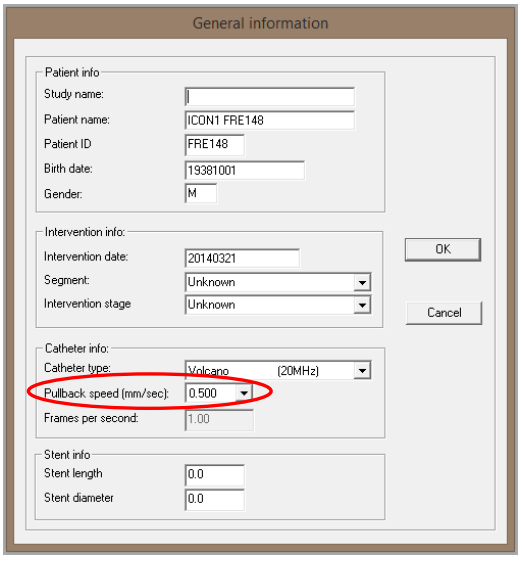
6. The panel below "Image file information" shows the patient study ID, date of study and vessel imaged. Before opening the image run, ensure that each patient has a separate analysis storage folder by clicking **Change Analysis Storage Folder...** and making a new folder (labelled with the patient study number) in an easy to find location. This is where all the previous analyses for

that patient will be stored. The software defaults to the last analysis storage folder used when opening a new file.

7. Open a new analysis by clicking New analysis, or select a previously started analysis.



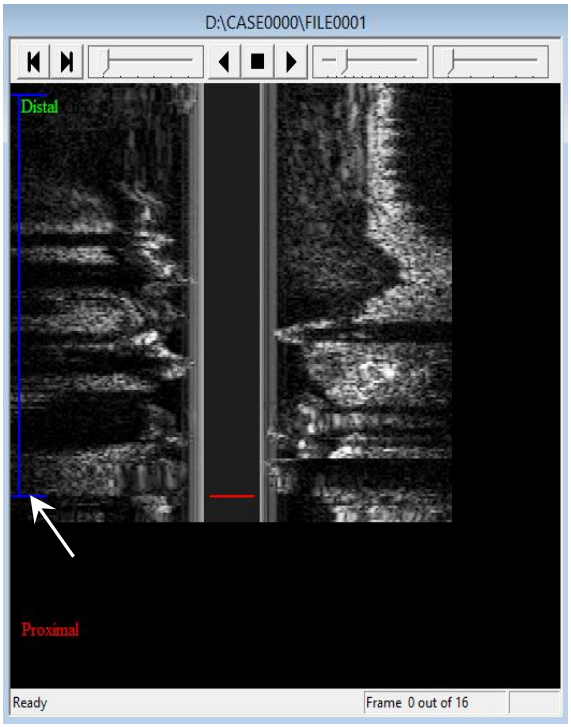
8. A dialogue box will pop up with further information about the image run. Enter the Segment and Intervention stage. Ensure that the pullback speed is set at 0.500 mm/sec and click **OK**.



Preparing The Image For Analysis

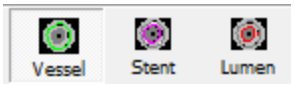
1. Remove any artefacts from the image by clicking 

2. Define the length of the segment to be analysed by clicking and dragging the blue segment markers to contain all frames of interest in the longitudinal view. Do not include frames at the beginning of the image run (distal) that are duplicated because the imaging catheter had not started moving, and do not include frames at the end of the run (proximal) where the guide catheter is visible.



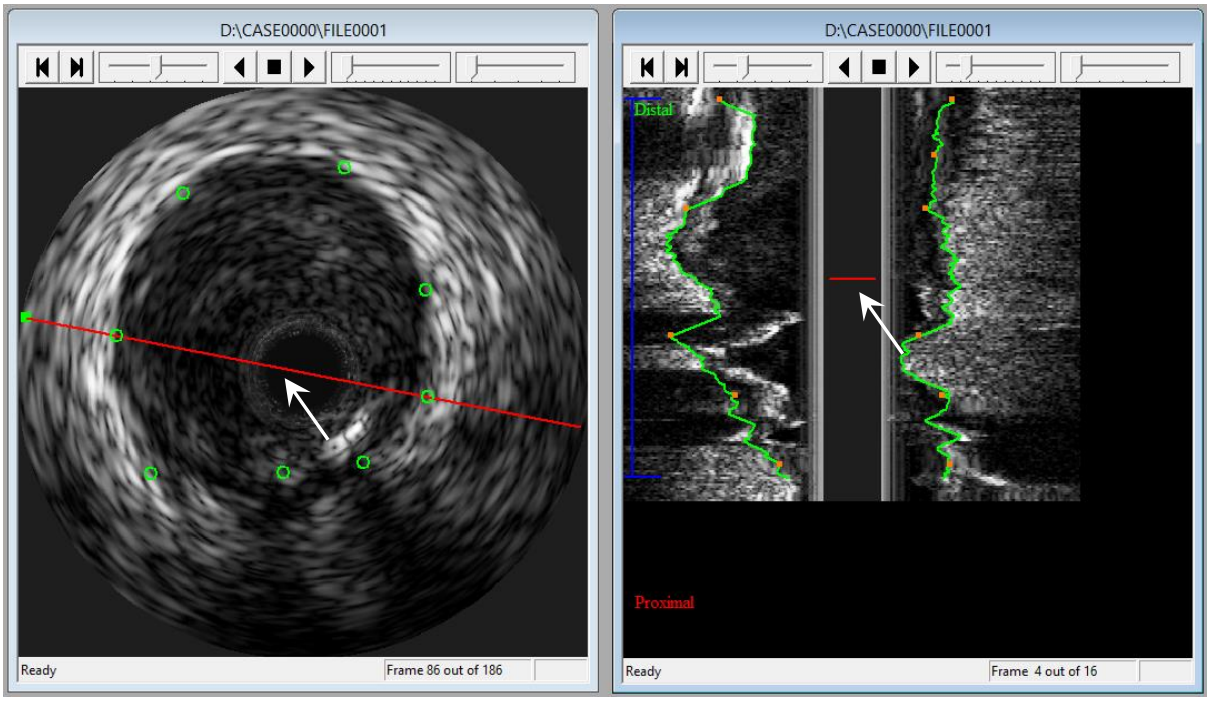
3. Make a note of any frames that are duplicated when the imaging catheter has become stuck (usually occurs at points of heavy calcification or tight stenoses). These will be excluded from the analysis later.

