Real world clinical outcomes and health-related quality of life following revascularisation for left main coronary artery disease

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"The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others."

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Proverbs 4:7

Wisdom is the principal thing; therefore get wisdom: and with all thy getting get understanding

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Abstract

Introduction:

Percutaneous coronary intervention (PCI) for unprotected left main coronary artery (ULMCA) disease has emerged as a viable alternative to coronary artery bypass graft (CABG) surgery in specific patterns of coronary involvement. Recent evidence suggests it is best utilised in patients with limited overall coronary disease burden and complexity, yet in current practice it is often employed for those with high surgical risk. While there are published data on outcomes following ULMCA PCI is selected groups of patients, there are limited data describing current real-world practice. Current revascularisation guidelines apply data from randomised studies using traditional outcome measures to stratify the appropriate use of treatment modalities. Although measures of health-related quality of life (HRQOL) are recognised to be important to patients, they are rarely taken into consideration in contemporary guidelines or clinical decision making. While there is limited knowledge surrounding the HRQOL outcomes from randomised studies of LMCA revascularisation, no published studies have assessed HRQOL outcomes in the 'real world' population treated for LMCA disease, including those who are medically managed.

Methods:

First, we undertook a retrospective analysis of patients undergoing PCI for ULMCA at a single cardiac centre in the UK. We identified a retrospective cohort of patients who received LMCA PCI between March 2005 and March 2013. We applied Cox proportional hazards model to identify the major predictors of poor survival and clinical outcomes. The primary composite outcome was major adverse cardiac and cerebrovascular events (MACCE), comprising all-cause mortality, myocardial infarction, stroke and repeat revascularisation. In separate analyses, we excluded patients with cardiogenic shock, while other subgroups analysed included LMCA bifurcation cohorts and octogenarians.

Second, we recruited a prospective cohort of patients with LMCA disease managed conservatively or by PCI or CABG and applied an HRQOL questionnaire at 4 times points over the course of 1 year follow-up. Multilevel modelling using linear mixed models was used to conduct longitudinal analyses of HRQOL outcomes.

Results:

The Kaplan-Meier estimate of MACCE at 1 year was 26.2% and at the median (IQR) follow-up of 584 (1036) days it was 41.8%. Significant factors associated with MACCE include SYNTAX score(SS) [Hazard ratio (HR) 1.01; 95% Confidence Interval (CI): 1.00 - 1.02; p<0.05], presentation in cardiogenic shock [adjusted Hazard Ratio (aHR) 5.88, 95% CI 3.81-9.06, p<0.05], previous MI [aHR 1.94, 95% CI 1.37-2.75, p<0.05] and a history of diabetes [aHR 1.61, 95% CI 1.12-2.31, p<0.05] after long term follow-up. With a separate analysis excluding patients with cardiogenic shock we found SS [aHR 1.02, 95% CI 1.00-1.04, p<0.05], previous MI [aHR 1.89, 95% CI 1.28-2.80, p<0.05], peripheral vascular disease [aHR 1.68, 95% CI 1.09-2.61, p<0.05] and renal impairment [aHR 1.89, 95% CI 1.05-3.43, p<0.05] were significantly associated with MACCE; for every 10 unit increase in SS there was a 2% increase in the risk of MACCE. In a separate analysis of patients with 'True' LMCA bifurcation disease, there was no difference in survival from a single or two stent strategy. Residual coronary disease amongst octogenarians was assessed using the residual SS, each 10 unit increase in rSS was associated with a 3% increase in all-cause mortality (aHR 1.03; 95% CI, 1.00-1.06; p=0.04]. HRQOL was found to deteriorate significantly over 1 year for patients managed conservatively, while despite earlier improvement in HRQOL following PCI, the HRQOL for patients treated with CABG overtook these and showed greater and more sustained improvement over 1 year.

Conclusion:

This database describes a real world cohort of patients with LMCA, with significantly greater coronary disease burden and comorbidity than most published studies. While cardiogenic shock was a strong predictor of poor outcomes, the SS was also associated with poor outcomes. Other measures of coronary disease burden, such as 'True' bifurcation disease are significant predictors of poor outcomes. Diabetes is a predictor of outcome, yet after excluding cardiogenic shock, the association is no longer evident. After adjusting for the sequelae of the diabetes, such as renal impairment and burden of atheromatous disease (SS and PVD), these variables become significant predictors of poor outcomes.. Residual SS following PCI was associated with poor outcomes in this long-lived population, suggesting that untreated coronary disease is undesirable,

although it is not clear that more aggressive revascularisation is indicated. HRQOL measures suggest that, despite selection bias, patients currently selected for conservative management for LMCA may benefit from some form of targeted revascularisation despite limited prognostic benefit.

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Abbreviations

ACC: American College of Cardiology

ACS: Acute Coronary Syndromes

AHA: American Heart Association

aHR: adjusted hazard ratio

ARC: Academic Research Consortium

BARC: Bleeding Academic Research Consortium

BBC ONE: British Bifurcation Coronary study: Old, New and Evolving strategies trial

BIP: Brief Illness Perception

BMI: Body mass index

BMS: Bare metal stents

CABG: Coronary artery bypass graft

CAG: Confidentiality Advisory Group

CASS: Coronary Artery Surgery Study

CI: Confidence interval

CTO: Chronic total occlusion

CRN: Clinical Research Network

DELTA registry: Drug Eluting stent for LefT main coronary Artery disease registry

Delta SYNTAX score (ΔSS): The difference between the baseline SS and the rSS.

DES: Drug eluting stents

DGH: District General Hospital

EBC: European Bifurcation Club

ECSS: European coronary surgery study group

eGFR: Estimated glomerular filtration rate

ESC: European Society of Cardiology

EXCEL trial: Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization

EuroSCORE: EuroSCORE (European System for Cardiac Operative Risk Evaluation), a 17 point risk model for calculating the risk of death after heart surgery. The predicted mortality (in percent) is calculated by adding the weights assigned to each factor.

GP: General practitioner

HRA: Health Research Authority

HRQOL: Health Related Quality of Life

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th edition

IMD: Indices of Multiple Deprivation

IPQ-B: The Brief Illness Perception Questionnaire (Brief IPQ) is a widely used multifactorial pencil-and-paper questionnaire which assesses the five cognitive illness representations. It uses a single-item scale, across nine items, approach to assess perceptions on a continuous linear scale. It was developed by forming one question that best summarised the items contained in each subscale of the IPQ-R (Illness Perception Questionnaire-Revised).

IQR: Interquartile range

LAD: Left anterior descending

LCx: Left circumflex artery

LMCA: Left Main Coronary Artery

LSOA: Lower super output area

LST: Late stent thrombosis

LTHT: Leeds Teaching Hospitals Trust

MACE: Major Adverse cardiac events

MACCE: Major adverse cardiac and cerebrovascular events

MB: Main branch

MDT: Multi-disciplinary Team

Medina classification: The Medina classification was proposed to classify coronary bifurcation disease in 2006, it is a binary system indicating the angiographic presence of disease in the main vessel (MV), main branch (MB) and side branch (SB) around the bifurcation (i.e. disease present in all three vessels MV,MB,SB = 1,1,1).

MI: Myocardial Infarction

MV: Main vessel

NHS: National Health Service

NIGB: National Information Governance Board (for Health and social care)

NIHR: National Institute for Health Research

NOBLE trial: Nordic-Baltic-British Left Main Revascularization Study

NS: Not significant

NSTEMI: Non-ST segment Elevation Myocardial Infarction

N3 Network: This is a Wide Area IP Network (WAN) which is the national broadband network of the NHS. It runs over a high-speed IP-based Virtual Private Network which connects all locations within NHS England & Scotland. Acute hospitals and GP surgeries in England are linked through 58 points of presence (POPs), with a further 5 POPs in Scotland. Other networks, such as the Internet, are connected via Gateways, eg. Internet Gateway. British Telecom was awarded the contract to deliver and manage N3 on behalf of the NHS in 2004

NOBLE: Nordic–Baltic–British left main revascularisation study

Non-WB: Non-whole bifurcation

ONS: Office for National Statistics

OR: Odds ratio

PAS: Patient Administration System

PatID: patient identifier

PCI: Percutaneous Coronary Intervention

PIS: Patient Information Sheet

PRECOMBAT: PREmier of Randomized COMparison of Bypass Surgery Versus AngioplasTy Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease

QOL: Quality of life

RCT: Randomised controlled trial

Residual SYNTAX score (rSS): the sum of all residual coronary disease after coronary intervention as calculated using the SS. The baseline score for a treated lesion is subtracted from the overall baseline score. In most published studies of rSS, the lesion characteristics of calcification, tortuosity, angulation and thrombus are deducted. However in this study these measures of jeopardy of treated lesion were retained for calculation of the rSS.

SB: Side branch

SD: Standard deviation

SQL: Structured Query Language

SS: SYNTAX score. The SS is a comprehensive anatomical assessment derived from various pre-existing classifications. It is calculated by analysing diagnostic angiograms. Each lesion producing ≥50% luminal obstruction in vessels ≥1.5 mm is defined based on the modified AHA coronary tree segment classification and separately scored regarding

bifurcations or trifurcations or aortic ostial localisation, chronic occlusion, vessel tortuosity, length, calcification and thrombus formation. Finally, the score of each lesion is added to obtain the patient's raw SS. Thus, the SS reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33.

SSL: Secure Sockets Layer, communication between a user web browser and a secure website requires this layering of security. SSL certificates assure users that the website is legitimate and not a copycat website. Communications between the web browser and study website is encrypted. This level of security is commonly employed on websites transferring sensitive information such as credit card details -the URL protocol https// instead of http:// is used to designate an SSL secure website. The encryption is automatically employed by the website. Certificates are validated by the Certificate Authority for a fee after registering company details. The certificate is installed on the server where the website is hosted.

ST: Stent thrombosis

STEMI: ST segment Elevation Myocardial Infarction, indicating transmural infarction of myocardium usually due to a complete occlusion of the coronary artery.

SYNTAX trial: Synergy between PCI with Taxus and Cardiac Surgery trial

TLR: target lesion revascularisation

TVR: Target vessel revascularisation

ULMCA: Unprotected Left Main Coronary Artery is considered 'unprotected' if there is no functioning graft to any of the left coronary arteries.

WB: Whole bifucation

VLST: Very late stent thrombosis

1. Introduction

1.1 LMCA disease background

Significant left main coronary artery (LMCA) disease, defined as >50% diameter stenosis, may be found in 5-7% of patients undergoing coronary angiography [1, 2]. A more recent meta-analysis of published studies suggests a prevalence of greater than 12% amongst patients who are treated for coronary disease [3]. Intuitively, those with the largest amount of myocardium at risk, such as unprotected LMCA (ULMCA) disease or multivessel coronary disease, would suffer worse outcomes if left untreated. The LMCA supplies 100% of the blood to the left ventricle in a left dominant circulation and about 75% in a right dominant circulation [4]. Studies have confirmed that coronary artery bypass grafting (CABG) in patients with LMCA disease improves long term survival when compared with conservative treatment (**Table 1)** [5-8]. While amongst those who are revascularised for multivessel coronary disease, ULMCA disease is an independent predictor of poor long term outcomes [9].

The evidence in support of CABG for ULMCA disease dates back to the Coronary Artery Surgery Study (CASS) registry in the 1970s, soon after the introduction of CABG in the 1960s. Over a 15-year follow-up, CABG conferred a median survival advantage which was double that of medical management. Median survival in the surgical group was 13.3 years (12.8-13.8 years, 95% Confidence interval [CI]) compared with 6.6 years (5.4-7.9 years) in the medically managed group (difference, 6.7 years; $p < .0001$) [4]. Randomised trials of CABG compared to medical management consistently identify ULMCA disease as an independent predictor of poor survival over long term follow-up [10], these studies include patients with single or multivessel coronary disease [11, 12]. It is further shown in these studies that ULMCA disease confers higher operative risk than all other subsets of multivessel coronary disease.

Table 1: Studies comparing CABG to medical management for LCMA disease

Author	Year	Study design	CABG	Medically managed	Survival for CABG vs medically managed		
					1 year	3 year	5 year
Talano[5]	1975	registry	89	32	89% vs. 61% (p<0.05)		
ECS study group[10]	1980	RCT	395	373			93% vs 84% (p=NS)
Chaitman[6, 7]	1981	registry	1183	309		91% vs. 69% (p<0.05)	88% vs 57% (p=0.02)
Takaro[8]	1982	RCT LMCA subgroup	48	43		88% vs. 65% (p=0.05)	

CABG – coronary artery bypass grafting; LMCA – left main coronary artery; RCT – randomised controlled trial; ECS – European Coronary Surgery; NS – not significant

1.2 PCI of LMCA disease

Percutaneous coronary intervention (PCI) as treatment of the ULMCA was performed sporadically at first and was limited to balloon angioplasty in patients ineligible for CABG. The proximal, readily accessible, muscular and large calibre LMCA would seem the ideal target for this form of revascularisation. The initial observational data on LMCA PCI from registry analysis revealed high rates of 'bail out' surgery and the subsequent need for surgical revascularisation during medium-term follow-up [13]. These adverse outcomes were related to acute vessel closure, vessel recoil and subsequent restenosis; the solution seemed to be the introduction of bare metal stents (BMS) which reduced the peri-procedural risk of acute vessel failure [14]. However, the early benefits of BMS were offset by the high restenosis rates, of up to 23%, resulting in subsequent target vessel revascularisation (TVR) or target lesion revascularisation (TLR) [15]. Drug-eluting stents (DES) have reduced the restenosis rates compared to BMS in coronary arteries [16, 17], these results were subsequently replicated in the LMCA [18, 19] (**Table 2**).

Data exploring outcomes from DES and BMS are derived mainly from registries and reflect the transition of practice in interventional cardiology from BMS to DES during the early noughties. The first studies comparing DES to BMS in the LMCA included matched retrospective cohorts of patients, confirming the benefit of reducing the risk of myocardial infarction (MI) and TVR [18]. There remains only one randomised trial comparing DES to BMS in the LMCA using a paclitaxel-eluting stent; this study showed a significantly reduced binary angiographic restenosis rate with DES [20]. First generation DES including sirolimus- [21] and paclitaxel-eluting [20, 22] platforms were studied independently and in mixed cohorts [23, 24]. Despite high-risk cohorts including worse coronary anatomy, such as more distal LMCA disease and smaller calibre vessels, both DES platforms reduced the risk of major adverse cardiac and cerebrovascular events (MACCE), concerning TVR and TLR, when compared with BMS for the treatment of the LMCA [21, 22]. While these studies confirmed the reduced restenosis rates, a meta-analysis of studies comparing DES to BMS in ULMCA disease suggests there is a better survival from DES treatment in addition to the reduced TVR/TLR [25].

Table 2: Bare metal stents vs. drug eluting stents for LMCA disease

Author	Year	Study design	Adjustment	DES	BMS	Duration (months)	Outcomes			
							MACCE		TLR/TVR	
Chieffo [21]	2005	Historical cohort	Propensity score matching	85	64	6	OR-0.27 (0.09-0.73)	p<0.05	OR- 0.28(CI0.09-0.73)	p<0.05
Erglis [20]	2007	Randomised	Randomisation	53	50	6	OR- 0.36 (0.13-0.96)	p<0.05	OR-0.10 (0.01-.84)	p<0.05
Gao [23]	2008	Cohort study	Propensity score matching	220	224	15	OR- 0.53 (0.30-0.94)	p<0.05	OR- 0.48 (0.24-0.96)	p<0.05
Palmerini [24]	2008	Multicentre registry	Propensity adjusted	1111	342	24	aHR 0.49 (0.32 -0.77)	p<0.05		
Han [22]	2009	Cohort study	Propensity score matching	178	109	35	OR- 0.23 (0.09-0.58)	p<0.05	OR- 0.26 (0.08-0.83)	p<0.05
Kim [26]	2009	Prospective cohort	Probability weighting	864	353	36	aHR- 0.81 (0.54–1.21)	p<0.05	aHR - 0.32 (0.17–0.61)	p<0.05
Tamburino [18]	2009	Multicentre registry	Propensity score matching	187	187	18			aHR - 0.68 (0.21-0.69)	p<0.05
Tamburino [27]	2009	Multicentre registry	Propensity score matching	334	145	15	aHR- 0.73 (0.44-1.21)	NS	aHR - 0.79 (0.33-1.90)	NS

BMS – bare metal stent; DES – drug eluting stent; LMCA – left main coronary artery; MACCE – major adverse cardiac and cerebrovascular disease; TLR – target lesion revascularisation; TVR – target vessel revascularisation; OD – odds ratio; aHR – adjusted hazard ratio; NS – not significant

1.2.1 DES vs CABG, data from published registries

Early published registries with follow-up of up to 5 years have demonstrated favourable survival from LMCA PCI using DES when compared to CABG. A meta-analysis of 16 observational studies, including 1278 patients, demonstrated the safety of DES for treating ULMCA disease with a 2.3% in-hospital mortality rate and 5.5% mortality rate at a median follow-up of 10 months [28]. While virtually all these studies showed no significant difference in MACCE at one year, there were significantly higher rates of TVR and TLR for DES PCI (**Table 3**).

Despite the growing evidence supporting the safety endpoints of DES PCI for treating patients with ULMCA disease, given the heterogeneous study cohorts, it remained uncertain whether PCI would be appropriate for treating all presentations, especially those with a greater burden of coronary artery disease. In keeping with the nature of observational studies, there were huge disparities between treatment groups for the burden of coronary disease; patients considered for PCI had less extensive coronary involvement when compared with those treated with surgery [29-33]. While other studies with well-matched cohorts, despite no significant difference in death or MACCE, continued to show higher rates of TVR/TLR with DES PCI [34]. A randomised trial comparing CABG to PCI in patients suitable for both procedures would identify the threshold of coronary disease burden at which the short term benefits of PCI are outweighed by the poor long term outcomes [35].

Table 3: PCI vs CABG for LMCA disease

Author	Year	Study design	PCI (%DES)	CABG	Duration (months)	Outcomes					
						Death		MACCE		TLR/TVR	
Lee [36]	2006		50(100%)	123	12			17.0% vs. 25.0%	p= NS		
Palmerini [37]	2006	Prospective	157(60%)	154	14	13.4% vs. 12.3	p= NS			25.5% vs. 2.6%	p<0.05
Sanmartin [38]	2007	Retrospective	96(100%)	245	12	5.2% vs. 8.4%	p= NS	10.4% vs. 11.4%	p= NS	0.8% vs. 5.2%	p<0.05
Rodes-Cabau [39]	2008	Retrospective	104(46%)	145	23			43.3% vs. 35.3%	p= NS		
White [40]	2008	Retrospective	67(100%)	67	24			aHR-1.8 (1.0-3.3)	p= NS		
Brener [41]	2008	Retrospective	97	190	36	20.0% vs. 15.0%	p= NS				
Shimizu [32]	2010	Prospective	64(100%)	89	18	8.1% vs. 6.6%	p= NS	37.3% vs. 17.8%	p= NS		
Kang [31]	2010	Retrospective	205(100%)	257	36	14.1% vs. 12.1%	p= NS	35.1% vs. 21.8%	p<0.05	22.4% vs. 5.1%	p<0.05
Wu [30]	2010	Prospective	131(100%)	245	48	4.6% vs. 9.4%	p= NS	27.0% vs. 22.0%	p= NS	18.0% vs. 9.4%	p<0.05
Park [29]	2010	Prospective	1102(71%)	1138	60	aHR-1.1(0.9-1.4)	p= NS			aHR-5.1 (3.5-7.4)	p<0.05
Chieffo[34]	2010	Prospective	107(100%)	142	60	15.9% vs 18.3%	p= NS	32.4% vs. 38.3%	p= NS	18.7% vs. 8.4%	p<0.05
Park [42]	2011	Prospective	645(100%)	501	55	10.4% vs 16.2%	p= NS			14.4% vs 3.4%	p<0.05
Chieffo [43]	2012	Retrospective	1874 (100%)	901	43	14.1% vs 11.4%	P=NS	30.3% vs 20.1%	P<0.05	25.7% vs 8.9%	P<0.05

PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; DES – drug eluting stent; LMCA – left main coronary artery; MACCE – major adverse cardiac and cerebrovascular disease; TLR – target lesion revascularisation; TVR – target vessel revascularisation; aHR – adjusted hazard ratio; OD – odds ratio; NS – not significant

1.2.2 Overall results from randomised trials DES vs CABG for LMCA disease

In the first published randomised trial comparing outcomes from LMCA PCI to CABG, DES was only used when the LMCA measured ≤3.8mm [44] (see Table 4). The results indicated equivalent outcomes from PCI and CABG. However, the trial was underpowered. Notably, almost two-thirds of patients screened were excluded from the study. Similarly, more than half the patients screened were excluded from a trial reported by Boudriot et al [45]. This study was the first designed to show non-inferiority of LMCA PCI to CABG when using DES. While the study failed to demonstrate non-inferiority using the composite end-point of MACCE, non-inferiority was demonstrated using the composite of safety endpoints death, MI and stroke. As with the previous non-randomised studies, there was significantly more TVR and TLR with PCI treatment.

The randomised PREmier of Randomized COMparison of Bypass Surgery Versus AngioplasTy Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) study reported 5 year results, which are consistent with earlier registry findings, with no significant difference in MACCE between PCI and CABG (17.5% vs 14.3%, p=NS). However, significantly more TVR was reported with PCI (11.4% vs. 5.5%)[46]. The data did not quantify the specific burden of coronary disease for which DES PCI would achieve similar outcomes compared with CABG. A standardised, repeatable and reliable method for quantifying the burden of coronary disease would be required to allow the accurate matching of patients. The objective would be to establish cut-off values that would describe a distinct watershed of outcomes between scores; this would require an extensive trial incorporating all multi-vessel disease.

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial was a randomised multicenter trial designed to show non-inferiority of PCI, using Taxus DES, versus CABG in patients with multivessel coronary disease including LMCA disease [47]. The SYNTAX score (SS) was formulated to quantify the amount and complexity of coronary disease [35]. The SS is a comprehensive anatomical assessment calculated when analysing the diagnostic angiogram, which was derived from various pre-existing classifications. The coronary tree was divided into segments according to the modified

American College of Cardiology/American Heart Association (ACC/AHA) coronary tree segment classification [48, 49]. Application of a weighting factor per significant coronary lesion is based on the Leaman score and the expected obstruction to the blood flow of the left ventricle [50]. Lesions with a luminal narrowing of $\geqslant$50% in vessels $\geqslant$1.5 mm in size were considered significant. A weighting factor of 2 was added for a complete total occlusion and 1 for lesions with 50-99% stenosis. Tandem lesions were counted as a single lesion if within three reference vessel diameters of each other. Characteristics which define lesion complexity according to the ACC/AHA lesion classification system were considered additive [51], such as bifurcations or trifurcations or aortic ostial localisation, chronic total occlusion, vessel tortuosity, length, calcification and thrombus formation. Additional scores were given for the specific characteristics of a chronic total occlusion [52] and for bifurcation or trifurcation lesions according to the Duke and ICPS bifurcation lesion classification systems [53][54]. Finally, the scores for each coronary obstruction were added together to obtain the patient's overall SS. Thus, the SS reflects a comprehensive anatomical assessment, with higher scores indicating more complex and extensive coronary disease. The study cohort was ordered by SS and then divided into tertiles, a low score was defined as $\leqslant$22, an intermediate score as 23 to 32, and a high score as $\geqslant$33 [55].

The primary non-inferiority end-point was not met for the overall study population in the SYNTAX trial. The subgroup analysis of the LMCA group, therefore, should be considered observational and hypothesis generating as it was underpowered. In the LMCA subgroup, 348 patients were randomised to CABG and 357 to PCI. The MACCE rate at 12 months and three years were comparable for the two groups. However, the rate of repeat revascularisation was significantly higher in patients randomised to PCI (Table 5). In this study, patients with an intermediate SS (23-32) or high SS ($\geqslant$33) had worse outcomes from PCI than CABG, which was driven mainly by higher rates of TVR [12]. At 12 months there was no significant difference in survival or MACCE between the two groups. However, the rate of repeat revascularization among patients treated with PCI was significantly higher. Pooled results from a meta-analysis of all randomised trials of ULMCA PCI vs. CABG have confirmed these results [56-58]. At three years

follow-up the MACCE rate was comparable (26.8% vs. 22.3%; p = NS), however rates of repeat revascularisation remained higher in the PCI group (20.0% vs. 11.7%; p<0.05). When considering the composite safety endpoint (death, CVA or MI), there was a statistical trend towards better outcomes from PCI. Pooled results from over fourteen thousand patients with five years of follow-up confirmed the comparable survival from PCI and CABG, with the ongoing trend towards increased need for repeat revascularisation from PCI [58].

The recently published Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and the Nordic-Baltic-British Left Main Revascularization Study (NOBLE) randomised trials reported conflicting results for revascularisation of intermediate complexity coronary disease [59, 60]. While both studies aimed to recruit patients with a low to intermediate burden of coronary disease, the EXCEL investigators defined this according to a SS $\leqslant$32 while the NOBLE investigators did not use the SS. Instead they included patients with a significant lesion (>50.0% stenosis or FFR<0.80) of the LMCA (ostium, mid-shaft and/or bifurcation) AND with no more than three additional non-complex PCI lesions. Complex lesions were defined as calcified/tortuous coronary artery lesions, >25 mm in length, Chronic Total Occlusion (CTO) or a bifurcation lesion requiring treatment with a 2-stent strategy.

After three years follow-up, the EXCEL investigators reported non-inferior outcomes from PCI compared to CABG for MACCE. However, they reported an increased risk of repeat revascularisation from PCI. The NOBLE investigators reported significantly worse outcomes from PCI for the composite outcomes of MACCE and the secondary outcomes of non-procedural myocardial infarction, any revascularisation and stroke.

Table 4: Randomised studies of PCI vs. CABG

Author	Year	Study design	PCI (%DES)	CABG	Duration (months)	Outcomes					
						Death		MACCE		TLR/TVR	
Buszman [44]	2008	Randomised	52(35%)	53	12	1.9% vs. 7.5%%	p=NS	28.8% vs. 25.5%	p=NS	9.6% vs. 9.4%	p=NS
Morice [61]	2010	Randomised, multicentre	357(100%)	348	12	4.2% vs. 4.4%	p=NS	15.8%% vs. 13.6%	p=NS	11.8% vs. 6.5%	p<0.05
Boudriot [45]	2011	Randomised	100(100%)	101	12			19.0% vs. 13.9%	p=NS	13.0% vs. 4%	p<0.05
Park [62]	2011	Randomised	300(100%)	300	24			12.2% vs. 8.1%	p=NS	9.0% vs. 4.2%	p<0.05
Mäkikallio [60]	2016	Randomised, multicentre	598	603	60	12.0% vs 9.0%	p=NS	29.0% vs 19.0%	p<0.05	16.0% vs 10.0%	p<0.05
Stone [59]	2016	Randomised, multicentre	948	957	36	8.2% vs 5.9%	p=NS	23.1% vs 19.1%	p=NS	12.9% vs 7.6%	p<0.05

PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; DES – drug eluting stent; LMCA – left main coronary artery; MACCE – major adverse cardiac and cerebrovascular disease; TLR – target lesion revascularisation; TVR – target vessel revascularisation; aHR – adjusted hazard ratio; OD – odds ratio; NS – not significant

1.2.3 Implications for clinical practice from the randomised data

The SS is a useful measure which allows the valid comparison of the burden of coronary disease among patients [35], even when applied across different studies. The SS has been validated when applied retrospectively to assess observational registries with results consistent with the randomised trials. One such study confirmed equivalent outcomes from PCI and CABG amongst the low SS group (score $\leqslant$22), but inferior outcomes from PCI in the high SS (score $\geqslant$33) group [42]. Another registry confirmed the discriminative ability of the SS to predict worse outcomes for patients with high SS [63]. The very low event rates reported in the PRECOMBAT trial, when compared to all other randomised trials and registries, may be explained by the less extensive coronary disease burden (median SYNTAX score only 25) [64].

While the SS is predictive of outcomes amongst patients with ULMCA disease treated with PCI [63, 65, 66], there is disagreement when it comes to predicting outcomes from CABG. Some studies have shown that it is a predictor of MACCE amongst patients treated with CABG [67], while others suggest it is not as useful as other clinical scores [65, 68]. There is significant interobserver variability with calculating the SS, which may explain some of the conflicting data, yet it creates doubt when comparing SS across various studies [68].

Randomised trials inform clinical revascularisation guidelines, yet one could argue they do not represent the 'real world' patient population to which these guidelines are applied. The SYNTAX trial was an all-comers study design, yet failed to recruit more than 58% of all patients screened while almost 30% of all patients were enrolled into a separate registry as they were ineligible for one or other of the treatment modalities [55]. A screening log was maintained at only five centres which recruited 506 of the 1201 patients in the NOBLE trial; these five centres rejected close to half of all patients screened [60]. Similarly, the EXCEL trial kept a screening log for the first 1747 patients only, of whom they were able to recruit 747 (42.7%) patients, thereafter they closed the registry and recorded only patients recruited to the study.

1.2.4 Current guidelines:

The evidence from observational studies and randomised trials indicate that CABG is superior to PCI due to increased need for repeat revascularisation with PCI. The randomised studies have not shown a different signal compared to the observational data, but the SYNTAX trial and more recently the EXCEL trial have allowed us to identify a cohort of patients which may have similar outcomes from PCI, those with a SS≤32. Given the NOBLE trial data, we should weigh up the risks and benefits for each patient individually. So while we may conclude that particular coronary disease patterns and patient risk profiles could indicate favourable outcomes from PCI if used as an alternative to CABG [69], management decisions should continue to be made by a multi-disciplinary team (MDT). Thus CABG remains a Class I recommendation to improve survival for significant (angiographic stenosis $\geqslant$ 50% diameter) LMCA stenosis.

PCI is a Class IIa recommendation to improve survival as a reasonable alternative to CABG in selected stable patients with significant (≥ 50% diameter stenosis) unprotected LMCA disease (ULMCA). These patients include:

1. Anatomical characteristics indicating a low PCI procedural risk and a likely good long-term outcome [e.g., a low SYNTAX score (≤ 22), ostial or trunk LMCA disease]; and

2. Patient characteristics associated with increased risk of adverse outcomes from surgery (high surgical operative risk scores) [70].

It is considered a Class IIb recommendation for PCI to be used as a reasonable alternative to CABG in patients with:

1. Anatomic characteristics indicating a low to intermediate PCI procedural risk with an intermediate to high probability of good long-term outcome (e.g., a low to intermediate SS of ≤33, LMCA bifurcation disease); and

2. Patient characteristics predicting increased risk from surgery (e.g. history of chronic obstructive pulmonary disease (COPD), previous stroke and previous cardiac surgery) [70].

The SYNTAX score is a useful tool to describe various study populations. Notwithstanding these benefits, the vast majority of patients excluded from these trials represent the real population requiring careful decision making. While the published literature has identified a cohort of patients for whom PCI is a viable alternative for revascularisation of the LMCA, the findings may not apply to the patients for whom PCI is the only option. It is for these patients that observational studies present an ideal means to identify the particular challenges of PCI for which further studies could be designed.

1.3 LMCA bifurcation disease

LMCA bifurcation stenoses have been identified as an independent predictor of long term MACCE [26, 28, 71-77]. The left main coronary artery is divided into three anatomical sections, the ostium, the body and the bifurcation. The ostium and body can be treated with great success using PCI; however the treatment of the bifurcation is fraught with procedural complications and long term poor outcomes [78], yet debate still remains as to the best approach to treat the LMCA with PCI.

1.3.1 Approach to coronary bifurcations

Coronary bifurcation disease represents one of the more challenging lesion types to treat with PCI; procedural success depends on operator experience. Compared with non-bifurcation coronary PCI there is a greater chance of procedural complications when attempting PCI of the coronary bifurcation, such as acute vessel closure of the side branch (SB) [79, 80], while poor long-term outcomes include high rates of TLR [81]. The choice of stent strategy, either a provisional single stent or elective two stent strategies, are influenced by the distribution of disease in the branches, the size of the side branch and the branch angle. One should first consider whether a stent should be inserted into the SB electively, as this dictates further treatment strategies. A provisional single stent, where the first stent is placed from the main vessel (MV) into

the main branch (MB) across the SB, is recommended. If the SB becomes compromised, further 'bail out' strategies could be considered where the SB may be treated with an additional stent. Data supporting this approach comes from large randomised clinical trials, such as the BBC ONE and Nordic trials [82, 83]. These trials' populations, however, included less than 4% of cases with LMCA bifurcation disease. One should note that these studies analysed on an 'intention to treat' basis and employed rigorous treatment protocols for decision making.

The European Bifurcation Club (EBC) consensus favours a provisional single stent approach for all coronary bifurcations with certain caveats [84]. The operator may decide to use a two stent approach depending upon: (1) the size of the side branch (SB), and therefore the myocardium at risk; and (2) the distribution of disease around the side branch. A two stent approach, securing the SB with a stent from the outset, may be considered in patients with a large SB with significant ostial disease extending further into the side branch vessel.

1.3.2 Specific features of LMCA bifurcation disease

While significant (>50% stenosis) LMCA disease may be found in up to an eighth of patients undergoing coronary angiography for chest pain [85], up to 80% of these stenosed LMCA's involve the bifurcation, and up to 80% of patients with left main disease will have associated multi-vessel coronary artery disease [45, 61, 86-88]. There are specific features which present a challenge when considering PCI of the LMCA bifurcation including: (1) usually a large calibre (>2.5mm) SB, the circumflex (LCx) vessel; (2) atheromatous disease of the bifurcation is often more extensive involving the ostia of both branches; and (3) there is a large amount of myocardium at risk. Due to the acute angulation of the bifurcation, the distribution of atheroma is not always apparent on conventional angiography; one may have to consider unusual and steeper views or the use of intravascular imaging to delineate the anatomy and the involvement of branch ostia [89]. The LMCA bifurcation presents the operator with different challenges when compared with other coronary bifurcations; outcomes from

elective two stent strategies for the LMCA bifurcation are worse than those for left anterior descending (LAD) bifurcations with higher TLR rates in LMCA bifurcations [90, 91].

1.3.3 Classification of atheromatous burden at the bifurcation

Six different classification systems were used to report outcomes amongst studies of LMCA bifurcation PCI. Consequently, this creates difficulty with comparing the results due to the heterogeneous populations [92][93][94][95][53]. Extensive plaque involvement at the bifurcation is strongly associated with high TLR rates regardless of the stent strategy used [96]. These classification systems rely on the accurate identification of significant plaque burden, which can be difficult, with angiography alone. Significant LMCA atheroma may be detected with intra-vascular ultrasound (IVUS) assessment when angiography is equivocal [97-100]. IVUS findings may help determine the distribution of disease around the LMCA bifurcation [89, 101, 102] and influence the choice of treatment strategy due to predicted change in LMCA geometry and side branch stenosis [103].

A recent study suggested the use of 'whole bifurcation' (WB) and 'non-whole bifurcation' (non-WB) to describe the atheroma burden at the LMCA bifurcation. WB's were associated with worse outcomes. However, this classification system was considered impractical for everyday use [96]. Rather the Medina classification has been proposed, it is a simplified way to describe the distribution of significant atheroma burden around the bifurcation [104]. This classification system allowed the standardised reporting of results across studies (**Figure 1**) [92, 105]. To indicate the absence or presence of disease within 5mm of the bifurcation in either the main vessel (MV), main branch (MB) or side branch (SB), one uses binary coding, e.g. disease in all three (MV, MB, SB) vessels is designated as 1,1,1. More recently lesions have been classified as 'True' and 'Non-true' bifurcation disease, this simply relies on the Medina classification and has been adopted by the European Bifurcation Club (EBC) [106, 107].

'True' bifurcation disease includes Medina classes 1,1,1. 1,0,1 and 0,1,1, where the SB is diseased in all categories, these lesions are typically associated with worse outcomes [108-110].

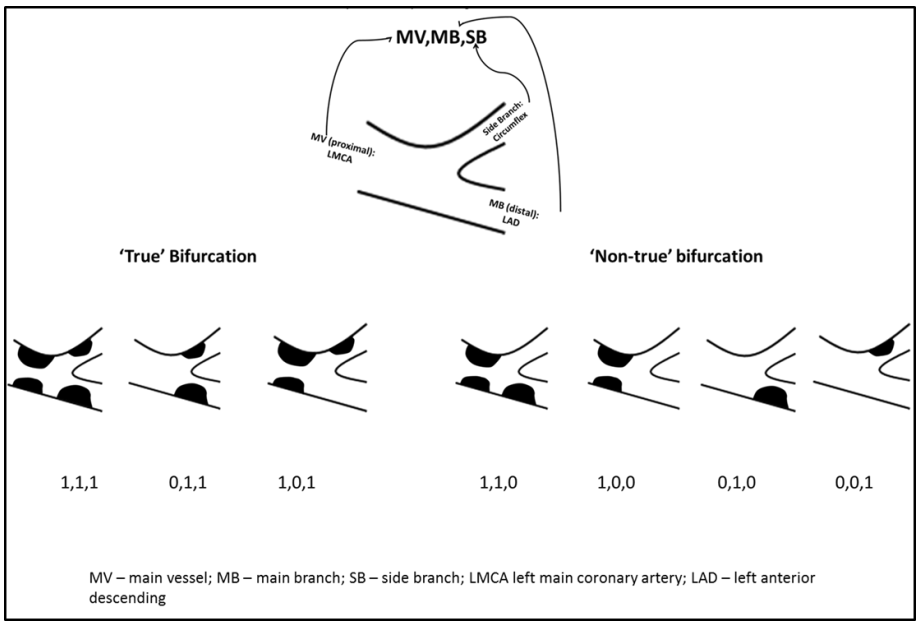

Figure 1 Medina Classification of bifurcation disease, adapted to the LMCA

The LMCA bifurcation contributes up to 2 points to the SYNTAX score if it involves the side branch ostium otherwise only 1 point. So this would include all 'True' bifurcation lesions by Medina classification, except the 1,0,1 lesion [35]. The stenosed distal LMCA represents a small addition to the SYNTAX score, yet it is a significant independent factor contributing to poor long-term outcomes.

1.3.4 LMCA bifurcation PCI outcome measures

The use of DES in the distal LMCA has reduced the risk of TLR when compared with BMS use [26]; however poor outcomes from PCI of the LMCA bifurcation are mainly

driven by repeat revascularisation [71, 111]. Repeat revascularisations are reported to include various combinations of target vessel revascularisation (TVR) and TLR [26, 28, 71-73]. Distal LMCA disease is typically associated with a greater burden of multi-vessel disease; this could, therefore, confound outcomes when reporting 'repeat revascularisations' as TVR may be secondary to distal vessel coronary disease rather than restenosis of the LMCA bifurcation. Repeat revascularisation reported in these studies may also include the subsequent treatment of non-ischaemic lesions; routine angiographic follow-up after LMCA PCI was considered standard clinical practice previously, which may result in additional TLR [96, 112].

1.3.5 Stent strategy for the LMCA bifurcation

Evidence from LMCA bifurcation PCI registries

There are limited data to guide the choice of stent strategy for the treatment of LMCA bifurcation disease. Registries of LMCA bifurcation PCI have reported conflicting results (**Table 5**). Some studies indicate there is no difference in outcome between single and two stent strategies [113, 114] while others report fewer MACCE from a provisional single stent approach [77]. Inherent selection bias may account for this conflict due to the differences between treatment groups. One large registry reported a higher risk of TLR and MACCE when using two stents compared with one stent [115]. However, the two treatment groups differed with regards to comorbidity, and another criticism of this study was the lack of reporting the atheroma burden for the left main bifurcation and the rest of the coronary tree. The choice of PCI strategy is guided by the atheroma burden, while the distribution of atheroma around the bifurcation predicts the outcome; extensive atheroma at the LMCA bifurcation is associated with worse outcomes [96, 113]. Patients with less extensive atheroma of the LMCA bifurcation tend to receive a single stent treatment and have less TLR in the long term, while those with complex lesions tend to have a two stent strategy [116]. This bias may lead to excess repeat revascularisations when MACCE includes TVR rather than TLR. Therefore,

to assess the outcome of the LMCA bifurcation stent strategy, it would be more accurate to assess TLR rather than TVR [73].

Evidence from LMCA bifurcation PCI RCT's

The only published randomised trial compared two complex stent strategies for the treatment of LMCA bifurcation disease, the culotte versus the double kiss crush techniques. They included Medina 1,1,1 and 0,1,1 lesions only, where treatment of the side branch may be considered necessary [117]. In this trial, where the side branch was treated in all cases, they showed significantly better outcomes from the double kiss crush technique compared to the culotte technique for PCI of the LMCA bifurcation. However this did not answer the question of whether a provisional single stent technique would offer equal or superior results to a 2 stent strategy.

The EBC recommends the provisional single stent strategy for treatment of the LMCA bifurcation but notes that the circumflex is 'almost always' considered a major SB which would favour a two stent technique. They recommend assessing the MB and SB with fractional flow reserve (FFR) [118], if FFR is not possible, due to downstream disease, they recommend the use of IVUS [119]. Intravascular imaging should be used to size the bifurcation stents [120]. Questions remain regarding the choice of stent strategy in 'True' LMCA bifurcation disease and how the distribution of disease around the LMCA bifurcation impacts on the outcome.

Table 5: Single stent vs Two stent strategy for LMCA bifurcation

Author	Year	Study design	Stent Strategy		Duration (months)	Outcomes					
			Single	Two		Death		MACCE		TLR/TVR	
Kim[112]	2006	Prospective cohort	67	49	18	0%				0% vs 12.2%	P<0.05
Valgimigli [113]	2006	Prospective cohort	48	46	19			28% vs 31%	p = NS	10.0% vs 13.0%	p = NS
Toyofuku [90]	2011	Retrospective cohort	741	204	12	5.8% vs 8.8%	p = NS			5.6% vs 24.2%	p<0.05
Palmerini [115]	2008	Retrospective cohort	456	317	24			24.7% vs. 32.4%	p<0.05	13.0% vs 26.9%	p<0.05
Song [116]	2014	Retrospective cohort	509	344	36	1.6% vs 4.1%	P<0.05			15.5% vs. 38.1%	P<0.05

LMCA – left main coronary artery; PCI – percutaneous coronary intervention; MACCE – major adverse cardiac and cerebrovascular disease; TLR – target lesion revascularisation; TVR – target vessel revascularisation; aHR – adjusted hazard ratio; OD – odds ratio; NS – not significant

1.4 LMCA disease in Octogenarians

1.4.1 Epidemiology

World and UK populations are expected to experience acceleration in the proportion of older people in the next 20-30 years [121-123]. The elderly are more likely to suffer with extensive and complex coronary disease, including a greater incidence of ULMCA disease [3, 124-126]. Patients undergoing revascularisation for ULMCA disease are older than those with no ULMCA disease [127]. Octogenarians have been identified as a group of patients with a significantly greater risk from revascularisation and have been studied extensively within national registries [1, 126, 128-132]. This is not surprising given that amongst the elderly, cardiac death remains a significant cause of death [133]. The proportion of the population over the age of 80, is predicted to rise from less than 5% currently to 20% by 2050 [134]. Coupled to this is the increasing life expectancy for octogenarians, a recent report suggesting a life expectancy of 7 years in North America and Western Europe for this age group [135]. According to the published Office of National Statistics (ONS) life tables the life expectancy of an 80 year old has increased from two years in 1981 up to ten years in 2015 [136].