Vessel Contour Drawing

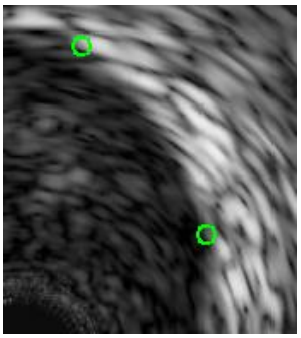
1. By default, the vessel contour is selected. 

2. Click to analyse the longitudinal image. 

3. Review the attraction points (green circles) in the longitudinal view by dragging the red marker line. The red line in the transversal view corresponds to the red marker line in the longitudinal view.



4. Refine the attraction points in the cross-sectional view so that they sit at the boundary of the media (dark) and the adventitia (bright) of the vessel.



5. Moving an attraction point automatically updates the longitudinal contour and thus moves other attraction points that have not already been edited. Start with

refining the attraction points that are most inaccurate and continue until all points are on the vessel border. It is worth spending some time doing this accurately, as it reduces the time spent manually correcting the border.

6. When happy with the position of the attraction points, click to analyse the contour in the transversal view. 

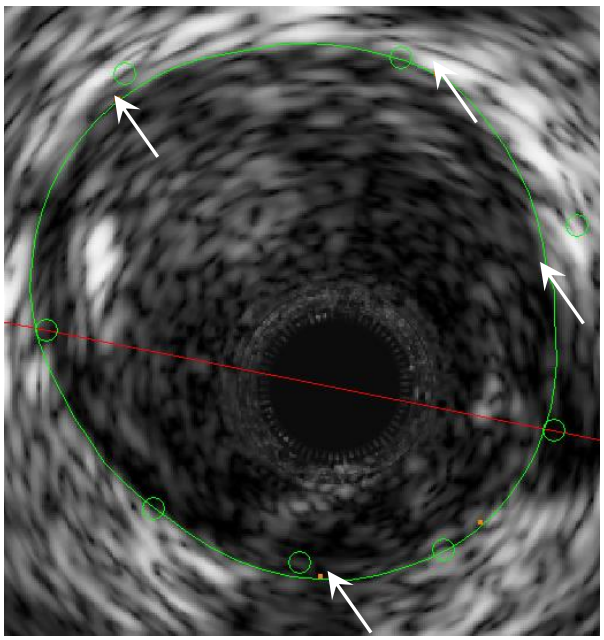
7. Select **Options** > **Graphics line thin**.