1.4.2 Revascularisation in the elderly

Age is a major predictor of death from cardiac surgery [137]. PCI and CABG are both viable options for revascularisation in the elderly; however advanced age is often given as a reason to defer CABG in patients undergoing non-emergent ULMCA PCI [138, 139]. Indeed the higher incidences of perioperative morbidity and mortality, coupled with longer in-hospital stay, after CABG in elderly patients make PCI an attractive alternative to surgery [132, 140]. Notwithstanding the higher peri-procedural risk, age alone should not be given as a reason to defer coronary revascularisation amongst the elderly [141, 142].

For LMCA stenosis treated by CABG, advancing age is strongly correlated with poor survival [78]. However, when carefully selecting appropriate patients, ULMCA PCI in octogenarians may achieve similar [39, 143] or better outcomes [144] than CABG without incurring the penalty of longer post-operative stays and greater cost to the healthcare system [128]. Less extensive coronary disease burden and higher surgical risk favour PCI.

Evidence supporting revascularisation strategies amongst octogenarians is sparse and is mainly described by non-randomised data [39, 141-144]. Revascularisation in the elderly carries a higher risk of complications than in younger patients [1, 126, 129, 132, 133, 142, 145, 146] with nearly four times the procedural mortality rate compared to younger patients [1, 128], where the largest difference is amongst the unstable patients [126]. Notably, coronary revascularisation offers greater absolute gains in survival in the elderly in comparison to the young [130, 142], where octogenarians receiving revascularisation can achieve similar survival to the general octogenarian population [128]. Indeed the survival benefit is highest amongst octogenarians treated with ULMCA PCI compared to the young across all clinical syndromes [147], Revascularisation with PCI or CABG achieves a better risk-adjusted survival in octogenarians compared with patients under 70 years old [130]. The number needed to treat for those under 70 years old was four times greater than for octogenarians. It is not surprising that coronary revascularisation could be so effective in improving outcomes given that Ischaemic heart disease is the leading cause of death amongst men and women over the age of 80 [148][149, 150] .

1.4.3 Complete revascularisation and residual coronary disease

Up to three quarters of patients with significant left main coronary artery disease have associated multi-vessel coronary artery disease [151]. Octogenarians are more likely to have multivessel disease, left main disease and more complex lesions compared to younger patients [1, 126, 130, 141, 146, 152]. The prevalence of left main coronary

artery disease in patients investigated for angina increases with age from 10-15% in the 5th and 6th decades to 25% in the 8th decade of life [151]. Among octogenarians, the prevalence of LMCA disease requiring revascularisation may be as high as 40% [153]. Octogenarians represent up to 24% of all patients treated with PCI to the ULMCA in a recent national linked cohort study [154]. In each clinical category, STEMI/NSTEMI/Stable angina, octogenarians were found to have higher 1 year mortality.

Notably, with greater complexity of coronary disease one finds incremental levels of incomplete revascularisation [47, 155] while residual coronary disease is significantly associated with increased mortality [156-158]. The mortality benefit of complete revascularisation was found in the context of CABG [159, 160]. CABG is considered superior to PCI in achieving complete revascularisation [161, 162], even more so in the treatment of ULMCA disease [39, 47, 143, 144]. In addition to the prognostic benefit, quality of life improves to a greater extent with complete revascularisation [163].

Complete revascularisation is defined either as either anatomical [164] or functional [165]. Within the anatomical definitions there are variations [166], such as 1) a graft to each disease main vessel artery; 2) a graft to all diseased main or primary segmental vessels; 3) all disease coronary segments subtended by a distal anastomosis; and 4) all main coronary artery systems subtended by at least one anastomoses. Functional complete revascularisation can be defined where all ischaemic, and viable territories, have been reperfused.

Residual coronary disease, post revascularisation, is an independent predictor of increased mortality in multi-vessel coronary disease [9, 156-158]. The SYNTAX score (SS) [47], was developed as a quantification of multi-vessel disease by adding lesion scores based on angiographic analysis. The residual SS (rSS)[167], is a novel measure of residual coronary disease calculated after revascularisation. It allows us to describe a

continuum of values from incomplete to complete anatomical revascularisation by subtracting scores for all treated lesions. The residual SYNTAX score (rSS) is a quantitative and reproducible measure of the severity and complexity of residual coronary disease after PCI, which is predictive of long term clinical outcomes in younger populations [47, 167]. Patients with rSS >8 have higher all-cause mortality at long term follow-up [155] and are at increased risk of recurrent ischaemic events [167]. In patients who receive PCI for ULMCA disease, rSS is a prognostic discriminator and has been identified as an independent predictor of cardiac mortality at two years [168]. However, the patients included in this study were relatively young (mean age 71 years) and the results may not be applicable to older individuals. Both, the SS and rSS, have been shown to be predictive of long term outcomes amongst a younger population [155, 167, 168]. In these studies complete revascularisation was achieved in at least 60% of patients treated.

Greater coronary artery lesion severity and complexity as well as the presence of multi-morbidity may introduce challenges in achieving complete revascularisation in elderly patients with ULMCA disease. Indeed while it is known that incomplete revascularisation following CABG in elderly is associated with worse survival compared with complete revascularisation [169]; it is uncertain whether the residual coronary disease burden, as measured by the rSS, is associated with poor long term outcomes among octogenarians treated with ULMCA PCI. A recent study of fewer than 100 patients suggested that residual coronary disease was associated with poor outcomes in octogenarians presenting with ACS [170]. However, a much larger retrospective study, including the largest ever analysis of angiograms calculating the SS and rSS, found no association between rSS and poor outcomes in octogenarians [171]. Neither of these studies assessed patients with LMCA disease exclusively, with fewer than 10.0% of patients in the larger study and fewer than a third of patients in the smaller study having LMCA disease. Furthermore, the larger study included a fairly low risk population: the median SS was only 18.3 with a median rSS of 10.1 [171], compared with those patients included in the study which initially validated rSS for predicting mortality [155]. Given the sparsity of data for outcomes in Octogenarians with LMCA

disease, we sought to determine whether the residual coronary artery disease burden, as measured by the rSS, was associated with mortality in the elderly treated with ULMCA PCI.

1.5 Indices of multiple deprivation

1.5.1 Definition of deprivation

Deprivation indices are commonly used to describe spatial health heterogeneity. Deprivation is a relative term, comparing different populations across local communities, regions within countries and the world. Deprivation has been quantified using a score obtained by summing standardised variables, each measuring different ecological dimensions derived from census data. The indices of deprivation cover seven distinct domains: health deprivation and disability, crime and the living environment, barriers to housing services, income, employment, education skills and training.

1.5.2 The English indices of multiple deprivation

Local measures of deprivation for England have been calculated since the 1970s by the Department for Communities and Local Government (DCLG). The DCLG commissioned the Social Disadvantage Research Centre at Oxford University to develop the English Indices of deprivation; the aim was to develop a broader definition of multiple deprivation which would include several dimensions of deprivation. The local measures of deprivation are derived from the census data, and the indices of deprivation which are produced by DCLG are measures of deprivation for every Lower Layer Super Output Area (LSOA) and local authority area in England. Separate Indices at LSOA level are provided for each of the seven domains of deprivation. This information is then combined into one overall Index of Multiple Deprivation. Thus all 32,844 LSOAs can then be ranked according to how deprived they are relative to each

other. Using this information one can identify and explore the causes of unmet needs in the local communities.

The scores for each domain are derived from subjective self-assessment by the individual. For example, assessment of the 'health deprivation and disability' domain included asking respondents whether they felt limited in daily activities due to a health problem or disability lasting or expected to last 12 months or more (see Box 2).

The individual scores for each deprivation domain are then summated to give an overall score which allows ranking of the LSOAs. The seven domains, including their relative of weighting in the combined score, are as follows:

- Employment Deprivation (22.5%)
- Income Deprivation (22.5%)
- Health Deprivation and Disability (13.5%)
- Education, Skills and Training Deprivation (13.5%)
- Living Environment Deprivation (9.3%)
- Crime (9.3%)
- Barriers to Housing and Services (9.3%)

The Index of Multiple Deprivation (IMD) is the official measure of relative deprivation for LSOAs in England. The indices of deprivation are calculated every few years for many local areas across England; previous publications include 2004, 2007, 2010 and more recently 2015. The indices are comparable over time; however, the 2015 score is not directly comparable due to significant changes in the way the indices were measured. The LSOAs can include several postcode territories; they have on average about 1,600 residents or 650 households and may include adjacent output areas.

LSOAs are the smallest geographical unit within a Clinical Commissioning Group (CCG) for which most indicators are available and are non-overlapping. Comparisons between CCGs, enable sensitive identification of pockets of deprivation. The IMD scores are divided into quintiles which allow comparisons to be made between similar areas of deprivation and between different quintiles. Quintile group IMD score range:

1 $\leqslant$ 8.49 (Least deprived)

2 8.5 - 13.79

3 13.8 - 21.35

4 21.36 - 34.17

5 $\geqslant$ 34.18 (Most deprived)

The IMD 2010 has been adjusted to reflect the LSOA boundary changes of 2011.

1.5.3 Relationship between coronary disease outcomes and deprivation

Deprivation has been linked to the greater incidence of cardiac death [172], coronary artery disease [173], peripheral vascular disease and cerebrovascular disease [174]. It is known if there is an earlier onset of coronary artery disease amongst the more deprived [173, 175-177]. Patients from more deprived backgrounds have worse outcomes following PCI [178]. It is not known if the burden of disease within the coronary arteries, in particular subsets of left main coronary artery disease, are related to deprivation nor if the survival post PCI is related to deprivation indices.

1.6 Revascularisation outcome measures

1.6.1 MACCE

Composite endpoints include measures of safety and effectiveness of treatments employed. However, questions surround the specificity and sensitivity of these composite end-points. The choice of outcomes in the composite end-point, through their weighted contribution, may change the interpretation of results significantly [179]. Furthermore, the nature of the study population and length of follow-up may alter the specificity of the outcome measures. There remain some controversy and inconsistency in the choice of composite endpoints for various studies reporting on coronary revascularisation.

All cause death may be a reasonable measure of treatment safety and effectiveness at thirty days or one year following revascularisation procedures; however, with longer-term follow-up in an older population, it may be less specific due to the greater proportion of non-cardiac deaths in this cohort. The Academic Research Consortium (ARC) recommendations indicate that all-cause death is the most unbiased method to report outcomes but does recognise that over longer term follow-up cardiac cause of death would be a more specific outcome measure [180]. After all, death is inevitable.

It has been suggested for several reasons that all-cause death, rather than cause-specific death, should be reported in clinical studies. The data recorded on the death certificate may be incorrect [181]. There is an incremental incidence of wrongly identifying coronary disease as a cause of death with increasing age of the patient [182]. Up to a third of published data includes disagreement between autopsy findings and death certificates [182-184]. Based on clinical records, one cannot exclude significant pre-existing cardiac disease as a major contributor to the cause of death despite other present mechanisms [185]. However, the ARC gives clear guidance, albeit a conservative approach, to attributing a cardiac cause of death after independent review [180]. In randomised controlled trials the cause of death will not

affect the interpretation of the outcome; however the further away one moves from the intervention the less precise death becomes as a measure of treatment effect. For example in the long term follow-up of the left main subgroup of the CASS registry, after 15 years, the survival curves of medically managed and surgically managed patients converged [186]. Finally, it is asserted that 'dead is dead' when assessing outcomes, based on the critical evaluation of amiodarone in the CAMIAT and EMIAT trials; in this trial, there was no benefit from amiodarone when evaluating all-cause death but significant benefit with using 'arrhythmic death' [187-189]. However, in this situation where the drug therapy itself may be toxic, it may be more appropriate to use all-cause death. This approach may not apply to procedural interventions, where the presumed 'harm' from the treatment would be limited by early events and would be restricted to cardiac-specific events.

Repeat revascularisation is defined in various ways resulting in differing levels of sensitivity for outcomes. Some studies report target lesion revascularisation (TLR) and/or target vessel revascularisation (TVR) in the composite endpoint of MACCE. TVR and TLR may contribute over half of all MACCE, so it is important to define the diagnostic criteria, the circumstances in which these events arise and the approach to management. In studies which employ routine angiographic follow-up, one could end up with over-reported TLR; asymptomatic restenosis may only require 'ischaemia driven' revascularisation in less than half of these cases [190]. More recently in trials reporting upon the effect of completeness of revascularisation, non-TVR repeat revascularisations have also been reported [59].

Due to the binary nature of MACCE end-points, an uncomplicated PCI for TVR is measured as severely as a disabling stroke. Furthermore, the first event results in censorship of patients who may suffer two or more consecutive events; and due to the time-to-event analysis, significant or more informative second events are excluded from analysis. For example in the EXCEL trial, despite significantly greater ischaemia driven repeat revascularisations amongst the PCI group, the composite secondary

endpoint did not differ between the two groups, presumably as patients were censored for an earlier event [59].

MACCE as a composite end-point may not present an appropriate measure of long-term outcomes; there is a debate about which endpoints should be included in the composite [179, 191]. Depending on the context or patient group studied different composite end-points may inform specific questions about treatment effectiveness. The application of trial data to real world populations may not always be appropriate. So death as an end-point in the long-lived, with limited life expectancy, may be an inappropriate outcome measure, as the benefit of the intervention would be negated by other factors. In these populations, the benefit may lie in freedom from hospitalisation or improvement in the quality of life rather than longevity.

Health-related quality of life (HRQOL) is a multifaceted idea of well being including physical, emotional, social and mental spheres. It is not known whether quality of life may help better define which of these end-points are significant life events. Could we establish a method of weighting outcomes based on their influence on quality of life? In this way, the change in quality of life would act as an indicator of whether the end-point had a significant impact on quality of life or whether it is a minor inconvenience.

1.7 Study hypothesis

Hypotheses

1. PCI represents a safe and effective strategy for treatment of ULMCA disease, for which predictors of clinical outcomes can be identified by studying a real-world all-comers population.
2. Revascularisation leads to improved quality of life in patients with LMCA disease in comparison to conservative management.

Aims and Objectives

Aims: To identify the main factors associated with adverse outcomes following PCI and to assess changes in quality of life measures following revascularisation in a real-world population with LMCA disease.

Study objectives

i. to determine the factors associated with adverse long-term outcomes, such as death, myocardial infarction, repeat revascularisation and stroke, in patients treated with LMCA PCI.

ii. To investigate the influence of (i) the Medina class of bifurcation disease or (ii) the PCI treatment strategy on clinical outcomes in patients with bifurcation disease requiring ULMCA PCI.

iii. To investigate whether residual coronary artery disease after ULMCA PCI is associated with survival in octogenarians.

Iv. To study patient recorded outcome measures of HRQOL before and after treatment for LMCA disease according to mode of revascularisation.

2. Methods chapter

2.1 Study Design

The Leeds left main revascularisation registry was developed for the purpose of measuring outcomes for LMCA revascularisation amongst patients treated at the Leeds Teaching Hospitals NHS Trust (LTHT) for left main coronary artery disease.

Chief investigator: Prof U.M. Sivananthan

Co-Investigators: Dr S.B. Wheatcroft, Dr C.P. Gale, Dr F. Astin, Dr I.R. Pearson and Dr D. Barmby

Medical co-ordinator: Dr C. A. Maart

Nurse co-ordinators: Mrs R. Maindonald, Mrs R. Dickinson and Mrs E. Ikon.

Database manager: Mr R. Gillott

This was an observational study of all patients undergoing LMCA revascularisation at the Yorkshire Heart Centre, comprising:

1) a retrospective cohort of patients who had LMCA PCI between June 2005 and March 2013 and;

2) a prospective cohort of patients undergoing revascularisation with PCI/CABG or medical management for LMCA disease between March 2013 and August 2015.

2.2 Ethics

We were granted approval for the retrospective study under Section 251 of the NHS Act 2006 (Control of Patient Information Regulations 2002, http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/#sthash.h8Rt8nlc.dpuf). For the purposes of data collection the common law duty of confidentiality had to be overridden in order for the LTHT trust and general practices (GP's) to disclose confidential patient information for purposes of this research. It was not possible to use anonymised information and seeking retrospective

consent was not practical. Formerly this approval was granted by the National Information Governance Board for Health and Social Care (NIGB) in 2010, this body has now been replaced by the Health Research Authority's Confidentiality Advisory Group (CAG) in April 2013.

2.3 Funding

Initial funding for the project through the Jimmy Savile Trust was withdrawn in August 2012. Ongoing funding for research fellow salaries was provided by a local Imaging fund for 12 months and further funding continued for 6 months through support from LTHT. Additional funds for the licensing and printing of quality of life questionnaires were provided by the School of Healthcare, University of Leeds, under the supervision of Professor Felicity Astin. In January 2014 ongoing salary support was withdrawn, the post of research fellow associated with the study was terminated. The study was adopted onto the National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio and a research nurse, employed by the NIHR, provided support for the consenting of patients. Furthermore, a data clerk and the database manager were provided similarly through the NIHR CRN portfolio.

2.4 Review of literature strategy

Relevant literature related to Left main coronary artery revascularisation was identified from Pubmed between January 1966 to May 2017 and was restricted to English articles using search terms: left main stem/left main stem revascularisation/left main coronary artery/left main coronary artery revascularisation/incomplete coronary revascularisation. The results were transferred to Endnote and duplicates were removed. I then re-applied additional search terms: CABG/percutaneous coronary intervention/PCI/bifurcation/bifurcation PCI/ bifurcation stenting/SYNTAX score/residual coronary disease/residual SYNTAX score/octogenarians/quality of life. Abstracts of articles were scanned and relevant articles were reviewed including a

further search of their bibliographies and citation trees were followed in order to identify other pertinent articles.

2.5 Leeds left main registry

2.5.1 Retrospective study

Data collection

We studied patients who received PCI for ULMCA disease at LTHT, a large UK cardiothoracic centre, between 10th May 2005 and 30th May 2013. All patients who received ULMCA PCI during the study period were identified from a bespoke procedural electronic health records database (Cardiobase®). We included clinical syndromes of chronic stable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), defined according to the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) consensus on definition of myocardial infarction [192]. Baseline clinical and demographic data were extracted from medical case notes and procedural details collected from the electronic health record database. Where additional patient data were required, the hospital notes and correspondence were reviewed. In addition the following referring hospitals were contacted to provide additional data: York Teaching Hospital National Health Service (NHS) Foundation Trust, Mid-Yorkshire NHS Hospital trusts, Bradford Teaching Hospitals NHS Foundation Trust, Calderdale and Huddersfield NHS Foundation Trust, Harrogate and District NHS Foundation Trust and the Airedale General Hospital. GP summaries were collected for all patients where available, for deceased patients these were not available. All cause mortality was tracked through linkage to the Office of National Statistics (ONS) using the NHS number. An enquiry was raised through the Patient Administration Systems (PAS) at the LTHT and local hospitals to verify subsequent admissions to hospital after the date of the ULMCA PCI. We were then able to identify potential MACCE events using International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) codes.

As a research group we decided to accept the diagnosis of comorbidities as recorded on the bespoke procedural electronic health records database (Cardiobase®). We did not define specific criteria for the diagnosis of relevant comorbidities, so accepted the adjudication of the treating physician.

Derived Data

Indices of multiple deprivation

Using post-code identifiers for patients, indices of deprivation were derived from the Office of National statistics. Pseudonymised patient identifier's (PatID's) were used to order post-codes and these were entered into an online indices of multiple deprivation (IMD) Postcode search tool (https://tools.npeu.ox.ac.uk/imd/) to find the associated IMD quintile group and score. Indices for the periods covering the date of treatment were used, thus the 2011 Indices were used for all patients as the 2015 indices were derived from data for the period 2012-2013.

Data storage and database design

A bespoke database was designed on the Google™ Structured Query Language (SQL) platform. The database is hosted on the NHS secure N3 network. The design allows multicentre recruitment and data input using the N3 network. Security includes password protected accounts; data encryption and pseudonymised patient data using sequentially allocated PatID's.

Research committee meetings, headed by the Chief Investigator Prof Sivananthan, were held to discuss the design of the database. Our aim was to integrate automated EuroSCORE, SYNTAX score, eGFR/BMI calculators into the design. The platform could be used in the cathlab for the imputation of data directly by cathlab staff.

The database set out to include a robust drug history including antiplatelet initiation, use of anti-anginals at the time of the procedure through the entire follow-up.

Database management is through a central management structure including the Chief investigator, Prof Sivananthan and database manager Richard Gillott. Applications for research on the data held can be made to the research committee. Account access for data entry and data downloads is made through a similar process.

Missing Data

Missing values were checked against the existing in-house database and clinical notes. Local GP practices and district general hospitals were contacted in order to collect the missing data. Any contradictory data points were discussed with the CI, generally the data held on Cardiobase was taken in preference as they were entered by the clinician prospectively at the time of the procedure.

The analysis and handling of missing data will be explored in the statistical analysis section below.

Patient follow-up

All retrospective patients received a telephone follow-up or outpatients follow-up which recorded any clinical events after the PCI. This follow-up date was taken as the censorship time point. All patient-reported clinical events were investigated by collecting GP summaries or discharge summaries from local general hospitals

2.5.2 Prospective study design

Recruitment: referral process

Correspondences from referring district cardiologists were to a named surgeon involved in the LTHT LMCA revascularisation clinic or to the cardiac interventionist.

Patients referred to the LTHT multidisciplinary team meeting (MDT) were approached for consent at the time of admission for revascularisation to the LTHT.

Patients who were diagnosed after angiography at the LGI were at the time of their revascularisation procedure, either as an in-patient or upon elective admission. In the case of emergency revascularisation, such as STEMI, we sought consent from these patients after their revascularisation procedure.

The heart team is a concept approved by the ESC and AHA for patients considered for LMCA revascularisation. All patients were considered for a multidisciplinary discussion in the following ways:

Elective patients were either discussed at their local district general hospitals (DGH's) and then referred to a named surgeon at the LTHT, or referred to the LTHT MDT. Urgent admissions to the LTHT were discussed at the LTHT MDT. Patients admitted as an emergency, often had treatment in their best interest, but where possible discussions between the interventional cardiologist and on-call surgeon were documented.

Issues with recruitment

We recognised potential issues relating to recruitment, and instituted strategies to address these as follows:

1) Direct referrals to a named surgeon would bypass the discussion at an MDT and lead to missed recruitment – The project outline was presented to the Yorkshire Consultant Cardiology Regional Working Group in November 2012. All DGH centres were invited to participate as research centres or to refer patients to the LTHT MDT. Furthermore, the study design and ethics application made possible the recruitment from multiple centres.

2) Emergency admissions at night may be repatriated to regional hospitals following treatment, representing a missed opportunity for recruitment– We placed posters in the cathlab area with contact details of the research team. Our research team would go to coronary care unit (CCU) on a daily basis to recruit overnight emergency admissions.

Follow-up of prospectively-recruited patients

Prospectively-recruited patients had a planned telephone or clinic follow-up conducted at 6 months post-procedure and then yearly. The HRQOL measures we used and questionnaire design was planned with the advice of Dr F. Astin, formerly of the School of Healthcare, University of Leeds. HRQOL questionnaires were completed by patients at the following time points to allow for longitudinal analysis:

- 2 weeks prior to procedure (either PCI or CABG): MacNew [66], Brief illness perception [70]
- 1-Month post-procedure: MacNew, Brief illness perception and PPE-15(Picker Questionnaire) posted
- 6 month post-procedure/recruitment: MacNew, Brief Illness perception
- 1 year post-procedure/recruitment: MacNew and Brief Illness perception

Documents approved for the recruitment and collection of data include the Patient information leaflet (PIS) (Appendix 1), consent form (Appendix 2) and letter to the GP. The HRQOL measures include the combined questionnaires for use at 2 weeks prior, 1, 6 and 12 months post-procedure (sample questionnaire, Appendix 3). These questionnaires are validated for use in measuring outcomes from cardiovascular disease.

Inclusion and exclusion criteria

All consenting patients with significant left main coronary artery disease were included. These include patients treated with PCI or CABG revascularisation as well as those on medical treatment. Patients with a predicated lifespan of less than 90 days, with some other terminal diagnosis, were excluded from the study.

2.6 Angiographic data

All angiograms were reviewed by an experienced interventional cardiologist who was blinded to all outcomes. Baseline coronary angiograms were reviewed to confirm the presence of *de novo* left main coronary artery disease (defined as a stenosis >50%) and to exclude patients with patent bypass grafts to the left coronary artery tree (denoting a protected circulation).

2.6.1 SYNTAX score (SS)

The SS is a comprehensive anatomical assessment derived from various pre-existing classifications. It is calculated by analysing diagnostic angiograms. Each lesion producing ≥50% luminal obstruction in vessels ≥1.5 mm is defined based on the modified AHA coronary tree segment classification and separately scored regarding bifurcations or trifurcations or aortic ostial localisation, chronic occlusion, vessel tortuosity, length, calcification and thrombus formation. Finally, the score of each lesion is added to obtain the patient's raw SS. Thus, the SS reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33. The SYNTAX score was calculated the syntax score (SS) using an online calculator (www.syntaxscore.com).

2.6.1 Residual SYNTAX score (rSS) and Delta SYNTAX score (deltaSS)

The residual SS (rSS) was derived by subtracting all treated lesion scores from the SS, thus, representing the complexity of the remaining coronary artery disease. The amount of coronary artery revascularisation undertaken was estimated using the Delta SS (defined as the difference between baseline SS and rSS).

2.6.2 Medina classification

Left main bifurcation disease was classified according to the Medina classification [104]. The Medina classification uses the binary notation to describe the presence (1) or absence (0) of significant coronary atheroma at the bifurcation within the Main vessel, main branch and side branch. The annotation for disease at all segments is as follows:

Main Vessel,Main Branch,Side Branch = 1,1,1

Through this annotation, bifurcation disease can be classified as 'True' bifurcation disease (1,1,1 and 0,1,1 and 1,0,1) and 'non-true' bifurcation disease.

2.6.3 Procedural Complications

Complications reported at the time of the procedure were recorded on Cardiobase® and then verified by angiographic review. At the time of angiographic review if further complications were recorded or if those on the database were recorded in error, the complications logged at the time of the angiographic review were taken as final.

2.7 Outcome measures

Traditional measures of outcome from revascularisation studies include hard endpoints of MACCE such as all cause death, myocardial infarction, repeat revascularisation events (target lesion and vessel revascularisation) and stroke.

Definitions of these outcomes are provided in original research articles but may differ between studies.

2.7.1 Major adverse cardiovascular and cerebrovascular events

Definitions

For the purpose of this study outcomes were defined using the ARC guidelines [180], here the ARC recommends using all-cause mortality in preference to cardiac death.

Further, it recommends the diagnosis of MI according to biomarker rise in accordance with the current guidelines [193, 194].

For the purposes of this study we adopted the classification of repeat revascularisation. After MACCE review with an independent interventional cardiologist, we included all ischaemia driven non-TVR and TVR.

Stroke was defined as a new and persistent neurologic deficit developing over a short period of time, which is caused by an obstruction to cerebral blood flow and/or cerebral hemorrhage in the absence of a non-vascular cause (e.g. infection/trauma/ tumour)

Data collection

All retrospective patients received a telephone follow-up or outpatients follow-up which recorded any clinical events after the PCI. The research nurse or doctor would use a prescribed questionnaire to direct the interview. All patient-reported clinical events were investigated by collecting transcripts of treatment summaries from primary care or discharge summaries from local general hospitals. Hospital electronic database systems, such as Patient Administration Service (PAS), were searched using

the patient NHS number for unreported MACCE events. Details of the date and cause of death was tracked through linkage of the registry to the Office for National Statistics.

Independent MACE review

All clinical events were independently reviewed by a consultant interventional cardiologist, Dr C.J. Malkin. Events were classified according to the academic research consortiums (ARC) definitions for myocardial infarction, repeat revascularisations and stent thrombosis (ST) [180]. Events were classified as either definite/probable/possible ST.

Patient deaths were also investigated to establish the likelihood of ST. ONS data on cause of deaths were used to identify cardiac deaths and then further investigation included Cardiobase®, discharge summaries, clinical notes and investigations to diagnose ST. In a small number of cases post-mortem reports were used for review.

2.7.2 Quality of life measures

Quality of life measures were used in the prospective study including the MacNew and the Brief illness perception.

The MacNew questionnaire has 27 items with a Likert-type, single response questionnaire to assess the three domains of quality of life; emotional, social and physical. The global and subscale scores are used to assess quality of life over time. To calculate, divide the sum of the scores by the number of questions aggregated, to assess a particular domain [195, 196].

The Brief illness perception score uses a 0-to-10 Likert scale to assess responses to 8 questions. Each question assesses a separate item of the cognitive and emotional illness representations [197]. An increase in the score represents an increase in the domains measured. The means of the score are calculated and allow us to observe change over time.

2.1.1.1 Public consultation

We conducted a public consultation with the West Yorkshire Cardiovascular Network Patient and Public group on the 6th September 2013. This consultation process informed the study design, implementation and the recoding of outcome measures. Of note, their consensus opinion (refer to Appendix 4: West Yorkshire Cardiac patient and public group consultation) was that the components of MACCE should not be considered as equal.

In summary:

- ''The group felt that 'quality of life is the single most important indicator' for patients who survive the initial procedure.

- They also felt that stroke should be weighted more heavily than the risk of MI or repeat revascularisation, however

-The severity of each MACCE event should be measured individually, that is, for an MI which results in the need for CABG should carry more weight than a simple TIA/Stroke from which a patient makes a full recovery.

Indeed, the impact that these events would have on a patient's quality of life was considered the main factor when weighing the decision between two treatments.''

While the consultation process emphasised that weighting MACCE may better inform the impact of outcomes, no validated weighting exists. We felt that using quality of life as a separate outcome measure would adequately demonstrate the impact a MACCE event has on the patient.

2.8 Statistical methods

Statistical analysis was performed with IBM SPSS statistics version 20 (IBM Corporation, NY, USA).

2.8.1 Data descriptors

Baseline characteristics were described using numbers and percentages for categorical data. Means and standard deviations (SD) or medians and interquartile ranges (IQR) were used for normally and non-normally distributed continuous variables respectively. Categorical data were compared using a Pearson Chi-squared test. Continuous variables were compared using one way ANOVA for normally distributed variables and the Kruskal-Wallis test for non-normally distributed data.

2.8.2 Survival analysis

Kaplan-Meier Survival analysis

We used Kaplan-Meier estimates for cumulative event rates and constructed survival curves. Survival curves were compared using the log-rank test.

Cox Regression analysis

Test variables, with a plausible association to adverse outcomes were entered into an unadjusted regression analysis. Resultant significant variables, $p<0.10$, were used to study adjusted survival using Cox proportional hazards model, with the stepwise removal of non-significant factors. The final model adjusted for mode of presentation, comorbidity (renal impairment, diabetes, previous cardiac surgery, previous myocardial infarction, peripheral vascular disease) and PCI strategy. Final estimates were represented as adjusted hazard ratios (aHR) with associated 95% confidence intervals (CI). The proportional assumptions were tested and not violated. We adjusted

for varying levels of baseline disease severity using the baseline SS in the Cox model. All tests were two-sided, and statistical significance was considered as $p<0.05$.

2.8.3 Methods to deal with confounders and bias

We addressed potential confounders by exploring causal relationships using a directed acyclic graph. In the case of collinearity of variables, we included those variables with a perceived greater discrimination, such as Syntax Score (SS) used in preference to specific lesion-level data, such as coronary lesion calcification or length of the coronary atheromatous lesion.

2.9 Missing data

Missing data are a common finding in retrospective studies. A significant amount of LV function assessments were missing in spite of investigating clinical notes as well as contacting local hospitals. I received assistance from Mr Sami Saeed S Almudarra, Biostatistics University of Leeds, with the analysis and statistical methods used to assess missing data including building multiple imputation models.

2.9.1 Defining missing data and tests of missing data

A sensitivity analysis was conducted to test associations and potential confounders. We were then able to explore the mechanisms which lead to the missingness of data allowing us to classify missing data into several types. By understanding the nature of our missing data, we were able to consider appropriate ways to mitigate the effects of missing data on the analysis. We therefore applied the following missing data classification:

-Missing Completely at Random (MCAR), where the missing value (y) neither depends on x nor y. No observed data or values can explain the missing data, and there is no systematic or recurrent issue which makes some data more likely to be missing than others.

-Missing at Random (MAR), where the missing value (y) depends on x, but not y. In this case, the missing values show an association with observed data but not with the missing data; there IS a systematic relationship. For example, in a survey of incomes within a community, the income data are missing for high earners as they are unwilling to submit the information.

-Missing not at Random (MNAR), where the probability of a missing value is dependent on the variable that is missing. For example, poor LV function is missing because the LV function is indeed poor.

2.9.2 Methods of dealing with missing data

Once the missing data were classified, we considered appropriate methods to deal with them. Statistical methods which deal with missing data assume MCAR or MAR, yet most often we find data MNAR [198]. Due to the limited number of patients and the potential for increased bias with MNAR we did not consider either list-wise or pairwise deletion techniques. Similarly, we decided against single imputation techniques, such as mean/mode substitution or conditional mean substitution, due to the potential for reduced variability and bias [199]. While a maximum likelihood estimation would use all the available cases, it produces significant bias with data which is MNAR; we opted for multiple imputation as there is evidence it may offer unbiased estimates of the missing data even when the data are MNAR [200]. We used the regression method of multiple imputation [201] . Using this method, a regression model is fitted for each variable with missing values, with the previous variables as covariates. This regression model is used to impute the missing values for each variable. Multiple imputation replaces missing data with imputed values. An appraisal of the distribution of the observed data, allows us to use predictor variables to impute missing values. In this way multiple imputation incorporates a robust bayesian

approach and thereby reduces bias. An acyclic directed graph was used to identify the predictor variables related to the missing values. Five datasets were imputed in this analysis, in this way we can create the necessary variability to accommodate for the unpredictability of the missing data. By applying the model to all of the datasets we can then draw valid conclusions.

2.10 Logistical problems

Regular research team meetings between co-investigators UMS, IRP, DB, CAM, RGG and RM were held to discuss the database design and to troubleshoot. The database evolved over time with additional fields added at different stages of the recruitment process. The intention was to develop a database which could collect the clinical data fields recommended in the British Cardiac Interventional Society's (BCIS) guidance on database design. The goal was a database with the dual purpose of live research data collection as well as serving as an in-house working database for interventional procedures.

The resultant ongoing changes in the database design resulted in the unfortunate delay in data entry while ongoing recruitment continued. Furthermore, this created significant amounts of missing data and led to a recurring data re-entry on the same group of patients. Where our intention was to collect data prospectively, these issues naturally created problems aligning data, and therefore some of the data was 're-entered' several times over.

Data were regularly re-validated which again created a time-consuming treadmill of data collection. We considered this a learning experience; the lesson learnt was that the database design was probably the most important initial step in this research process.

3. Overall retrospective cohort of left main coronary PCI

3.1 Study cohort

We studied all patients who received percutaneous coronary intervention (PCI) of the unprotected left main coronary artery (ULMCA) at the Leeds General Infirmary from March 2005 up to March 2013. A search of the bespoke in-house procedural database identified 491 patients. We reviewed angiograms and procedural notes to determine if any patients had a patent graft to the left coronary artery, a protected left coronary circulation. We excluded 125 patients with a protected LMCA from further analysis. We were left with 366 patients for further analysis. The number of patients treated increased year upon year from 2005-2008 and then continued above 50 patients per year apart from the year 2009, during which only 40 patients were treated (see **Table 6**).

The median (IQR) age of the cohort was 76.0(18.0) years (**Table 7**), with 42.1% (154) of patients in the octogenarian/nonagenarian age group (see **Figure 2**). Patient profiles varied depending upon the mode of presentation, and there was a significant difference in age with younger patients presenting with STEMI. A third of the patients were female. Almost three-quarters of patients presented with an acute coronary syndrome (ACS), close to a third (29.0%) presented with STEMI. Patients presenting with STEMI were more likely to be haemodynamically compromised with over a third presenting in cardiogenic shock, and greater chances of developing cardiac arrest during the procedure.

Comorbidity showed considerable variation across the modes of presentation, with generally more comorbidity in patients presenting with stable coronary disease or NSTEMI. Diabetes was present in 22.1% of patients. However, patients presenting with STEMI were least likely to have diabetes. Peripheral vascular disease was present in 15.6% of patients and was more prevalent in patients with stable coronary disease and NSTEMI on presentation. While up to 38.8% of patients had a history of previous MI,

this was the first presentation with an MI for 86% of patients suffering an STEMI. STEMI patients were also less likely to give a history of previous coronary revascularisation with either PCI or CABG. Despite 5.8% of patients having had previous cardiac surgery, none of these patients had protected left coronary arteries. The EuroSCORE II (IQR), was 8.4% (13.7), with only 34 (9.3%) of patients with a EuroSCORE of less than 2%. Of these 34 patients, 26 (7.1%) had a SS of under <32 and 22(6.0%) had distal LMCA disease. Given this background, about 32.2% of patients had missing LV function assessments.

Table 6: Unprotected LMCA PCI in calendar year

Year	Number of LMCA PCI	%DES
2005	17	52.9
2006	31	61.3
2007	31	54.8
2008	57	49.1
2009	40	82.5
2010	58	93.1
2011	57	89.5
2012	59	96.6
2013 (up to March)	16	75.0

LMCA – left main coronary artery; PCI: percutaneous coronary intervention; DES: drug eluting stent

Table 7: Patient characteristics (n=366)

	Overall n=366	Stable angina (1) 99 (27.0%)	NSTEMI (2) 163 (44.5%)	STEMI (3) 104 (28.4%)	p (1v3)	p (1v2)	p (2v3)	Missing data %
Median age (IQR), years	76.0 (18.0)	78.0 (17.0)	75.6 (12.0)	66.9 (24.0)	p<0.05	p=NS	p<0.05	0
Female Sex	122 (33.3%)	27 (27.3%)	65 (39.9%)	30 (28.8%)	p=NS	p<0.05	p=NS	0
Cardiac arrest	8 (2.4%)	0	3 (1.9%)	5(4.95%)	p<0.05	p=NS	p=NS	0
Cardiogenic shock	46 (12.6%)	0	9 (5.5%)	37 (35.6%)	p<0.05	p<0.05	p<0.05	0
Hyperlipidaemia	172 (47.0%)	57 (60.0%)	86 (54.8%)	29 (30.9%)	p<0.05	p=NS	p<0.05	0
Diabetes	81 (22.1%)	20 (20.2%)	50 (30.7%)	11 (10.6%)	p=NS	p=NS	p<0.05	0
Hypertension	174 (47.5%)	56 (32.2%)	90 (55.2%)	28 (26.9%)	p=NS	p<0.05	p<0.05	0
Current or ex-smoker	172 (47.0%)	49 (53.8%)	75 (54.3%)	48 (58.5%)	p=NS	p=NS	p=NS	0
Previous Stroke	37 (10.1%)	13 (13.1%)	16 (9.8%)	8 (7.7%)	p=NS	p=NS	p=NS	0
Peripheral vascular disease	57 (15.6%)	20 (20.2%)	29 (17.8%)	8 (7.7%)	p<0.05	p=NS	p<0.05	0
Previous MI	142 (38.8%)	40 (40.4%)	87 (53.4%)	15 (14.4%)	p<0.05	p<0.05	p<0.05	0
Previous PCI	60 (16.4%)	24 (24.2%)	31 (19.0%)	5 (4.8%)	p<0.05	p=NS	p<0.05	0
Previous Cardiac surgery	21 (5.8%)	8 (8.1%)	11 (6.7%)	2 (1.9%)	p<0.05	p=NS	p=NS	0
Renal Impairment	38 (10.4%)	8 (8.1%)	24 (14.7%)	6 (5.8%)	p=NS	p<0.05	p<0.05	0
Moderate to severe LV impairment	128 (35.0%)	26 (26.2%)	66 (40.4%)	36 (34.6%)	p<0.05	p<0.05	p=NS	32.2%
Logistic EuroSCORE (IQR)	8.4(13.7)	5.7(8.7)	8.4(13.)3)	15.0(27.2	p<0.05	p<0.05	p<0.05	

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV: left ventricular; NS: not significant

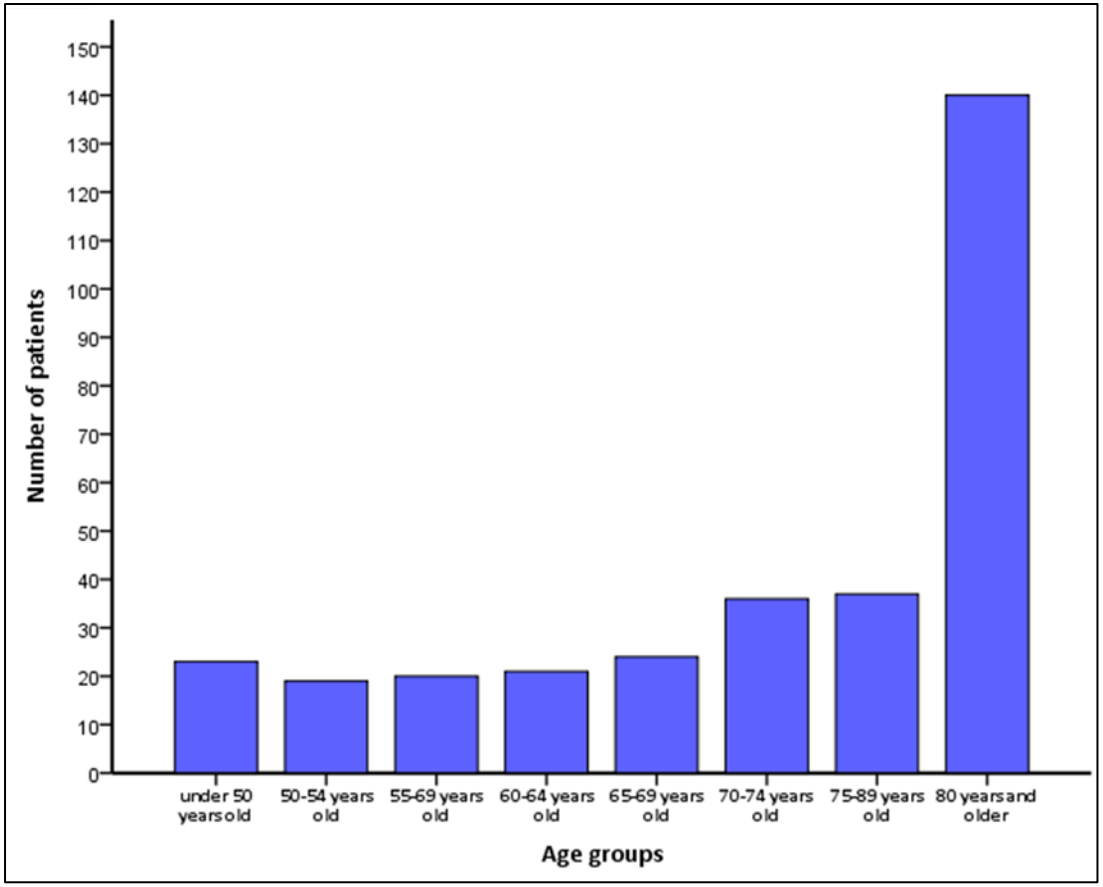

Figure 2: Number of ULMCA PCI according to 5 year age groups

3.1.1 Missing LV function

For those with a valid LV assessment, moderate to severe LV impairment was present in 128 (35.0%), which included 27 patients with cardiogenic shock on presentation. While amongst those with no LV assessment, 19 patients presented in cardiogenic shock. Therefore, with no further way to assess LV function at the time, we were unable to include LV function in modelling predictors of outcome.