8. Click and drag the window with the transversal view to maximise its size.

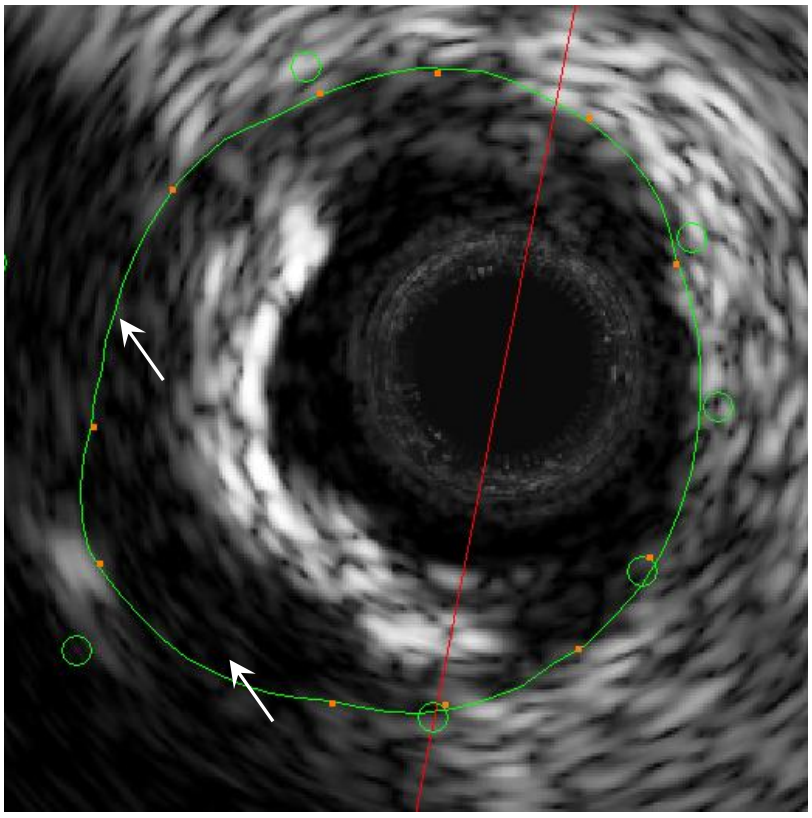
9. Exclude the frames identified as duplicates above. 

10. Starting at the first (distal) frame, correct the vessel contour of each frame of the segment using correction points. 

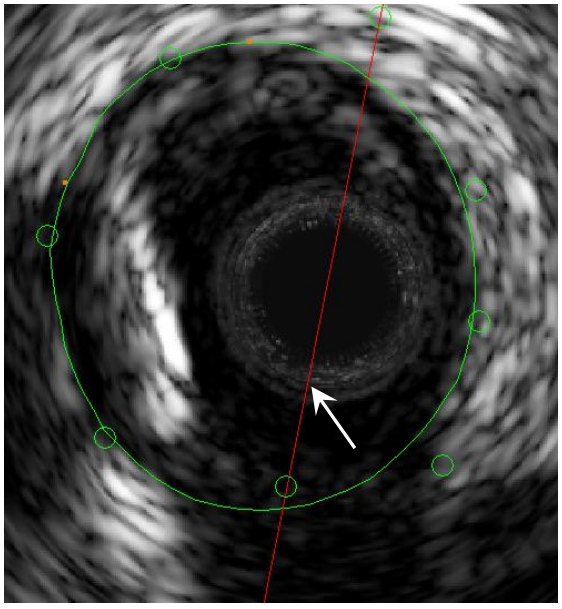
11. These correction points edit the contour in one frame only. They can be picked up and moved, or removed by clicking the left and right mouse buttons simultaneously.



12. The vessel contour should be extrapolated as accurately as possible where it is not possible to see the boundary of the media and adventitia e.g. behind calcium.



13. Where a side branch is entering a vessel, the vessel contour should be drawn to follow the original (distal) vessel boundary until the side branch is fully incorporated into the main vessel.

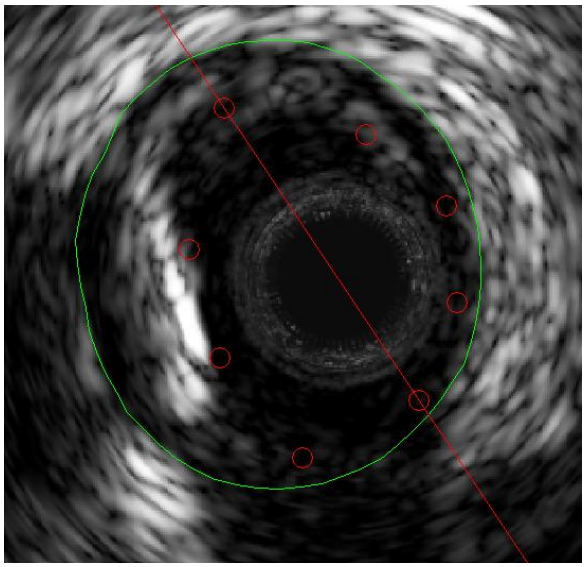


Lumen Contour Drawing

1. Select the lumen contour. 

2. Click to analyse the longitudinal image. 

3. Move the red attraction points to the lumen border for the whole segment. These do not have to be as accurate as the vessel contour attraction points, as the lumen border will be manually corrected frame by frame.