Significant differences in clinical characteristics were apparent between patients with missing LV function assessments and those with assessments present (see **Table 8**). Those with missing LV function assessments were more likely to present with an ACS and in particular an STEMI. Those with LV assessments present were more likely to have hypertension, renal impairment, a history of previous MI, previous PCI and were older at presentation. Furthermore, those with missing LV assessments were significantly younger.

The burden of coronary disease did not differ between the two groups; neither was there a difference in the history of diabetes or peripheral vascular disease. Interestingly, concerning the presentation with cardiogenic shock, there was no significant difference between the groups.

Table 8: Comparison of patients with missing LV assessment to those with LV assessments present

	Missing LV, n=118 (%)	LV assessment present, n=246 (%)	p-value
Female gender	36 (30.5%)	86 (35.0%)	p=NS
Median age(IQR), years	72.0(28.0)	77.0(14.0)	p<0.05
Acute coronary syndrome	97 (82.2%)	168 (68.3%)	p<0.05
STEMI at presentation	55 (46.6%)	47 (19.1%)	p<0.05
Cardiogenic shock	19 (16.1%)	27 (11.0%)	p=NS
Renal impairment	6 (5.1%)	32 13.0%)	p<0.05
History of diabetes	26 (22.0%)	55 (22.4%)	p=NS
Peripheral vascular disease	15 (12.7%)	42 (17.1%)	p=NS
Hypertension	44 (37.3%)	130 (52.8%)	p<0.05
Previous PCI	12 (10.2%)	48 (19.5%)	p<0.05
Previous MI	30 (25.4%)	112 45.5%)	p<0.05
Median(IQR) SYNTAX score	30.0 (20.8)	31.0 (18.3)	p=NS
DES used	83 (70.3%)	197 (80.1%)	p=NS

LV: left ventricular; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; IQR: interquartile range; PCI: percutaneous coronary intervention; MI: myocardial infarction; SYNTAX: synergy between PCI with taxus and cardiac surgery; STEMI: ST-elevation myocardial infarction; DES: drug eluting stent; NS: not significant

3.1.2 Angiographic data

The majority of patients presented with extensive coronary artery disease with a median (IQR) SS of 31.00 (18.5), with no significant difference between the three clinical syndromes (**Table 9**). In the overall cohort, 163 (44.5%) of patients were grouped in the high (⩾32) SYNTAX tertile [55] (see **Table 9** and **Figure 3**). The majority of patients in each clinical syndrome group fell in the high SYNTAX tertile. There was no significant difference in the distribution of the SYNTAX scores across tertiles for the mode of presentation.

We found significant stenoses of the LMCA bifurcation in close to three-quarters of patients. Only 124 (33.8%) patients presented with associated multi-vessel disease, including LM +2VD and LMCA +3VD. Over half of patients had a significant coronary stenosis in the RCA. Chronic total occlusions (CTO's) were present in 17.5% of patients and were within the proximal to mid segments of vessels in 16.7% of patients.

3.1.3 PCI procedural data

Table 10 includes the procedural data for the coronary interventions. The majority of procedures were carried out via femoral artery access with only 106 (29.0%) procedures via radial artery access. Change of access from the radial to the femoral route occurred in 15 (4.1%) patients; numerically this occurred more frequently in patients presenting with STEMI. Larger sheath sizes, 7Fr and 8Fr, were favoured in the stable and NSTEMI patient groups, those presenting with STEMI were more likely to be treated using a 6Fr sheath. 7/8Fr catheters were used more frequently in patients with LMCA bifurcation stenosis compared to those with no stenosis at the bifurcation (82.6% vs. 65.8%, $p<0.05$).

The intra-aortic balloon pump (IABP) was used pre-PCI in a 15.8% of patients, with STEMI patients more likely to have an IABP before PCI. Patients with STEMI were more likely to receive Bivalirudin than stable patients or those with NSTEMI, where heparin was preferred.

The proportion of drug eluting stents (DES) used increased from about half in the years 2005-2008, to close to 90% in the years 2009-2013 (see **Table 6**). DES use differed significantly across modes of presentation, those with stable angina and NSTEMI were more likely to receive a DES than those presenting with STEMI. Still, in all these groups the majority of patients were treated with a DES. The proportion of second generation DES to 1st generation DES was more than fourfold. The median total stent length (IQR) was 35mm (25mm) per patient. The single stent strategy was favoured in patients with LMCA bifurcation disease; while only 115 patients, or 43.9% of patients with LMCA bifurcation disease, received a two-stent strategy.

Intravascular imaging, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), was used in 81 (22.1%) of cases, including 18.3% of STEMI patients. There was no relationship to the presence of LMCA bifurcation disease and the use of IVUS/OCT. Rotational atherectomy was successfully applied to segment 5 in over 10.0% of patients, with only one STEMI patient treated with this modality. PCI was considered successful after angiographic review in 340 (92.9%) of cases.

Table 9: Angiographic data for overall study population (n=366)

Characteristic	Overall 366	Stable angina (1) 99 (27.0%)	NSTEMI (2) 163 (44.5%)	STEMI (3) 104 (28.4%)	p (1v2)	p (1v3)	p (2v3)
LMCA Bifurcation lesion	264 (72.1%)	77 (77.8%)	118 (72.4%)	69 (66.3%)	p=NS	p=NS	p=NS
'True' LMCA bifurcations	193 (52.7%)	57 (57.6%)	95 (58.2%)	42 (40.4%)	p = NS	p<0.05	p<0.05
LM+1VD	147 (40.2%)	46 (46.5%)	58 (35.6%)	43 (41.3%)	p<0.05	p=NS	p=NS
LM+2VD	88 (24.0%)	20 (20.2%)	47 (28.8%)	21 (20.2%)	p=NS	p=NS	p=NS
LM+3VD	36 (9.8%)	9 (9.1%)	16 (9.8%)	11 (10.6%)	p=NS	p=NS	p=NS
Median SYNTAX score (IQR)	31.0(18.5)	31.0 (14.0)	30.0 (18.0)	34.8 (23.9)	p=NS	p<0.05	p<0.05
Lower SS tertile ≤23	90 (24.6%)	19 (19.6%)	45 (27.8%)	26 (25.5%)	p=NS	p=NS	p=NS
Intermediate SS tertile 23-32	108 (29.5%)	38 (39.2%)	48 (29.6%)	22 (21.6%)	p=NS	p<0.05	p=NS
High SS tertile ≥32	163 (44.5%)	40 (41.2%)	69 (42.6%)	54 (52.9%)	p=NS	p<0.05	p=NS
Dominant RCA	336(95.5%)	93 (96.9%)	148 (94.3%)	95 (96.0%)	p=NS	p=NS	p=NS
Significant RCA disease	177 (50.6%)	47 (49.5%)	83 (53.2%)	47 (47.5%)	p=NS	p=NS	p=NS
CTO present	64 (17.5%)	14 (14.1%)	26 (16.0%)	24 (23.1%)	p=NS	p=NS	p=NS
CTO of proximal/mid vessel segments	61 (16.7%)	13 (13.1%)	26 (16.0%)	22 (21.2%)	p=NS	p=NS	p=NS

NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; LMCA: left main coronary artery; LM: left main; VD: vessel disease; SYNTAX: synergy between PCI with taxus and cardiac surgery; IQR: interquartile range; SS: SYNTAX score RCA: right coronary artery; CTO: chronic total occlusion; NS: not significant

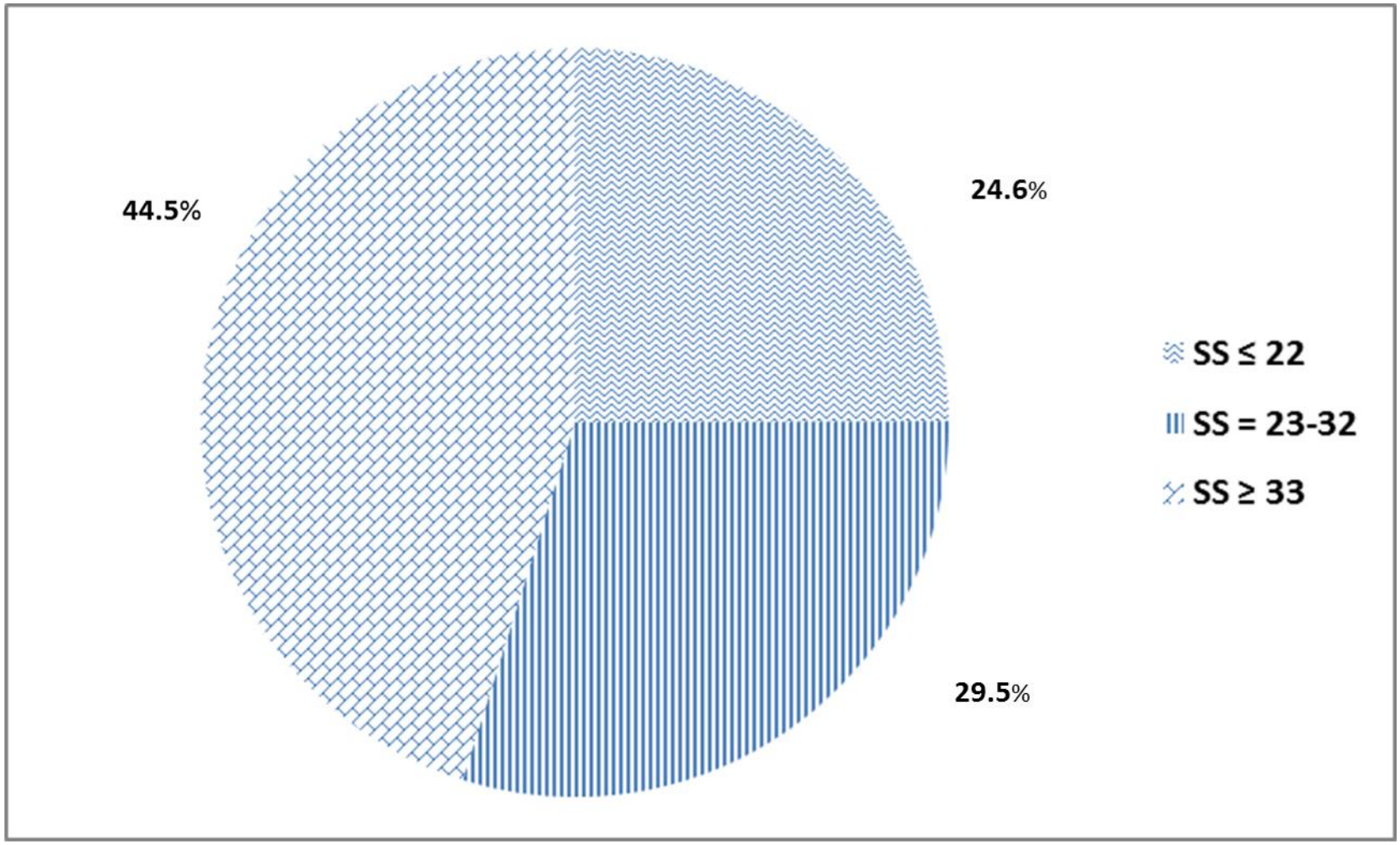

Figure 3: Distribution of SYNTAX Score (SS) tertiles for the overall study population (n=366)

Table 10: PCI data for overall study population (n=366)

	Overall	Stable angina 99 (27.0%)	NSTEMI 163 (44.5%)	STEMI 104 (28.4%)	p (1v2)	p (1v3)	p (2v3)
Femoral access	245 (66.9%)	74 (74.7%)	114 (69.9%)	57 (54.8%)	p=NS	p<0.05	p<0.05
Radial Access	106 (29.0%)	24 (24.2%)	44 (27.0%)	38 (36.5%)	p=NS	p<0.05	p<0.05
Radial and Femoral access	15 (4.1%)	1 (1.0%)	5 (3.1%)	9 (8.7%)	p=NS	p<0.05	p<0.05
6 Fr Sheath	91 (24.9%)	12 (12.4%)	33 (20.2%)	47 (45.2%)	p<0.05	p<0.05	p<0.05
7 Fr Sheath	218 (59.6%)	65 (67.0%)	104 (63.8%)	49 (47.1%)	p=NS	p<0.05	p<0.05
8 Fr Sheath	36 (9.8%)	15 (15.5%)	19 (11.7%)	2 (1.9%)	p=NS	p<0.05	p<0.05
IABP use pre – PCI	58 (15.8%)	4 (4.1%)	17 (10.4%)	37 (35.6%)	p<0.05	p<0.05	p<0.05
IABP use during PCI	15 (4.1%)	2 (2.0%)	5 (3.1%)	8 (7.7%)	p=NS	p<0.05	p<0.05
Heparin	229 (62.5%)	78 (78.8%)	117 (71.8%)	43 (41.3%)	p=NS	p=NS	p=NS
Bivalirudin	115 (31.4%)	21 (21.2%)	45 (27.6%)	58 (55.8%)	p=NS	p<0.05	p<0.05
Abciximab	114 (31.1%)	27 (27.3%)	48 (29.4%)	39 (37.5%)	p=NS	p<0.05	p<0.05
Tirofiban	12 (3.3%)	1 (1.0%)	10 (6.1%)	1 (1.0%)	p<0.05	p=NS	p<0.05
2 stent strategies for LMCA bifurcation	115 (32.8%)	33 (33.3%)	57 (35.0%)	25 (24.0%)	p=NS	p<0.05	p<0.05
DES use (patient level data)	284 (77.6%)	89 (89.9%)	129 (79.1%)	66 (63.5%)	p<0.05	p<0.05	p<0.05
1st generation DES	48 (13.1%)	15 (15.2%)	25 (15.3%)	8 (7.7%)	p=NS	p<0.05	p<0.05
2nd Generation DES	236 (64.5%)	74 (74.7%)	104 (63.8%)	58 (55.8%)	p<0.05	p<0.05	p<0.05
Median (IQR) total stent length	35.0 (25.0)	36.0 (26.0)	32.0 (25.3)	36.0 (27.0)	p<0.05	p=NS	p=NS

Rotational atherectomy	39 (10.7%)	20 (20.8%)	18 (11.0%)	1 (2.6%)	p=NS	p<0.05	p<0.05
IVUS	79 (21.6%)	27 (27.3%)	33 (20.2%)	19 (18.3%)	p<0.05	p<0.05	p=NS
OCT	2 (0.5%)	1 (1.0%)	1 (1.0%)	0	p=NS	p=NS	p=NS
Operator reported successful PCI	340 (92.9%)	97 (98.0%)	153 (93.9%)	91 (87.5%)	p=NS	p<0.05	p<0.05

PCI: percutaneous coronary intervention; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; Fr: french size; IABP: intra-aortic balloon pump; LMCA: left main coronary artery; IVUS: intravascular ultrasound; OCT: optical coherence tomography; NS: not significant

3.1.4 PCI complications

Over a quarter of patients, 92 (25.1%), were reported to have suffered a procedural or access site complication (T**able 11**). The vast majority of complications were procedural, coronary dissections were identified in 48 (13.1%) of patients and occurred with equal frequency amongst STEMI, NSTEMI and stable patients. Arterial access complications were reported on Cardiobase® in 21 (5.7%) of cases (see T**able 12**). In all but two cases of access site complications a 7 or 8 Fr sheath was used from the femoral artery. Only one case out of seven femoral arterial haemorrhages required surgical intervention. The two reported arterial occlusions were not further defined. Patients presenting with STEMI were more likely to develop cardiogenic shock during the procedure, and were more likely to suffer a cardiac arrest.

Table 11: PCI procedural complications for overall study population (n=366)

Complication	Overall	Stable angina 99 (27.0%)	NSTEMI 163 (44.5%)	STEMI 104 (28.4%)	P (1v2)	P (1v3)	P (2v3)
Coronary dissection	48(13.1%)	14 (24.1%)	22 (13.5%)	12 (11.5%)	p<0.05	p<0.05	p=NS
Coronary perforation	6(1.6%)	2 (2.1%)	2 (1.2%)	2 (2.0%)	p=NS	p=NS	p=NS
Cardiac tamponade	3(0.8%)	2 (2.0%)	0	1 (1.0%)	p=NS	p=NS	p=NS
Cardiogenic shock developing during procedure	8(2.2%)	2 (2.0%)	6 (3.7%)	13 (12.5%)	p<0.05	p<0.05	p<0.05
Pulmonary oedema	2(0.5%)	0	2 (1.2%)	0	p=NS	p=NS	p=NS
Cardiac arrest	9(2.5%)	1 (1.0%)	1 (0.6%)	7 (6.8%)	p=NS	p<0.05	p<0.05
Propagation of thrombus	6(1.6%)	0	4 (2.5%)	2 (1.9%)	p=NS	p<0.05	p<0.05
Side branch occlusion	8(2.2%)	2 (2.0%)	3 (1.8%)	3 (2.9%)	p=NS	p=NS	p=NS
Stroke	1(0.3%)	0	1 (0.6%)	0	p=NS	p=NS	p=NS
Underdeployed stent	6(1.6%)	0	5 (3.1%)	1 (1.0%)	p<0.05	p=NS	p<0.05

PCI: percutaneous coronary intervention; BARC: Bleeding Academic research consortium defined bleeding complications; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; NS: not significant

Table 12: Access site complications for the overall study population (n=366)

Arterial complication	Overall	Stable angina 99 (27.0%)	NSTEMI 163 (44.5%)	STEMI 104 (28.4%)
Retroperitoneal bleed	1(0.3%)	0	1 (0.6%)	0
Surgical intervention	1(0.3%)	0	1 (0.6%)	0
Arterial dissection	6(1.6%)	0	6 (3.7%)	0
Arterial occlusion	2(0.5%)	0	0	2 (1.9%)
Arterial haemorrhage	7 (1.9%)	3 (3.0%)	3 (1.8%)	1 (1.0%)
False aneurysm requiring thrombin injection	1(0.3%)	0	1 (0.6%)	0
False aneurysm requiring compression	1(0.3%)	1 (1.0%)	0	0
False aneurysm conservative management	1(0.3%)	1 (1.0%)	0	0

NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; NS: not significant

3.1.5 Indices of multiple deprivation (IMD)

Based on the postcodes on record for patients, we allocated English indices of multiple deprivation (IMD) for lower super output areas (LSOA's). The office for national statistics supplied the LSOA's and IMD's; we used the recognised national quintiles for further analysis (**Table 13**). The quintiles represent five groups of increasing levels of deprivation from the 1st to the 5th. There was a significant difference in age between the quintiles with older patients in the 1st and 2nd quintiles, representing the least deprived areas. Patients in the most deprived quintiles had significantly more diabetes and renal impairment compared to the least deprived quintiles. There was no significant difference in the mode of clinical presentation, between the quintiles. Previous cardiac disease was prevalent amongst all quintiles equally with no difference in previous PCI or MI. The burden of coronary disease did not differ between the groups either; the high burden of left main coronary bifurcation disease was similar between groups. The SS did not differ between groups, and neither did the distribution of SS across the three tertiles.

Table 13:Overall study population characteristics by quintile of indices of multiple deprivation

Characteristic	1st Quintile (n=53)	2nd Quintile (n=93)	3rd Quintile (n=51)	4th Quintile (n=76)	5th Quintile (n=91)	p-value
Female gender	15 (28.3%)	30 (32.3%)	13 (25.5%)	30 (39.5%)	34 (37.4%)	p=NS
Median (IQR) age, years	78.0 (19.0)	80.0 (16.0)	76.0 (20.0)	76.0 (17.0)	74.0 (20.0)	p<0.05
NSTEMI	22 (41.5%)	39 (41.9%)	24 (47.1%)	35 (46.1%)	42 (46.2%)	p=NS
Stable Angina	15 (28.3%)	29 (31.2%)	13 (25.5%)	18 (23.7%)	24 (26.4%)	p=NS
STEMI at presentation	16 (30.2%)	25 (26.9%)	14 (27.5%)	23 (30.3%)	25 (27.5%)	p=NS
Cardiogenic shock	7 (13.2%)	10 (10.8%)	7 (3.7%)	12 (15.8%)	9 (9.9%)	p=NS
Renal impairment	1 (1.9%)	5 (5.4%)	4 (7.8%)	11 (14.5%)	16 (17.6%)	p<0.05
History of diabetes	10 (18.9%)	13 (14.0%)	6 (11.8%)	22 (28.9%)	29 (31.9%)	p<0.05
Previous stroke	7 (13.2%)	7 (7.5%)	8 (15.7%)	3 (3.9%)	12 (13.2%)	p=NS
Peripheral vascular disease	9 (17.0%)	9 (9.7%)	12 (23.5%)	13 (17.1%)	14 (15.4%)	p=NS
Hypertension	22 (41.5%)	47 (50.5%)	29 (56.9%)	32 (42.1%)	43 (47.3%)	p=NS
Previous PCI	9 (17.0%)	18 (19.4%)	6 (11.8%)	9 (11.8%)	18 (19.8%)	p=NS
Previous MI	21 (39.6%)	38 (40.9%)	16 (31.4%)	30 (31.4%)	37 (40.7%)	p=NS
Median(IQR) SYNTAX score	34.0 (17.0)	31.0 (17.0)	28.5 (20.0)	32.0 (20.0)	29.0 (19.9)	p=NS
LMCA Bifurcation lesion	39 (73.6%)	68 (73.1%)	34 (66.7%)	53 (69.7%)	68 (74.7%)	p=NS
LM+1VD	20 (37.7%)	41 (44.1%)	21 (41.2%)	26 (34.2%)	37 (40.7%)	p=NS
LM+2VD	10 (18.9%)	21 (22.6%)	13 (25.5%)	20 (26.3%)	24 (26.4%)	p=NS
LM+3VD	7 (13.2%)	9 (9.7%)	5 (9.8%)	12 (15.8%)	3 (3.3%)	p=NS

Dominant RCA	46 (92.0%)	84 (95.5%)	48 (94.1%)	70 (95.9%)	86 (97.7%)	p=NS
Significant RCA disease	26 (51.0%)	41 (47.1%)	26 (52.0%)	40 (55.6%)	42 (47.7%)	p=NS
CTO present	15 (28.3%)	9 (9.7%)	10 (19.6%)	14 (18.4%)	15 (16.5%)	p=NS
CTO of proximal/mid vessel segments	13 (24.5%)	8 (8.6%)	10 (19.6%)	14 (18.4%)	15 (16.5%)	p=NS

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; PCI: percutaneous coronary intervention; PCI: percutaneous coronary intervention; MI: myocardial infarction ; LMCA: left main coronary artery; SYNTAX: synergy between PCI with taxus and cardiac surgery; LM: Left main; CTO: chronic total occlusion; NS: not significant

3.2 Outcomes

Median (IQR) follow-up was 584 (1036) days. The crude 30-day mortality rate was 12.0%, one-year mortality was 20.2% and the overall mortality rate for the follow-up period was 35.2%. Table 14 shows a breakdown of all the MACCE during the study follow-up. The MACCE rate for the overall follow-up was 41.8%, where death makes up 81.7% of all MACCE. The MACCE rate at 30 days was 13.1% consisting of a high proportion of cardiac deaths. Cardiac deaths made up 85% of all MACCE at one month, 62.5% at one year and 52.2% for the entire follow-up period.

The proportion of non-cardiac cause of death rose steadily from 6.8% in one month to 18.9% at one year and 36.0% for the entire follow-up. At one year we report a repeat revascularisation rate of 2.5% and 5.2% over the whole follow-up period.

Myocardial infarction occurred in 10.1% of patients for the entire follow-up. We report definite and probable ST rates in this analysis. The early and late ST rates are 1.6% (6 cases) and 0.3% (1 case) respectively, with a VLST rate of 0.6 % (2 cases).

Table 14: MACCE at 30 days, 1year and median follow-up period for overall study population (n=366)

	0-30 days	1 year	Overall follow-up
All-cause death	44 (12.0%)	74 (20.2%)	125 (34.2%)
Cardiac Death	41 (11.2%)	60 (16.4%)	80 (21.9%)
MI	6 (1.6%)	32 (8.7%)	37 (10.1%)
Repeat revascularisation	2 (0.8%)	9 (2.5%)	19 (5.2%)
Stroke	1 (0.3%)	1 (0.3%)	4(1.1%)
Definite/Probable ST	6 (1.6%)	7 (1.9%)	9 (2.5%)
MACCE	48 (13.1%)	96 (26.2%)	153 (41.8%)

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; ST: stent thrombosis

3.2.1 Survival Analysis

Unadjusted Kaplan-Meier survival estimates

Unadjusted Kaplan-Meier survival curves show a significant difference in outcomes for the 3 SYNTAX score tertiles, see **figure 4**. There is a definite visual separation of the curves for the low and intermediate SS groups from the curve for the high SS group.

Survival curves for the three modes of presentation (**Figures 5-7**) show a significant difference in survival for the stable patients compared to those presenting with STEMI (**Figure 5**). The survival curve for STEMI patients show a large number of early events, and then a plateau, the survival curve of NSTEMI patients seem to converge with the survival curve of STEMI patients at about two years (**Figure 6**). A further analysis comparing patient presenting with NSTEMI to stable patients also showed no significant difference, although there seem to be more early events within the NSTEMI patients the two curves run in parallel after that with a similar attrition rate (**Figure 7**).

Patients presenting with cardiogenic shock suffered significantly worse outcomes, with a thirty-day mortality of 65.9% compared with 9.6% for those who did not suffer cardiogenic shock (**Figure 8**).

Unadjusted survival curves for quintiles of indices of deprivation showed no significant differences between the quintiles for survival free from MACCE (**Figure 9**). A separate analysis comparing the upper and lower quintiles did not reveal any significant differences (**Figure 10**).

Unadjusted survival of all patients older than 80 years old was similar to those under 80 years old, (**Figure 11**).

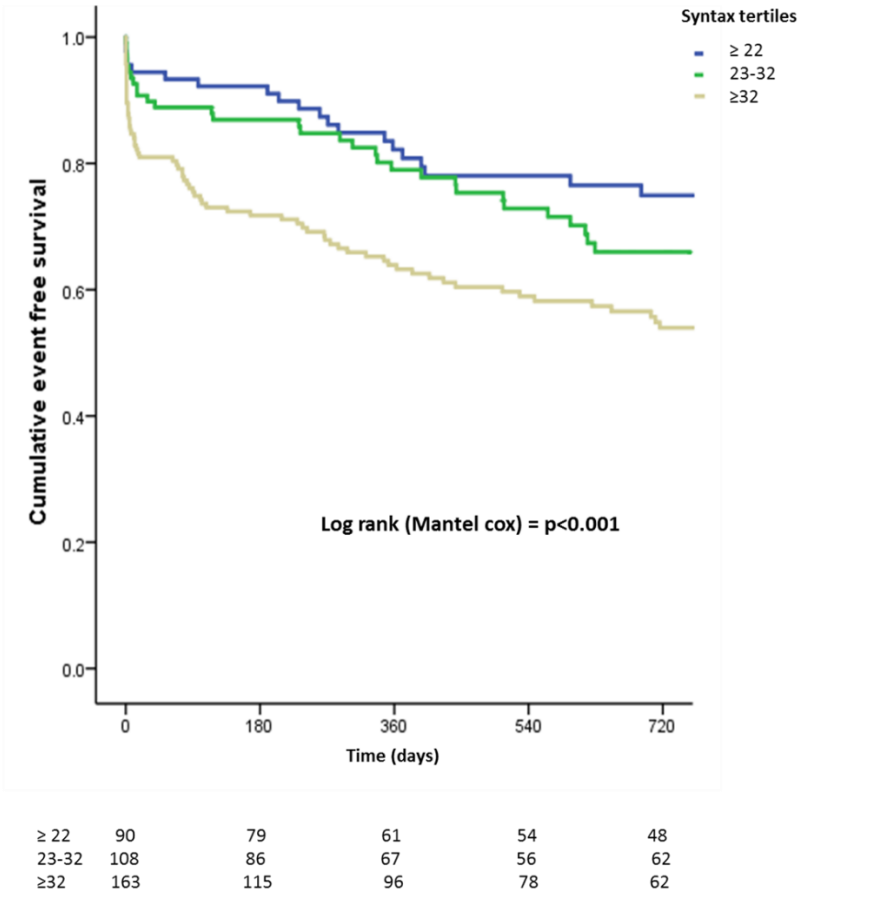

Figure 4: Kaplan-Meier (KM) survival curve of all LMCA PCI by SYNTAX score

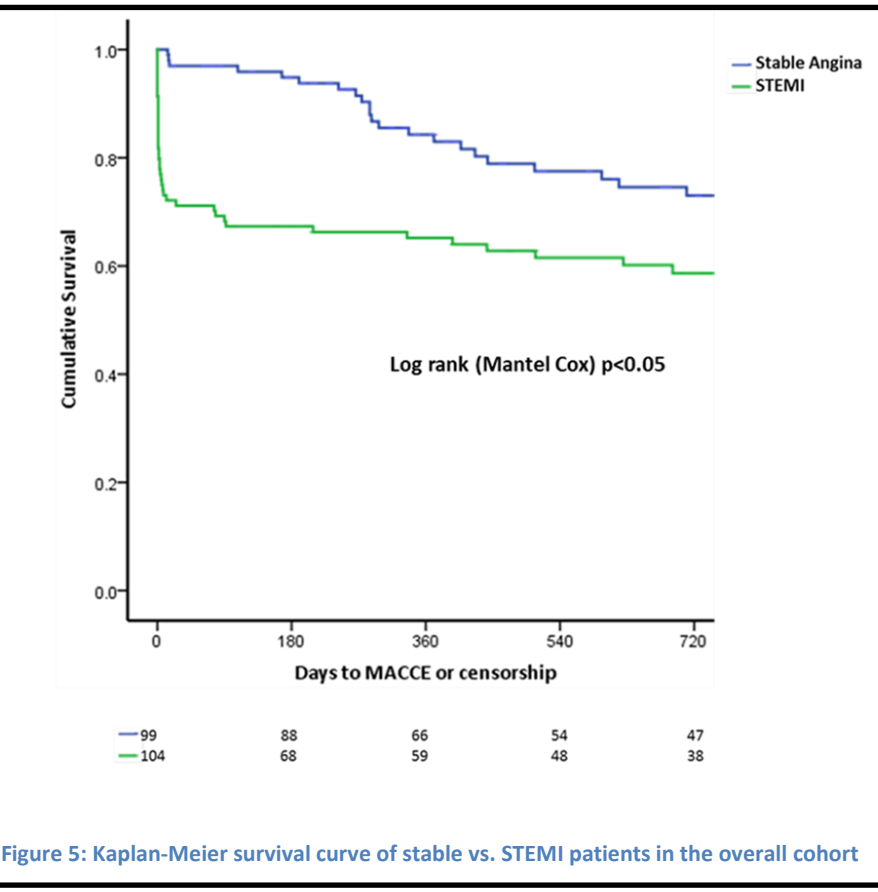

Figure 5: Kaplan-Meier survival curve of stable vs. STEMI patients in the overall cohort

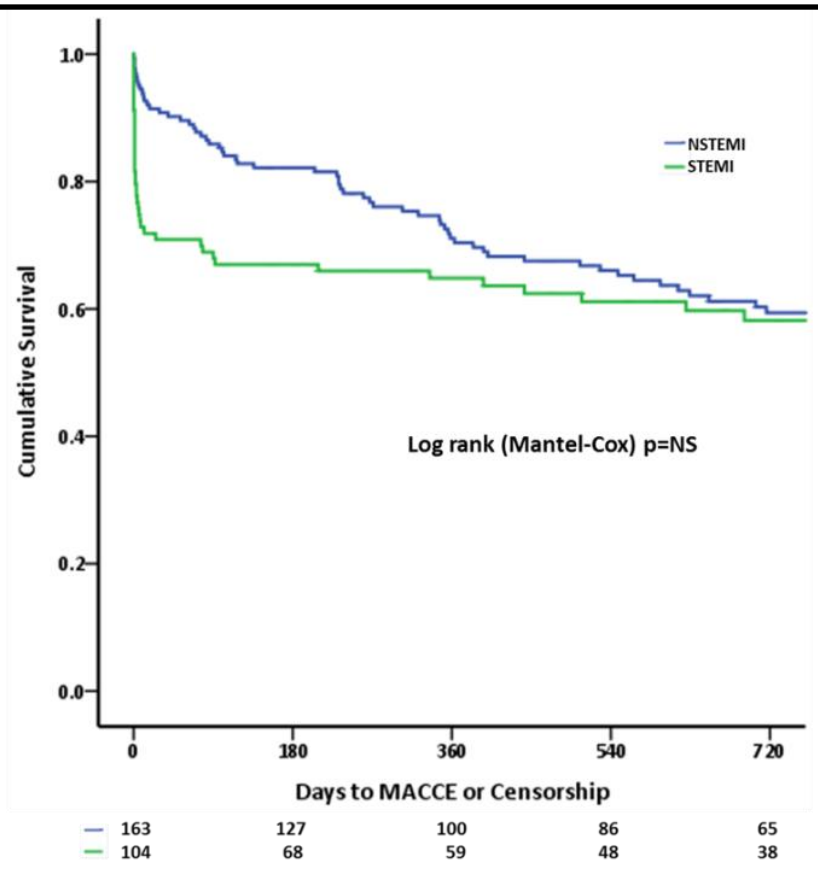

Figure 6: Kaplan-Meier survival curve of patients with NSTEMI vs STEMI in the overall cohort.

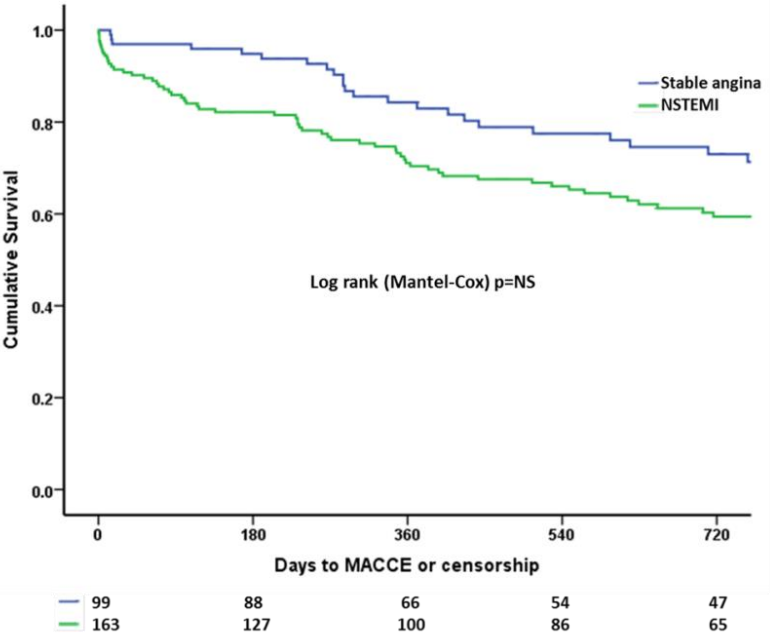

Figure 7: Kaplan-Meier survival curve of stable vs NSTEMI patients in the overall cohort

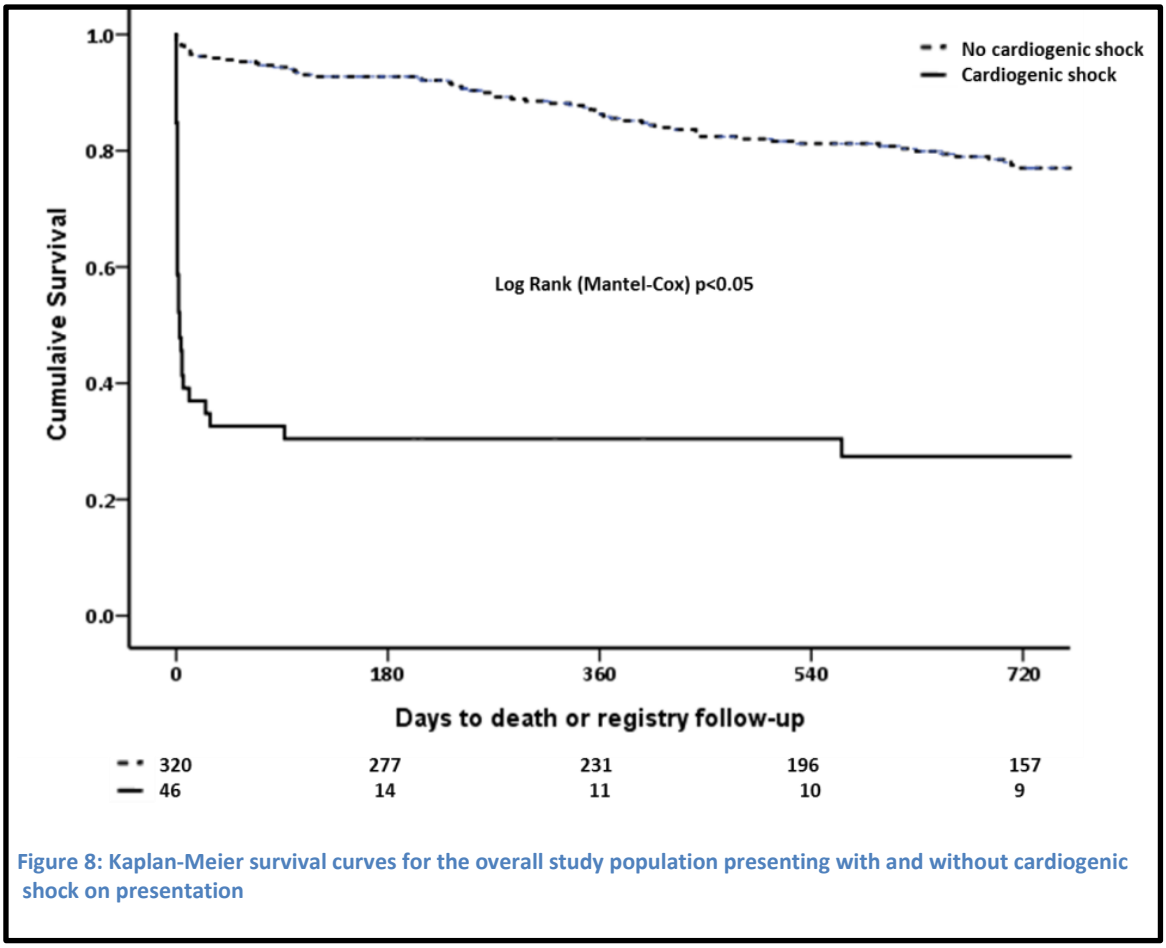

Figure 8: Kaplan-Meier survival curves for the overall study population presenting with and without cardiogenic shock on presentation

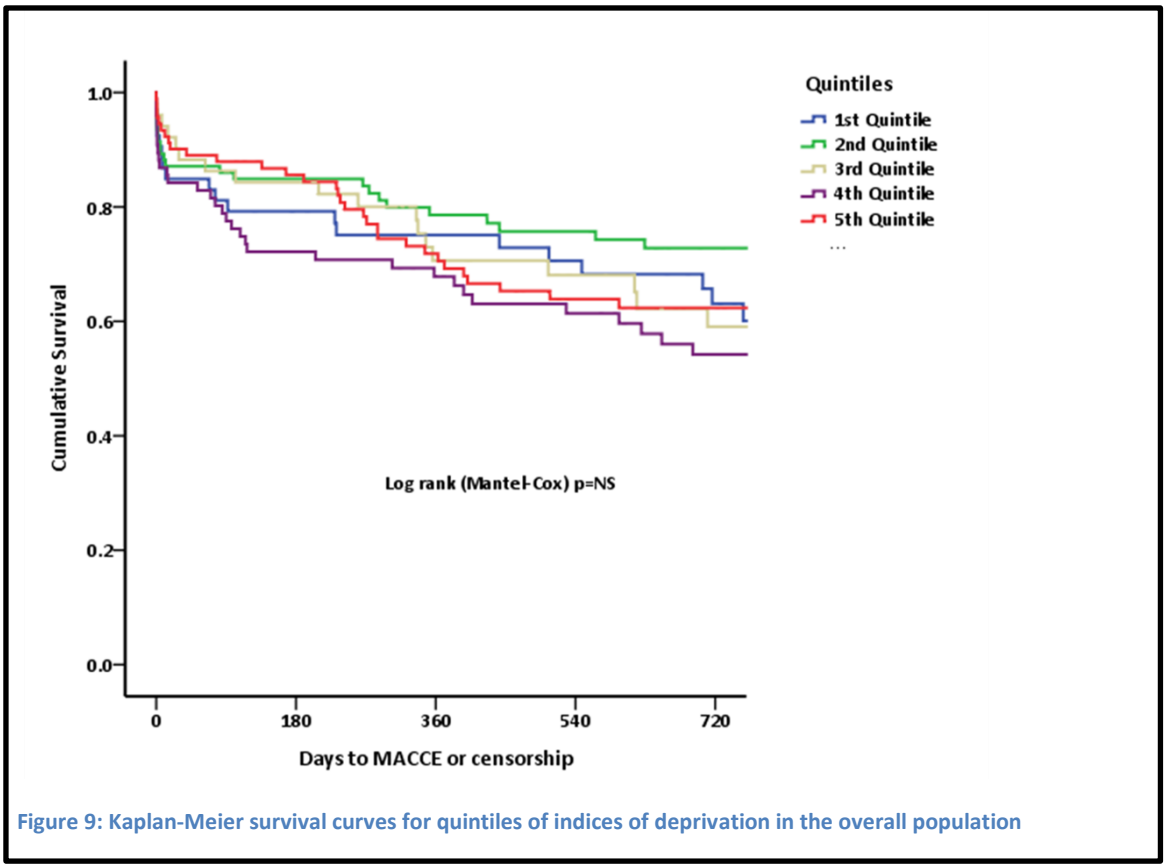

Figure 9: Kaplan-Meier survival curves for quintiles of indices of deprivation in the overall population

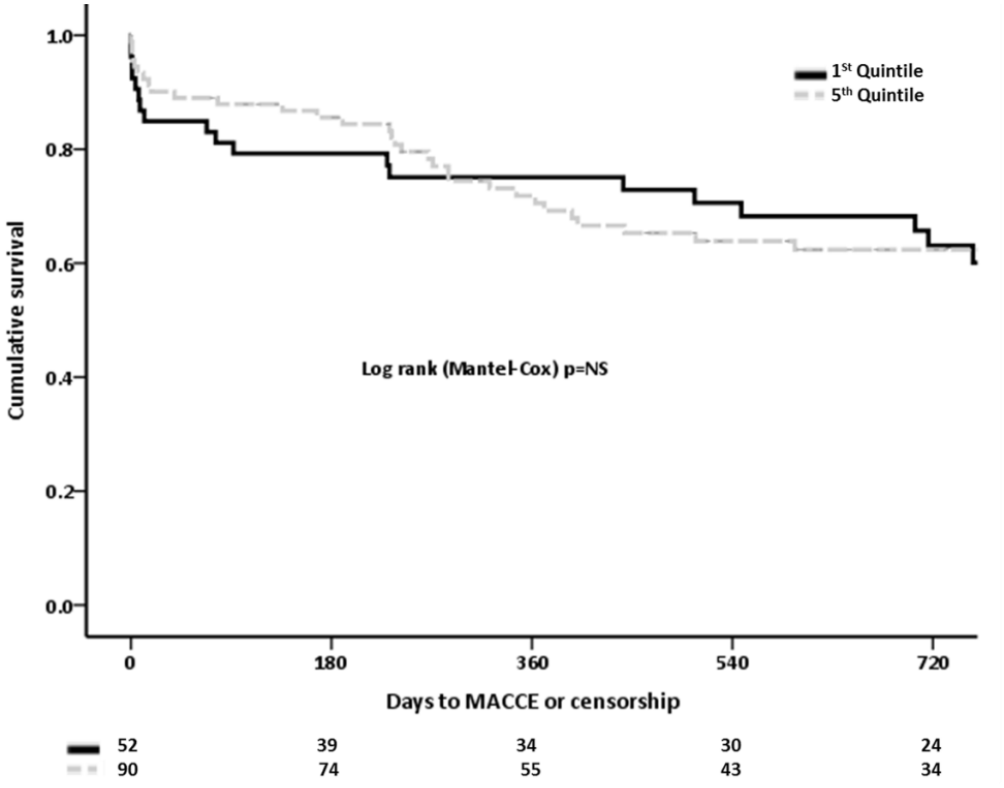

Figure 10: Kaplan-Meier survival curves of 1st and 5th Quintiles of indices of multiple deprivation

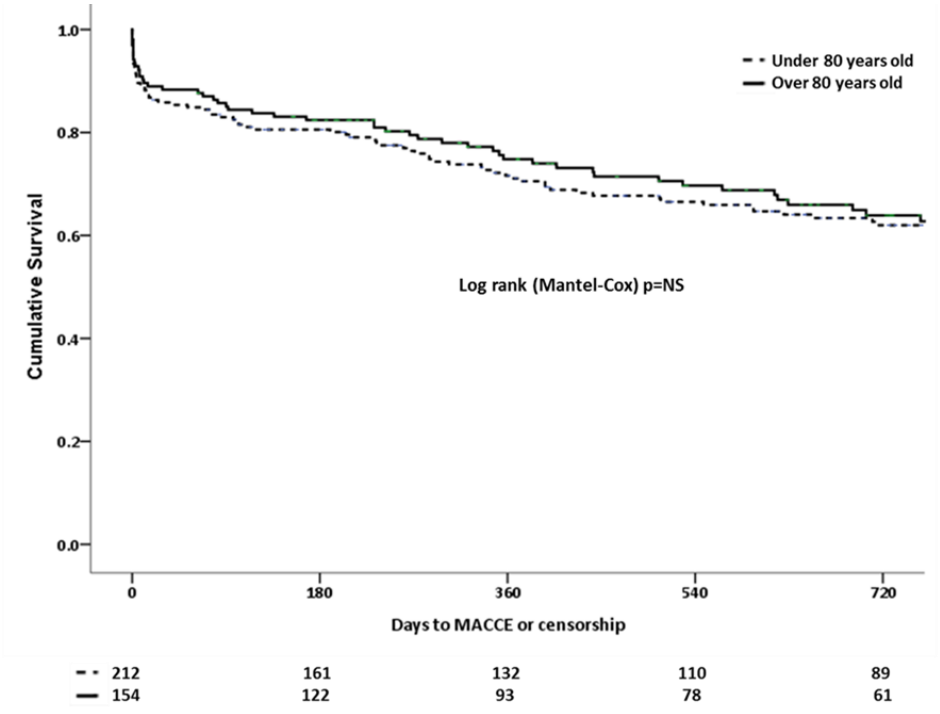

Figure 11: Kaplan-Meier survival curves comparing patients over 80years old to those less than 80 years old

Cox proportional hazards regression

Up to 14 explanatory covariates could be included in developing the regression model [12]:

$$N=10k/p$$

Where, N=number of cases in the study, k =the number covariates in the study, and p = the proportion of cases with events to those with no events. The model did not include LV function due to the high rate of missing values; however, we have reported the results of the analysis of multiple imputation datasets separately. The regression model used included: Age, gender, clinical syndrome on presentation, presentation with cardiogenic shock, renal impairment, diabetes, previous stroke, previous MI, previous PCI, peripheral vascular disease, median SYNTAX score and left main bifurcation disease.