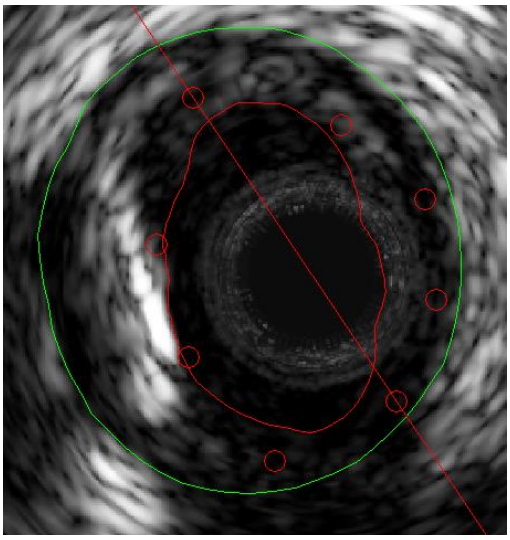


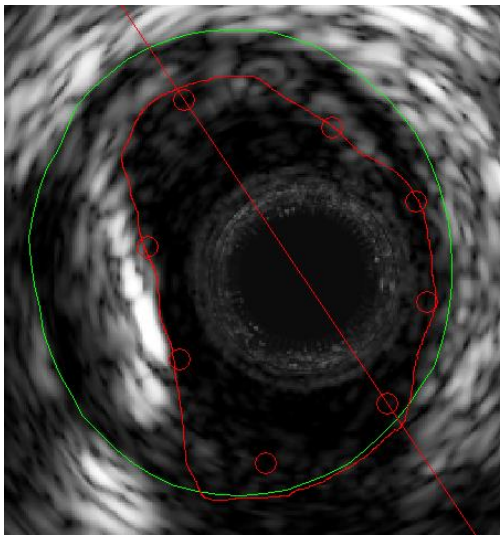
4. When happy with the position of the attraction points, click to analyse the contour in the transversal view. 

5. Starting at the first frame, manually re-trace the lumen contours for each frame of the segment of interest. Omit any artefacts from the lumen contour. Use the zoom slider to zoom in on the image and more accurately define the contour.

The loop review button can help to visualise the lumen contour. 

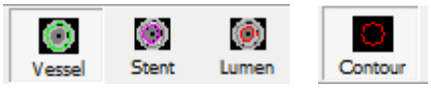
At side branches, draw the lumen contour slightly outside the vessel contour to ensure that the software does not automatically add an area of media when doing the VH analysis.





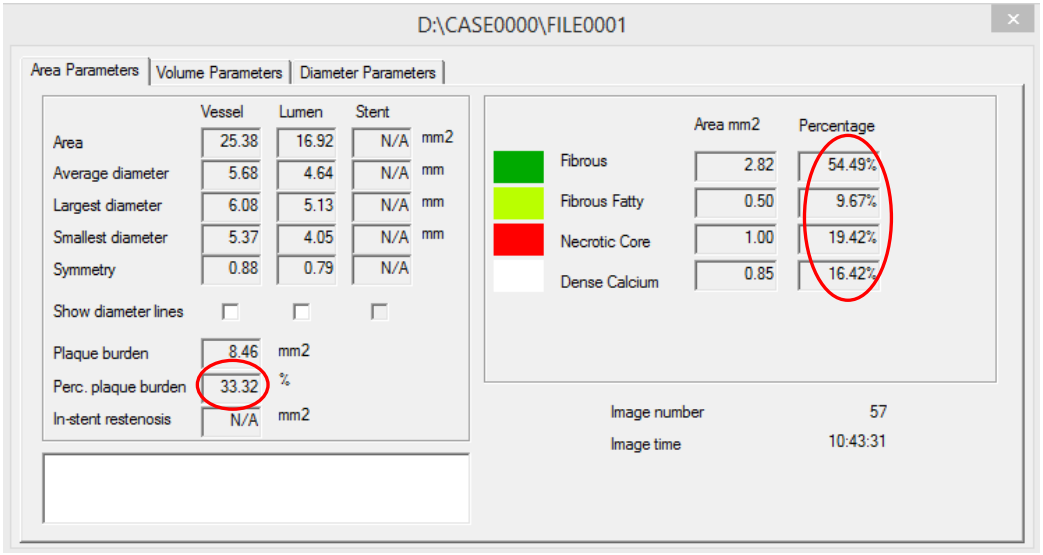
Lesion Classification

1. Click to load the VH overlay. 

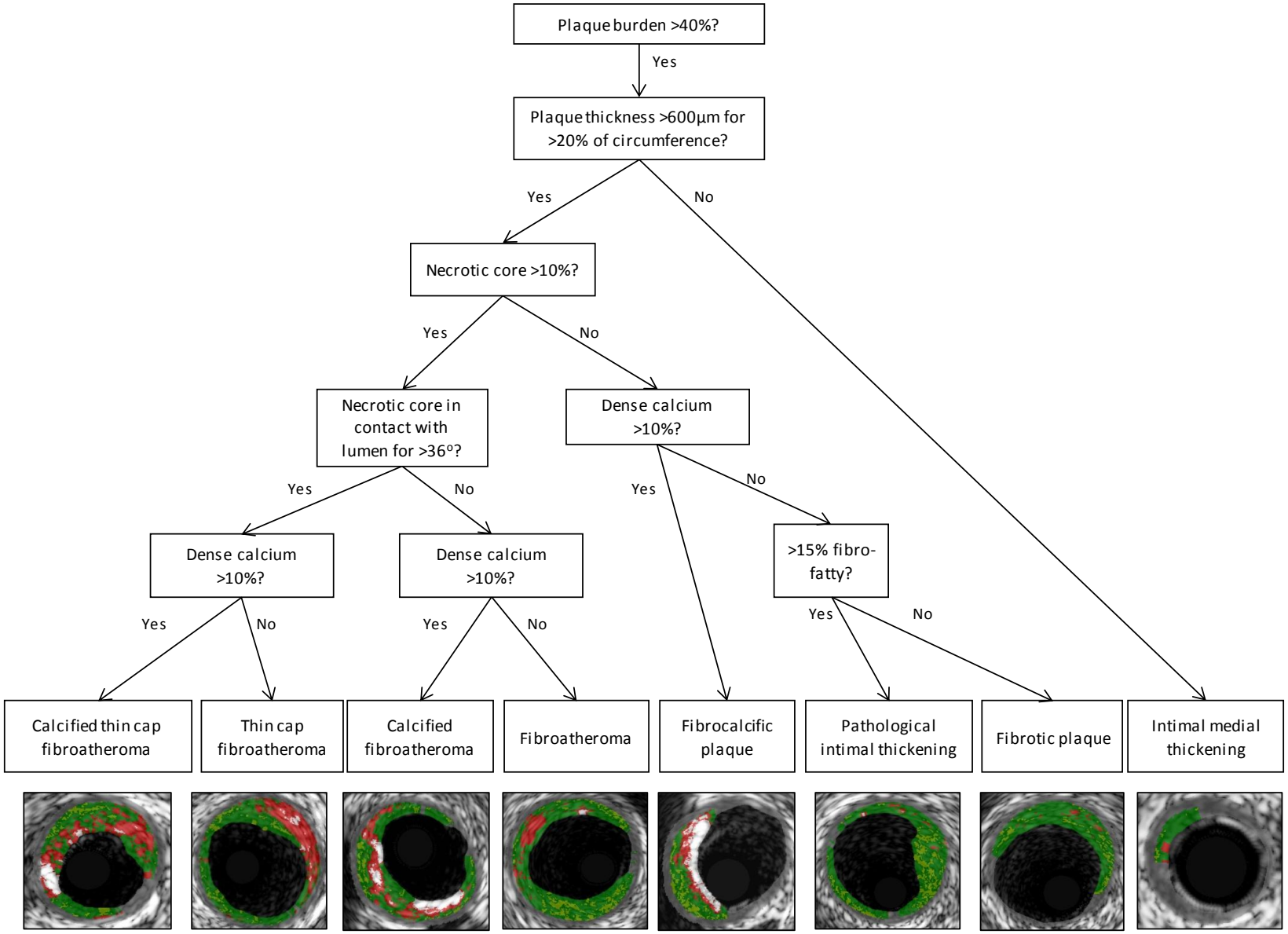
2. Hide the contour lines by choosing either **Vessel** or **Lumen** and clicking **Contour** for each. 

3. Click on **Results**. 

4. In the results dialog box, the overall percentage plaque burden and percentages of each plaque component for this image frame are displayed.

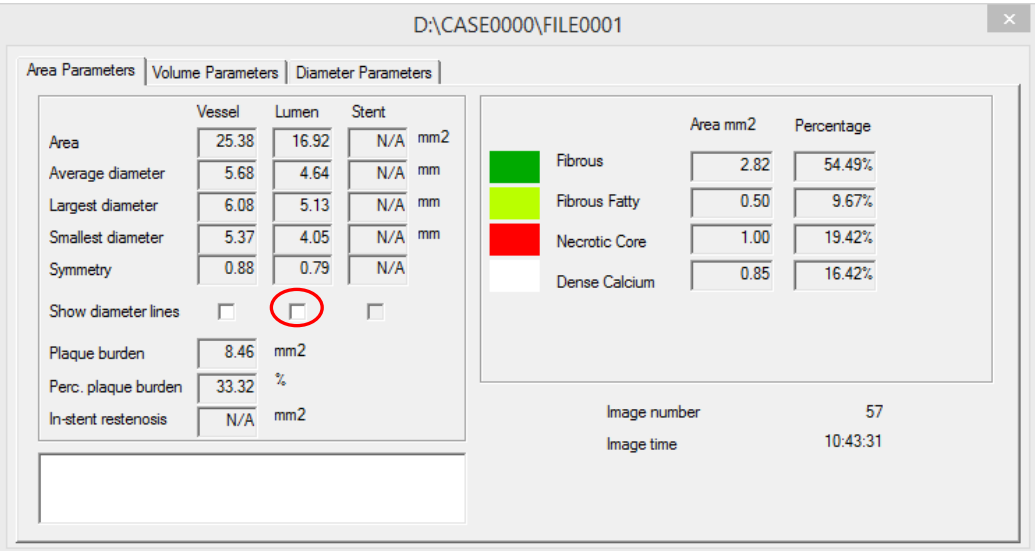


5. Use the decision tree below to decide which lesion subtype each frame represents, and enter the name of the lesion in the comments box. This will be saved to the Excel report at the end of analysis.