After adjustment for baseline clinical and procedural characteristics, we found that the SS [aHR 1.01, 95% CI 1.00-1.02, $p<0.05$], presentation in cardiogenic shock [aHR 5.88, 95% CI 3.81-9.06, $p<0.05$], previous MI [aHR 1.94, 95% CI 1.37-2.75, $p<0.05$] and a history of diabetes [aHR 1.61, 95% CI 1.12-2.31, $p<0.05$] were significantly associated with MACCE (see **Table 15**). When the regression analysis was repeated using a composite adverse endpoint of cardiac death, myocardial infarction, stroke and unplanned repeat revascularisation, SS was no longer found to have a significant association with poor outcomes (**Table 16**).

Table 15: Independent predictors of MACCE over long term follow-up in patients treated with LMCA PCI

Covariate	aHR (95%CI)	p-value
SYNTAX score (mean – 31.70)	1.01 (1.00-1.02)	<0.05
Cardiogenic shock	5.88 (3.81-9.06)	<0.05
Previous MI	1.94 (1.37-2.75)	<0.05
Any history of diabetes	1.61 (1.12-2.31)	<0.05

MACCE: major adverse cardiac and cerebrovascular events; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; aHR: Adjusted Hazard ratio; CI: confidence interval; SYNTAX: synergy between PCI with taxus and cardiac surgery

Table 16: Independent predictors of the composite end-point of cardiac death, myocardial infarction, stroke and unplanned repeat revascularisation over long term follow-up in patients treated with LMCA PCI

Covariate	aHR (95% CI)	p-value
Cardiogenic shock	8.89 (5.75-13.75)	<0.05
Previous MI	1.91 (1.28-2.83)	<0.05
Any history of diabetes	1.93 (1.28-2.90)	<0.05

LMCA: left main coronary artery; PCI: percutaneous coronary intervention; aHR: Adjusted Hazard ratio; CI: confidence interval; MI: myocardial infarction

Patients with cardiogenic shock

Patients with cardiogenic shock on admission were more likely to present with STEMI, while only a fifth presented with NSTEMI (T**able 17**). They were less likely to have any cardiac history prior to this presentation, such as a previous MI or PCI, but were otherwise equally matched with regards to comorbidity. Coronary disease burden was similar between the two groups with no significant difference in SS; however acute occlusion of the LMCA was more likely in patients with cardiogenic shock. Patients with cardiogenic shock on presentation were more likely to have a CTO of the main epicardial vessels.

Those presenting in cardiogenic shock were more likely to receive treatment with an intra-aortic balloon pump (IABP) prior to PCI, and significantly more procedures were performed using femoral access. Bare metal stents were twice as likely to be used in shocked patients as non-shocked patients. Total radiation dose was significantly higher in the shocked group. There was no significant difference in the rate of procedural complications; however, the only retroperitoneal bleed was found in the non-shocked group.

The thirty day and one-year mortality for shocked patients was 67.4% and 69.6% respectively (**figure 8**). Cardiac death accounts for over 93.8% of all deaths at 30 days and 96.9% of all deaths at one-year in this group.

Table 17: Characteristics of 46 patients with cardiogenic shock on presentation compared with 320 patients with no cardiogenic shock

Characteristic	Cardiogenic shock	No Cardiogenic shock	p-value
Female gender	12 (26.1%)	110 (34.4%)	p=NS
Median (IQR) age, years	72.0 (15.0)	76.0 (20.0)	p=NS
NSTEMI	9 (19.6%)	154 (48.1%)	p<0.05
Stable Angina	0 (0.0%)	99 (30.9%)	p<0.05
STEMI at presentation	37 (80.4%)	67 (20.9%)	p<0.05
Cardiogenic Arrest on presentation	4 (8.7%)	4(1.4%)	p<0.05
Renal impairment	7 (15.2%)	31 (9.7%)	p=NS
History of diabetes	8 (17.4%)	73 (22.8%)	p=NS
Previous stroke	4 (8.7%)	33 (10.3%)	p=NS
Peripheral vascular disease	4 (8.7%)	53 (16.6%)	p=NS
Previous PCI	2 (4.3%)	58 (18.1%)	p<0.05
Previous cardiac surgery	1 (2.2%)	20 (6.3%)	p=NS
Previous MI	8 (17.4%)	134 (41.9%)	p<0.05
Median(IQR) SYNTAX score	43.0(20.0)	27.5(19.0)	p=NS
LMCA Bifurcation lesion	37 (80.4%)	227 (70.9%)	p=NS

LMCA acute occlusion	17 (42.5%)	26 (10.8%)	p<0.05
LM+1VD	15 (32.6%	132 (41.3%)	p=NS
LM+2VD	15 (32.6%)	73 (22.8%)	p=NS
LM+3VD	3 (6.5%)	33 (10.3%)	p=NS
Significant RCA disease	27 (61.4%)	150 (49.0%)	p=NS
CTO present	14 (30.4%)	50 (15.6%)	p<0.05
CTO of proximal/mid vessel segments	13 (28.3%)	48 (15.0%)	p<0.05
Femoral access	38 (82.6%)	20 (64.7%)	p<0.05
Total radiation dose Units(IQR)	8345.0 (7307)	7461 (5569)	p<0.05
Inotropes	6 (13.0%)	2 (0.6%)	p<0.05
IABP prior o PCI	35 (76.1%)	23 (7.2%)	p<0.05
BMS used	22 (47.8%)	58 (18.2%)	p<0.05
Total stent length, mm (IQR)	36.0 (35.0)	33.0 (30.0)	p=NS
Cardiac arrest during PCI	6 (13.0%)	3 (0.9%)	p<0.05

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; PCI: percutaneous coronary intervention; PCI: percutaneous coronary intervention; MI: myocardial infarction ; LMCA: left main coronary artery; SYNTAX: synergy between PCI with taxus and cardiac surgery; LM: Left main; CTO: chronic total occlusion; IABP – intra-aortic balloon pump

Patients with cardiogenic shock excluded

The median survival of patients with cardiogenic shock was three days. The SHOCK trial and registry show that cardiogenic shock on presentation with a myocardial infarction is strongly associated with early in-hospital death independent of the burden of coronary disease [202]; for these patients, better outcomes are dependent on the speed with which cardiac reperfusion is restored and multi-organ dysfunction is corrected. To better assess the long-term outcomes from LMCA PCI, we excluded patients with cardiogenic shock. Thus we performed a separate survival analysis. After excluding patients presenting with cardiogenic shock, we show the breakdown in MACCE in **Table 18**. The one-month mortality was now only 4.1%, compared with 12.0% for the overall cohort (**Table 14**).

The baseline characteristics of 320 patients with no cardiogenic shock on presentation reveal a smaller proportion of STEMI patients with only a marginal reduction in the percentage of patients presenting with NSTEMI (see **Tables 19** and **20**). The burden of coronary disease, as measured by the median SYNTAX score, has not changed significantly. A similarly sized majority of patients were within the high SYNTAX score tertile.

Table 18: MACCE at 30 days and overall follow-up in 320 patients with no cardiogenic shock on presentation

	0-30 days	1 year	Overall follow-up
All-cause death	13 (4.1%)	42 (13.1%)	90 (28.1%)
Cardiac Death	11 (3.4%)	29 (9.1%)	48 (15.0%)
MI	5 (1.6%)	22 (6.9%)	33 (10.3%)
Repeat revascularisation	2 (0.6%)	9 (2.8%)	16 (5.0%)
Stroke	1 (0.3%)	1 (0.3%)	4 (1.3%)
Definite/Probable ST	5 (1.6%)	6 (1.9%)	7 (2.2%)
MACCE	17 (5.3%)	64 (20.0%)	116 (36.3%)

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; ST: stent thrombosis

Table 19: Patient characteristics for 320 patients with no cardiogenic shock (n=320)

	Number (Percentages)	Missing data %
Median (IQR)Age	77.0 (19.0)	0
Female Sex	110 (31.4%)	0
Stable Angina	99 (30.9%)	
NSTEMI	154 (48.1%)	0
STEMI	67 (20.9%)	0
Unstable angina	1 (0.3%)	0
Cardiac arrest	2 (0.6%)	0
Hyperlipidaemia	164 (51.2%)	0
Diabetes	73 (22.8%)	0
Hypertension	158 (49.4%)	0
Current or ex-smoker	159 (49.7%)	0
Previous Stroke	33 (10.3%)	0
Peripheral vascular disease	53 (16.6%)	0
Previous MI	134 (322%)	0
Previous PCI	58 (18.1%)	0
Previous Cardiac surgery	19 (5.9%)	0
Renal Impairment	31 (9.7%)	0
Moderate to severe LV impairment	103 (32.2%)	30.9%

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV: left ventricle

Table 20: Angiographic data in patients with no cardiogenic shock (n=320)

Characteristic	Number (%)
LMCA Bifurcation lesion	227 (70.9%)
LM+1VD	132 (41.3%)
LM+2VD	73 (22.8%)
LM+3VD	33 (10.3%)
Median SYNTAX score (IQR)	30.0(18.0)
Lower SS tertile ≤23	85 (24.6%)
Intermediate SS tertile 23-32	98 (29.5%)
High SS tertile ≥32	134 (44.5%)
Dominant RCA	150 (46.9%)
Significant RCA disease	50 (15.6%)
CTO present	48 (15.0%)
CTO of proximal/mid vessel segments	45 (14.1%)

LMCA: left main coronary artery; LM: left main; VD: vessel disease; SYNTAX: synergy between PCI with taxus and cardiac surgery; IQR: interquartile range; SS: SYNTAX score; RCA: right coronary artery; CTO: chronic total occlusion

The median follow-up was 710 (1118) days. The 30 day, 1 year and overall mortality rates are 4.1%, 13.1% and 28.1% respectively. After adjustment for baseline clinical, angiographic and procedural characteristics, SS [aHR 1.02, 95% CI 1.00-1.04, p<0.05], previous MI [aHR 1.89, 95% CI 1.28-2.80, p<0.05] , peripheral vascular disease [aHR 1.68, 95% CI 1.09-2.61, p<0.05] and renal impairment [aHR 1.89, 95% CI 1.05-3.43, p<0.05] were significantly associated with MACCE (see **Table 21**). Thus, for every 10 point change in SS there is a 2% increase in risk of MACCE.

Cox regression analysis of covariates was used to detect predictors of the composite adverse end-point of cardiac death, MI, stroke and repeat revascularisation. After adjustment for covariates, we found: that for every 10 point increase in SS there was a 2% increase in risk of the composite adverse endpoint [aHR 1.02, 95% CI 1.02-1.04, p<0.05]. In addition previous MI [aHR 1.82, 95% CI 1.15-2.88, p<0.05] and diabetes [aHR 1.81, 95% CI 1.13-2.91, p<0.05] were associated with poor outcomes (see **Table 21**).

Diabetes was not significantly associated with MACCE when adjusting for other variables (see **Table 21**). However, it was significantly associated with the composite of cardiac death, MI, stroke and repeat revascularisation (see **Table 22**). Diabetic patients had more commonly experienced previous MI or undergone cardiac surgery. They were more likely to have suffered a stroke in the past and were more likely to have a history of hyperlipidaemia. Despite a similar SYNTAX score, diabetic patients were more likely to have LMCA bifurcation disease. DES use did not differ between the groups, and the mean total stent length was similar between the two groups (see **Table 23**).

Table 21: Independent predictors of MACCE over long term follow-up in 320 patients treated with LMCA PCI, all cardiogenic shock patients excluded

Covariate	aHR (95% CI)	p-value
SYNTAX score	1.02 (1.00-1.04)	<0.05
Previous MI	1.89 (1.28-2.80)	<0.05
Peripheral vascular disease	1.68 (1.09-2.61)	<0.05
Renal impairment	1.89 (1.05-3.43)	<0.05

LMCA: left main coronary artery; PCI: percutaneous coronary intervention; aHR: Adjusted Hazard ratio; CI: confidence interval; MI: myocardial infarction

Table 22: Independent predictors of the composite end-point (cardiac death, MI, stroke and repeat revascularisation) over long term follow-up in 320 patients treated with LMCA PCI, all cardiogenic shock patients excluded

Covariate	aHR (95% CI)	p-value
SYNTAX score	1.02 (1.00-1.04)	<0.05
Previous MI	1.82(1.15-2.88)	<0.05
Diabetes	1.81(1.13-2.91)	<0.05

LMCA: left main coronary artery; PCI: percutaneous coronary intervention; aHR: Adjusted Hazard ratio; CI: confidence interval; MI: myocardial infarction

Table 23: Diabetic patients compared to non-diabetic patients, cardiogenic shock patients excluded (n=320)

	Diabetic patients, n=73 (%)	No diabetes, n=247 (%)	p-value
Median (IQR)Age	74.7(9.4)	72.5(13.9)	p=NS
Female Sex	24 (32.9%)	86 (34.8%)	p=NS
Hyperlipidaemia	48 (65.8%)	116 (47.0%)	p<0.05
Hypertension	47(64.4%)	111 (44.9%)	p<0.05
Previous Stroke	12(16.4%)	21 (8.5%)	p<0.05
Peripheral vascular disease	16 (21.9%)	37 (15.0%)	p=NS
Previous MI	41 (56.2%)	93 (37.7%)	p<0.05
Previous PCI	15 (20.5%)	43 (17.4%)	p=NS
Previous Cardiac surgery	10 (13.7%)	9 (3.6%)	p<0.05
Renal Impairment	11 (15.1%)	20 (8.1%)	p=NS
ACS	53 (72.6%)	166 (67.2%)	p=NS
Median (IQR) SS	32.0 (11.8)	30.0(13.6)	p=NS
LMCA bifurcation disease	59 (80.8%)	168 (68.0%)	p<0.05
All CTO's	16 (21.9%)	34 (13.8%)	p=NS
DES used	60 (82.2%)	196 (79.4%)	p=NS
Median (IQR)Total stent length	38.5(21.6)	37.5(22.3)	p=NS

IQR: interquartile range; MI: myocardial infarction; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; SS: SYNTAX score; LMCA: left main coronary artery; CTO: chronic total occlusion; DES: drug eluting stent; NS: not significant

Imputed data

5 datasets were imputed with co-morbidity, clinical presentation and severity of coronary disease used as predictors of LV function. All 5 datasets were used in the Cox proportional hazards regression analysis, which included the imputed LV function assessment as a covariate. Adjusted hazard ratios and 95% confidence intervals are displayed in **Table 24**.

The imputed data confirm that patients with cardiogenic shock had a greater than five times hazard of MACCE; other independently associated covariates include a previous MI, diabetes and the SS. Additionally, we can conclude that moderate to severe LV impairment was an independent predictor of MACCE. The analysis has also identified renal impairment, age and DES use as independent predictors of poor outcomes.

Table 24: Independent predictors of MACCE over long term follow-up for imputed data of patients treated with LMCA PCI

Covariate	aHR (95% CI)	p-value
SYNTAX score (mean – 31.6)	1.013(1.008-1.018)	p<0.05
Cardiogenic shock	5.081(4.165-6.197)	p<0.05
Previous MI	1.774(1.527-2.061)	p<0.05
Any history of diabetes	1.551(1.331-1.807)	p<0.05
Age	1.01(1.004-1.016)	p<0.05
Renal impairment	1.250(1.002-1.558)	p<0.05
Moderate to severe LV impairment	1.407(1.206-1.641)	p<0.05
DES used	1.245(1.061-1.460)	p<0.05

LMCA: left main coronary artery; PCI: percutaneous coronary intervention; aHR: Adjusted Hazard ratio; CI: confidence interval; SS: SYNTAX score; MI: myocardial infarction; LV: left ventricular; DES: drug eluting stent

3.3 Summary

3.3.1 Key results

In this retrospective analysis of unselected patients with ULMCA disease treated with PCI, cardiogenic shock before intervention contributed more than fivefold hazard to the risk of MACCE when compared to other significant covariates. Other independent covariates associated with MACCE include the burden of coronary disease, as measured with the SS, previous MI and a history of diabetes.

Left Ventricular function was missing in over 30.0% of patients; to assess the association between LV function and outcomes, we conducted multiple imputation. After imputation of 5 datasets, using predictor variables identified with a directed acyclic graph, we analysed the data using Cox proportional hazards modelling. The results were consistent with the first analysis and confirm the independent association between SS, cardiogenic shock, previous MI and diabetes with poor outcomes. In addition to this, moderate to severe LV dysfunction was confirmed to be independently associated with MACCE. Furthermore, we identified age, renal impairment and DES used as predictors of poor outcomes; however, these findings should be viewed with caution.

Cardiac death represents more than half of all the MACCE events throughout the follow-up period. Cardiac death in patients with cardiogenic shock contributed more than 60% of all MACCE in the first month; this represents 27% of all MACCE for the entire follow-up period. The one-year survival for our patients presenting with cardiogenic shock, 30.1%, was less than that reported for patients treated with revascularisation in both the SHOCK trial and the SHOCK trial registry [202, 203]. Less than a quarter of patients in both of these study cohorts had significant LMCA stenosis though; while patients with LMCA disease in the SHOCK trial registry had a much worse survival compared to those in our study [204]. We can conclude from these studies that with increasing severity of coronary disease, patients presenting with cardiogenic

shock have worse outcomes and those with LMCA stenosis or three vessel disease have the worst survival rates overall. MACCE in this context becomes a sensitive indicator of covariates associated with early cardiac death. Thus we identified cardiogenic shock, with the consequent multi-organ dysfunction, as a predictor of poor short-term outcomes [180]. Indeed, with a change in the composite outcome measure from MACCE (Table 15) to one which replaced all cause death with cardiac death (Table 16), we see that the SS was no longer predictive of worse outcomes. Where cardiogenic shock is so closely related to early cardiac death, it blunts the sensitivity of covariates on the sample, and the regression analysis becomes less discriminatory of long term outcomes.

We conducted a separate analysis, excluding patients presenting with cardiogenic shock, to assess more specifically the predictors of long-term outcomes. The MACCE rate for this cohort was 20.0% at one year and 36.3% over the median follow-up period of almost two years. We found that the SS, previous MI, peripheral vascular disease and renal impairment were associated with MACCE. Furthermore, when one assesses the components of MACCE, we report a repeat revascularisation rate of only 2.8% in 1 year; while in other retrospective studies the repeat revascularisation rates are between 5-10% [18, 73, 205]. The incidence of myocardial infarction though was comparable to these studies. Death therefore makes up the largest component of our MACCE. There may be two reasons for the differences in composite event rates between our study and other published studies. Firstly, there may be a tendency to manage subsequent ischaemic events in this older cohort conservatively compared with other studies [18, 73, 170, 206, 207]. Secondly, death may be the earlier event in this older population, so it may be appropriate to measure cardiac death.

It is known that the choice of outcome indicators included in a composite end-point, through their weighted contribution, may change the interpretation of results of studies significantly [179, 191]. Death is recommended by the ARC as a safety indicator within the composite end-point of MACCE [180]. All-cause death contributed over 80.0%

of all of the MACCE in our study. Considering the individual components of MACCE, with a proportionately large weighting of all-cause death on the composite end-point in the context of our relatively aged study population, cardiac death would seem a more specific measure of treatment safety and effectiveness. The ARC considers cardiac death a useful alternative to all-cause death in long term studies [180], the further one moves away from the treatment the less specific all-cause death becomes as a measure of treatment outcomes. In older populations we would argue the same principle applies. Cardiac death can be considered a specific measure of target lesion failure following LMCA PCI [111, 208]. Thus, we assessed the separate composite end-point of: cardiac death, MI, stroke and repeat revascularisation. For this composite end-point we found that SS, previous MI and diabetes were associated with worse outcomes.

3.3.2 Discussion

This retrospective registry represents a unique study population with respect to demographics, comorbidity and coronary disease burden. Compared with other published observational studies and randomised trials, this study has an older population with a median age almost 10 years greater than other published LMCA revascularisation studies in the drug-eluting stent era[25, 30, 31, 33, 59-61, 209, 210]. The proportion of patients 80 years and older in our study is near twice that reported in a recently published British Cardiovascular Interventional Society (BCIS) national dataset [147, 154]. Our study population had more comorbidity than previously published studies; including higher rates of previous MI, CKD and more than three times the level of peripheral vascular disease [25, 33, 210]; but similar levels of diabetes were observed. So this represents a higher surgical risk population compared with other published studies [211].

The SS was independently associated with MACCE within the overall cohort such that for every 10 point increase in the SS there was a 2.0% increase in risk of MACCE. It was

independently associated with the composite end-point when substituting all-cause death with cardiac death. The SS is predictive of death and MACCE following PCI and has been consistently demonstrated in multivessel revascularisation [47, 212] as well as LM revascularisation [61-63, 213]. However the interaction between SS and outcomes are not consistent depending on the distribution of coronary atheroma [46, 62, 64], as well as in it's application in individual studies depending on different median SS between studies thus affecting the tertile cut points [64, 212]. The revascularisation guidelines recognise that the SS may not reflect all the individual factors in a case which may predict hazard from PCI [64, 214]. While the SS describes the 'total' burden of significant coronary stenoses as well as the complexity, the specific distribution of atheroma within the LM may impact on outcomes [73]. Despite a similar median SS, we found a greater proportion of patients with a high SS (SS ≥32) when compared with the SYNTAX trial [61]. Compared with the left main subgroup of the SYNTAX trial our study population had more distal left main coronary disease (72% vs. 54% respectively), but less multi-vessel disease (LM + 2VD and LM +3VD in 33.9% vs. 65.6%) and fewer chronic total occlusions [61]. The SYNTAX trial included all-comers and was designed to study PCI vs. CABG in multivessel disease, the posthoc analysis of the LMCA subgroup, therefore, reflects this selection bias for multivessel disease. In the SYNTAX trial the SS therefore was a measure of the burden of multi-vessel disease, while in our study the SS weighting seemed to reflect the complexity of distal LMCA disease [61]. So while our patients may have a similar median SS, they have different distribution of coronary atheroma. In agreement with other studies, we found that the SS was significantly associated with MACCE [47, 63] and furthermore, patients in the high SS tertile had the worst survival compared to the other two groups [215].

In comparison to our study, the EXCEL and NOBLE trials reported a similar burden of distal LMCA disease and multi-vessel disease, yet the median SS was significantly lower [59, 60]. Both EXCEL and NOBLE included over 80.0% pf patients with significant left main bifurcation disease; however they did not disclose the number of patients with 'True' bifurcation disease. While these two studies did not show an association between left main bifurcation disease and poor outcomes, it is known that long term

outcomes from PCI of the left main bifurcation are worse when compared with ostial or mid-shaft disease [73], particularly when complex two stent strategies are required [114]. While we did not identify the left main bifurcation as a specific predictor of outcomes, there is significant collinearity with the SS. A further analysis of this specific coronary lesion for which a separate results chapter is included, vide infra.

We report similar levels of diabetes amongst the study cohort compared with other reported registries [36, 113-115] and randomised trials of left main coronary artery disease [61, 62, 216]. In our study diabetes was independently associated with MACCE in the overall cohort, but it was not found to be associated with MACCE when we excluded patients with cardiogenic shock. DM was associated with a nearly twofold increase in the combined adverse event rate (cardiac death, stroke, repeat revascularisation and MI) in patients with no cardiogenic shock on admission. Diabetic patients have an increased risk of cardiac death [217-219], which may explain the difference in sensitivity between the composite endpoints. Cardiac death may provide a more specific examination of the cardiovascular system effects of diabetes in this aged population.

Diabetic patients have an earlier onset of more extensive coronary disease [220, 221], including LMCA disease [125]. It is known that diabetic patients do worse from multivessel revascularisation than non-diabetics, where CABG offers better survival than PCI for individuals with diabetes [212, 222]. However, there is some conflict in the published data on revascularisation of diabetic patients with significant LMCA disease. A registry of multivessel and LMCA revascularisation showed no interaction between diabetes and outcomes [223]. Some registries reporting outcomes from PCI for LMCA disease have not identified DM as a predictor of poor outcomes [18, 24, 224]; yet other registries reporting on LMCA revascularisation have shown diabetes was a predictor of poor outcomes [36, 225, 226]. However, these studies were not designed to examine outcomes from LMCA revascularisation in diabetic patients. Despite early results from the SYNTAX trial and left main subgroup which identified diabetes as a

predictor of worse outcomes [61, 227]; in a later analysis at 4 years the association was no longer evident [228]. Indeed diabetes was not included in the SYNTAX II model of predictors of long term outcomes [229]; the SYNTAX II was later externally validated in the Drug Eluting stent for LefT main coronary Artery disease (DELTA) registry [43]. Other randomised studies of left main revascularisation, comparing CABG and PCI, found no excess hazard with diabetes [62, 216]. These studies can be criticised for significant differences in the burden of coronary disease between diabetic and non-diabetic groups.

It is suggested that the end-organ consequences, rather than the presence of diabetes are strongly predictive of poor outcomes [229-231]. The burden of coronary disease can be viewed as an end-organ effect of diabetes. This is evident in the BARI registry, where patients received physician-led choice of treatment strategy; they found no difference in outcome between CABG and PCI for diabetic patients [232]. As the majority of patients screened ended up in the registry, the choice of revascularisation strategies were based on the merits of treating the specific pattern of coronary disease burden. Similarly in the LMCA, where the choice of revascularisation strategy was based on the burden of disease, we find no interaction between diabetes and poor outcomes [216]. However, randomised studies of ULMCA revascularisation comparing groups with similar burdens of coronary disease have found significantly worse outcomes in diabetic patients [233]. While there is a lack of data for outcomes amongst diabetic patients with ULMCA disease, after correction for SS and other comorbidities, we found a significant association between diabetes and adverse outcomes. Our study indicates diabetes may be an important factor with respect to outcome in ULMCA revascularisation independent of SS.

A meta-analysis of patients with multivessel disease has shown a survival advantage of CABG over PCI over long term follow-up in diabetic patients [234]. Our findings therefore could indicate that diabetic patients may benefit from consideration for high risk CABG. However, while we report a significantly greater burden of coronary disease

than the studies included in this meta-analysis, our patients have more comorbidity and therefore higher surgical risk. Further studies evaluating the effect of diabetes on outcomes in patients with ULMCA disease is warranted.

We identified previous MI as a significant predictor of MACCE. However, as LV dysfunction was not included in the multivariate analysis it is not clear to what extent previous MI was merely a surrogate of LV dysfunction. LV dysfunction is known to be an independent predictor of adverse outcomes of MACCE following revascularisation across all patient age groups and presentations [235, 236]. A similar proportion of missing LV function has been observed in the BCIS national database of left main disease [147], and for almost half of all patients who undergo PCI in the UK [235]. Those with LV assessments present had significantly greater comorbidity with higher rates of previous MI, previous PCI and renal impairment. The patients with missing LV function were more likely to present with a STEMI and were younger than those with LV function assessments available. This indicates the data were MNAR. The PPCI service in West Yorkshire operates on a 'spoke and wheel' design, patients presenting with STEMI are treated at the tertiary centre and then discharged to the districts hospitals where LV assessments may not have been completed. While we could not confirm the reason for missing LV function assessments, this is a recognised mechanism for missing LV function assessments [237]. Five multiple imputation datasets were analysed for predictors of the adverse end-point, thereby allowing us to assess the independence of these two factors, MI and moderate to severe LV dysfunction. The adjusted model revealed both of these covariates were independently associated with worse outcomes. Possible mechanisms for this association should include not only pump failure but also scar related arrythmogenesis.

Older patients are more likely to suffer with LMCA disease [3, 124, 125] and considering the median age of this study population, it was surprising that age was not a predictor of poor outcomes in the overall cohort. Other studies have shown a significant correlation with increasing age and poor outcomes from LMCA PCI [78, 228]. Cox regression analysis of the multiple imputation datasets suggests that age has a weak association with poor outcomes, for every 10 year increase in age there was a 1%

increase in the risk of MACCE. Renal failure too was identified as a predictor of MACCE in the analysis of the multiple imputation datasets, while this finding is similar to other studies [78], we had three times the proportion of renal failure within our study population. It was reassuring that the findings from the analysis of the multiple imputation datasets correlated with the initial findings from our overall cohort and with other published data despite the data MNAR.

Patients from more deprived LSOAs, as indicated by high IMD quintiles, were significantly younger than with those in the least deprived quintiles. There were significant differences in co-morbidity between the quintiles of deprivation. We found a significantly greater prevalence of diabetes and renal impairment amongst the 4th and 5th quintiles of deprivation, this is congruous with other studies of PCI populations [178], as well as large national and international studies of unselected patients [238]. While peripheral vascular disease is a marker of severity of coronary artery disease and is predictive of poor outcomes from revascularisation [228], we did not show a significant difference in the prevalence of peripheral vascular disease between the quintiles of deprivation. This differs to studies of deprivation in unselected populations where the prevalence of peripheral vascular disease was highest amongst the most deprived [174], but this finding is not always consistent [178].

While it is known the there is an earlier onset of subclinical coronary disease amongst the more deprived [239], we found no difference in the burden of coronary disease amongst the quintiles of deprivation when measured with the SS. Nor did we find an excess of multivessel disease in the more deprived. However, no study has identified a specific pattern of coronary disease associated with deprivation. This may reflect the earlier development of worse categories of coronary artery disease, such as left main coronary artery disease amongst the more deprived. Coronary artery disease has a prolonged incubation period from the onset of subclinical disease [175, 239] to the presentation of severe disease. So, while we were unable to demonstrate a significant difference in survival after PCI between the quintiles of deprivation, the period of

deprivation which antecedes the manifestation of coronary disease may lead to an earlier onset of severe coronary artery disease in the more deprived. Hence the younger more deprived with severe disease. Other studies though have found worse outcomes following PCI amongst the more deprived [178, 240, 241]. However, it is not known if these studies were comparing patients with similar burdens of coronary disease while in our study we found a similar burden of coronary disease across the quintiles of deprivation.

We report a large number of complications, over 25.1%. While one may accept this high complication rate is due to the significantly older cohort of patients it is five times that reported for elderly patients in other studies [133]. These complications represent a combination of operator-reported complications, recorded on Cardiobase® at the time of the procedure, and those identified at the time of angiographic review for this analysis. The interventionalist who reviewed the angiograms was blinded to the procedural notes; complications were imported directly into the database and were not allocated separately to the reviewer or operator. Due to this method of data collection and coding, we were unable to discriminate those reported by the operator from those reported at the time of angiographic review. Complications are divided into procedural or access site related complications.

Over half of our reported complications include coronary dissections. Untreated coronary dissections post-angioplasty may result in poor long term outcomes whether in the context of balloon angioplasty or post-stenting [242-244]. As a consequence additional stenting to cover the dissection flap may be indicated. In the pre-stent era it was recognised that the risk of acute complications, such as side branch occlusion and MI, were associated with angiographically higher grades of dissections post-angioplasty [244, 245]. There is debate as to whether dissections detected on intravascular imaging are of significant clinical consequence with some studies advocating additional stenting [246, 247] , while other data suggests a conservative approach would be appropriate [248, 249]. Due to the way in which our data were

collected we were unable to elucidate whether these reported dissections were edge dissections post-stenting and whether these resulted in unplanned additional stenting. In addition there was lack of information concerning the angiographic grades of dissection being reported. Nevertheless, we did not demonstrate an association between poor long term outcomes and angiographic LMCA dissection during angioplasty.

Access site complications were reported in 5.7% of all patients, 90.4% of these were reported in cases of femoral access with a large (7/8Fr) sheath and over three quarters of these patients had LMCA bifurcation disease. Arterial sheaths greater than 7 Fr in size were used in almost 70.0% of our patients which is ten times the proportion reported in other studies [250, 251]. As a consequence of these larger sheaths and the much higher levels of PVD in our study, we report access site complications in nearly twice the number of patients compared with these studies. However, the pattern of coronary disease and PCI strategy is not known for these published studies. The large burden of distal LMCA disease in our study may account for the need to use larger sheaths and catheters. There could be a number of reasons for this, one consideration is potentially one operator with a preference for the femoral approach, yet we do not have the data to speculate. Another reason could be the consideration that distal LMCA disease may require a two stent strategy, further analysis is required to determine the mechanisms and decision making leading to the use of large catheters in a population with higher than reported rates of peripheral vascular disease.

We report a definite and probable stent thrombosis ST rate of 1.9% in the first year, rising to 2.2% over the course of the follow-up. While this is similar to that reported for other LMCA PCI cohorts [31, 252], it is twice the number reported in a multi-centre registry of ULMCA PCI [253]. There could be a few of reasons for this increased ST rate in our study compared to this registry, including: 1) significantly longer median stent length used in our study [253]; 2) our patients have significantly more comorbidity [254]. While LMCA bifurcation requiring a two-stent strategy may be a risk of ST [31,

77], we had a similar burden of distal LMCA disease and similar usage of the two stent approach compared to this multicentre registry. Despite using fewer DES in our cohort compared to the meta-analysis, we reported cases of very late ST (VLST), while they reported none. Unfortunately, we were unable to exclude premature cessation of DAPT in our patients. One other factor which may explain the significantly lower ST rate in this multi-centre registry is that the study authors may have under-reported ST in unexplained deaths [253].

3.3.3 Limitations

Despite a similar median SS, diabetic patients had significantly more distal left main disease. Distal LMCA disease is a predictor of MACCE [26, 28, 71-77]. The SS incorporates the total burden of coronary disease and additional points are given for LMCA bifurcation disease and complexity [35]. In this way we have significant collinearity of data. So despite including the SS in the multivariate regression analysis, there may be significant confounding from distal LMCA disease.

Selection bias was inherent in this retrospective study of a group of individuals for whom one can only presume CABG was not an option. Whether it is due to the acuteness of their presentation or high surgical risk, this heterogeneous study population would not be included in a randomised trial of ULMCA revascularisation. Considering the mode of presentation, this alone would bias the results in favour of those presenting free of cardiogenic shock. This is reflected in the significant differences between patients with and without cardiogenic shock. Therefore it was appropriate to consider these two groups separately for further analysis. While it is unavoidable for this type of study, by dividing the patients into subgroups, e.g. excluding cardiogenic shocked patients; it is possible to explore some research questions. If we are to consider a prospective registry examining this patient group, we should include strict exclusion and inclusion criteria.

Missing data presents a specific confounding on the analysis of outcomes, in particular when considering that poor LV function is accepted as a significant factor predicting poor outcomes from revascularisation. While accepting this was unavoidable given the retrospective nature of the study, it is noted that similar studies of more robustly audited databases, such as the BCIS national database, the data here too were found wanting in a greater proportion of patients. Furthermore, other randomised trials have reported similarly high proportions of missing LV function data, up to a quarter in some instances [110]. Nevertheless, in order to diminish this confounding, we used multiple imputation. While this imputed data cannot be used to provide conclusions, we were able to confirm the findings from the initial analysis.

The choice of composite outcomes could be argued lack specificity and may in fact be inaccurate. The inaccuracy relates to the follow-up, as the data were collected retrospectively and a proportion of the patients were followed up at district hospitals. However, every effort was made, as stated in the methods section to ameliorate this by gathering information from each hospital and GP practices. Furthermore, the specificity is directly related to the selection bias, e.g. measuring all cause death in older patients doesn't necessarily examine the treatment effect of revascularisation. We addressed this issue earlier and by using two different composite end-points have provided alternative interpretations of outcomes. These two issues could easily be addressed by constructing a prospective registry with regular follow-up and independent review of end-points. Exclusion criteria should provide a study population which allows longer term follow-up where appropriate measures of treatment effectiveness can be examined.

There may be significant confounding for the lack of data on medical management for these patients. The study sample was accrued over a number of years and during this time there were significant advances in medical therapy, so these were not taken into account. Nor is there any knowledge of whether medications were optimised during at follow-up.

There are hints that some of the practices at the LGI were not conforming to other centres, take for instance the use of large sized femoral catheters. In this way we should be cautious to generalise the findings of this study to the wider community. Of particular note is seemingly low numbers of repeat revascularisation, which is out of keeping with all published data. There could be a few reasons for this; 1) conservative management of subsequent coronary events, 2) recurrent MACCE events not being included, which is possible given the retrospective nature of this study.

3.3.4 Conclusion

This unique study population gives insight into the challenges of delivering ULMCA revascularisation for those patients who are not usually included in published studies and for whom CABG is not appropriate according to accepted guidelines/practice. Our study population is older, has more comorbidity and has a significantly different burden of coronary disease compared with currently published observational and randomised study populations.

Patients with cardiogenic shock had poor outcomes which are consistent with findings from historical cardiogenic shock study cohorts, despite advancing PCI techniques. This probably reflects the limited progress in the management of cardiogenic shock rather than a failing of PCI revascularisation techniques.

We have shown diabetes is independently associated with poor outcomes amongst patients with ULMCA disease. While risk factors, such as smoking and high cholesterol decline in the population, diabetes continues to increase amongst the more deprived [255]. The role of diabetes in cardiovascular disease is potentially confounded by the timing of diagnosis and initial management, which is often at the time of onset of clinically apparent coronary disease, such as presentation with an ACS.

Despite significant missing data, multiple imputation provided results which were consistent with other analyses. While future studies should improve the completeness of data collection, multiple imputation can be considered a useful tool in dealing with missing data.

Finally, MACCE in our cohort was relatively high with a high mortality rate, repeat revascularisation represented less than 3.0% of all MACCE. This may reflect the conservative approach to further revascularisation. Patients and clinicians embark on treatment to achieve two goals, prognostic and symptomatic benefit. This retrospective study indicates that amongst this older group of patients, where prognostic benefit may be limited, a closer analysis of the symptomatic benefit is warranted with a prospective quality of life study.

4. Results chapter: Left main coronary bifurcation percutaneous coronary intervention

We demonstrated significant stenosis of the left main coronary bifurcation in 262 patients. In this analysis of outcomes from left main bifurcation percutaneous coronary intervention we excluded 27 patients presenting with cardiogenic shock, which is in keeping with the other studies of bifurcation PCI [106, 110, 114].

4.1 Patient characteristics

We identified 162 patients with 'True' left main bifurcation disease compared with 63 patients with 'Non-true' bifurcation disease.

4.1.1 Demographics

The 'Non-true' and 'True' bifurcation groups were equally matched for most baseline characteristics (**Table 25**). There was a preponderance of females in the 'True' bifurcation group, while age did not differ between the two groups. There was no significant difference in the median age for the 'Non-true' and 'True' bifurcation groups, 75.0 (21.0) years and 79.0 (14.0) respectively. Almost two-thirds of patients presented with an ACS in each group, with a significantly greater proportion of STEMI in the 'Non-true' compared to the 'True' groups, 17 (27.0%) vs. 24 (14.8%); $p<0.05$. The proportion of patients treated electively for stable angina was not significantly different between the groups and represented just over a third of all patients, 22 (34.9%) in the 'Non-true' group compared with 55 (34.0%) in the 'True' group.

Baseline comorbidity was similar with a significantly smaller proportion of patients with a history of previous MI in the 'Non-true' bifurcation group, 20 (31.7%), compared with the 'True' bifurcation group, 82 (50.6%); $p<0.05$. Close to a third of patients had missing LV function assessments, and for those with LV function, a third had moderate to severe LV impairment. Over a quarter of patients presented with diabetes in the 'Non-true' and 'True' groups, 16 (25.4%) and 42 (25.9%) respectively. A little over 17.0% of all patients had a history of peripheral vascular disease (PVD), with no significant difference between the two groups.

Table 25: Patient characteristics in 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	p-value
Median (IQR)Age	75.0 (21.0)	79.0 (14.0)	p=NS
Female Sex	12 (19.0%)	59 (36.4%)	p<0.05
Stable Angina at time of presentation	22 (34.9%)	55 (34.0%)	p=NS
NSTEMI at time of presentation	24 (38.1%)	83 (51.2%)	p=NS
STEMI at time of presentation	17 (27.0%)	24 (14.8%)	p<0.05
Cardiac arrest at presentation	3 (5.6%)	0 (0%)	p=NS
Hyperlipidaemia	31 (51.7%)	83 (53.5%)	p=NS
Diabetes	16 (25.4%)	42 (25.9%)	p=NS
Hypertension	27 (42.9%)	83 (51.2%)	p=NS
Current or ex-smoker	34 (58.6%)	76 (53.1%)	p=NS
COPD	7 (11.1%)	19 (11.7%)	p=NS
Previous Stroke	4 (6.3%)	21 (13.0%)	p=NS
Peripheral vascular disease	10 (15.9%)	29 (17.9%)	p=NS
Previous MI	20 (31.7%)	82 (50.6%)	p<0.05
Previous PCI	1 (15.9%)	31 (19.1%)	p=NS
Previous Cardiac surgery	3 (4.8%)	14 (8.6%)	p=NS
Renal Impairment	5 (7.9%)	16 (9.9%)	p=NS
Moderate to severe LV impairment*	13 (20.6%)	62 (38.3%)	p=NS

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV: left ventricular; *missing values = 63 (28.0%)

4.1.2 Angiographic data

There were significant differences in the burden of coronary disease between the two groups beyond the left main bifurcation (**Table 26**). We identified aorto-ostial disease in a slightly greater proportion of 'Non-true', 18 (28.6%), versus 'True' group patients, 36 (22.2%); $p<0.05$. The median (IQR) SYNTAX score (SS) was significantly lower in the 'Non-true' group, 25.5 (14.3) vs. 35.0 (14.0). Close to a third of 'Non-true' group patients, 18 (29.0%), and almost two-thirds of patient with 'True' bifurcation disease, 98 (60.9%), were in the high SS tertile. A significantly smaller proportion of patients in the 'Non-true' group presented with left main (LM) +2 vessel disease (VD) and LM+3VD, 12 (19.0%), compared with 63 (38.9%) of 'True' bifurcation patients. An American Heart Association (AHA) Type C lesion classification for the left main bifurcation stenosis was given for half of all 'Non-true' bifurcation lesions, 31 (49.2%) compared with almost four-fifths, 127 (78.3%); $p<0.05$, in the 'True' group. The right coronary artery (RCA) was significantly diseased in over half of patient with 'True' bifurcation disease, 92 (58.6%), which was a significantly greater proportion when compared with the 'Non-true' bifurcation cohort, 21 (34.4%); $p<0.05$. There was no significant difference in the proportion of patients with chronic total occlusions (CTO) in the 'Non-true', 9 (14.3%), and 'True', 28 (17.3%), bifurcation groups.

Table 26: Angiographic characteristics of 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	p-value
Aorto-ostial lesion	18 (28.6%)	36 (22.2%)	p=NS
LM+1VD	23 (36.5%)	68 (42.0%)	p=NS
LM+2VD	6 (9.5%)	43 (26.5%)	p<0.05
LM+3VD	6 (9.5%)	20 (12.3%)	p=NS
AHA Type C lesion	31 (49.2%)	127 (78.3%)	p<0.05
Median SYNTAX score (IQR)	25.5 (14.3)	35.0 (14.0)	p<0.05
Lower SS tertile ≤23	19 (30.6%)	9 (5.6%)	p<0.05
Intermediate SS tertile 23-32	25 (40.3%)	54 (33.5%)	p=NS
High SS tertile ≥32	18 (29.0%)	98 (60.9%)	p<0.05
Dominant RCA	58 (95.1%)	152 (95.6%)	p=NS
Significant RCA disease	21 (34.4%)	92 (58.6%)	p<0.05
CTO present	9 (14.3%)	28 (17.3%)	p=NS
CTO of proximal/mid vessel segments	8 (12.7%)	28 (17.3%)	p=NS

LMCA: left main coronary artery; LM: left main; VD: vessel disease; SYNTAX: synergy between PCI with taxus and cardiac surgery; IQR: interquartile range; SS: SYNTAX score RCA: right coronary artery; CTO: chronic total occlusion

4.1.3 PCI procedure data

Femoral access was favoured for the majority of patients in both groups, whereas radial access was used in just over a quarter of 'True', and a third of 'Non-true' left main bifurcation cases (see **Table 27**). There was a cross over from radial to femoral access in fewer than 5% of patients in both groups. A larger sized catheter, at least 7Fr, was favoured in 43 (68.2%) of 'Non-true' and 133 (82.1%) of 'True' bifurcation cases. There was significantly more use of the smaller 6Fr sheath in the 'Non-true' bifurcation group. An intra-aortic balloon pump (IABP) for inotropic support was required pre-PCI in 11 (6.8%) of patients with 'True' bifurcation disease and 2 (3.2%) patients with 'Non-true' bifurcation disease. Numerically more patients with 'True', 7 (4.3%), than 'Non-true', 1 (1.6%), bifurcation disease had an intra-aortic balloon pump insertion during PCI. Heparin was the preferred anticoagulant for two-thirds of patients in both groups. Heparin and Bivalirudin were used together in less than 3% of all cases.

There was a significant difference in choice of bifurcation treatment strategies between the two groups. The single-stent strategy was employed in the majority of patients with 'Non-true' bifurcation disease, 53 (84.1%), whereas a two-stent strategy was preferred in the majority of 'True' bifurcation cases, 88 (53.4%); $p<0.05$. A similar proportion of patients in both groups had a final kissing balloon inflation, with 15 (23.8%) of 'Non-true' bifurcation cases and 39 (24.2%) of 'True' bifurcation cases. While we report significant RCA disease in half of all patients, only 14 (6.2%) had a coronary intervention to this artery at the time of LMCA intervention, with no significant difference between the two groups. A drug-eluting stent (DES) was used in over 80% of all cases, including the use of 2nd generation DES in 45 (71.4%) of 'Non-true' and 111 (68.5%) of 'True' bifurcation cases. Despite a numerically greater median (IQR) stent length for patients with 'True' bifurcation disease, there was no significant difference between the two groups. A larger proportion of 'True' bifurcation patients had rotational atherectomy to the LMCA than 'Non-true' bifurcation, 27 (16.7%) compared with only 4 (6.5%); $p<0.05$. Intravascular ultrasound was employed in significantly more patients with 'Non-true' bifurcation disease than those with 'True' bifurcation disease, 24 (38.1%) vs. 30 (18.5%) respectively.

Rotational atherectomy of the calcified LMCA was required in 31(13.8%) of all patients where femoral access was preferred in 26(83.9%) using a large sized sheath, greater than 7Fr, in 30(96.8%) of these cases.

4.1.4 PCI complications

There were fewer procedural complications in the 'Non-true' bifurcation groups, 9 (14.2%), compared with 43 (26.5%) in the 'True' bifurcation group. Nevertheless, there was no significant difference between the two groups (see **Table 28**). Coronary complications, including coronary dissection/perforation/side branch occlusion, accounted for the majority of complications in the 'True' bifurcation disease group making up two-thirds of all the complications, whereas in the 'Non-true' group this represented fewer than half of all complications. The proportion of coronary dissection in patients with 'True' bifurcation disease, was more than twice that of patients with 'Non-true' bifurcation disease, 17 (10.5%) vs. 3 (4.8%) respectively. Access site complications occurred in a similar proportion of patients in the two groups, 4 (5.6%) of 'Non-true' bifurcation disease and 7 (4.6%) of 'True' bifurcation disease (see **Table 29**).

Of the 31 patients who required rotational atherectomy, 7 (22.6%) suffered a procedural complication. Four patients had coronary dissections, of these one patient had an additional coronary perforation, and one other developed a cardiac arrest during the procedure. Of the two patients with coronary perforations, one resulted in a cardiac tamponade. Only one patient developed cardiogenic shock during PCI, while none suffered side branch occlusions, neither pulmonary oedema nor underdeployed stents were reported. Access site complications were limited to those treated by the femoral route. These complications included: 1 femoral artery dissection, two haematomas and one false aneurysm requiring injection.

Table 27: PCI procedure details in 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	p-value
Femoral access	39 (61.9%)	113 (69.8%)	p=NS
Radial Access	21 (33.3%)	44 (27.2%)	p=NS
Radial and Femoral access	3 (4.8%)	5 (3.1%)	p=NS
6 Fr catheters	16 (25.4%)	23 (14.2%)	p<0.05
7 Fr catheters	38 (60.3%)	111 (68.5%)	p=NS
8 Fr catheters	5 (7.9%)	22 (13.6%)	p=NS
IABP use pre – PCI	2 (3.2%)	11 (6.8%)	p=NS
IABP use during PCI	1 (1.6%)	7 (4.3%)	p=NS
Heparin	42 (66.7%)	108 (66.7%)	p=NS
Bivalarudin	23 (36.5%)	54 (33.3%)	p=NS
Abciximab	14 (22.2%)	47 (29.0%)	p=NS
Tirofiban	3 (4.8%)	4 (2.5%)	p=NS
2 stent strategies for LMCA bifurcation	10 (16.1%)	88 (53.4%)	p<0.05
Final kissing balloon	15 (23.8%)	39 (24.2%)	p=NS
DES use (patient level data)	55 (87.3%)	135 (84.4%)	p=NS
1st generation DES	10 (15.9%)	24 (14.8%)	p=NS
2nd Generation DES	45 (71.4%)	111 (68.5%)	p=NS
Median (IQR) total stent length	30.0 (22.3)	42.0 (26.0)	p=NS
Rotational atherectomy	4 (6.5%))	27 (16.7%)	p<0.05
IVUS	24 (38.1%)	30 (18.5%)	p<0.05
OCT	0 (0%)	0 (0%)	p=NS
Operator reported unsuccessful PCI	0 (0%)	5 (3.1%)	p=NS

PCI: percutaneous coronary intervention; IABP – intra-aortic balloon pump; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; Fr: french size; IABP: intra-aortic balloon pump; LMCA: left main coronary artery; IVUS: intravascular ultrasound; OCT: optical coherence tomography

Table 28: Procedural complications in 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	p-value
Coronary dissection	3 (4.8%)	17 (10.5%)	p=NS
Coronary perforation	0 (0%)	5 (3.1%)	p=NS
Cardiac tamponade	0 (0%)	2 (1.2%)	p=NS
Cardiogenic shock developing during procedure	1 (1.6%)	5 (3.1%)	p=NS
Pulmonary oedema	0 (0%)	1 (0.6%)	p=NS
Cardiac arrest	0 (0%)	1 (0.6%)	p=NS
Propagation of thrombus	2 (3.2%)	3 (1.9%)	p=NS
Side branch occlusion	1 (1.6%)	5 (3.1%)	p=NS
Stroke	1 (1.6%)	0 (0%)	p=NS
Underdeployed stent	1 (1.6%)	3 (1.9%)	p=NS
Emergency CABG	0 (0%)	1 (0.6%)	p=NS

CABG: coronary artery bypass surgery

Table 29: Access site complications in 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	p-value
Retroperitoneal bleed	0 (0%)	1 (0.6%)	p=NS
Surgical intervention	0 (0%)	1 (0.6%)	p=NS
Arterial dissection	0 (0%)	1 (0.6%)	p=NS
Arterial haemorrhage	1 (1.6%)	4 (2.5%)	p=NS
False aneurysm requiring thrombin injection	1 (1.6%)	0 (0%)	p=NS
False aneurysm requiring compression	1 (1.6%)	0 (0%)	p=NS
False aneurysm conservative management	1 (1.6%)	0 (0%)	p=NS

4.2 Outcomes

The median (IQR) follow-up of all patients with left main bifurcation disease was 642 (1069) days with a mortality rate of 28.4% over this period. The crude 30-day mortality rate was 4.9 % and the one-year mortality rate was 15.1%. A breakdown of all MACCE events during the study follow-up is shown in **Table 30**. The overall MACCE rate for the entire follow-up period was 37.3%, and the 30-day MACCE rate was 5.8%. There was significantly less MACCE over the follow-up period for the 'Non-true' bifurcation group, 15 (23.8%), compared with the 'True' bifurcation group, 69 (42.6%). There were no repeat revascularisations in patients with 'Non-true' bifurcation disease, 0 (0%), whereas 10 (14.5%) patients with 'True' bifurcation disease underwent further unplanned coronary revascularisation.

Myocardial infarction (MI) occurred in 10.2% of patients for the entire follow-up. 2.2% of all patients suffered either a definite or probable ST, all of these were in the 'True' left main bifurcation disease group. Early and late stent thrombosis (ST) rates were 1.8 % and 0.4% respectively, while there were no reported very late ST (VLST) for either group.

4.2.1 Survival Analysis

Unadjusted Kaplan-Meier survival analysis showed a significantly worse outcome for patients with 'True' left main bifurcation disease over 642 (1069) days follow-up (**figure 12**). After adjustment for baseline clinical and procedural characteristics, which are considered in the directed acyclic graph, we found that there was a two fold increase in the risk of MACCE in patients with 'True' bifurcation disease, [aHR 2.0; 95% Confidence Interval (CI), 1.1-3.6; $p<0.05$] (**Table 31**). Other covariates which were independently associated with MACCE include: significant right coronary artery (RCA) disease [aHR 1.8; 95% CI, 1.1-2.9; $p<0.05$], diabetes [aHR 1.7; 95% CI, 1.1-2.7; $p<0.05$] and peripheral vascular disease [aHR 1.7; 95% CI, 1.0-2.8; $p<0.05$].

Table 30: MACCE in 225 patients with left main bifurcation disease

	'Non-true' bifurcation disease (n=63)	'True' bifurcation disease (n=162)	**p-value**
All-cause death	11 (17.5%)	53 (32.7%)	p<0.05
Cardiac Death	3 (4.8%)	33 (20.4%)	p<0.05
MI	5 (7.9%)	18 (11.1%)	p=NS
Repeat revascularisation	0 (0%)	11 (14.7%)	p<0.05
Stroke	0 (0%)	2 (1.2%)	p=NS
Definite/Probable ST	0 (0%)	5 (3.1%)	p=NS
MACCE	15 (23.8%)	69 (42.6%)	p<0.05

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; ST: stent thrombosis

Table 31: Independent predictors of MACCE over long term follow-up in 225 patients with left main bifurcation disease

Covariate	**aHR (95%CI)**	**p-value**
'True' left main bifurcation disease	2.0 (1.1-3.6)	p<0.05
Significant RCA disease	1.8 (1.1-2.9)	p<0.05
Peripheral vascular disease	1.7 (1.0-2.8)	p<0.05
Diabetes	1.7 (1.1-2.7)	p<0.05

MACCE: major adverse cardiac and cerebrovascular events; aHR: Adjusted Hazard ratio; CI: confidence interval; RCA: right coronary artery

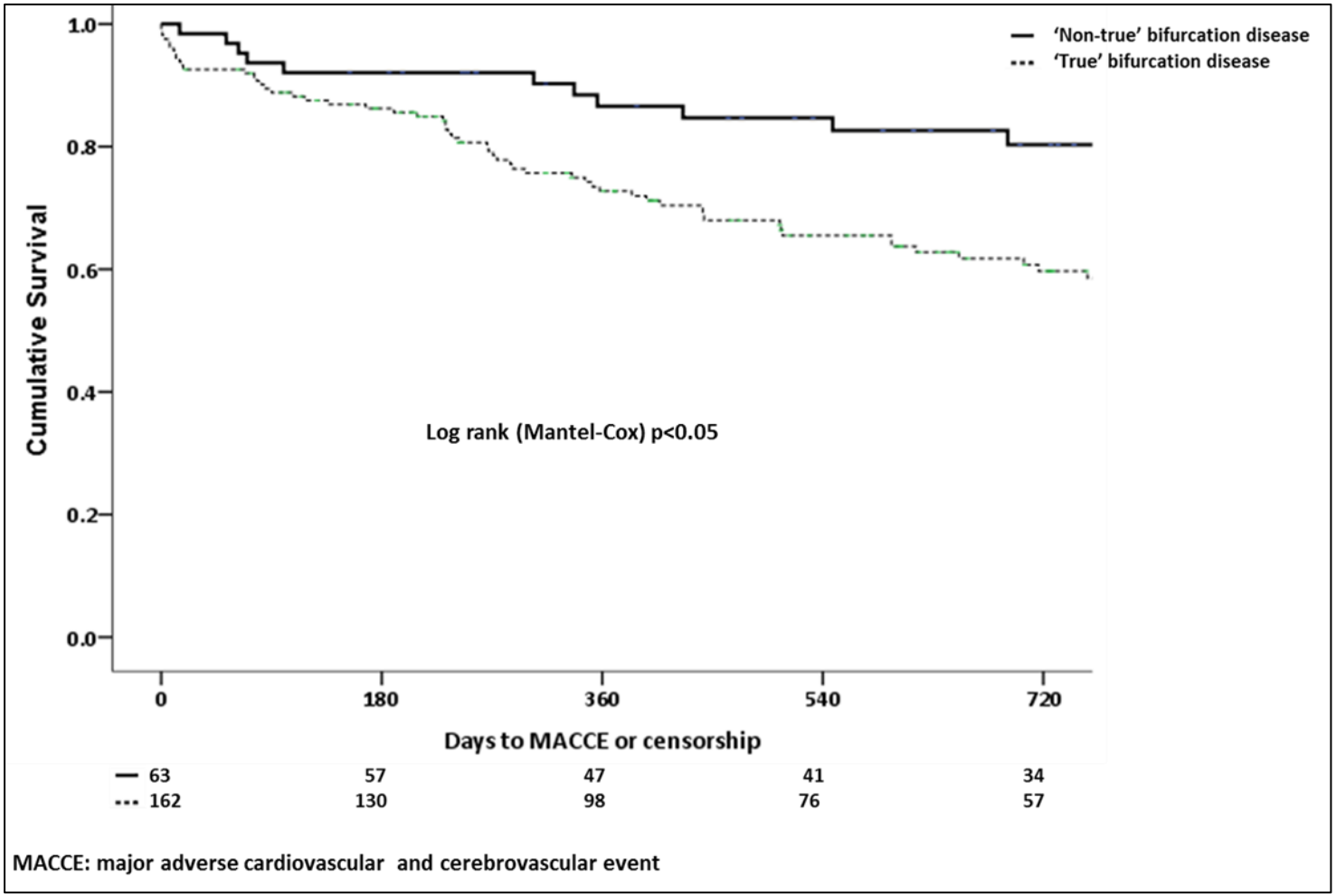

Figure 12: Kaplan-Meier estimates of survival to MACCE in 162 patients with 'true' and 63 patients with 'non-true' left main bifurcation disease

4.3 One-stent vs Two-stent strategies

A separate analysis of 162 patients with 'True' bifurcation disease was made comparing 74 patients treated with a single stent strategy to 88 patients treated with a two-stent strategy.

4.3.1 Patient characteristics

The cohort treated with a two-stent strategy were significantly older than those treated with a single stent strategy, median (IQR) 81.0 (11.0) years old vs. 75.5 (20.0) years old; $p<0.05$ (see **Table 32**). Approximately two-thirds of patients presented with an acute coronary syndrome (ACS) with no significant difference between the two groups. Those patients treated with a single stent strategy had a numerically higher proportion of patients who had a previous MI at presentation, 43 (58.1%) vs. 38 (43.2%), but this was not significantly different between the two groups. Those treated with a two-stent strategy had significantly more chronic obstructive pulmonary disease (COPD), 16 (18.2%) vs. 3 (4.1%); $p<0.05$. They were also more likely to suffer from hypertension, 50 (56.8%) vs. 31 (41.9%); $p<0.05$. There were no other significant differences between the groups for comorbidity.

4.3.2 Angiographic details

Aorto-ostial disease was present in over a quarter of patients treated in the single stent group and a fifth of those in the two stent group with no significant difference between the two groups (see **Table 33**). The median (IQR) SYNTAX score was significantly higher in the single stent group. Despite proportionately more patients in the higher SS tertile for those treated with a single stent, there was no significant difference between the treatment groups for the three SYNTAX tertile groups. The right coronary artery was the dominant vessel in over 90.0% of patients and was significantly diseased in over half of patients in both treatment groups. Chronic total occlusions (CTO's) were present in 17 (23.0%) patients treated with a single stent

strategy and only 12 (13.6%) of patients treated with the two-stent strategy. Multivessel disease, LM+2VD and LM+3VD, was present in half of the patients in the single stent groups and only a third of patients in the two stent group. There were a significantly larger proportion of patients with LM+2VD in the single stent group, 26 (35.1%) vs. 17 (19.3%); $p<0.05$, than in the two stent group.

4.3.3 PCI procedural data

The femoral route was preferred in over two-thirds of patients, with no significant difference between the groups, 47 (67.1%) in the single stent group and 59 (72.0%) in the two stent group (see **Table 34**). Larger sized catheters, 7Fr and 8Fr, were preferred in the two stent group, 77 (95.1%) vs 52 (70.3%); $p<0.05$. Heparin use was not significantly different between the two groups. However, the two stent group had significantly higher Bivalirudin use, 35 (42.7%) vs. 16 (22.9%); $p<0.05$. Final kissing balloon inflations were employed in almost a third of patients in the two stent group and just 11.6% of patients in the single stent group. Drug-eluting stents were used in the majority of patients, 136 (84.0%), with significantly more DES used in the two stent group, 74 (90.2%), compared with 53 (75.7%) in the single stent group. In the light of this, we found a significantly greater use of second generation DES used in the two stent group, over three-quarters, compared with just over half in the single stent group. The ‘Trouser, legs and seat’ two-stent strategy was preferred in the majority of patients, 28 (31.8%), while the T-stent was the second most commonly employed two-stent technique, used in 24 (27.3%) of patients. The 'Shotgun' method was the next most common with 21 (23.9%) of patients treated using this strategy, see **Table 35**. The V-stent and Culotte were used in equal frequency, 7 (8.0%), while the ‘T and small protrusion’ technique was used in a single patient. It is not known whether some patients treated with these two stent techniques had failed a provisional single stent approach.

Table 32: Patient characteristics in 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
Median (IQR)Age	81.0 (11.0)	75.5 (20.0)	p<0.05
Female Sex	32 (36.4%)	27 (36.5%)	p=NS
Stable Angina at time of presentation	28 (31.8%)	26 (35.1%)	p=NS
NSTEMI at time of presentation	50 (56.8%)	33 (44.6%)	p=NS
STEMI at time of presentation	10 (11.4%)	15 (20.3%)	p=NS
Cardiac arrest at presentation	0 (0%)	0 (0%)	p=NS
Hyperlipidaemia	45 (51.1%)	39 (52.7%)	p=NS
Diabetes	26 (29.5%)	17 (23.0%)	p=NS
Hypertension	50 (56.8%)	31 (41.9%)	p<0.05
Current or ex-smoker	39 (44.3%)	36 (48.6%)	p=NS
COPD	16 (18.2%)	3 (4.1%)	p<0.05
Previous Stroke	13 (14.8%)	8 (10.8%)	p=NS
Peripheral vascular disease	13 (14.8%)	16 (21.6%)	p=NS
Previous MI	38 (43.2%)	43 (58.1%)	p=NS
Previous PCI	16 (18.2%)	15 (20.3%)	p=NS
Previous Cardiac surgery	5 (5.7%)	8 (10.8%)	p=NS
Renal Impairment	9 (10.2%)	7 (9.5%)	p=NS
Moderate to severe LV impairment*	32 45.7%)	29 (52.7%)	p=NS

IQR: interquartile range; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; LV: left ventricular; *missing values = 35 (22.9%)

Table 33: Angiographic characteristics of 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
Aorto-ostial lesion	17 (19.3%)	19 (25.7%)	p=NS
LM+1VD	40 (45.5%)	28 (37.8%)	p=NS
LM+2VD	17 (19.3%)	26 (35.1%)	p<0.05
LM+3VD	10 (11.4%)	10 (13.5%)	p=NS
AHA Type C lesion	62 (91.2%)	65 (95.6%)	p=NS
Median SYNTAX score (IQR)	34.0 (11.0)	40.5 (18.0)	p<0.05
Lower SS tertile ≤23	5 (5.7%)	4 (5.4%)	p=NS
Intermediate SS tertile 23-32	34 (39.1%)	20 (27.0%)	p=NS
High SS tertile ≥32	48 (55.2%)	50 (67.6%)	p=NS
Dominant RCA	81 (93.1%)	70 (97.2%)	p=NS
Significant RCA disease	47 (55.3%)	44 (61.1%)	p=NS
CTO present	12 (13.6%)	17 (23.0%)	p=NS
CTO of proximal/mid vessel segments	12 (13.6%)	17 (23.0%)	p=NS

LMCA: left main coronary artery; LM: left main; VD: vessel disease; SYNTAX: synergy between PCI with taxus and cardiac surgery; IQR: interquartile range; SS: SYNTAX score RCA: right coronary artery; CTO: chronic total occlusion

Table 34: PCI procedure details in 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
Femoral access	62 (70.5%)	51 (68.9%)	p=NS
Radial Access	23 (26.1%)	21 (28.4%)	p=NS
Radial and Femoral access	3 (3.4%)	2 (2.7%)	p=NS
6 Fr catheters	5 (5.7%)	18 (25.7%)	p<0.05
7 Fr catheters	68 (78.2%)	44 (62.9%)	p<0.05
8 Fr catheters	14 (16.1%)	8 (11.6%)	p=NS
IABP use pre – PCI	6 (6.8%)	4 (5.4%)	p=NS
IABP use during PCI	3 (3.4%)	5 (6.8%)	p=NS
Heparin	54 (61.4%)	54 (73.0%)	p=NS
Bivalarudin	37 (42.0%)	17 (23.0%)	p<0.05
Abciximab	21 (23.9%)	26 (35.1%)	p=NS
Tirofiban	2 (2.3%)	2 (2.7%)	p=NS
Final kissing balloon	30 (34.1%)	9 (12.3%)	p<0.05
DES use (patient level data)	80 (90.9%)	56 (75.7%)	p<0.05
1st generation DES	10 (11.4%)	14 (18.9%)	p=NS
2nd Generation DES	70 (79.5%)	42 (56.8%)	p<0.05
Median (IQR) total stent length	45.0 (24.0)	34.5 (23.0)	p=NS
Rotational atherectomy	14 (16.3%)	13 (17.8%)	p=NS
IVUS	14 (15.9%)	17 (23.0%)	p=NS
OCT	0 (0%)	0 (0%)	p=NS
Operator reported unsuccessful PCI	2 (2.3)	2 (2.7%)	p=NS

PCI: percutaneous coronary intervention; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; Fr: french size; IABP: intra-aortic balloon pump; LMCA: left main coronary artery; IVUS: intravascular ultrasound; OCT: optical coherence tomography

Table 35: Two stent strategies used in 88 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)
T-Stent	24 (27.3%)
V-stent	7 (8.0%)
Trouser legs and seat	28 (31.8%)
Culotte	7 (8.0%)
TAP	1 (1.1%)
Shotgun	21 (23.9%)

TAP: T and small protrusion

4.3.4 Procedural complications

Procedural complications occurred in 19 (21.6%) patients in the two stent group and 24 (32.4%) patients in the single stent group with no significant difference between the groups (p=NS). There was a fourfold higher rate of side branch occlusion in the single stent group (see **Table 36**). Coronary dissection was by far the commonest complication in 7 (8.0%) patients in the two stent group and 10 (13.5%) patients in the single stent group. Only one patient in the single stent group underwent emergency bypass. Cardiogenic shock developed in 3 (4.1%) patients in the single stent group and 2 (2.3%) patients in the two stent group. All of these patients with cardiogenic shock, apart from one patient in the two stent group, required intra-aortic balloon pump insertion.

There was a single retroperitoneal bleed in the two stent group (see **Table 37**) however; there were no significant differences between the two groups for the incidence of arterial access site complications.

Table 36: Procedural complications in 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
Coronary dissection	7 (8.0%)	10 (13.5%)	p=NS
Coronary perforation	2 (2.3%)	3 (4.1%)	p=NS
Cardiac tamponade	2 (2.3%)	0 (0%)	p=NS
Cardiogenic shock developing during procedure	2 (2.3%)	3 (4.1%)	p=NS
Pulmonary oedema	1 (1.15)	0 (0%)	p=NS
Cardiac arrest	0 (0%)	1 (1.4%)	p=NS
Propagation of thrombus	2 (2.3%)	1 (1.4%)	p=NS
Side branch occlusion	1 (1.1%)	4 (5.4%)	p=NS
Stroke	0 (0%)	0 (0%)	p=NS
Underdeployed stent	2 (2.35)	1 (1.4%)	p=NS
Emergency CABG	0 (0%)	1 (1.4%)	p=NS

CABG – coronary artery bypass grafting

Table 37: Access site complications in 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
Retroperitoneal bleed	1 (1.1%)	0 (0%)	p=NS
Surgical intervention	0 (0%)	1 (1.4%)	p=NS
Arterial dissection	0 (0%)	1 (1.4%)	p=NS
Arterial haemorrhage	1 (1.1%)	3 (4.1%)	p=NS
False aneurysm requiring thrombin injection	0 (0%)	0 (0%)	p=NS
False aneurysm requiring compression	0 (0%)	0 (0%)	p=NS
False aneurysm conservative management	0 (0%)	0 (0%)	p=NS

4.3.5 Outcomes

The median (IQR) follow-up of the patients with 'True' bifurcation disease was 603 (1077) days. The overall mortality rate for the follow-up period was 32.7%. The crude 30-day mortality rate was 6.2%, and the one-year mortality rate was 17.2%. **Table 38** shows a breakdown of all MACCE during the study follow-up. The MACCE rate for the overall follow-up was 41.4%, where death makes up 76.8% of all MACCE. The MACCE rate at 30 days was 7.4% consisting of a high proportion of cardiac deaths. Cardiac deaths made up two-thirds of all MACCE at one month, 58.5% of all MACCE at one year and 47.8% for the entire follow-up period. Patients treated with a single stent strategy had a higher MACCE rate compared with those treated with a two-stent strategy, 38 (51.4%) vs. 31 (35.2%). At one year we report a repeat revascularisation rate of only 3.1%, and for the entire follow-up period, this was 4.9%. Myocardial infarction occurred in 11.1% of all patients for the entire follow-up. Definite and probable ST rates are reported in this analysis at a rate of 3.1%, with 3 (3.4%) cases of ST in the two stent group and 2(2.7%) cases in the single stent group. The early and late ST rates are 2.5% (4 cases) and 0.6% (1 case) respectively. No very late stent thrombosis was reported.

4.3.6 Survival analysis

While there seems to be a nominal advantage in survival from a two stent strategy when assessing the separation of the Kaplan-Meier curves in **figure 13**, this is not evident with unadjusted survival analysis. After adjustment for baseline clinical and procedural characteristics, we found that peripheral vascular disease [aHR 1.9; 95% CI, 1.1-3.3; $p<0.05$] and diabetes [aHR 1.7; 95% CI, 1.0-2.9; $p<0.05$] were independently associated with MACCE (see **Table 39**).

Table 38: MACCE in 162 patients with 'true' left main bifurcation disease

	Two stent strategy (n=88)	Single stent strategy (n=74)	p-value
All-cause death	23 (26.1%)	30 (40.5%)	p=NS
Cardiac Death	13 (14.8%)	20 (27.0%)	p=NS
MI	7 (8.0%)	11 (14.9%)	p=NS
Repeat revascularisation	4 (4.5%)	7 (9.5%)	p=NS
In-stent restenosis	7 (8.0%)	4 (5.4%)	p=NS
Stroke	2 (2.3%)	0 (0%)	p=NS
Definite/Probable ST	3 (3.4%)	2 (2.7%)	p=NS
MACCE	31 (35.2%)	38 (51.4%)	p<0.05

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; ST: stent thrombosis

Table 39: Independent predictors of MACCE over long term follow-up in 162 patients with 'true' left main bifurcation disease

Covariate	aHR (95%CI)	p-value
Peripheral vascular disease	1.9 (1.1-3.3)	p<0.05
Diabetes	1.7 (1.0-2.9)	p<0.05

MACCE: major adverse cardiac and cerebrovascular events; aHR: Adjusted Hazard ratio; CI: confidence interval;

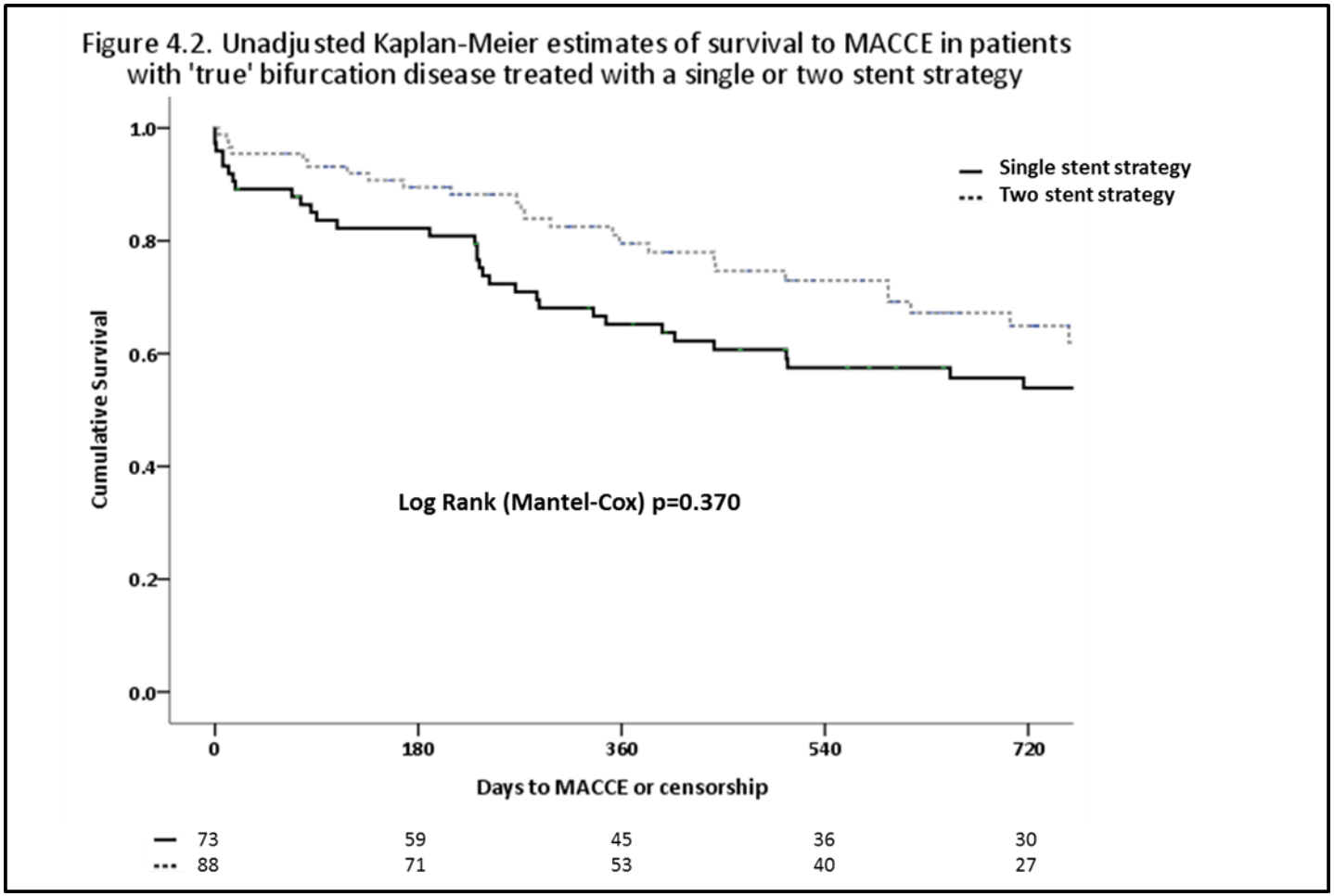

Figure 13: Kaplan-Meier estimates of survival to MACCE in patients with 'true' bifurcation disease treated with a single or two stent strategy

4.4 Summary

4.4.1 Key results

In this analysis of patients with left main coronary artery bifurcation disease, the presence of 'True' bifurcation disease was associated with a two-fold increase in the risk of MACCE over long-term follow-up. Other factors independently associated with MACCE include the presence of significant right coronary artery disease, peripheral vascular disease and diabetes.

A separate analysis of patients with 'True' bifurcation disease identified peripheral vascular disease and diabetes as independent predictors of MACCE over long-term follow-up. Unadjusted survival analysis showed while there appears to be a separation of the Kaplan-Meier survival curves for the two stent strategy and single stent strategy, that there was no significant difference in unadjusted survival when comparing patients treated with a single or two-stent strategy.

4.4.2 Discussion

In order to study long-term outcomes from ULMCA bifurcation disease, and given the known association of cardiogenic shock with early mortality [256-259], we did not include patients with cardiogenic shock in this analysis. This methodology is in keeping with the study design of prospective left main bifurcation studies and other bifurcation studies where patients with cardiogenic shock were excluded [106, 110].

The MACCE rate in this study population was 13.1% at 30 days and 26.2% at 1 year, which is similar to that reported in registries of LMCA PCI with first generation DES [21], while it is almost twice the MACCE found in other LMCA PCI registries of 1st generation DES which include close to 80.0% distal LMCA disease [22, 23, 26]. However, the burden of coronary disease may not be comparable as these studies do not specify the Medina class of LMCA bifurcation disease, nor do they use the SYNTAX score to

quantify associated coronary involvement. Our MACCE rate seems to be comparable with the treatment of complex LMCA bifurcations [73].

We found a significant association between ‘True’ left main bifurcation disease and MACCE. There is a known association between significant distal LMCA disease and poor long-term outcomes [78]. While ‘True’ coronary bifurcations have worse outcomes when compared to 'Non-true' [260], no study has demonstrated this within the LMCA bifurcation. Other studies of left main bifurcation disease inform us that the greater the burden of atheroma at the bifurcation, the worse the long-term outcomes [78, 96]. However, this is the first study reporting outcomes in ‘True’ versus ‘Non-true’ left main bifurcation disease using the Medina classification of bifurcation disease [104, 107, 114]. While other studies of LMCA disease demonstrate a prevalence of 'True' LMCA bifurcation in around one third of all patients, our study reports almost half all patients have ‘True’ LMCA bifurcation stenosis [61, 90, 114, 261]. Similar to our study, these studies did not use QCA to assess the size of the SB and the severity of disease in this vessel, while IVUS use was limited to a between one and two thirds of patients in two of these studies only. While there is a more than two fold increase in MACCE for patients with ‘True’ left main bifurcation disease in our study, they have a more than 5 fold greater proportion of cardiac death, repeat revascularisation and stent thrombosis.

The presence of RCA disease was associated with a nearly two-fold increase in the risk of MACCE. While this supports the notion that total coronary disease burden contributes to poor outcomes in LM revascularisation [155, 213], more specifically significant RCA stenosis is predictive of worse outcomes from surgical revascularisation for LM disease [78]. Incomplete revascularisation of the RCA at the time of LMCA revascularisation may account for the association with poor outcomes. A number of factors may contribute to incomplete revascularisation. We describe an older cohort of patients with a median age of 78.0(16.0) years compared with other observational [113-115, 127, 261] or randomised trials [61, 117] reporting on outcomes from LMCA bifurcation PCI. While some studies report exclusively on patients with stable or unstable angina [113, 114, 117], others include less than a third [61, 127, 261] or close

to half of patient of patients presenting with ACS [115]. Our cohort of patients has the largest proportion, two-thirds, presenting with an acute coronary syndrome when compared with these studies with a larger proportion of patients with STEMI on presentation than any of these studies. National BCIS data have displayed a similar proportion of stable to ACS for all PCI [262]. Taken together, this preponderance of ACS in an older cohort may lead to selective revascularisation [170] and may have led to the incomplete revascularisation of the RCA. Indeed, residual coronary disease is a significant factor in determining outcomes from coronary revascularisation [9, 156-158]. However, while we failed to revascularise the RCA in only 14 (6.2%) of our patients, the other study reporting RCA disease as a predictor of poor outcomes, failed to declare the number of unrevascularised RCAs [78]. Given the small number it is not certain that incomplete revascularisation of the RCA is the mechanism for poor outcomes.

Compared with other studies of LMCA bifurcation disease, our study cohort has a similar burden of diabetes [113-115, 261], yet only one other study has demonstrated the association between diabetes and poor outcomes in distal LMCA disease [115]. While the burden of diabetes in our cohort is similar to that reported for this retrospective study by Palmerini et al [115], they failed to demonstrate this association after propensity-adjusted Cox regression analysis. This was mainly due to significant differences between groups with respect to comorbidity and coronary disease burden. In our study after multivariate regression analysis, correcting for coronary disease burden and comorbidity, we found the presence of diabetes was associated with almost twice the risk of adverse long-term outcomes in patients with ULMCA bifurcation disease. While Palmerini et al's and our study were not designed to examine the outcomes between diabetic and non-diabetic patients, the choice of outcome measures may account for the conflicting results. While we used MACCE they used a composite of cardiac death and MI; MACCE would encompass the multi-organ effects of diabetes, while cardiac death and MI would be a measure of the cardiac specific effects of the PCI.

There was a two-fold increased risk of MACCE in patients with peripheral vascular disease (PVD). PVD is associated with an increased risk of coronary artery disease [263, 264], and is an independent predictor of poor long-term outcomes following revascularisation [137, 228, 265]. While our cohort had less PVD compared to other published registries of LMCA PCI [72, 73], only one other LMCA PCI registry has reported PVD as an independent predictor of worse outcomes [37]. However, in this study, patients had almost twice the burden of PVD compared with our study patients. We did not find a significant difference in the prevalence of PVD between the 'True' and 'Non-true' groups, indeed no study has demonstrated an association between PVD and the burden of coronary disease. PVD is a marker of whole body atherosclerosis, and in this context is associated with MACCE in our population.

In the separate analysis of patients with 'True' left main bifurcations, we showed no difference in outcomes for single and two stent strategies. There is conflict in the available evidence supporting either a single or two stent strategies in the treatment of LMCA bifurcation disease. No randomised trials have compared single to two stent strategies for 'True' LMCA bifurcation PCI; while observational studies may report unequally matched treatment groups. Some studies have reported favourable outcomes from a single-stent strategy [90, 112, 115, 127] . Criticisms of these studies include: a) unequally matched groups with significantly more 'True' bifurcation disease in the two stent group [90, 112], or b) a lack of reporting atheroma burden in the left main bifurcation [115, 127], or c) significant differences in the burden of comorbidity between treatment groups, such as more diabetic patients in the single stent group compared to the two stent group [115]. Similarly, studies which report no difference between the stent strategies have inherent issues [113, 114, 261, 266]. These issues include: a) the inclusion of up to 20% of patients with a protected left coronary circulation [113], b) there may be a mismatch between the treatment groups with more 'true' bifurcation disease in the two stent group [113, 114, 266], c) they include only a third of patients with 'true' left main bifurcation disease [261], d) there may be significant differences in accepted practice between the treatment groups, such as significantly fewer final kissing inflations in the single stent group compared with the

two stent group [114]. To our knowledge this is the first study reporting outcomes from a two stent versus single-stent strategy in 'True' left main bifurcation disease, other studies have considered culotte versus double kiss crush and another considered culotte versus T-stenting [111, 267]. Yet our findings should be considered with caution, the study is underpowered and this is reflected in the unadjusted survival curves. There appears to be a nominal advantage from a two stent strategy, yet the unadjusted survival analysis did not show significant differences. While our findings seem to suggest a provisional strategy could be considered up front for all patients, we await the result of the EBC MAIN study which will examine this question [106].