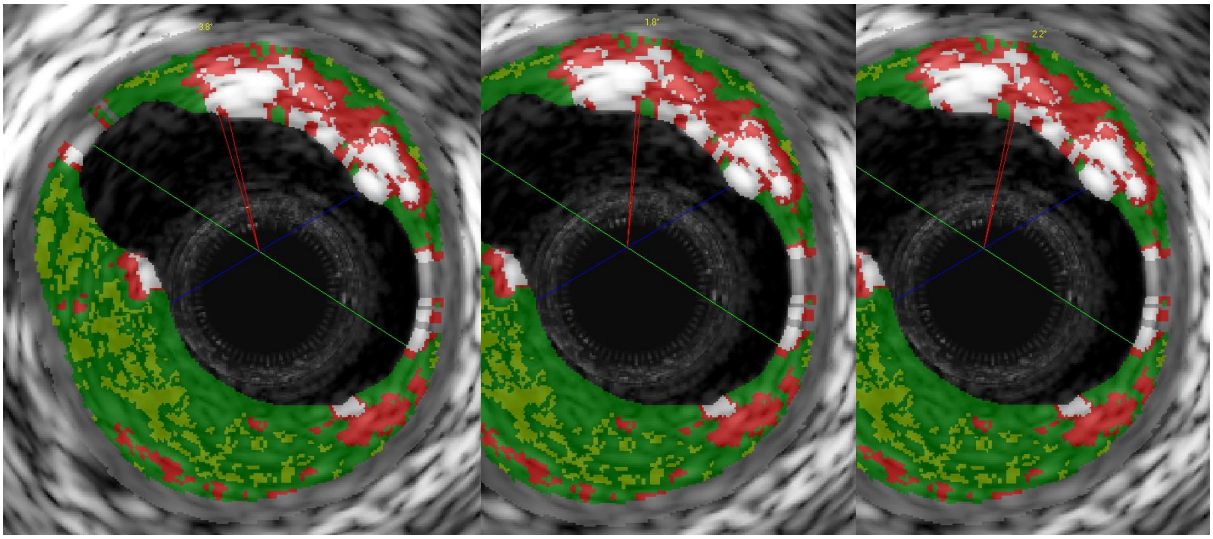

Plaque burden >40%?
Yes
Plaque thickness >600µm for >20% of circumference?
Yes
No
Necrotic core >10%?
Yes
No
Necrotic core in contact with lumen for >36°?
Dense calcium >10%?
Yes
No
Yes
No
Dense calcium >10%?
Dense calcium >10%?
>15% fibro-fatty?
Yes
No
Yes
No
Yes
No
Calcified thin cap fibroatheroma
Thin cap fibroatheroma
Calcified fibroatheroma
Fibroatheroma
Fibrocalcific plaque
Pathological intimal thickening
Fibrotic plaque
Intimal medial thickening

6. Measure the plaque thickness by selecting **Options** > **Transversal caliper** and clicking **Indicate distance**.

7. Measure angles from the centre of the lumen by ticking the box marked **Show diameter lines** under the **Lumen** column in the **Results** dialog box.



8. Open the angle caliper by selecting **Options** > **Transversal caliper** > **Indicate angle**. Drag the corner of the angle into the centre of the lumen, where the diameter lines intersect. Measure the angle of every area of necrotic core that is in contact with the lumen and add them to obtain the total angle of necrotic core in contact with lumen.



Recording Results

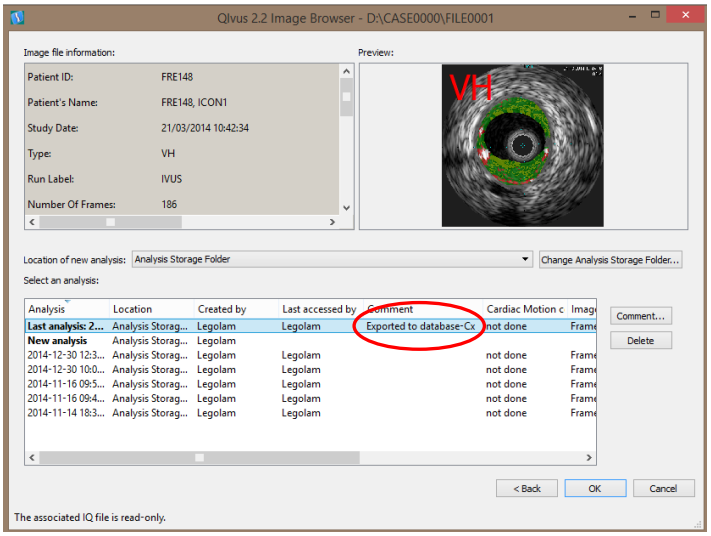
1. Once finished classifying each frame, click the Excel button. 

2. An Excel spreadsheet will open automatically. Save the sheet in a separate folder entitled "completed analyses" and name the file based on the study ID and vessel analysed e.g. FRE148-Cx.

3. Record the relevant data in the master database.

4. A plaque becomes a lesion when the plaque burden is >40% for 3 consecutive images, and lesions separated longitudinally by >5mm of artery with a plaque burden <40% should be considered separate lesions. Where different plaque subtypes co-exist within a lesion, the lesion should be classified according to the highest risk subtype i.e. thin capped fibroatheroma (TCFA) > fibroatheroma (FA) > pathological intimal thickening (PIT) > fibrotic plaque (FP) > intimal medial thickening (IMT). TCFA, FA and FP are further subdivided into calcified and non-calcified lesions (if >3 consecutive frames are calcified, it is a calcified lesion).