While we show equal outcomes from two and single stent procedures, there may be considerable crossover between treatment groups. In our cohort, it could be presumed that almost two thirds of our patients treated with a two stent procedure, including the 'Trouser, legs and seat'/ 'V-stent'/ 'Shotgun', were treated electively, while those treated with a 'T-stent'/'Culotte'/'TAP' may have crossed over from a provisional single stent procedure to a two stent procedure [92]. The 'Crush' and 'Culotte' techniques were employed in over 85.0% of patients treated with an elective two stent strategy in the Nordic and BBC ONE studies of coronary bifurcations [82, 83, 268], while the 'Culotte' technique was preferred in the EBC TWO study of large coronary bifurcation disease [110]. After intention to treat analysis they concluded that a single stent technique was superior to a these two stent strategies for complex coronary lesions, however these studies include fewer than 5.0% of patients with LMCA disease. The 'T-stent' and 'Crush' were preferred in over 70.0% of patients treated with two stents in retrospective studies of LMCA bifurcation PCI [22, 114, 115]. While these studies suggest equal outcomes from two or single stent procedures for the LMCA bifurcation, the crossover from a single to two stent procedure due to SB stenosis may be as high as 16% for these patients [82]. While in the BBC ONE trial crossover was allowed when the side branch was compromised, we report 4 times as many SB occlusions in the single stent cohort [82]. It is therefore not clear from these studies, nor our data, whether equal outcomes from single or two stent strategies were confounded by considerable crossover. The only randomised trial of PCI for LMCA bifurcation disease suggested that the double kiss crush was superior to the 'Culotte' for LMCA bifurcation

disease [117]. It is therefore not known which elective two stent procedure is preferable for the LMCA bifurcation. Yet the protocol for the EBC MAIN study, which will examine single stent vs two stent procedures for LMCA bifurcations, limit operators to a choice of either 'Culotte', 'Minicrush' (the double kiss variety), 'T-stenting' or 'TAP' [106]. While our data cannot be analysed on an intention to treat analysis, they suggest that other two stent techniques, such as the 'Trouser, legs and seat'/'V-stent'/'Shotgun', should be included in a randomised study against the single stent technique.

While it is known that PCI of the distal LMCA carries a higher risk of ST compared to other LMCA lesions [127], our study demonstrates a numerically more definite or probable ST in the 'True' bifurcation group compared to the 'Non-true' LMCA group, 3.1% vs 0.0, however this was not statistically significant. The ST rate for 'True' left main bifurcation disease in our study was three times the rate reported for all other PCI [69, 269], yet it was similar to that reported in other left main bifurcation PCI studies [114, 127]. Furthermore, while other studies report a greater risk of ST amongst patients treated with a two stent strategy compared with a single stent strategy [127, 261], we found no difference between the single and two stent treatment groups with respect to ST rates. Other studies confirm our findings that the ST rate is similar for single and two stent groups, however while we report on 'True' LMCA bifurcation disease, these studies report both 'True' and 'Non-true' [113, 114].

IVUS guided PCI was not associated with better outcomes in our study. Only one study suggests a specific IVUS measurement, the minimum luminal area (MLA) of the polygon of confluence, may be predictive of long term outcomes following LMCA bifurcation PCI [101], while other evidence suggests there is no significant improvement in outcomes from IVUS guided LMCA PCI [270]. While SB stenosis at the distal LMCA is predictive of poor outcomes [96], IVUS is superior to angiography in delineating the LMCA bifurcation disease into 'Non-true' or 'True' bifurcation disease [89]. In this way IVUS might influence the PCI management strategy. We report double

the rate of use of IVUS for 'Non-true' compared with 'True' bifurcation patients. The benefit of using IVUS in the 'Non-true' group may lie in confirming the lack of obstructive atheroma in the SB [89], where this modality may be used to assess the appropriateness of a provisional single stent strategy while 'True' bifurcation disease would motivate the operator to consider an elective two stent approach. The operators in our study may well have used IVUS to identify adverse features, such as acute bifurcation angle, which may predict carina shift and SB occlusion [103]. Indeed for patients with 'True' bifurcation disease, IVUS was employed in greater numbers amongst those treated with a single-stent compared with the two-stent group, albeit this was not statistically significant. In another retrospective study, IVUS was favoured in patients for whom an elective two-stent strategy was preferred to a provisional single-stent to treat 'True' LMCA disease; it is not clear whether the IVUS findings influenced the choice of stent strategy [114]. Yet, we used IVUS in only 24.0% of all our patients, while other LMCA bifurcation PCI studies report IVUS use in over two thirds of patients [90, 112, 114, 127]. While IVUS seems to be employed selectively in our study this practice does not seem to be consistent with other observational studies [90, 112, 127], nor is it in agreement with the EBC recommendation to use IVUS in all LMCA bifurcation PCIs [271]. Indeed beyond the assessment of SB involvement, additional advantages of IVUS in bifurcation PCI include: 1) determining the main and sidebranch vessel reference diameters, 2) assessing adequate stent expansion, 3) assessment of the sidebranch ostium post PCI and 4) excluding stent edge dissections. There seems to be evidence indicating the data from the IVUS influenced the choice of stent strategy in our study population. Indeed this influence has been studied for other diagnostic modalities, such as pressure wire [272]. While there is no proven outcome benefit from IVUS use in LMCA PCI, our study suggests that management strategies are influenced by the data gathered through IVUS, so further studies designed to quantify this influence is warranted.

While rotational atherectomy of the ULMCA is considered 'off-label' [273-275], there is evidence of improved outcomes in this subgroup of patients [276]. We report rotational atherectomy of the ULMCA bifurcation in 31 (13.8%) of the overall cohort.

However, a recent analysis of the use of rotational atherectomy in the UK national database has found that rotational atherectomy was used to treat the LMCA in only 5.5% of all LMCA PCI [276], and other studies have shown it is a safe option [277]. In younger observational cohorts, less than half the proportion of patients with LMCA disease required rotational atherectomy [32, 43], with even lower usage rates amongst LMCA bifurcation registries [112]. Our older cohort of patients may be expected to have more calcified lesions than the younger patients reported in other studies [278-280], which may account for this increased usage.

While coronary rotational atherectomy is associated with a two-fold greater risk of complications compared with standard PCI, we report an incidence of double that number, 22.6% vs. 9.7% [276]. Over half of our reported complications were coronary dissections, 4(12.9%), while other data suggest the risk of coronary dissections from rotational atherectomy could be as low as 2.0% to 6.0% [276, 281-287]. Indeed the risk of coronary dissection after rotational atherectomy is lower than for standard PCI [288-290]. There could be various mechanisms for this increased number of dissections in our cohort, including an older cohort compared with other studies or the concurrent use of balloon angioplasty. Additionally one has to consider there is a small pool of operators who perform rotational atherectomy, indeed there is a possibility that these represent the complications of a single operator. One other consideration would be that of operators with lack of experience, such as registrar operators. These considerations though would be difficult to assess given the lack of identification of operators in our data.

Nearly three times as many patients with 'True' than 'Non-true' bifurcation disease were treated with rotational atherectomy. Side branch occlusion rates in our study were numerically higher amongst 'True' left main bifurcations; however, none were reported for patients treated with rotational atherectomy. While there was no statistically significant difference in our study, there is evidence from other studies that debulking of bifurcation lesions results in less SB occlusion from main vessel across side branch stenting [274, 283]. More patients with 'True' bifurcation disease treated with a single stent suffered SB occlusion than the two stent group, 5.4% vs.

1.1%. However, this was not statistically significant. While 16 patients had rotational atherectomy and single stent treatment, none suffered SB occlusion. SB occlusion is a recognised complication of bifurcation PCI and may occur in up to 8.0% of all cases [80, 291-293]. It is commonly due to carina shift after main across side branch stenting [103]. While some studies suggest that 'True' bifurcations are at risk of side branch occlusion [260, 291, 294], other studies have found no difference in side branch occlusion rates comparing 'True' to 'Non-true' bifurcations [293]. Our study suggests a trend to more SB occlusion from the single-stent strategy in 'True' LMCA bifurcation disease but not after rotational atherectomy; while this is hypothesis generating the number of patients in our study are too small to draw conclusions.

A third of patients in the two-stent group and only and eighth of those treated with a single stent had final kissing balloon (FKB) inflations; however the lack of use of FKB's was not associated with poor outcomes. FKB inflations are recommended for provisional single stenting when the SB requires further ballooning [295], indeed it may be required in less than a third of these patients [82, 114]. The data suggest potential benefit from the use of final kissing balloons as a routine strategy in single stent procedures of the LMCA bifurcation. For LMCA bifurcation studies with high FKB inflations, over 50.0%, in the single stent group, they report better outcomes from the single stent compared with the two stent technique, despite FKB inflations in over 90.0% of those treated with two stents [73, 90, 115, 127]. While in other studies where FKB inflations were used in less than a third of patients treated with a single stent, they found no difference in outcomes [113, 114]. These studies suffer from confounding due to the difference in Medina class of bifurcation involvement, indeed after matching the benefit of FKB's seem to extend only to patients treated with a two stent strategy [115]. Yet there is conflict in the data examining FKB in single stent treatment of LMCA bifurcation disease, with some reporting benefit [115], while others report no benefit in the routine FKB inflations for a single stent in the LMCA bifurcation [296]. These studies report almost double the FKB usage compared with our study and were undertaken amongst 'Non-true' and 'True' LMCA bifurcation lesions. Questions remain

regarding the benefit of routine FKB inflations for a single stent strategy in 'True' bifurcation disease.

We report a similar rate of arterial access complications, only 4.9%, compared with other LMCA PCI registries [297], and we report an equal incidence of complications between 'True' and 'Non-true' cohorts. This is surprising given that the femoral route was used for almost two thirds of our patients with a slightly higher frequency amongst those with 'True' bifurcation disease. Femoral access is associated with worse outcomes from LMCA PCI [297]. The radial route has been used successfully for left main bifurcation PCI [297], however the femoral route seems to be the preferred access for patients with 'True' left main bifurcation stenosis [114, 298]. In these studies the femoral route was preferred for elective two-stent strategies. We found no difference in access site preference for one or two stent strategies; femoral access was used in over two thirds of patients in both groups. The size of catheter used may have influenced the choice of access, close to 80.0% of all our patients were treated using at least a 7Fr catheter. While the 6Fr catheter can be used successfully for treating left main bifurcations [297], for those treated with an elective two stent strategy, larger catheters have been preferred in the past [298]. Current randomised studies seem to suggest a trend to using 6Fr catheters for elective two stent procedures in up to two thirds of patients [110]. While larger catheters allow the option of using kissing stents, more conventional two stent strategies can be performed with a 6Fr catheter even when kissing balloons are used. Amongst the 'True' bifurcation group those treated using a two stent technique were more likely to have larger catheters compared with the single stent group. However, due to lack of knowledge of intention to treat, it is not known the number of patients treated as a provisional single stent strategy with a view to possible conversion to a two stent strategy. In spite of the larger sized catheters and preference for femoral access amongst the two stent group, there was no significant difference in access site complications between the one and two stent groups.

Notably, while early expert consensus suggested that 'True' left main bifurcation disease should be considered a strong indication for a two stent strategy [119], the most recent consensus remains deliberately ambiguous in the light of observational non-randomised data and pending the results of EBC MAIN [271] . The only randomised trial assessing 'True' LMCA bifurcation disease compared the Culotte to double kiss crush, both two stent strategies [117]. However the question of whether a provisional single stent or two stent strategy for the treatment of 'true' bifurcation disease has not been assessed in a randomised trial. Our study therefore sheds some light on the problem given some obvious limitations.

4.4.3 Limitations

Our study suffers from considerable confounding for a number of reasons. While there were a significantly greater proportion of patients with a past medical history of myocardial infarction amongst the 'True' LMCA bifurcation group, the 'True' and 'Non-true' bifurcation groups were otherwise equally matched with regards to comorbidity. Missing LV function, on almost a third of patients, would act as a confounder given the greater number of patients in the 'True' group with previous myocardial damage.

Given that all cause death makes up three quarters of the MACCE, age may be considered a confounder as patients treated with a two stent strategy were significantly older than those treated with a single stent strategy. One other study showed that despite patients treated with a single stent being older patients with greater comorbidity they had better outcomes [115]. However, in this study the treatment groups differed with respect to the extent of LMCA bifurcation disease.

In the analysis of 'True' bifurcation disease, patients treated with a single stent had a significantly greater median SS compared with patients in the two stent group. The greater SS is mainly accounted for by the associated coronary vessel disease, LM+2VD and LM+3VD, where half of patients in the single stent group had associated coronary

disease as opposed to only a third of those in the two stent group. In contemporary registries up to 80% of patients with LMCA bifurcation disease are reported to have LM+2VD and LM+3VD [112, 113]. In another study, patients had worse outcomes from a two stent strategy in the context of significantly more mulitvessel disease as compared to the single stent group [112]. Patients with a greater SYNTAX score generally do worse [55]. The higher SYNTAX score for patients with 'True' bifurcation disease in our study is not accounted for alone by the burden of atheroma around the LMCA bifurcation. A 'True' left main bifurcation stenosis contributes only 2 points to the SYNTAX score when compared with a 'Non-true' lesion [35, 299].Another study which report no difference in outcomes for single and two stent strategies, have treatment groups which are matched for SYNTAX scores and where the SS was in the low-intermediate tertiles [114]. Despite the criticism that the groups differed with regards to coronary disease burden, in the multivariate analysis, SS was not an independent predictor of poor outcomes.

Future studies examining the PCI strategy for distal LMCA disease should be designed to reduce the confounding created by this associated multivessel disease. Indeed the EBC MAIN study excludes patients with a SS of greater than 32 [106]. However, bearing in mind that we treated significantly older patients with more extensive coronary disease, the data should be applied cautiously to the 'real world' patient cohorts.

Distal left main disease is associated with a greater burden of multivessel disease [62, 300-302] and indeed this is the case for 'True' left main bifurcation disease, more so than 'Non-true' bifurcation disease. We report significantly more multivessel disease, LM +2VD and LM+3VD, amongst the 'True' bifurcation cohort compared with the 'Non-true' cohort. However, other studies of PCI for unselected distal LMCA disease have reported associated multivessel coronary disease in up to four-fifths of patients [113, 115], twice the proportion in our study. They show no difference in the burden of coronary disease between the 'True' and 'Non-true' groups [72]. Despite this association with multivessel disease, after multivariate analysis including the SS, we can conclude that the association of 'True' LMCA bifurcation disease with poor outcomes were independent of the greater coronary disease burden.

Despite only a numerically greater median stent length for the 'True' group, given the significant differences in coronary disease burden between the 'True' and 'Non-true', one cannot ignore possible confounding. We did not report the coronary territory involved in ST, other LM PCI studies have suggested the risk of ST may be related to the treatment of extensive coronary disease beyond the LMCA [127].

Prospective trials, such as the BBC ONE and Nordic trials include clear study treatment protocols which allow the identification of treatment crossover due to an unsuccessful stent strategy [83]. In this respect, while our retrospective study reports equal outcomes from a two stent vs single stent treatment for the LMCA, for those patients treated with 'T-stent'/'Culotte'/'TAP' strategies, there may have been considerable crossover from a provisional single stent to a T-stent strategy. In the EBC II trial the crossover was up to 16% [110]. Other confounders of an intention to treat analysis would include the lack of QCA data to confirm the size of the SB, while the viability of the subtended myocardial bed was unknown for a number of patients.

While we report MACCE, including death, MI, repeat revascularisation and stroke, we did not report on TLR due to a lack of lesion-level outcome data. TLR in the stented left main bifurcation is reported in up to a fifth of patients over long term follow-up [127], so it remains an important determinant of outcomes. However, restenosis after LMCA bifurcation PCI was commonly asymptomatic and was often diagnosed after routine angiographic follow-up [190]. Only a small number of our patients suffered repeat revascularisations, while MACCE was mainly driven by death. In this older cohort it could be suggested that a lack of access to revascularisation procedures may have led to an underreporting of TLR .

4.4.4 Conclusions

This study cohort is older and has more extensive coronary disease than study populations included in current published data from which LMCA bifurcation PCI guidelines have been drawn. This study is the first to show that 'True' LMCA bifurcation disease is associated with worse outcomes following PCI. Diabetes is associated with a two-fold increase in the risk of poor outcomes in patients with LMCA bifurcation disease, albeit patient-level rather than lesion-level outcomes. Our study sample is representative of current clinical practice, which include high risk patients with complex coronary lesions. These data highlight the challenges facing both clinicians and researchers.

So while our data support the notion that a single or two-stent strategy is acceptable for the treatment of 'True' LMCA bifurcation disease, given the lack of lesion-level outcomes, including TLR, this is hypothesis generating rather than conclusive. Future research to assess single vs. two stent strategies for 'True' LMCA bifurcation disease should include a more specific outcome measure and the selection of patients with limited associated coronary disease to minimise confounding. The challenge, therefore, would be to design a study which can answer the narrow question of how to treat the LMCA bifurcation while acknowledging that the typical patient presenting with LMCA bifurcation disease would usually have extensive coronary disease and may well be older with more comorbidity. These patients, therefore, may not be appropriately managed with CABG. While we await the results of the EBC MAIN study, our findings seem consistent with the EBC recommendations for treating LMCA bifurcations.

5. Results chapter: Octogenarians with Left main coronary artery disease

We identified 154 octogenarians who presented with unprotected left main coronary artery (ULMCA) disease, the numbers of octogenarians treated increased year on year (see **table 40**). It is known that amongst an unselected group of octogenarians treated with PCI, cardiogenic shock is the single greatest predictor of in-hospital death, with a risk greater than five fold compared with other patients [1, 126, 303]. For the following analysis of long term outcomes amongst octogenarians, 15 patients presenting with cardiogenic shock were excluded and here follows the analysis of outcomes amongst 139 octogenarians following left main coronary intervention.

Up to three quarters of patients with LMCA disease have concomitant multi-vessel coronary artery disease [151]. There is increasing recognition that incomplete revascularisation of all diseased coronary arteries in multi-vessel disease is associated with increased mortality [156-158]. However, complete revascularisation is less commonly achieved in patients with anatomically more complex disease [47, 155]. If one considers that as one approaches the 8th decade the prevalence of LMCA disease is over 25% [151, 304],[305],[306], even up to 40% in one study [153], and it often presents with concomitant multivessel coronary disease [151], then the elderly would be at risk of incomplete revascularisation [170, 206].

The residual SYNTAX score (rSS) is a quantitative and reproducible measure of the severity and complexity of residual coronary disease after PCI, which is predictive of long term clinical outcomes in younger populations [47, 167]. Patients with rSS >8 have higher all-cause mortality at long term follow-up [155] and are at increased risk of recurrent ischaemic events [167]. In patients who receive PCI for ULMCA disease, rSS is a prognostic discriminator and has been identified as an independent predictor of cardiac mortality at two years [168]. However, the patients included in this study were relatively young (mean age 71 years) and the results may not be applicable to older individuals. A recent study of less than 100 patients suggested that residual coronary disease was associated with poor outcomes in octogenarians presenting with ACS [170]. This study did not assess patients with LMCA disease exclusively, with less than a third of patients had LMCA disease.

5.1 Patient characteristics

5.1.1 Demographics

Of 139 octogenarians (median age 84.0 [IQR 5.0] years; 40.7% female), over two thirds (67.1%) presented with an acute coronary syndrome, 12.1% of whom had STEMI (**Table 41**). Over half of patients 78 (56.1%) presented with a history of some form of cardiovascular disease including 21 (15%) with peripheral vascular disease, 16 (11.4%) with a history of stroke, 62 (44%) patients had a history of previous MI, while 25 (17.9%) had previous PCI and 4(2.9%) patients had a history of previous cardiac surgery. No patients were found to have a protected left coronary circulation. There were 26 (18.6%) patients with diabetes and nearly half of patients, 69 (49.3%) were treated for hypercholesterolaemia. Other significant comorbidity in this study cohort includes 14 (10.1%) patients with renal impairment and 4 out of 10 patients had a history of smoking. While the median EuroSCORE (IQR) was 10.4 (11.8), there were 19 patients with a EuroSCORE of less than 5.0. The decision for PCI over surgery was not available in the retrospective data enquiry.

The patients were ordered by rSS and divided into equal tertiles, the rSS score corresponding to the separate groups was used to describe the categories by rSS groupings. There were no significant differences in comorbidity between the three tertiles.

Table 40: Number of unprotected left main coronary artery (ULMCA) percutaneous coronary intervention (PCI) in octogenarians per calendar year

Year	Number of ULMCA PCI	%DES
2005	6	50%
2006	10	80%
2007	10	30%
2008	22	36.4%
2009	17	82.4%
2010	24	100%
2011	27	88.9%
2012	32	96.9%
2013 (up to March)	6	100%

ULMCA – unprotected left main coronary artery; PCI – percutaneous coronary intervention; DES – drug eluting stent

Table 41: Baseline clinical characteristics for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17

Variable	All patients (n=139)	rSS≤8 (n=48)	rSS >8-17 (n= 44)	rSS >17 (n=47)	p-value
Median Age (IQR)	84.0 (5.0)	84.0 (5.0)	84.0 (4.0)	85.0 (6.0)	NS
Female sex	57 (40.7%)	19 (39.6)	16 (36.4%)	22 (46.8%)	NS
Stable angina	46 (32.9%)	16 (33.3%)	14 (31.8%)	16 (34.0%)	NS
NSTEMI	76 (54.3%)	27 (56.3%)	25 (56.8%)	24 (51.1%)	NS
STEMI	17 (12.1%)	5 (10.4%)	5 (11.4%)	7 (14.9%)	NS
Previous MI	62 (44.3%)	21 (43.8%)	16 (36.4%)	25(53.2%)	NS
Previous cardiac surgery	4 (2.9%)	1 (2.1%)	1 (2.3%)	2 (4.3%)	NS
Previous PCI	25 (17.9%)	10 (20.8%)	6 (13.6%)	9 (19.1%)	NS
Hypertension	77 (55.0%)	27 (56.3%)	23 (52.3%)	27 (57.4%)	NS
Peripheral vascular disease	21 (15.0%)	6 (12.5%)	6 (13.6%)	9 (19.1%)	NS
Chronic Lung disease	13 (9.3%)	4 (8.3%)	5 (11.4%)	4 (8.5%)	NS
Previous CVA	16 (11.4%)	2 (4.2%)	7 (15.9%)	7 (14.9%)	NS
Renal impairment	14 (10.1%)	5 (10.4%)	6 (13.6%)	3 (6.4%)	NS
Diabetes	26 (18.6%)	8 (18.2%)	9 (19.1%)	9 (19.1%)	NS
Hyperlipidaemia	69 (49.3%)	25 (55.6%)	17 (38.6%)	27 (60.0%)	NS
Ex or current smoker	56 (40.0%)	20 (45.5%)	13 (37.1%)	23 (52.3%)	NS
Median logistic EuroSCORE (IQR)	10.4 (11.8)	10.0 (13.0)	11.5 (10.5)	10.4 (12.2)	NS

IQR – interquartile range; MI – myocardial infarction; PCI – percutaneous coronary intervention; CVA – cerebrovascular accident

5.1.2 Angiographic data

Over 60% of the cohort had 'true' bifurcation disease of the LMCA (medina 1,1,1/0,1,1/1,0,1) (**Table 42**). The median SS was 32.0 (IQR 12.8) with almost half (47.1%) of patients falling within the high SS group (SS ≥33) (see **figure 14**). Over a third of patients, 53 (34.1%), had at least 2 other coronary vessels with a significant stenosis in addition to the diseased LMCA, where the RCA had a significant stenosis in over half of patients, 73 (52.1%). Chronic total occlusions (CTO) were present in 21 (15.0%) patients, and involved the proximal to mid coronary artery segments in all but one patient.

There were significant differences with respect to coronary disease burden for the three tertiles of residual SS. For patients with an rSS>17, none had a baseline of SS≤22, while half of all patients in the rSS≤8 and rSS <8-17 tertiles had a baseline SS ≤ 22. Only 10.4% of patients with a rSS≤8 had a SS≥33, consequently those patients within the rSS>17 tertile had significantly greater baseline SS. Almost three quarters of patients in the rSS≥17 group had 'True' LMCA bifurcation disease, while this was the case in less than half of the patients with rSS≤8. Over a quarter of patients in the rSS≥17 tertile had a CTO, while only one patient had a CTO in the rSS≤8 tertile. Close to half of patients in the rSS≤8 tertile had LMCA+1VD, while more than half of patients in the rSS≥17 group had at least 2 vessels disease in addition to the LMCA.

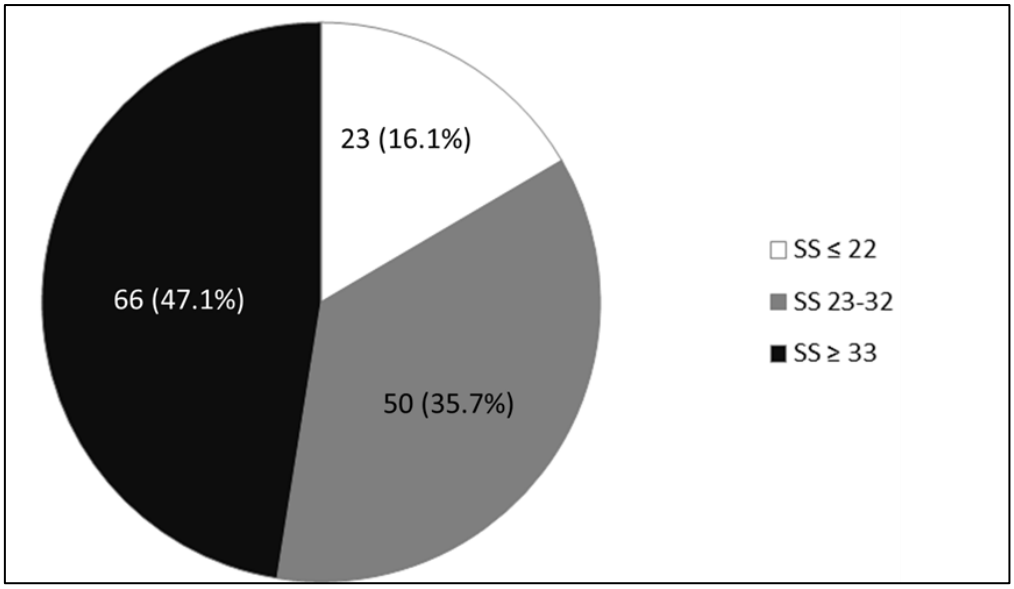

Figure 14: Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery (SYNTAX) Score tertiles in 139 Octogenarians. Patients were divided into low (SYNTAX score ≤22), intermediate (SYNTAX score =23-32) and high (SYNTAX score ≥33) tertiles.

Table 42: Baseline angiographic features for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17

Variable	All patients (n=139)	rSS≤8 (n=48)	rSS >8-17 (n= 44)	rSS >17 (n=47)	p-value
Median SS (IQR)	32.0 (12.8)	25.0 (11.8)	31.0 (8.0)	45.0 (14.5)	<0.001
Lower tertile ≤ 22	23 (16.4%)	19 (39.6%)	4 (9.1%)	0 (0%)	<0.001
Intermediate tertile 23-32	50 (35.7%)	24 (50.0%)	22 (50.0%)	4 (8.5%)	<0.001
High tertile ≥33	66 (47.1%)	5 (10.4%)	18 (40.9%)	43 (91.5%)	<0.001
LMCA bifurcation disease	109 (78.4%)	35 (72.9%)	35 (79.5%)	39 (83.0%)	NS
True LMCA Bifurcation disease *	84 (60.0%)	23 (47.9%)	26 (59.1%)	35 (74.5%)	<0.05
LMCA + 1 vessel	53 (37.8%)	22 (45.8%)	18 (40.9%)	13 (27.7%)	<0.05
LMCA + 2 vessels	34 (24.3%)	5 (10.4%)	13 (29.5%)	16 (34.0%)	<0.05
LMCA + 3 vessels	19 (13.6%)	3 (6.3%)	4 (9.1%)	12 (25.5%)	<0.05
Significant RCA disease	73 (52.1%)	15 (33.3%)	25 (56.8%)	33 (70.2%)	<0.05
Dominant RCA	132 (94.3%)	45 (95.7%)	41 (93.2%)	46 (97.9%)	NS
All CTO's	21 (15.0%)	1 (2.1%)	8 (18.2%)	12 (25.5%)	< 0.05
Proximal to mid vessel CTO's	20 (14.3%)	1 (2.1%)	8 (18.2%)	11 (23.4%)	<0.05

SS- SYNTAX score; IQR – Interquartile range; LMCA – left main coronary artery; RCA – right coronary artery; CTO – chronic total occlusion, *True left main bifurcation disease denotes (medina 1,1,1/0,1,1/1,0,1)

5.1.3 PCI procedural data

Almost three quarters of procedures were performed via the femoral artery with the radial and femoral artery employed in only 3 cases. Larger sized catheters were favoured, the 7 French (Fr) or 8Fr sized catheters were used in over 80.0% of patients (**Table 43**). The IABP was employed in a small number of patients, in 6 patients it was inserted prior to the PCI while in 5 patients the need arose during the angioplasty to insert the IABP. Unfractionated heparin was used in over two thirds of patients, while Bivalarudin was used in the rest. The additional use of intravenous IIb/IIIa-inhibitors was required in a quarter of patients. Rotational atherectomy was employed in a large proportion of patients, up to a fifth (27 cases) of patients. All rotational atherectomy was performed through a 7/8Fr catheter with all but 4 cases performed from the femoral access site. For LMCA bifurcation disease, a single stent strategy was undertaken in over half of the cases. While the median baseline SS was 32.0 (IQR 12.8) and the median residual rSS 13.0 (IQR 12.0), the median Delta SS was 20.0 (IQR 8.75). There was a significant positive correlation between the baseline SS and the rSS (Pearson's correlation coefficient 0.86, $p<0.001$), see **figure 15**.

There was no significant difference in the access site used for each of the three rSS tertiles as well as the preference for larger sized catheters in over 80.0% of patients. While the use of drug eluting stents (DES) was favoured in 4 out of 5 patients overall, only two thirds of patients in the highest rSS tertile, rSS≥17, received a DES. Compared with the rSS≥17 tertile, DES usage was significantly higher in the rSS≥8 and rSS >8-17 tertiles, 91.7% and 86.4% respectively. Median stent lengths did not differ between the three rSS tertiles; however there was a small but insignificant difference in the median Delta SS across the rSS tertiles.

While there was no significant relationship between access site and 'true' bifurcation disease X^2 (2, N = 139) = 2.76, p =0.25; there was a significant relationship between 'true' bifurcation disease and the use of at least 7Fr guide catheters, X^2 (1, N = 139) = 10.243, p =0.001. Furthermore, there is a significant relationship between the use of at least 7Fr guide catheters and the use of femoral access, X^2 (2, N = 139) = 30.34, p <0.001).

Table 43: Percutaneous coronary intervention (PCI) procedural details for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17.

Variable	All patients (n=139)	rSS⩽8 (n=48)	rSS >8-17 (n= 44)	rSS >17 (n=47)	p-value
Femoral access	101 (72.1%)	35 (72.9%)	32 (72.7%)	34 (72.3%)	NS
Radial Access	35 (25.0%)	13 (27.1%)	11 (25.0%)	11 (23.4%)	NS
Radial and Femoral access	3 (2.1%)	0 (0%)	1 (2.3%)	2 (4.3%)	NS
6 Fr Catheter	25 (17.9%)	9 (18.8%)	7 (15.9%)	9 (19.1%)	NS
7 Fr Catheter	89 63.6%)	32 (66.7%)	28 (63.6%)	29 (61.7%)	NS
8 Fr Catheter	22 (15.7%)	7 (14.6%)	8 (18.2%)	7 (14.9%)	NS
IABP Pre – PCI	6 (4.3%)	0 (0%)	3 (6.8%)	3 (6.4%)	NS
IABP During PCI	5 (3.6%)	3 (6.4%)	1 (2.3%)	1 (2.1%)	NS
Unfractionated Heparin	92 (65.7%)	30 (62.5%)	28 (63.6%)	34 (72.3%)	NS
Bivalarudin	47 (33.6%)	17 (35.4%)	16 (36.4%)	14 (29.8)	NS
Abciximab	28 (20.0%)	9 (18.8%)	12 (27.3%)	7 (14.9%)	NS
Tirofiban	7 (5.0%)	1 (2.1%)	1 (2.3%)	5 (10.6%)	NS
Rotational atherectomy	27 (19.3%)	7 (14.6%)	9 (20.9%)	11 (23.4%)	NS
Single stent to LMCA bifurcation	79 (56.4%)	26 (54.2%)	23 (52.3%)	30 (63.8%)	NS
DES used	113 (80.7%)	44 (91.7%)	38 (86.4%)	31 (66.0%)	<0.05
Median total stent length (IQR), mm	35.5 (23.3)	38.5 (22.8)	34.0 (27.0)	36.0 (28.0)	NS
Median rSS (IQR)	13.0 (12.0)	5.0 (3.0)	13.0 (4.0)	24.0 (13.0)	<0.001
Median deltaSS (IQR)	20.0 (8.75)	20.0 (8.5)	20.0 (7.0)	17.5 (8.0)	<0.001

Fr – French size; PCI – percutaneous coronary intervention; IABP – intra-aortic balloon pump; LMCA – left main coronary artery; DES – drug eluting stent; rSS – residual SYNTAX score; IQR – interquartile range; deltas – delta SYNTAX score

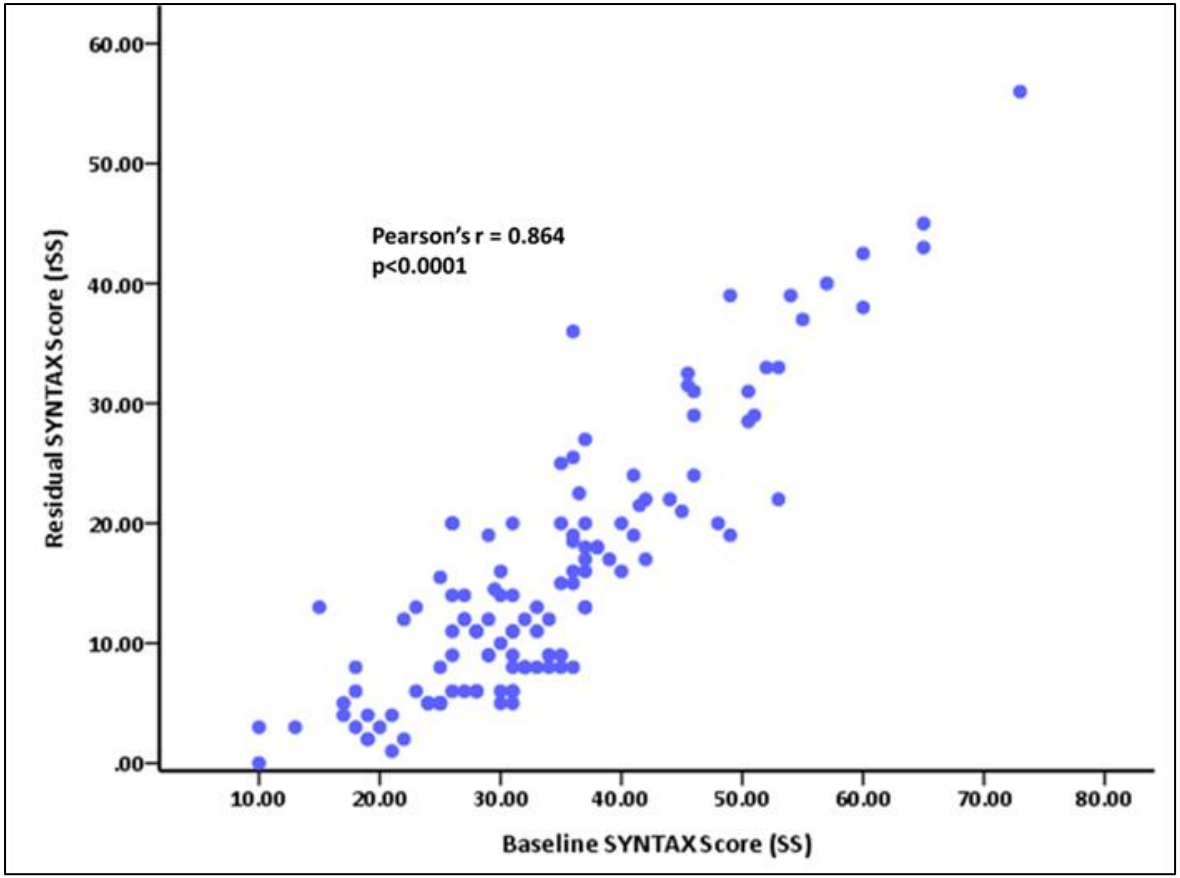

Figure 15: Correlation between the baseline and residual SYNERGY between Percutaneous Coronary Intervention with Taxus and Cardiac surgery (SYNTAX) Score. The baseline score is presented on the x-axis and the residual SYNATAX score on the y-axis. The paired scores are presented for the 139 octogenarians with unprotected left main coronary artery (ULMCA) disease. Each point on the graph may represent more than 1 value. SS- baseline SYNTAX score; rSS – residual SYNTAX score

5.1.4 PCI procedural complications

Procedural complications occurred in 9 (6.5%) patients, with 4 coronary perforations resulting in 2 cardiac tamponades, with cardiogenic shock in 1 of these patients (**Table 44**). Cardiogenic shock occurred in 3 additional patients. Of the 27 patients who were treated with rotational atherectomy, 2(7.4%) suffered a coronary perforation. All coronary perforations occurred in patients treated for LMCA bifurcation disease, 4(4.8%). Other procedural complications include 1 (0.7%) cerebrovascular accident (CVA) and 1 (0.7%) sidebranch occlusion.

5.1.5 Arterial access complications

Arterial access site complications occurred in 7 (5.0%), comprising 3 haemorrhages requiring blood transfusion and 1 which required surgical intervention (**Table 45**). All complications occurred in patients treated through the femoral artery and all occurred with catheters of at least 7Fr in size. Of the 27 patients treated with rotational atherectomy, 3(11.1%), suffered an access site complication. A chi-square test of independence was performed to examine the relation between all procedural and access site complications and rotational atherectomy. The relation between these variables was not significant, X^2 (1, N = 139) = 0.001, p =0.97.

Table 44: Post-procedure complications for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17

Complications	All patients (n=139)	rSS⩽8 (n=48)	rSS >8-17 (n= 44)	rSS >17 (n=47)	p-value
Cardiac Tamponade	2 (1.4%)	2 (5.4%)	0 (0%)	0 (0%)	NS
Cardiogenic shock	4 (2.9%)	2 (5.4%)	1 (1.6%)	1 (2.6%)	NS
Coronary perforation	4 (2.9%)	3 (8.3.%)	0 (0%)	1 (2.7%)	NS
CVA – infarct	1 (0.7%)	0 (0%)	1 (1.6%)	0 (0%)	NS
Sidebranch occlusion	1 (0.7%)	0 (0%)	1 (1.6%)	0 (0%)	NS

SYNTAX -Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score; rSS – residual SYNTAX score, CVA – cerebrovascular accident

Table 45: Arterial complications reported for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17

Arterial complication	All patients (n=139)	rSS≤8 (n=48)	rSS >8-17 (n= 44)	rSS >17 (n=47)	p-value
Retroperitoneal bleed	0	0	0	0	p=NS
Surgical intervention	1 (0.7%)	0	0	1 (2.1%)	p=NS
Arterial dissection	1 (0.7%)	1 (2.1%)	0	0	p=NS
Arterial occlusion	0	0	0	0	p=NS
Arterial haemorrhage	3 (2.2%)	1 (2.1%)	1 (2.3%)	1 (2.1%)	p=NS
False aneurysm requiring thrombin injection	1 (0.7%)	1 (2.1%)	0	0	p=NS
False aneurysm requiring compression	1 (0.7%)	1 (2.1%)	0	0	p=NS
False aneurysm conservative management	0	0	0	0	p=NS

NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; rSS – residual SYNTAX score

5.2 Outcomes

Over a median follow-up of 654 (IQR 1041) days, there were 43 (30.7%) deaths. At 30 days, the mortality rate was 5.0% and at one year it was 11.4%. **Table 46** shows a breakdown of all the MACCE events during the study follow-up. The MACCE rate for the overall follow-up was 38.1%, where death accounts for up to 81.1% of all MACCE. The MACCE rate at 30 days was 5.0%. Cardiac deaths accounted for over 85% of all MACCE at 1 month, 48.0% at 1 year and 35.8% for the entire follow-up period. The proportion of non-cardiac cause of death rose steadily from 14.3% at 1 month, to 25.0% at 1 year and 55.8% for the entire follow-up. At 1 year we report a repeat revascularisation rate of 2.9% and 5.8% over the entire follow-up period. No patients received repeat revascularisation with CABG, while further PCI was performed in the lower, middle and upper rSS tertiles in 3 (6.3%), 3 (4.5%) and 3 (6.4%) of patients respectively. Myocardial infarction occurred in 8.6% of patients for the entire follow-up. Definite and probable ST rates are reported in this analysis. The early and late ST rates are 1.4% (2 patients) and 0.0% (0 patients) respectively, with a VLST rate of 0.7 % (1 case).

5.2.1 Survival analysis

Unadjusted survival was worse for patients with an rSS in the upper tertile (**figure 16 and 17**). After adjusting for mode of presentation, co-morbidity (renal impairment, diabetes, previous cardiac surgery, previous myocardial infarction, previous PCI, peripheral vascular disease) and PCI strategy, the only variable independently associated with all cause death was SS [aHR 1.04, 95% CI 1.02-1.07, p=0.002]. Regression analyses were repeated after replacing SS with collinear variables including rSS, true left main stem coronary artery disease, significant right coronary artery disease and presence of a chronic total occlusion. After adjustment, rSS [aHR 1.03; 95% CI, 1.00-1.06; p=0.04] and true bifurcation LMCA disease [aHR 3.41; 95% CI, 1.31-8.83; p=0.01] were independently associated with all cause mortality, while 'True' LMCA bifurcation disease [aHR 2.78; 95% CI, 1.5-5.2; p=0.001] was independently associated with MACCE.

Table 46: MACCE at 30 days, 1 year and overall follow-up reported for 139 octogenarians, for the all patients and residual SYNATX score tertiles, rSS⩽8, rSS>8-17 and rSS⩾17

	0-30 days	1 year	Overall follow-up
All-cause death	7 (5.0%)	16 (11.5%)	43 (30.9%)
Cardiac Death	6 (4.3%)	12 (8.6%)	19 (13.7%)
MI	0	7 (5.0%)	12 (8.6%)
Repeat revascularisation	0	4 (2.9%)	8 (5.8%)
Stroke	0	0	3 (2.6%)
Definite/Probable ST	2 (1.4%)	2 (1.4%)	3 (2.6%)
MACCE	7 (5.0%)	25 (18.0%)	53 (38.1%)

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; ST: stent thrombosis

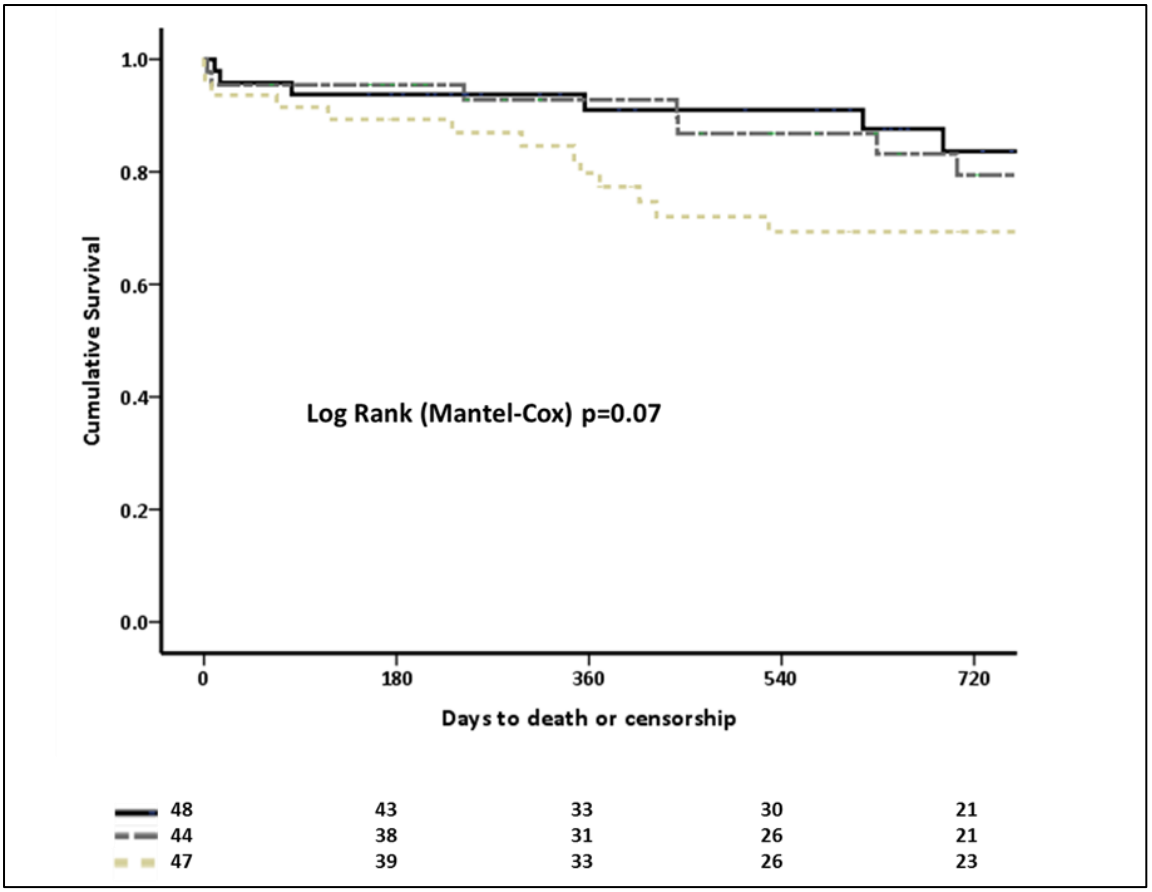

Figure 16: Unadjusted Kaplan-Meier estimates of survival from all-cause death in 139 Octogenarians with rSS ≤ 8; rSS >8-17 and rSS≥17.

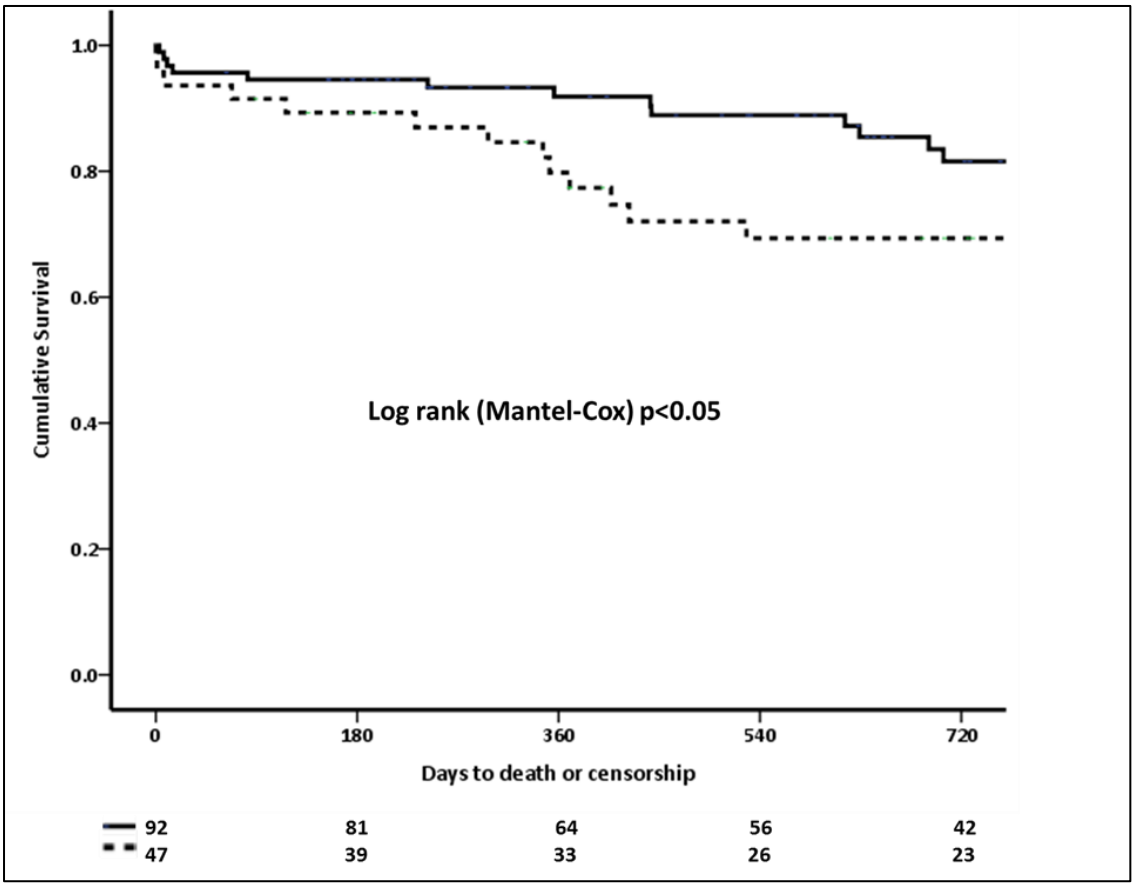

Figure 17: Unadjusted Kaplan-Meier estimates of survival from all-cause death in 139 octogenarians with rSS 0-17 and rSS>17

5.3 Summary

5.3.1 Key results

In this retrospective analysis of octogenarians treated with ULMCA PCI, we found that patients with incremental levels of residual coronary disease, as calculated from the residual Syntax score (rSS), were at greater risk of mortality over long-term follow-up. Each 10 unit increase in rSS was associated with a 3% increase in all-cause mortality. The thirty day and 1 year survival of patients within our cohort of octogenarians treated with ULMCA PCI is similar to other non-randomised studies of revascularisation amongst octogenarians despite significant comorbidity [152, 307]. Whilst one year survival amongst this aged population approached 90% and at about 2 years, was 77%, we found that, in addition, the Syntax score (SS) was significantly associated with poor long term outcomes. Furthermore, the presence of 'True' LMCA bifurcation disease was associated with a three-fold increase in risk of death after a median follow-up of 645 (IQR 1041) days.

5.3.2 Discussion

Our study population had a similar prevalence of comorbidities and burden of coronary disease compared with other reported registries of octogenarians treated with ULMCA PCI [126, 141, 143, 144, 308]. Elderly patients are more likely to present with complex, multivessel coronary disease [304, 309, 310]. This increased burden of atheroma in the elderly, which includes distal LMCA disease and multivessel disease, is confirmed by other observational studies of LMCA disease revascularisation in octogenarians [39, 146, 307]. Using the SS to quantify the atheroma burden, we can report a higher median baseline SS than those reported in randomised trials [47, 61].

In keeping with other observational studies, LMCA bifurcation disease was associated with poor outcomes [78]. Using the Medina classification of bifurcation disease, our study is the first to report this association with 'True' LMCA bifurcation disease

amongst octogenarians receiving PCI for LMCA disease. Despite a similar proportion of patients with LMCA bifurcation disease, our patients tended to have a provisional single stent when compared with younger study cohorts [31, 61]. It is not certain if the provisional single stent is inferior to the two stent strategies for treatment of the LMCA bifurcation disease [77, 113, 115]. Indeed, for the treatment of 'True' LMCA bifurcation disease, a provisional single stent would leave the large SB stenosis untreated. While poor outcomes from LMCA bifurcation revascularisation are driven by repeat revascularisation [115, 117], only 4.3% of our patients suffered repeat revascularisation. However, as LMCA bifurcation disease is associated with extensive coronary disease, repeat revascularisation was a major determinant of poor outcomes in these studies.

We reported almost twice the burden of residual coronary disease compared with other randomised studies [155, 167]. In our study rSS and SS were strongly correlated: we observed greater residual coronary disease in patients with higher baseline SS. This finding differs from that reported in the SYNTAX trial [155], in which there was no correlation between rSS and SS. In keeping with the design of this trial, complete revascularisation was achieved in almost 60% of patients in SYNTAX [155], whereas complete revascularisation was achieved in only 4.3% of patients in our observational study. Accordingly, median delta SS did not differ across the rSS tertiles confirming a tendency for selective rather than complete revascularisation in our series and this explains the significant collinearity of the SS with other measures of coronary disease, such as the rSS and distal LMCA involvement.

Selective revascularisation in the elderly has been reported in other studies [170, 206]. Over two thirds of our patients presented with an ACS compared with only 50-55% in other registries of octogenarians with ULMCA PCI [143, 144, 308] , while this is similar to UK national revascularisation trends [311]. Elderly patients are less likely to have access to revascularisation compared with younger patients [206, 207]. Octogenarians are more likely to receive treatment for unstable syndromes than stable angina when

compared with younger patients [126, 130, 133, 146], indicating a possible preference to manage stable symptoms conservatively for this age group. While haemodynamic compromise has been implicated in poor outcomes from revascularisation of ACS in the elderly [131] we excluded patients presenting with cardiogenic shock. Less extensive revascularisation and increasing rSS following the treatment of ACS in octogenarians has been associated with poor outcomes [170]. Nevertheless, ACS on presentation was not associated with poor outcomes.

The presence of a chronic total coronary occlusion is a major factor in failing to achieve complete revascularisation by PCI [312]. CTOs were more prevalent and tended to be left untreated in our patients when compared with a younger LMCA study cohort [61]. However, we were unable to assess whether CTO revascularisation was appropriately deferred due to lack of myocardial viability or ischaemia.

Diabetic patients tend to have more extensive coronary disease, indeed this has been confirmed amongst older patients with diabetes [313-315]. As a consequence of this, diabetic patients are at increased risk of incomplete revascularisation [316]. While we report a similar incidence of diabetes as reported in other non-randomised studies amongst octogenarians undergoing revascularisation [130, 141, 307], diabetes was not independently associated with adverse long-term outcomes in our cohort. Diabetes is implicated in excess cardiovascular deaths amongst the elderly [317]. Thus older patients with diabetes suffer excess mortality compared with older patients without diabetes [318]. Evidence suggests that tight glycaemic control amongst patients with established cardiovascular disease does not prevent excess cardiovascular deaths, and may in fact be harmful [319]. It is rather the macrovascular sequelae rather than the diabetes per se which is associated with poor outcomes. So within a cohort with a significantly high burden of established coronary disease, such as ours, there is no excess risk associated with diabetes following revascularisation.

Octogenarians suffer more complex coronary disease than younger patients, including more bifurcation disease [320] and more calcified lesions [278-280, 321]. Calcified lesions are identified as a major factor leading to selective revascularisation [322], and are markers of poor prognosis following revascularisation [323]. Rotational atherectomy was required to treat the LMCA in almost a fifth of our patients, while it is used in less than half the proportion of younger patients with LMCA disease [32, 43].

Octogenarians are more likely to suffer complications following PCI [1, 133], making clinicians less likely to consider complex revascularisation strategies [206]. The overall rate of complications amongst our cohort was 11.5 %; over half of these are related to coronary complications with the remaining related to access site complications. There are a number of factors potentially relating to this increased risk of complications. Compared with published data, we employed rotational atherectomy in nearly twice the proportion of octogenarians treated for all coronary artery lesions [141] and those treated for LMCA disease [39]. It is known that the elderly suffer an increased risk of procedural complications from standard PCI, including the use of rotational atherectomy, when compared with younger cohorts [133]. Due to the need for larger sized catheters, rotational atherectomy is often performed from the femoral route. All rotational atherectomy in our cohort was performed from the femoral access. Despite this, it should be noted that rotational atherectomy for LMCA disease can be performed from radial access using catheters no larger than 6Fr, thus offering an alternative approach with similar success rates [277].

Femoral artery access was favoured in close to three quarters of our patients, whereas in other reported studies of octogenarians the radial artery route was used in up to 90.0% of patients [39]. While the transradial approach is favoured by patients and clinicians alike due to reduced discomfort and less complications, there is a greater risk of failure of the transradial approach in the elderly [324]. Due to age related progression of vascular disease including increased tortuosity of the subclavian artery, unfolding of the aorta, dilation of the aortic root, less compliant vasculature with

increased atherosclerosis and calcification, the femoral route may be preferred [325, 326]. Evidence supports the use of the radial access in the context of STEMI, with fewer bleeding complications and improved survival compared with femoral access [250, 327, 328]. However, these trials include younger patients, fewer females and the LMCA was treated in only 1.0% of the population. There are significant benefits of radial access in the elderly [329, 330], however these data suffers from selection bias, where patients with greater clinical risk, such as cardiogenic shock, received femoral access [329]. Radial access is a viable option for LMCA PCI, there is only one observational study of access site use in octogenarians with LMCA disease, the findings suggest a 98.0% PCI success rate with fewer complications from the radial access [331].

This study cohort had a large burden of peripheral vascular disease, similar to the levels reported in other observational studies of coronary revascularisation in the elderly [39, 126, 141]. The burden of peripheral vascular disease is significantly higher amongst the elderly revascularisation population compared with younger patients [126, 129, 133, 141, 142]. Indeed the prevalence of peripheral vascular disease in octogenarians is more than twice that of younger patients [332], and is strongly correlated with coronary artery disease [333]. While the presence of peripheral vascular disease indicates widespread macrovascular disease, it has implications for the management of coronary disease in the elderly due to and increased risk of access site complications [133].

Women have smaller calibre vessels [334], present later with coronary artery disease [335] and consequently have greater clinical risk due to comorbidity. We report a greater proportion of female patients than found in randomised studies of ULMCA revascularisation [1, 59-61, 141, 213]. Given the survival bias due to significantly greater life expectancy for females in the overall population [121], it is unsurprising that we report a greater proportion of female patients than amongst the younger populations of randomised studies of ULMCA revascularisation. However, it is a similar prevalence to that reported in registries of revascularisation among the elderly, where

more women are represented [130, 131, 133, 141, 142, 303]. The combination of smaller coronary arteries and greater comorbidity also contributes to the increased risk of procedural complications [133].

In this cohort there seems to be a preference for the use of larger catheters for the treatment of 'true' left main bifurcation disease. While the treatment of 'True' LMCA bifurcation disease may necessitate the use of a two stent approach through a larger sized catheter, a provisional single stent technique could be performed through a 6Fr sheath [336]. Femoral access may be preferred when using larger sized catheter as there is a greater risk of radial artery spasm and greater long term occlusion rates. A single stent technique was favoured in up to three quarters of our patients with LMCA bifurcation disease, which is a significantly greater proportion of patients when compared with other studies reporting on LMCA bifurcation PCI in the elderly [39]. While in the Rodes-Cabau study they report taking a provisional single stent approach in over 80.0% of LMCA bifurcations, a sidebranch stent was required in over 90.0% of these patients. While we used at least 7Fr sized catheters in over four fifths of patients, there was a significant association between larger sized catheters using femoral access and 'True' left main bifurcation disease. So while the femoral route was preferred in our data set, and with IABP use in 7.9% of patients, it may be assumed that the radial route could have been considered in the over 90.0% of patients.

Bearing in mind the greater burden of peripheral vascular disease in octogenarians, the greater use of radial access for LMCA PCI may reduce the risk of complications amongst octogenarians. Despite a higher incidence of radial and brachiocephalic trunk anatomical tortuosity compared to younger subjects, similar success rates for PCI with low procedural complication rates are found even among the elderly [337, 338]. However this will be limited by the need for larger sized catheters employed for LMCA bifurcation PCI, rotational atherectomy and a greater proportion of female patients with smaller calibre radial arteries.

Despite a significantly higher number of females in this older cohort compared with other studies due to survival bias, gender was not identified as an independent predictor of worse outcomes. There is a gender-based difference in clinical outcomes from revascularisation which is pronounced in younger populations, with worse outcomes for women [206]. This gender-based difference in outcomes disappears amongst the elderly [307, 339]. It is not clear why these differences disappear, however, our data supports the findings that older female patients are at no greater risk of worse outcomes than men.

While death made up almost two thirds of all MACCE at 1 year and over 80.0% for the median follow-up, we report a repeat revascularisation rate of only 2.8% at 1 year and 5.9% over the median follow-up. It is known that poor outcomes from LMCA PCI are predominantly driven by repeat revascularisations in all major randomised controlled trials [47, 59, 60]. When compared with other observational studies of DES revascularisation in octogenarians, our repeat revascularisation rate is similar or slightly higher [303, 340], including a registry of ULMCA PCI in octogenarians [39]. The failure to use DES in a fifth of our patients may be causally linked to the risk of repeat revascularisation [341]. Older patients are less likely to receive DES, yet they are still likely to benefit from a DES compared with BMS [342, 343].

In this older cohort, with more baseline and residual coronary disease compared with the SYNTAX trial patients [155], we did not observe a difference in the risk of repeat revascularisation across the rSS groups. It should be noted that in our cohort all repeat revascularisation was performed in the context of subsequent acute coronary events rather than stable angina. The younger cohorts studied in the randomised trials seem to be at greater risk of repeat revascularisation [47, 59, 60]. This greater risk may in part be due to the difference in the pathology of the atheroma. Despite a greater burden of coronary disease in older age, the plaque morphology is more stable than in younger patients [321], and thus the older patient is less likely to re-present with further acute coronary events. In this way, while it is known that coronary

revascularisation offers greater gains in survival for the elderly than young [130], revascularisation also seems to offer a more robust form of treatment for the elderly.

5.4.3 Limitations

While there were 19 patients who may be considered low risk for CABG, a EuroSCORE of less than 5.0, we were unable to ascertain the reason for choosing PCI over CABG. One may therefore speculate that additional unmeasured confounders may account for this decision, such as frailty. Indeed frailty is linked with increased mortality following CABG [344, 345], and is a predictor of worse prognosis for patients with cardiovascular disease [346-349]. Other unmeasured confounders which should be considered include presentation with heart failure and dementia. While we have previously discussed the missing LV function, it is a major predictor of poor prognosis in the elderly [350, 351].

This observational study suffers from inherent limitations including referral and selection biases. More so amongst elderly patients, selection bias may play a huge impact on outcomes from observational studies of revascularisation [206]. The elderly patients who eventually have revascularisation represent those most likely to benefit from the procedure. While clinical judgement would no doubt result in a selection bias for patients included in this analysis, there is additional bias with regards to the decision to provide limited revascularisation in some patients. As this was a retrospective study we were unable to determine the revascularisation strategy on a per-patient level, and so can only speculate reasons for failure to achieve complete revascularisation in the majority of patients. However, elderly patients are at greater risk of selective revascularisation [171], which may account for over 15.0% of CTOs being left unrevascularised. While the rationale for this is not recorded, we also do not have the data describing the complexity of these lesions so can't make reasonable speculation about these lesions. While the techniques for CTO revascularisation have improved, these lesions remain difficult to treat and with high associated risk.

Our data lack functional lesion assessment, while rSS is an anatomical assessment of untreated coronary disease and does not necessarily imply functionally incomplete revascularisation Clinicians are more inclined to demonstrate lesion ischaemia, using fractional flow reserve (FFR), to assess appropriate revascularisation in multivessel disease [352, 353]. Functional lesion classification could change the SS for up to a third of patients and thus lead to a change in management decisions, from CABG to PCI and vice versa [354]. This would result in a change in SS and rSS. However, no study has demonstrated an advantage of functional complete revascularisation over anatomical complete revascularisation in multivessel disease [355]. Indeed, while we await the results of the SYNTAX II and FAME 3 studies which will assess the FFR guided revascularisation of multivessel disease, these studies will not include patients with left main disease [356, 357]. Similarly, as information on myocardial viability was unavailable we are unable to exclude the possibility that stenoses in vessels subtending non-viable myocardial segments may have been appropriately left untreated.

In an ideal world we should study the benefits of revascularisation in the elderly in a randomised controlled trial. Yet there are limited opportunities for this as most RCT's exclude long lived individuals. One other possibility is to introduce a control from the population using actuarially predicted survival as a control. One argument against this would be that it doesn't offer any reliable comparator for patients treated for this medical condition. This cohort with LMCA disease, suffered an ACS in about two thirds and had significant comorbidity. So any comparison to a predicted survival would not give a true reflection of the benefit or harm of the treatment. Therefore we did not consider it a useful exercise. It should be imperative that the cardiology community studies this group of patients in an RCT in the near future.

5.4.4 Conclusions

While several recently published studies have attempted to identify a cohort of patients with LMCA disease who could appropriately be treated with PCI, the proportion of octogenarians included in these studies is low. Nevertheless, we have demonstrated that amongst a high surgical risk cohort of octogenarians with LMCA

disease, survival can be similar if not better than other reported studies of revascularisation in octogenarians [307].

Bearing in mind the sample size and reduced statistical power, we are therefore limited in our capability of detecting clinically relevant factors associated with poor outcomes in revascularisation of octogenarians with LMCA disease. Yet we identified a few factors associated with poor outcomes which seem to be congruent with published studies.

Baseline coronary disease burden, measured by the SS, is associated with poor outcomes in octogenarians with ULMCA disease. While octogenarians suffer from selective revascularisation, octogenarians in our real-world series had levels of residual disease more than twice those reported in randomised studies of ULMCA revascularisation [155, 167]. Incremental residual coronary disease among octogenarians who received ULMCA PCI was significantly associated with mortality. Currently, we are unable accurately determine the benefit octogenarians would receive from more complete revascularisation, however further studies designed to quantify this are warranted. While we have applied an anatomical quantification of incomplete revascularisation, future studies should be designed with functional classification of completeness of revascularisation.

Furthermore, while repeat revascularisation remains a significant factor limiting the use of PCI for LMCA disease, we have found a very low repeat revascularisation rate amongst elderly patients despite the large burden of residual disease; this is probably related to the more stable nature of plaque disease in the elderly [321]. The main discriminator of outcomes in our study is mortality, rather than repeat revascularisation as we find in the younger trial populations. Thus in future consideration needs to be given to assessing outcomes including measures of quality of life given the high burden of comorbidity in this population.

While this study demonstrates an association between residual coronary disease and poor prognosis, we cannot conclude that increasing degrees of completeness of revascularisation in octogenarians would result in an improved prognosis. There is obviously a selection bias which would indicate that clinicians applied clinical judgement in assessing individuals for further revascularisation as well as in making decisions regarding which lesions were treated. Thus a risk-benefit analysis, balancing the increased risks of revascularisation against prognostic gains and quality of life gains, should be analysed in future studies. Quality of life is an important outcome measure in the success of revascularisation in patients with limited life spans [358].

6. Result chapter: Longitudinal health related quality of life outcomes of management in a prospective cohort with left main coronary disease

6.1 Introduction

Physician-oriented measures of revascularisation, including traditionally reported outcome measures, such as MACCE and mortality, describe the natural history of the pathophysiological processes as well as treatment effects [180]. These outcome measures inform treatment decisions of perceived prognostic benefit [69, 299]. Yet while mortality is an indisputable measure of prognosis; the composite outcome, MACCE, may not be as accurate. Due to binary censorship of MACCE, one may ascribe a minor MI as an equal outcome to a disabling stroke. In this way, for the treatment of LMCA disease, while PCI may be considered non-inferior to CABG on the basis of mortality [59, 60], for more extensive coronary disease, PCI is considered inferior to CABG on the basis of excess repeat revascularisations despite a higher risk of stroke with CABG [47, 215]. Only one recently published study found a greater risk of stroke with PCI compared to CABG for the treatment of LMCA disease [60]. These outcome measures inform the risk-benefit analysis for each patient when deciding between either PCI or CABG [47, 229]. In the case of high risk patients, where revascularisation may offer no prognostic benefit, these outcome measures do not inform us of symptomatic benefit to the patient. However, there also needs to be clarity on the benefit of revascularisation for symptom management as well. The problem of course is the significant placebo effect from undergoing a 'procedural' treatment. For less severe stable coronary disease, revascularisation with PCI offers no benefit over medical management for symptoms when employing a 'sham' procedure [359].

Observational data though suggest increasing proportions of patients are having PCI rather than CABG for coronary disease [360]. These include patients with high surgical risk, such as the elderly [360, 361] and others with more complex coronary disease [362], such as LMCA disease [2]. Revascularisation decisions are therefore not solely based on improving traditional outcome measures, such as mortality, but rather symptomatic improvement. There is a need for data which inform this management approach.

Quality of life outcome measures may nuance the risk-benefit analysis. Quality of life outcomes amongst patients with coronary disease are predictive of poor outcomes, such as death [363, 364], repeat revascularisation [365, 366] and hospitalisation [367]. Poor quality of life outcomes within the first year predicts mortality up to a decade following revascularisation [368], even extending to the elderly [369-371]. Several studies have compared quality of life outcomes in patients treated with coronary revascularisation using PCI or CABG [372-385], however the results are conflicting with some reporting no difference [377, 383, 386, 387], while other studies report greater benefit from CABG [376, 380-385, 388]. These observational studies compare patients with varying degrees of severity of coronary disease and apart from the SYNTAX trial; none of these studies includes a large cohort of patients with LMCA disease.

While it is known that CABG improves angina compared to medical management in patients with LMCA disease [389], there is only one study comparing QOL outcomes from CABG or PCI in patients with LMCA disease [390]. This study was an inadequate examination of QOL as it failed to assess the known longitudinal changes in QOL by using only a single time point measure. HRQOL changes have never been described over a 1 year longitudinal study in patients with left main coronary artery disease comparing patients who are medically managed to those undergoing revascularisation with CABG or PCI [377, 388, 390, 391].

6.2 Methods

6.2.1. **Study design**

This pilot study of comparative, prospective, longitudinal quality of life outcomes in patients with left main coronary disease, who are referred for consideration for revascularisation, was conducted at a single tertiary cardiac centre in the United Kingdom. The study narrative would describe the process of referral, the consideration

for revascularisation, the study recruitment process and the follow-up of QOL outcomes using repeated measure questionnaires over 1 year follow-up.

6.2.2. Public consultation

In accordance with the principles laid out in the UK Policy Framework for Health and Social Care Research [392] , we conducted a public consultation of the research project. It is recommended that patients, service users and the public be involved, where appropriate, in the design, management and conduct of research. Patient and public involvement in decision-making is regarded as a key feature of the provision and development of good quality health care [393]. The General Medical Council requires doctors to "work in partnership with patients, sharing with them the information they will need to make decisions about their care" [394]. A Patient and Public consultation was held with the West Yorkshire Cardiovascular Network Patient and Public group on the 6th September 2013. This consultation process informed the study design, implementation and the recording of outcome measures.

6.2.3. Patient recruitment

All patients referred to the Leeds General Infirmary (LGI) for consideration for LMCA revascularisation would be approached for consent to the prospective study. Patients would be identified after:

(i) review at the weekly multi-disciplinary team (MDT) coronary revascularisation meeting held on Wednesdays, or
(ii) outpatient referral to a named interventionalist/surgeon, or
(iii) emergency revascularisation for LMCA disease.

It is suggested by the European Society of Cardiology (ESC) that all patients considered for revascularisation of complex coronary disease, including LMCA disease, be discussed by the MDT or 'heart team' [299]. Guidelines suggest the MDT comprise

non-interventionalist cardiologists, interventional cardiologists and cardiothoracic surgeons [395]. For those patients discussed at the LGI weekly MDT, they were referred in the following ways:

1) Elective patients referred from the district general hospitals were discussed at their local MDT meeting and then referred to a named surgeon/coronary interventionalist at the Leeds General Infirmary.
2) Urgent admissions to the Leeds General Infirmary were discussed at the multi-disciplinary team meeting.

Treatment decisions were often made in the MDT meeting but for the purposes of recruitment to the study, all angiograms were first reviewed by a senior coronary interventionalist to confirm LMCA disease; patients were then approached by a member of the research team for informed consent. Elective patients referred to the LGI MDT were approached for consent at the time of admission for revascularisation to the LGI, while in-patients were approached for consent soon after MDT decisions of care.

For patients referred to a named interventionalist/surgeon, correspondence was sent to either the LGI LCMA revascularisation clinic or to the individual interventionalist/surgeon's clinic from a referring cardiologist. The treating surgeon/cardiologist would inform the research team of patients they felt were appropriate for inclusion in the study. Informed consent was obtained from patients admitted at the time of their procedure, in practical terms it was accepted this could occur about 1 week either side of the procedure. In the case of medically managed patients consent was obtained soon after the management decision was made either on the ward or in the clinic.

Patients admitted as an emergency often had treatment in their best interest, but where possible discussions between the interventional cardiologist and on-call surgeon were documented. These patients were approached for consent soon after their

procedure, usually the following day once they have been identified from angiographic review.

Recruitment of the prospective quality of life cohort began in March 2013, where the first 103 patients were included in this pilot study. Documents approved for the recruitment and collection of data include the Patient information leaflet (PIS) (appendix 1), consent form (appendix 2) and letter to the GP.

Inclusion and exclusion criteria

All patients with significant LMCA disease were invited to participate in the study, where significance was defined as a greater than 50.0% diameter angiographic stenosis of the LMCA. All patients presenting with ACS where the significant LMCA lesion was either the culprit or bystander lesion were included. Further diagnostic tests, including IVUS/OCT/pressure wire study of the LMCA were left to the discretion of the treating clinician. Patients managed with revascularisation, including PCI or CABG, as well as those for optimal medical treatment only, were invited. The only exclusion included patients with a lifespan of less than 90 days due to a significant life-threatening co-morbidity.

6.2.4. Follow-up

Prospective patients had a planned telephone or clinic follow-up conducted at 6 months post-procedure and then yearly. HRQOL questionnaires were completed by patients at the following time points to allow for longitudinal analysis:

- Within 1 week of the procedure (either PCI or CABG) or at the time of consent for medically managed patients: MacNew [66] and Brief illness perception [70] questionnaires were administered.
- 1 Month post-procedure: MacNew and Brief illness perception were posted.
- 6 month post-procedure/recruitment: MacNew and Brief Illness perception were posted.
- 1 year post-procedure/recruitment: MacNew and Brief Illness perception were posted.

The HRQOL measures include the combined questionnaires for use at 1 week prior, 1, 6 and 12 months post-procedure, a sample questionnaire can be found in appendix 3. The baseline questionnaire was issued to assess the HRQOL prior to treatment. However, when considering the event of patients presenting as an emergency, it was agreed by all investigators that the questionnaire would remain valid if administered within the first 1 week of the revascularisation procedure. It was felt that patients could still reflect on their premorbid state.

6.2.5. Questionnaires

The MacNew questionnaire

The MacNew questionnaire evaluates how emotional, physical and social functioning is affected by coronary disease and is therefore applicable to this research [196, 396]. Various studies have confirmed the validity, reliability and reproducibility of the MacNew questionnaire [397-399]. The questionnaire consists of 27 questions using multiple choice answers along a seven-point Likert-type response scale, where only one answer is allowed. The mean global score is a sum of all the scores divided by the number of questions. A mean subscale score for the three domains (social, physical and emotional) is similarly a sum of the scores divided by the number of questions aggregated to assess a particular domain [195].

The MacNew compares favourably to the other quality of life questionnaires commonly used to assess outcomes in coronary disease [379, 400, 401]. Questionnaire completion rates are higher than comparative questionnaires and the aggregated score is a valid and repeatable measure of quality of life [196], while its specificity for ischaemic heart disease has been confirmed [402].The MacNew mean global score is predictive of measurable clinical end-points: a relatively low mean score it is predictive of mortality in patients with coronary artery disease undergoing revascularisation [363]; while a comparatively high mean global score is associated with a decreased risk

of rehospitalisation over long term follow-up amongst patients following an MI [403]. Despite this, longitudinal studies in patients with left main coronary disease are limited.

Brief illness perception

Awareness of patients beliefs about an illness allows us to interpret self-reported quality of life outcomes as well as giving us an understanding of their behaviours [404]. Patients form cognitive and emotional representations of the illness in response to signs and symptoms leading to a change in coping behaviours. These beliefs/ideas about an illness are formed around five components which help them interpret their experiences and allow them to develop coping mechanisms [405]. They form ideas about the *nature or identity* (the label a patient uses to describe the illness or symptoms), *time-line* ('how long will my illness last'), *consequences* ('how does this impact on my life'), *cause* (what are the causal factors), and *control/cure* (feasibility of control or cure of the illness). Additional domains are measured by the BIP questionnaire including the *emotional representations* of the illness and *illness coherence*, and *control/cure* is separately assessed as *treatment control* and *personal control* [406].

The Brief Illness Perception (BIP) questionnaire assesses these components on a Likert scale where an increase in the score over time represents an increase in the domains measured [197]. It uses a single item scale, in the form of a question, to assess perceptions on a continuous linear scale rated 0-to-10. It assesses illness representations in the following domains:

- Cognitive illness representations: consequences (Question 1); timeline (Question 2), personal control (Question 3), treatment control (Question 4), and identity (Question 5).
- Emotional representations: concern (Question 6) and emotions (Question 8).
- Illness coherence/comprehensibility (Question 7).
- Causal attribution: This open-ended question asks the patient to list the three most important causal factors in their illness (Question 9). The unique patient responses

should be grouped into categories specific to the causality of coronary artery disease; e.g. hereditary, lifestyle, stress, comorbidity.

The BIP scale been shown to be predictive of poor outcomes, return to work, in patients following an MI [407]. Patients' beliefs that an MI will have long term negative impact can predict prolonged sick leave and greater levels of disability [408, 409]. Functional capacity in relation to return to work has been linked to causal attributions [410], the effect of which can be measured many years after the event [411]. Causal attributions contribute to changes in lifestyle behaviour after an MI [412], so effective interventions have been developed to promote positive lifestyle changes. Those patients with the strongest ideas concerning consequences, high scores for personal control and who attribute causation to lifestyle are more likely to attend rehabilitation programmes [413].

BIP interventions have been developed to influence these patterns of cognitive and emotional attributions following an MI and have been shown to improve angina and result in less time off work [407, 414]. Longitudinal studies are required to examine the change of illness perception following revascularisation procedures, none of which have been performed to date in a cohort of patients with left main coronary disease.

6.2.6. Ethics

Ethics approval was sought for the prospective study of patients treated with Left Main Coronary Artery revascularisation, the application was made in November 2012 and the study received approval in December 2012 (see appendix 5). An amendment to the application to allow the collection of quality of life measures using questionnaires was granted in December 2012. The application included provision for the study of prospective patients with quality of life questionnaires and for long term telephone or clinic follow-up for a period of ten years. Data would be held for 10 years. Prospective recruitment commenced in March 2013 and in April 2013 the first patient was recruited with HRQOL measures.

6.2.7. Data handling

Data storage

A bespoke database was designed with the consultation of all stakeholders. The database platform was then created on the Google™ Structured Query Language (SQL) platform by Mr R. Gillott, with constant clinical input from all members of the research team. The database is hosted on the NHS secure N3 network which allows multicentre recruitment and data input over all IT platforms. Security includes password protected accounts, data encryption and pseudonymised patient data using sequentially allocated patient identifiers (PatID's). The database platform was available in a rudimentary form by December 2012 with further ongoing modifications continuing based on research requirements.

Weekly research committee meetings, chaired by the Chief Investigator Prof Sivananthan, were held to discuss the design of the database and ongoing data entry. Our aim was to integrate automated EuroSCORE, SYNTAX score, eGFR/BMI calculators into the design. The platform could be used in the cathlab for the direct input of data by cathlab staff.

The database set out to include a robust drug history including use of anti-anginals at the time of the procedure and through the entire follow-up.

Database management is administered through a central management structure including the Chief investigator and database manager, Mr. Richard Gillott. Applications can be made to the research committee for research purposes. Individual password protected accounts are assigned to those involved in recruitment and data entry.

Data collection

Baseline clinical and demographic data were collected from medical case notes and referral correspondence. Procedural details were collected from the bespoke in-house procedural database, Cardiobase™. Where additional patient data were required GP summaries were collected including complete drug histories at baseline and at 1 year

follow-up. Specifically, baseline, prior to revascularisation, and 1 year medication lists were assessed to determine the change anti-anginals over the course of follow-up. A change in medication was noted as increased or reduced dose of anti-anginals including beta-blockers, calcium channel blockers, Ivabradine or Ranolazine. All data was entered prospectively at the time of the procedure, or at the time of consent. The data was regularly audited to ensure data completeness of the minimum dataset BCIS data fields. All cause mortality was tracked through linkage to the Office of National Statistics (ONS) using the NHS number.

Data completion was reviewed on a regular basis, but remained an issue due to delays in the database completion. While the database existed in a rudimentary form from December 2012, data entry was encouraged early on despite incomplete data fields. Many of these unfilled fields were then revisited at a later date during a separate data review.

6.2.8. Statistical methods

Statistical analysis was performed with IBM SPSS statistics version 20 (IBM Corporation, NY, USA). Baseline characteristics were described using numbers and percentages for categorical data and means and standard deviations (SD) or medians and interquartile ranges (IQR) for normal and non-normally distributed continuous variables. Categorical data were compared using a Pearson Chi-squared test or the ANOVA for more than 2 groups comparisons. Continuous variables were compared using one way ANOVA for normally distributed variables and the Kruskal-Wallis test for non-normally distributed data.

Longitudinal analyses are preferred for the analysis of changes over time [415]. Repeated measures analysis of variance (ANOVA) general linear model was applied to quality of life measures over the 4 time points to detect significant changes, this has the advantage over multiple T-tests as this could lead to type 1 error. However, for patients with only 2 time point measures present, due to missed time point sampling,

a paired T-test was applied to these 2 time points over the entire study cohort. An analysis thereof is presented separately. Individual predictors of health related quality of life at 1 year were determined by single variable linear regression analysis of variables related to presentation, comorbidity and treatment modality. A significance level, p value <0.1 was accepted and these variables were entered into a multivariate general linear regression model with stepwise removal of variables.

Multilevel modelling using linear mixed models were constructed in SPSS (SPSS 22.0; SPSS, Inc; Chicago). Mixed models analysis includes both random, the general variability within patients, and fixed effects, treatment or management used, in the analysis. These are analysed in a hierarchical way, which allow estimates for the means between upper levels, or treatment groups, with correlated measurements amongst the lower levels for each upper level group. We will use linear growth curves to assess variances, where the lowest levels of observation are the repeated measures and the predictor variable will be time [377, 416].Growth curves have the advantages over repeated measures ANOVA where it allows the inclusion of all cases despite a single missing measure by using maximum likelihood. Where we have unequal spacing of QOL measures we are able to use time as a predictor variable. Other predictor variables were identified based on their possible effect on HRQOL, this was through the use of a directed acyclic graph. We identified predictor variables from a literature review of studies of QOL in revascularisation including: demographic data (gender, age)[417-419] socioeconomic data (indices of multiple deprivation score)[379, 417, 420], presentation type (STEMI, NSTEMI, stable angina), comorbidity (renal dysfunction, diabetes, previous cardiac surgery or PCI, LV impairment). The predictor variables were added in a sequential way to determine the final growth model.

Bivariate correlation was performed using the Pearson Product Moment Correlation (PPMC) to establish possible causal links between two continuous variables. A high correlation was defined as a R2 value between 0.5 to 1.0 or -0.5 to 1.0; a medium

correlation was defined as a R2 value between 0.3-.05 or -0.3 to 0.5, while a low correlation was defined as a R2 value between 0.1 to 0.3 or -0.1 to -0.3.

Sample size calculation

In order to compare the MacNEW global score means of the three separate treatment groups using repeated measures analysis, the number required in each group is given by the equation:

$$n = f(\propto, \beta) \cdot \frac{2\gamma}{\delta}$$

Where:

$\propto$ is the significance level (using a two sided test) – i.e the cut-off for considering the result as statistically significant.

1-β is the power of the test

$f(\propto,\beta)$ is the value calculated from α and β – given in the table below

δ is the smallest difference in means that one would regard as being important to be able to detect, based on previous studies a difference on 0.5 in the global mean score at 1 year was correlated with poor long term outcomes [363].

γ is the standard deviation of the global mean score, this is estimated from previous studies to be ±1.0 [363]

$f(\propto,\beta)$ for the most commonly used values for $\propto$ and β:

$\propto$	β			
	0.05	**0.1**	**0.2**	**0.5**
0.05	13.0	10.5	7.9	3.8
0.01	17.8	14.9	11.7	6.6

An online calculator was used to determine the sample size for the study population given probability of type 1 error (a) of 0.05, power (1-β) of 0.1, difference between the

means of 0.5 and the expected background standard deviation of 1.0 (derived from previous studies) [421]. The sample size required per group is given as 77.

6.3. **Funding**

Ongoing funding for the research fellow salary was provided by a local research fund for 12 months and further funding continued for 6 months through the support through the LTHT. Additional funds for the licensing and printing of quality of life questionnaires was provided for by the School of Healthcare, University of Leeds, under the administration of Professor Felicity Astin. The study was adopted onto the NIHR CRN portfolio and a research nurse, employed by the NIHR, provided support for the consenting of patients. Furthermore, a data clerk and the database manager were provided similarly through the NIHR CRN portfolio.

6.4. Results

Recruitment to the prospective left main registry commenced in March 2013, while the first patient recruited for the HRQOL study was recruited in April 2013. A total of 103 patients completed 1 year follow-up in May 2015, ongoing recruitment continues. This analysis included the first 103 patients who completed one year follow up, recruitment continues, and is for review in this thesis alone. It provides pilot data to identify possible issues with recruitment thus allowing a feedback loop to improve recruitment and follow-up.

Baseline characteristics

This cohort of patients represents a heterogeneous group including patients considered for medical management, left main coronary artery (LMCA) percutaneous coronary intervention (PCI) and CABG. While the overall cohort of patients had a median age of 69.0 (IQR 14.0), the patients treated with LMCA PCI were significantly older than patients treated with CABG and those medically managed (**table 47**). It should be noted that of the patients treated for STEMI, the left main coronary artery was not the culprit vessel for these patients. The PCI group had the largest proportion of female patients, a third, compared with the medically manged, 15.0%, and CABG groups, 23.3%. Significantly more patients with STEMI were treated with CABG as compared to the PCI cohort.