5. Close the image run, then re-open the **Browse** dialog box. Make a comment on the completed analysis that the analysis has been exported to the master database.



Appendix D – ICON1 Study Follow up Case Report Form

A Study to **I**mprove **C**ardiovascular **O**utcomes in High Risk Patie**N**ts with Acute Coronary Syndrome.

ICON 1 Study
1 year Follow up - Case Report Form

Patient study no. _____

DOB _____

Date of enrolment _____

Date of Follow up _____

Clinic □ Telephone □ GP letter □

List of current medications

Aspirin	Yes □	No □	
Thienopyridine	Clop □	Pras □	Ticag □
Warfarin	Yes □	No □	
Statin	Yes □	No □	
ACEI/ARB	Yes □	No □	
Betablocker	Yes □	No □	
Furosemide	Yes □	No □	
Calcium channel blocker	Yes □	No □	
Long acting nitrate	Yes □	No □	
Nicorandil	Yes □	No □	
Vitamin D supplement	Yes □	No □	
Others (please specify)	_____		
	_____		
	_____		
	_____		

Height (cm) _____

Weight (kg) _____

Social history

Current smoker	Yes □	No □
Lives alone	Yes □	No □
Carers	Yes □	No □
If yes, how often per day	_____	
Residential home	Yes □	No □
Nursing home	Yes □	No □

Major Adverse Cardiovascular Events in the last year

Death	Yes □	No □

Date of death _____

Cause of death _____

Acute coronary syndrome Yes □ No □

Date of ACS _____

STEMI □ NSTEMI □ UA □

Stroke Yes □ No □

Date of stroke _____

Urgent repeat revascularisation Yes □ No □

Date of revascularisation _____

PPCI □ Urgent PCI □ Urgent CABG □

Bleeding problems Yes □ No □

Date of bleeding _____

Bleeding type _____

Bleeding Academic Research Consortium (BARC) definition for bleeding

Type 1	Bleeding that does not cause the patient to seek unscheduled investigation or treatment by a healthcare professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Any overt, actionable sign of haemorrhage that does not fit the criteria for Type 3, 4 or 5 but does prompting evaluation by a healthcare professional.
Type 3a	Overt bleeding plus haemoglobin drop of 3 to < 5 g/dl
	Any transfusion with overt bleeding
Type3b	Overt bleeding plus haemoglobin drop ≥ 5 g/dl
	Cardiac tamponade
	Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid)
	Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial or intraspinal haemorrhage (does not include haemorrhagic transformation)
	Intraocular bleed compromising vision
Type 4:	CABG-related bleeding:
	Perioperative intracranial bleeding within 48 hours
	Reoperation following closure of sternotomy for the purpose of controlling bleeding
	Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48-hour period
	Chest tube output ≥ 2 litres within a 24-hour period
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Stable angina	Yes □ No □
Elective PCI	Yes □ No □
Congestive cardiac failure	Yes □ No □
Transient ischaemic attack	Yes □ No □
Dialysis	Yes □ No □

Hospitalisation for any other reason	Yes □ No □
If yes, diagnosis/date	_____
	_____
	_____
	_____

Blood results at follow up

PT	_____
APTT	_____
Fibrinogen	_____
Vitamin D	_____
HS-CRP	_____
PTH	_____

Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status	Yes or No
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2	
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.	
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.	
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21	
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds	

Rockwood Frailty Scores

1	Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age	
2	Well – without active disease, but less fit than people in category 1.	
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4	
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.	
5	Mildly frail – with limited dependence on others for instrumental activities of daily living	
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living	
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.	

NYHA Symptom Class:

NYHA Symptom Class	Symptoms	Please tick
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.	
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.	
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.	
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.	

The Canadian Cardiovascular Society Angina Grading Scale:

0	No angina	
I	Angina only during strenuous or prolonged physical activity	
II	Slight limitation, with angina only during vigorous physical activity	
III	Symptoms with everyday living activities, i.e., moderate limitation	
IV	Inability to perform any activity without angina or angina at rest, i.e., severe limitation	

QOL Index (SF 36) Questionnaire

1. In general, would you say your health is:

□ 1. Excellent □ 2. Very good □ 3. Good □ 4. Fair □ 5. Poor

2. Compared to ONE YEAR AGO, how would you rate your health in general NOW?

□ 1. MUCH BETTER than one year ago.
□ 2. Somewhat BETTER now than one year ago.
□ 3. About the SAME as one year ago.
□ 4. Somewhat WORSE now than one year ago.
□ 5. MUCH WORSE now than one year ago.

3. The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	□	□	□
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	□	□	□
c) Lifting or carrying groceries?	□	□	□
d) Climbing **several flights** of stairs?	□	□	□
e) Climbing **one** flight of stairs?	□	□	□
f) Bending, kneeing or stooping?	□	□	□
g) Walking **more than a mile**?	□	□	□
h) Walking **several** blocks?	□	□	□
i) Walking **one** block?	□	□	□
j) Bathing or dressing yourself?	□	□	□

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Were limited in the **kind** of work or other activities?	□ 1. yes	□ 2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	□ 1. yes	□ 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Didn't do work or other activities as **carefully** as usual?	□ 1. yes	□ 2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1. Not at all □ 2. Slightly □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

7. How much **<u>bodily</u> pain** have you had during the **past 4 weeks**?
□ 1. None □ 2. Very mild □ 3. Mild □ 4. Moderate □ 5. Severe □ 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
□ 1. Not at all □ 2. A little bit □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week** …

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	□	□	□	□	□	□
b) Have you been a very nervous person?	□	□	□	□	□	□
c) Have you felt so down in the dumps that nothing could cheer you up?	□	□	□	□	□	□
d) Have you felt calm and peaceful?	□	□	□	□	□	□
e) Did you have a lot of energy?	□	□	□	□	□	□
f) Have you felt downhearted and blue?	□	□	□	□	□	□
g) Do you feel worn out?	□	□	□	□	□	□
h) Have you been a happy person?	□	□	□	□	□	□
i) Did you feel tired?	□	□	□	□	□	□

10. During the **past 4 weeks**, how much of the time has your **<u>physical health</u> or <u>emotional problems</u>** interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1. All of the time
□ 2. Most of the time.
□ 3. Some of the time
□ 4. A little of the time.
□ 5. None of the time.

11. How TRUE or FALSE is **each** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	□	□	□	□	□
b) I am as healthy as anybody I know?	□	□	□	□	□
c) I expect my health to get worse?	□	□	□	□	□
d) My health is excellent?	□	□	□	□	□

EuroQol EQ-5D™ - Please tick which statements best describe your own health state today.

1A. Mobility

I have no problems in walking about □
I have some problems in walking about □
I am confined to bed □

1B. Self-Care

I have no problems with self-care □
I have some problems washing or dressing myself □
I am unable to wash or dress myself □

1C. Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities □
I have some problems with performing my usual activities □
I am unable to perform my usual activities □

1D. Pain/Discomfort

I have no pain or discomfort □
I have moderate pain or discomfort □
I have extreme pain or discomfort □

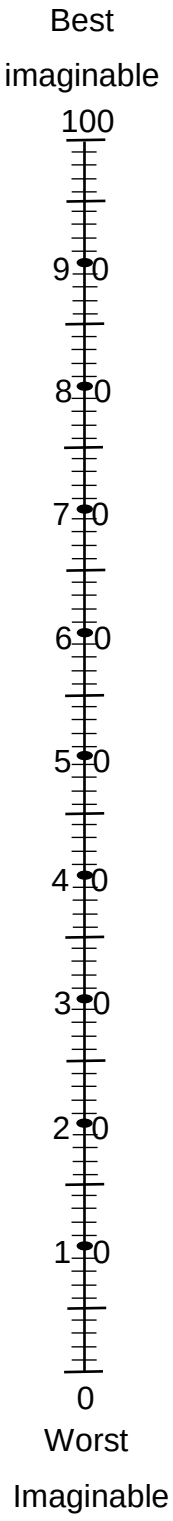
1E. Anxiety/Depression

I am not anxious or depressed □
I am moderately anxious or depressed □
I am extremely anxious or depressed □

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state

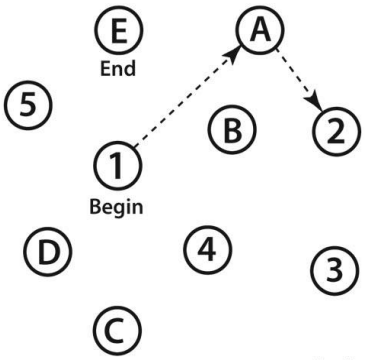


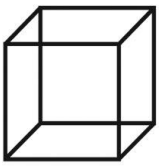
Cognitive Function Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : **Date of birth :**
Sex : **DATE :**

VISUOSPATIAL / EXECUTIVE





Copy cube

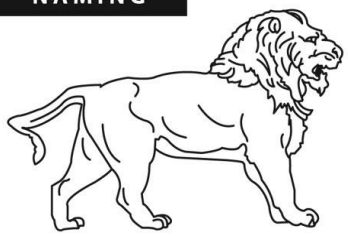
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

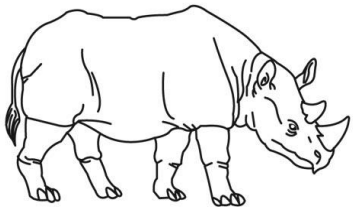
[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

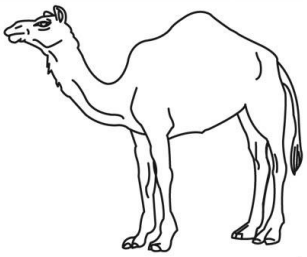
NAMING



[ ]



[ ]



[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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