Table 47: Baseline characteristics

Baseline characteristics	Overall cohort	Medically managed (n=20)	PCI (n=35)	CABG (n=48)	p-value
Median Age(IQR), years	69.0 (14.0)	69.5 (22.0)	76.0 (20.0)	66.0 (9.0)	<0.001
Female Gender	24 (23.3%)	3 (15.0%)	13 (37.1%)	8 (16.7%)	NS
NSTEMI	51 (49.5%)	8 (40.0%)	18 (51.4%)	25 (52.1%)	NS
STEMI	18 (17.5%)	7 (35.0%)	2 (5.7%)	9 (18.8%)	<0.05
Stable Angina	34 (33.0%)	5 (25.0%)	15 (42.9%)	14 (29.2%)	NS
Renal Impairment	8 (7.8%)	1 (5.0%)	4 (11.4%)	3 (6.3%)	NS
Diabetes	28 (27.1%)	8 (40.0%)	8 (22.9%)	12 (25.0%)	NS
Peripheral vascular disease	11 (10.7%)	4 (20.0%)	3 (8.6%)	4 (8.3%)	NS
Previous CVA	8 (7.8%)	2 (10.0%)	3 (8.6%)	3 (6.3%)	NS
Hypercholesterolaemia	54 (52.4%)	11 (55.0%)	11 (31.4%)	32 (66.7%)	NS
Previous MI	22 (21.6%)	8 (40.0%)	7 (20.0%)	7 (14.6%)	<0.05
Previous PCI	18 (17.5%)	4 (20.0%)	7 (20.6%)	7 (14.6%)	NS
Previous Cardiac surgery	8 (7.8%)	3 (15.0%)	4 (11.4%)	1 (2.1%)	NS
Protected	8 (7.8%)	3 (15.0%)	4 (11.4%)	1 (2.1%)	NS
Chronic lung disease	12 (11.7%)	3 (15.0%)	3 (8.6%)	6 (12.5%)	NS
Ex or current smoker	54 (52.4%)	9 (45%)	18 (51.4%)	27 (56.3%)	NS
Pulmonary hypertension	6 (5.8%)	1 (5.6%)	3 (11.1%)	3 (6.3%)	NS
Poor mobility	6 (5.8%)	2 (10.0%)	2 (5.7%)	2 (4.3%)	NS
Median(IQR) SYNTAX score					NS
Cardiogenic shock	1 (1%)	0	1 (2.9%)		NS

CABG – coronary artery bypass surgery; PCI- percutaneous coronary intervention; IQR – interquartile range; NSTEMI – non-ST elevation myocardial infarction; STEMI – ST elevation myocardial infarction; CVA – cerebrovascular accident; MI – myocardial infarction; SYNTAX - Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery

Surgical procedure details

CABG procedural data reflected current standard accepted practice, with over 80% of patients treated with a LIMA graft (**table 48**). Over 80% of patients required revascularisation of at least one other vessel and almost two thirds, 64.5%, required multivessel revascularisation with at least two vein grafts. Only two patients were treated with off-pump bypass and only one required circulatory support with an intra-aortic balloon pump during the operation.

PCI procedure details

Almost half of all patients treated had distal LMCA disease, while over a third had treatment of the ostium and body (**table 49**). Up to 20.0% of patients had rotational atherectomy during the procedure and almost half, 42.8%, had some form of intravascular imaging to aide the procedure. The femoral access route was favoured and larger sized catheters, 7Fr, in over 45.0%.

Anti-anginal medication

Full medication history was documented for 91 patients, and of these, the vast majority (48), reported no change in anti-anginal dose over the course of 1 year. However, 30 patients had an increase in anti-anginals while only 13 patients were taking fewer anti-anginals at the end of the 1 year follow-up. No patient within the medically managed group had a reduction in anti-anginals, while 10 patients had an increase in the anti-anginals over the course of follow-up. There was no significant difference between the treatment groups when considering a dose increase or no change vs reduced dose.

Table 48:CABG procedural details (n= 48)

	Numbers (%)	Missing data Number (%)
LIMA	40 (83.3%)	6 (12.5%)
RIMA	1 (2.1%)	6 (12.5%)
Three Vein Grafts	9 (18.8%)	6 (12.5%)
Two Vein Grafts	13 (27.1%)	6 (12.5%)
One vein Graft	18 (37.5%)	6 (12.5%)
Unrevascularised vessels –surgical report	5 (10.4%)	9 (18.8%)
AoV surgery (None=0/Tissue=1/Mechanical =2)	1 (2.1%)	7 (14.6%)
MV Surgery (None=0/Tissue=1/Mechanical =2)	0 (0%)	7 (14.6%)
Off-pump	2 (4.2%)	6 (12.5%)
Cardioplegia (Cold, Antegrade, Intermittent)	32 (66.7%)	6 (12.5%)
IABP used	1 (2.1%)	6 (12.5%)
Inotropes	3 (6.3%)	9 (18.8%)
Pacing	3 (6.3%)	6 (12.5%)
Bypass time (minutes)	93.0 [IQR 44.0]	11 (22.9%)
Cross clamp time (minutes)	49.0 [IQR 35.5]	11 (22.9%)
BMI	27.5 [IQR 7.6]	9 (18.8%)
Vasoconstrictors	0 (0%)	9 (18.8%)
Complications	2 (4.2%)	6 (12.5%)

CABG – coronary artery bypass surgery; LIMA – left internal mammary artery; RIMA – right internal mammary artery; IABP – intra-aortic balloon pump; BMI – body mass index

Table 49: Percutaneous coronary intervention (PCI) procedural details (n=35)

	Number (%)	Missing (%)
Femoral access	14 (40.0%)	
Radial Access	13 (37.1%)	
Radial and Femoral access	4 (11.4%)	
6 Fr Sheath	15 (42.8%)	
7 Fr Sheath	16 (45.7%)	
Heparin use	14 (40.0%)	4 (11.4%)
Bivalarudin only	16 (45.7%)	4 (11.4%)
Rotational atherectomy	7 (20.0%)	4 (11.4%)
Intravascular ultrasound	13 (37.1%)	4 (11.4%)
Optical coherence tomography	2 (5.7%)	4 (11.4%)
LMCA ostium/body treated	12 (34.2%)	5 (14.3%)
Distal LMCA treated	17 (48.6%)	5 (14.3%)
DES used	30 (85.7%)	4 (11.4%)
BMS used	1 (2.9%)	4 (11.4%)

Fr – French size; PCI – percutaneous coronary intervention; LMCA – left main coronary artery; DES – drug eluting stent; IQR – interquartile range; DES – drug eluting stent; BMS – bare metal stent

Table 50: Completed Questionnaires

	Baseline			1 month			6 months			1 year		
	Number (%)	Missing (%)	Deaths (%)	Number (%)	Missing (%)	Deaths (%)	Number (%)	Missing (%)	Deaths (%)	Number (%)	Missing (%)	Deaths (%)
Medical Management	17 (85.0%)	3 (15.0%)	1 (5.0%)	13 (65.0%)	7 (35.0%)	3 (15.0%)	10 (50.0%)	10 (50.0%)	3 (15.0%)	9 (45.0%)	11 (55.0%)	3 (15.0%)
PCI	30 (85.7%)	5 (14.3%)	1 (2.9%)	25 (71.4%)	10 (28.6%)	1 (2.9%)	23 (65.7%)	12 (34.3%)	1 (2.9%)	21 (60.0%)	14 (40.0%)	2 (5.7%)
CABG	41 (85.4%)	7 (14.6%)	0	38 (79.2%)	10 (20.8%)	0	40 (83.3%)	8 (16.7%)	1 (2.0%)	37 (77.1%)	11 (22.9%)	1 (2.0%)
Total	88 (85.4%)	15 (14.6%)	2 (1.9%)	76 (73.8%)	27 (26.2%)	4 (3.9%)	73 (70.9%)	30 (29.1%)	5 (4.9%)	67 (65.0%)	36 (35.0%)	6 (5.8%)
CABG – coronary artery bypass surgery; PCI- percutaneous coronary intervention;												

Patient and public consultation

Following the consultation process with the West Yorkshire Cardiovascular Network Patient and Public group consultation process in September 2013, we received a letter with the following:

- The group felt that 'quality of life is the single most important indicator' for patients who survive the initial procedure

- Their consensus opinion was that the components of MACCE should not be considered as equal.

- They also felt that stroke should be weighted more heavily than the risk of MI or repeat revascularisation, however

-The severity of each MACCE event should be measured individually, that is, for an MI which results in the need for CABG should carry more weight than a simple TIA/Stroke from which a patient makes a full recovery.

HRQOL outcomes

Completed questionnaires were included in the analysis; completion rates for the overall study population were over two thirds at each time point (**table 50**). Close to 85.0% of patients completed questionnaires at pre-intervention/baseline with equal rates of completion for each category of management. There was a significant and continued fall in completion rates down to two thirds at 1 year follow-up. The greatest fall in questionnaire completion rates occurred amongst the medically managed group with less than half completing 1 year questionnaires. Amongst 17 medically managed patients who completed the baseline questionnaire, there were 4 deaths within the first year of the follow-up. The PCI group too saw a fall in questionnaire completion rates down to 60.0% at 1 year. Amongst the 30 patients in the PCI group who completed the baseline questionnaire, there was only 1 death within the first year of follow-up. Patients who underwent CABG had the smallest fall in completion rates down to 77.1% at 1 year, with only 1 death amongst these patients over the course of the first year of follow-up.

While we did not record the patient's reason for not completing the initial questionnaire for the study, no patients refused on the basis of language difficulty. All patients were given baseline questionnaires either prior to treatment or within 1 week of receiving treatment. In the case of medically managed patients, they were given the baseline questionnaires at the time of assessment in the clinic, only 15.0% of all patients failed to complete the baseline questionnaires. Of the patients who had completed the initial baseline questionnaire, we compared those who completed the 1 year questionnaire to those who did not (**table 51**). Patients presenting with STEMI were more likely to fail to complete all their questionnaires. While patients treated by CABG were more likely to complete their questionnaires over 1 year follow-up. Medically managed patients as well as those with diabetes were more likely to fail to complete all questionnaires. There was no difference in age or indices of multiple deprivation scores for patients who did and did not complete the questionnaires.

Table 51:Comparison of patients who failed to completed the 1 year questionnaire

	Missing questionnaire	Completed questionnaire	p-value
Age	69.0 (10.0)	68.0 (12.0)	NS
Male gender	21 (75.0%)	49 (81.7%)	NS
Median Indices of multiple deprivation scores	27.0 (36.1)	12.0(20.0)	NS
CABG	8 (28.6%)	33 (55.0%)	p<0.05
Medically managed	9 (32.1%)	8 (13.3%)	p<0.05
PCI	11 (39.3%)	19 (31.7%)	NS
Previous CABG	3 (10.7%)	4 (6.7%)	NS
Stable	5 (17.9%)	23 (38.3%)	NS
STEMI	9 (32.1%)	7 (11.7%)	p<0.05
NSTEMI	14 (50.0%)	30 (50.0%)	NS
Chronic lung disease	2 (7.1%)	7 (11.7%)	NS
CVA	3 (10.7%)	4 (6.7%)	NS
Diabetes	11 (39.3%)	11 (18.3%)	p<0.05
Chronic kidney disease	1 (3.6%)	6 (10.0%)	NS
Recent MI	14 (50.0%)	27 (45.0%)	NS
Previous MI	9 (32.1%)	11 (18.6%)	NS
Previous PCI	5 (17.9%)	10 (16.7%)	NS
Ex or current smoker	16 (59.3%)	30 (50.8%)	NS

CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, CVA – cerebrovascular accident,, MI – myocardial infarction

MacNEW

Global scores

Mean (SD) MacNew global scores were calculated for each group of patients at baseline, 1 month, 6 months and 1 year. A one-way repeated measures analysis of variance (ANOVA) of the change in quality of life was calculated for a change in global MacNEW scores for the three groups (**table 52**).

The mean longitudinal MacNEW global score for completed questionnaires in the overall population show a trend to increase over time (**figure 18**). The paired sample T-test for baseline and 1 months mean global scores did not show a significant change in QOL (4.1 ±1.3 vs. 4.4 ±1.1; $p = 0.88$), however there was a significant increase from baseline to 6 months (4.1 ±1.3 vs. 5.3 ±1.2, $p<0.001$) which was maintained to 1 year (4.1 ±1.3 vs. 5.3±1.2, $p<0.001$) .

Subgroup analysis using paired T-tests revealed medically managed patients experienced no change in QOL over the course of the year. Patients managed with revascularisation, PCI and CABG, had significant improvements in QOL at 6 months ($p<0.05$ and $p<0.001$, respectively) and a year ($p<0.005$ and $p<0.001$, respectively) when compared to baseline scores (**figure 19**).

Table 52:MacNEW global scores over 1 year follow-up for all patients

	Baseline	1 month	6 months	1 year
All patients	4.33 (IQR1.81)	4.59 (IQR 1.59)	5.41 (IQR 1.69)	5.52 (IQR 1.45)
Medical Management (IQR)	4.33 (IQR 1.70)	4.78 (IQR 1.10)	5.13 (IQR 1.77)	4.33 (IQR 1.74)
PCI	4.36 (IQR 1.41)	4.37 (IQR 1.57)	4.89 (IQR 1.59)	5.48 (IQR 1.57)
CABG	4.11 (IQR 2.08)	4.75 (IQR 1.59)	5.85 (IQR 1.23)	5.89 (IQR 1.28)

CABG – coronary artery bypass surgery; PCI- percutaneous coronary intervention; IQR – interquartile range

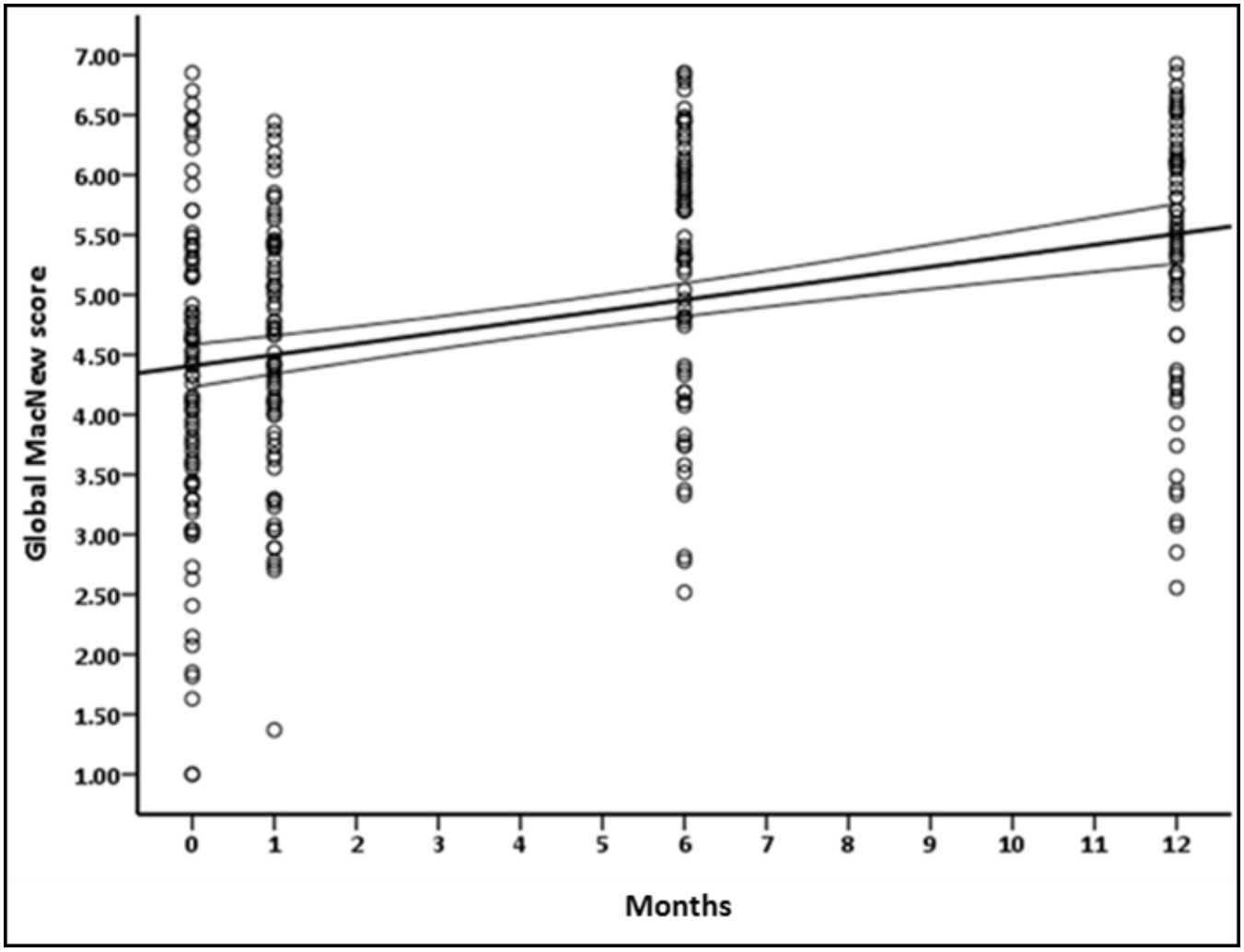

Figure 18: The scatter plot with linear regression prediction line of 95% confidence interval of the scores of global MacNew scores for time points: baseline (0 months), 1 month, 6 months and 12 months.

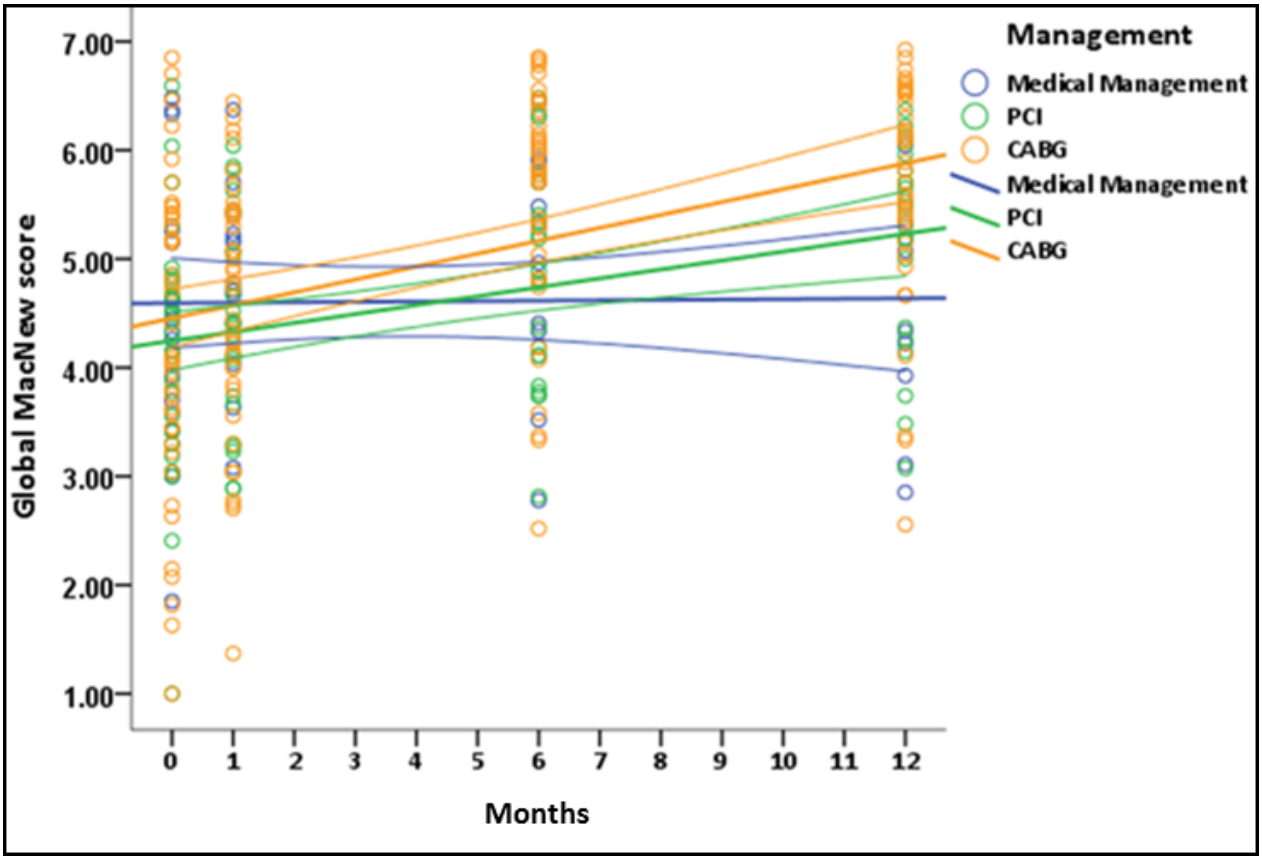

Figure 19: The scatter plot with linear regression predication line of 95% confidence interval of scores of global MacNew for patients treated with CABG, PCI and medical management of left main coronary artery disease for time points: baseline (0 months), 1 month, 6 months and 12 months.

Generalised linear model analysis

A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate if there was a significant change in the global MacNEW score over the period of one year for completed questionnaires at all time points up to 1 year (n=45). The results of the ANOVA indicated a significant change in quality of life over the four time points [Wilks' Lambda = 0.52, F(3, 42) = 12.89, W^2 = 0.48, p<0.001] but there was no significant difference between groups. Comparisons for the overall cohort indicated a significant pairwise difference in score was found between all time-points except between baseline and 1 month and between 6 months and 1 year. The QOL over the first and second time points did not significantly change. Between the management groups there was no significant difference between baseline HRQOL scores; however there was a significant difference between CABG and the medically managed groups over 1 year follow-up. There was no significant difference between PCI and the medically managed groups, or between PCI and CABG over 1 year follow-up.

All patient factors, management and MACCE were assessed in a general linear regression analysis to determine predictors of HRQOL outcomes. The HRQOL outcomes were used as the dependent variable. When predicting quality of life scores at 1 year it was found that elective procedures (β = -0.27, p < .05), previous MI (β = 0.28, p < .05), baseline quality of life scores (β= 0.35, p < .001) and CABG (β=0.45, p<0.001) were significant predictors of improved quality of life scores. Predictors of poor quality of life scores included previous cardiac surgery (β=0.40, p<0.001) previous CVA (β=0.27, p<0.05) and presentation with a STEMI (β=0.32, p<0.05). The overall model fit was R^2 = 0.63.

Mixed model analysis

Using multilevel analysis we identified three significant models. Firstly, data were converted to the long format. We used an unconditional means model, using a constant term only, to examine individual variation in the outcome without regard to time (n=98). This would allow the assessment of the amount of variation in the intra- and inter- individual levels. We found the intra-class correlation co-efficient (ICC), which describes the amount of variance in the outcome due to inter-individual

differences, to be 0.55/(0.96 + 0.55) = 0.36, which suggests that about 36% of the total variation in the global MacNew score was due to inter-individual differences. If the ICC is above 0.25, this indicates a better performance from growth curve models when compared with ANOVA [422].

Predictor variables were entered into the model sequentially. After each step, we assessed the goodness of fit by the difference in the deviance (-2*loglikelihood) between the sequential models. The best fitting model is determined by the lowest -2*loglikelihood. As a starting point we used the unconditional means model to describe and partition the variation across the 98 patients [423]. Then we proceeded to add time, thus constructing an unconditional growth model [424] and finally explanatory variables were identified and added to the model sequentially to fit an advanced model based on these possible predictor variables. The mixed model analysis is described in **table 53,** with the final best fitting model presented in the right hand column. Recent MI, within 90 days, CABG treatment and time, comparing all time points to the 1 year global mean MacNew score, significantly contributed to the model.

Table 53: Variables included in progressive stages of the model

Explanatory variables	Unconditional means model estimate (SE)	Unconditional growth model estimate (SE)	Final model Estimate (SE)
Fixed			
Constant	4.80(0.09)	5.29 (0.12)	3.64(0.15)
Time		-1.00 (0.16)	0.47(0.06)
Recent MI			0.52 (0.17)
CABG treatment			-0.36 (0.17)
-2*loglikelihood (IGLS)	946.7	828.2	816.1

All effects significant. SE – standard error

MacNEW domain scores

The questionnaire assesses the three major health related quality of life domains, the physical, emotional and social domains. The emotional, physical and social domain scores show a trend to improve over the 4 time points (**figure 20**). A one way repeated measures analysis of variance was conducted for all three domains over all time points. The emotional domain showed significant improvement in scores over the course of 1 year, Wilk's Lambda = 0.65, $F(3, 50) = 9.13$, $W^2 = 0.35$, $p<0.001$. Pairwise comparisons showed significant difference across all time points except between 1 month follow-up when compared with either baseline or 6 month follow-up.

Similar improvement in scores were found after analysis of the physical domain scores [Wilk's Lambda = 0.11, $F(3, 38) = 105.73$, $W^2 = 0.89$, $p<0.001$] and social domain scores [Wilk's Lambda = 0.45, $F(3, 42) = 16.9$, $W^2 = 0.55$, $p<0.001$] over the course of one year. Pairwise analysis revealed no significant change between baseline and 1 month scores and between 6 month and 1 year scores for both domains.

Medically managed patients did not experience an increase in emotional domain scores over 1 year, while patients treated with PCI or CABG did experience a progressive improvement in scores (**figure 21**). All treatment groups showed an increase in the physical domain (**figure 22**). The medically managed group was the only treatment group which showed no improvement in social domain scores (**figure 23**).

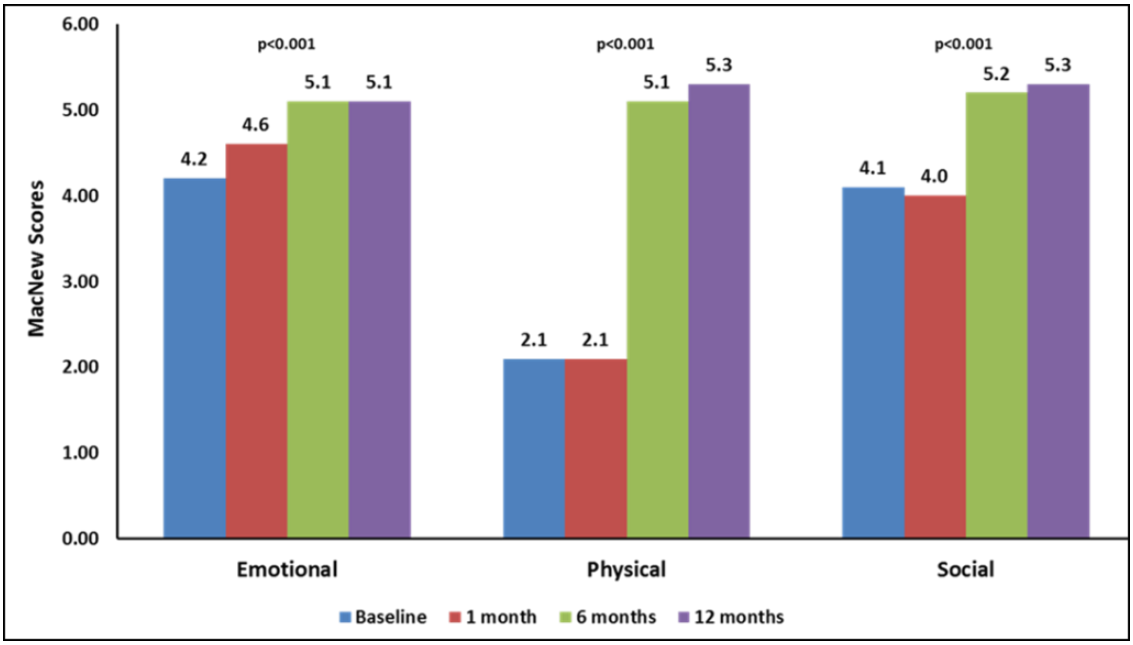

Figure 20: Change in MacNew score for emotional, physical and social domains over time points baseline, 1 month, 6 months and 12 months.

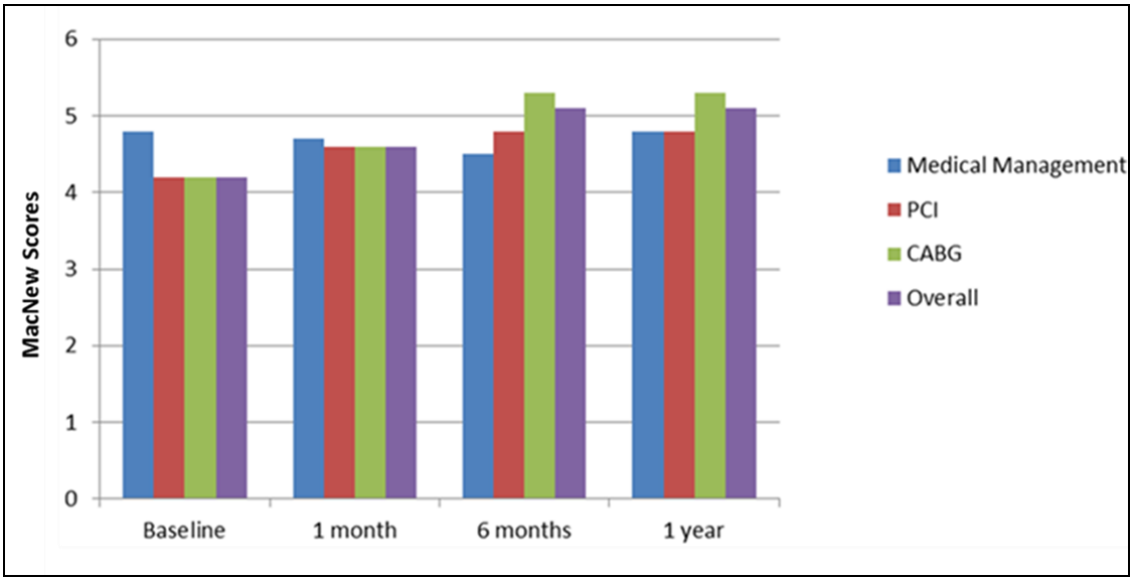

Figure 21: Changes in MacNew emotional domain score for the overall patient cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

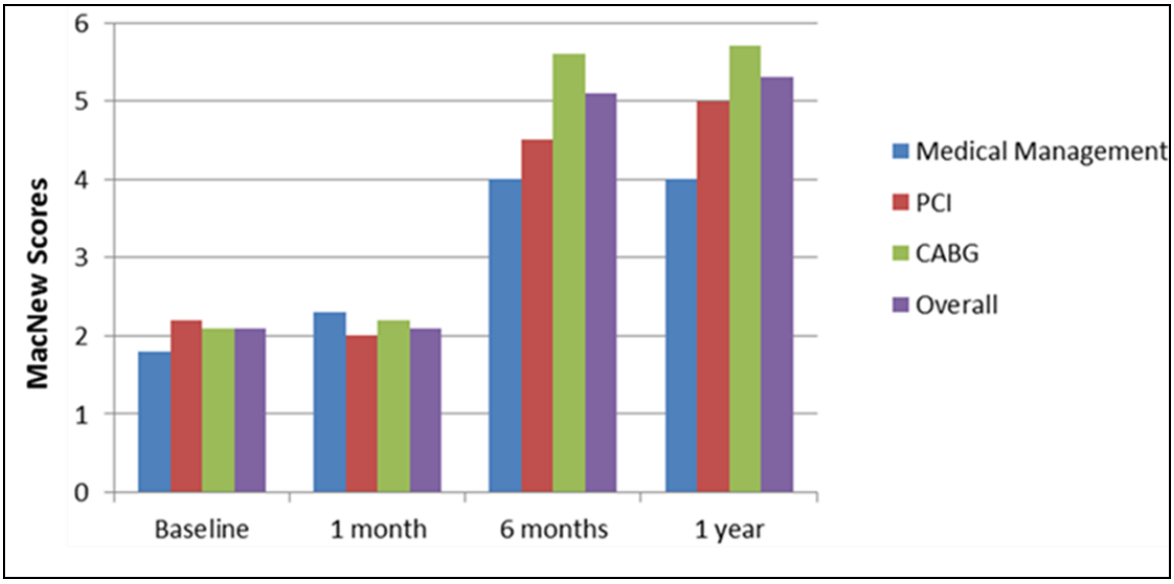

Figure 22: Changes in MacNew physical domain score for the overall patients cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

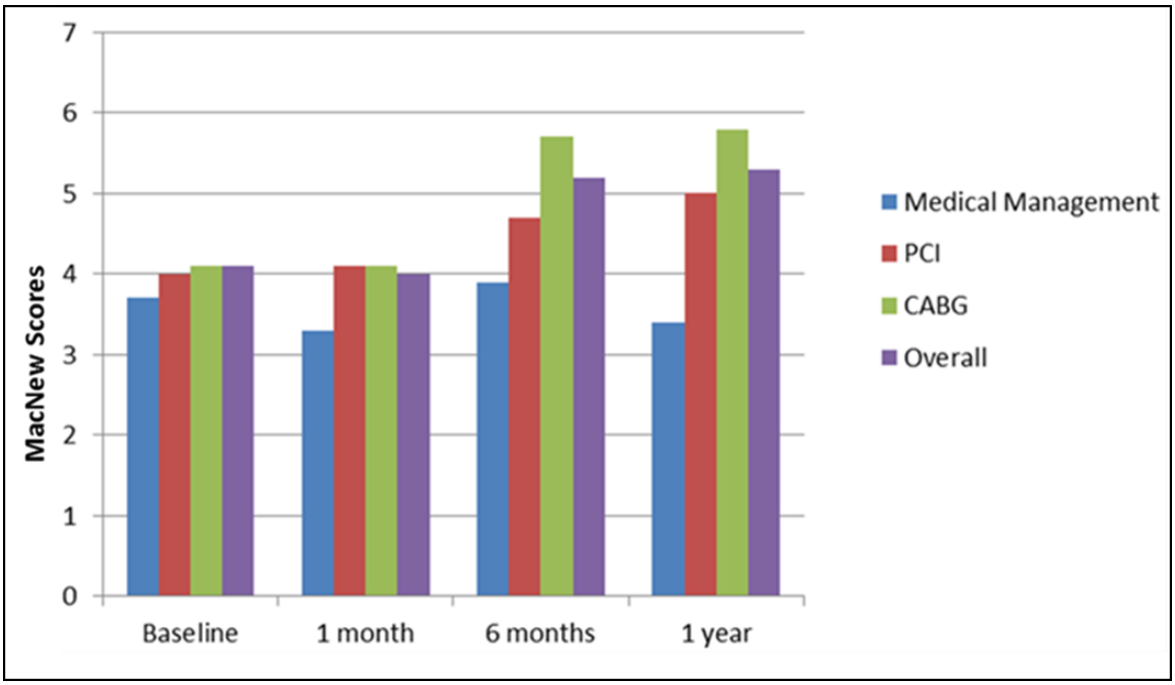

Figure 23: Changes in MacNew social domain score for the overall patients cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

Brief illness perception scores

The BIP questionnaire uses eight questions to assess illness comprehensibility, cognitive and emotional representations. Cognitive representations include consequences (Item 1- greater the score the worse the outcome) , timeline (Item 2- greater the score the worse the outcome), personal control (Item 3- greater the score the better the outcome), treatment control (Item 4 - greater the score the better the outcome), and identity (Item 5 - greater the score the worse the outcome). Two of the items assess emotional representations including concern (Item 6 - greater the score the worse the outcome) and emotions (Item 8 - greater the score the worse the outcome). One item assesses illness comprehensibility (Item 7 - greater the score the better the outcome). Causal representation is assessed by an open-ended response item, the patient is asked to list the three most important causal factors in their illness (Item 9).

All completed BIP questionnaires, n=41, were assessed across 4 time points for the 9 questions. Each domain was assessed for the overall cohort and management groups using the median scores for each time point (**figures 24-31**). Repeated measures analysis of variance was used to assess change in scores for the overall, PCI and CABG managed cohorts over 1 year for each of the domains. Only 3 medically managed patients completed questionnaires over all 4 time points, so are not analysed separately. There were significant improvement in the median scores over time for the following domains including, consequences [Wilk's Lambda = 0.41 F(3, 38) = 18.2, W^2 = 0.89, p<0.001] (**figure 24**), personal control [Wilk's Lambda = 0.61 F(3,39) = 8.5, W^2 = 0.39, p<0.001] (**figure 26**), identity [Wilk's Lambda = 0.74 F(3, 40), W^2 = 0.26, p<0.05] (**figure 28**), concern [Wilk's Lambda = 0.52 F(3, 40) = 12.5, W^2 = 0.48, p<0.001] (**figure 29**) and emotions [Wilk's Lambda = 0.75 F(3, 40) = 4.6, W^2 = 0.26, p<0.05] (**figure 31**). However, there was a significant decline in median scores over time for treatment control [Wilk's Lambda = 0.69 F(3,38) = 5.6, W2 = 0.31, p<0.05] (**figure 27**). The domains illness comprehensibility and timeline were not found to be significantly changed over the 4 time points. Visually medically managed patients did not have a significant change in consequence scores over time.

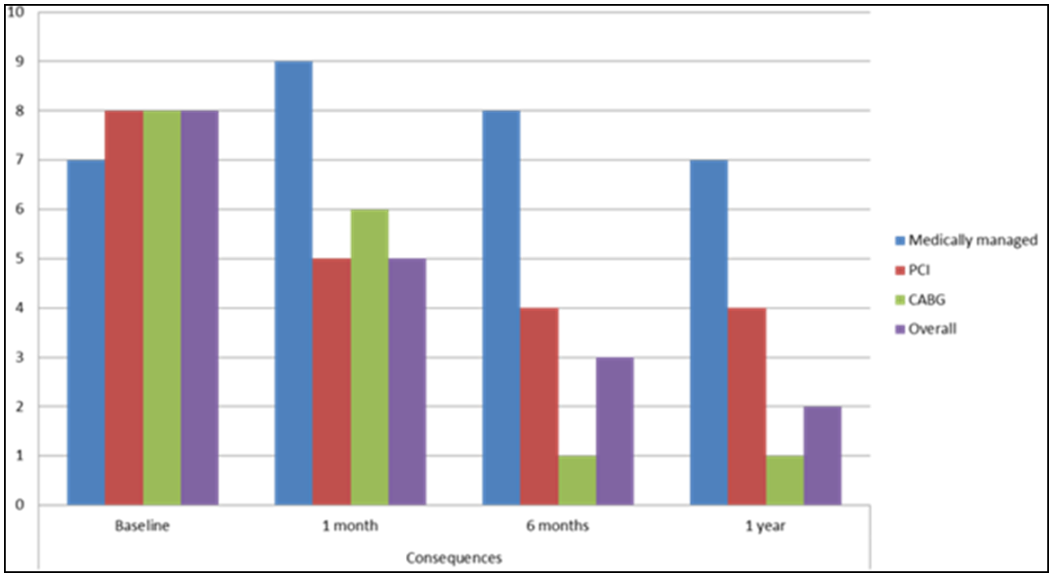

Figure 24: : BIP consequence score for the overall cohort for each treatment group over 1 year.

PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

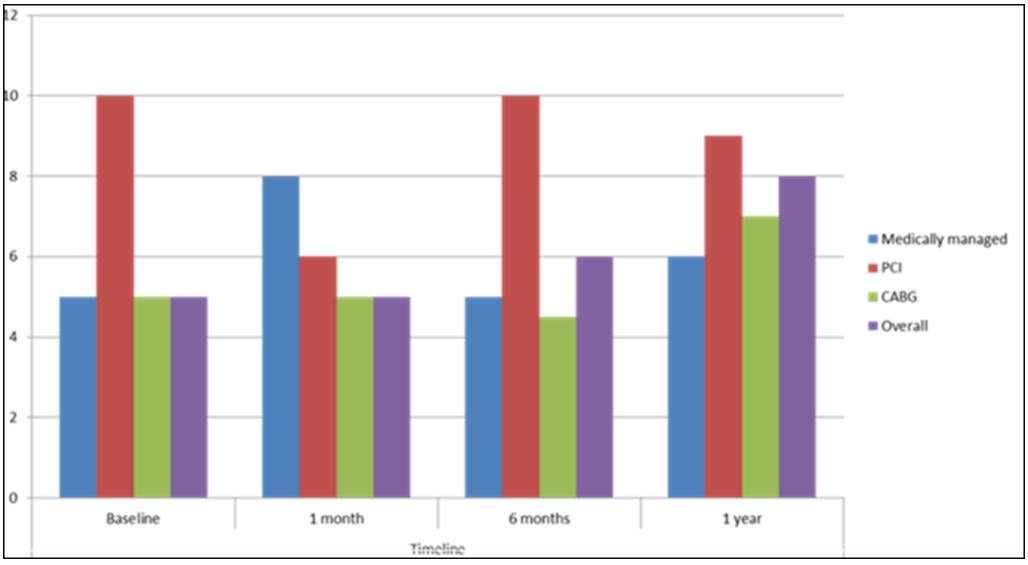

Figure 25: BIP timeline score for the overall cohort for each treatment group over 1 year.

PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting

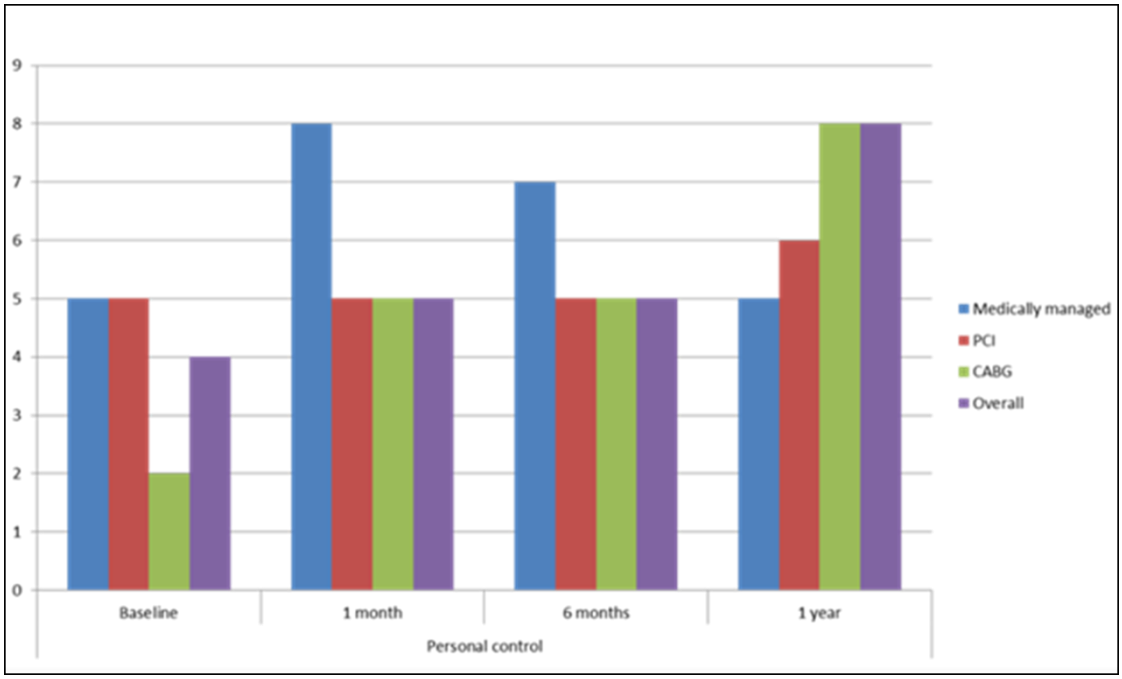

Figure 26: BIP personal control score for the overall cohort for each treatment group over 1 year follow-up.

PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

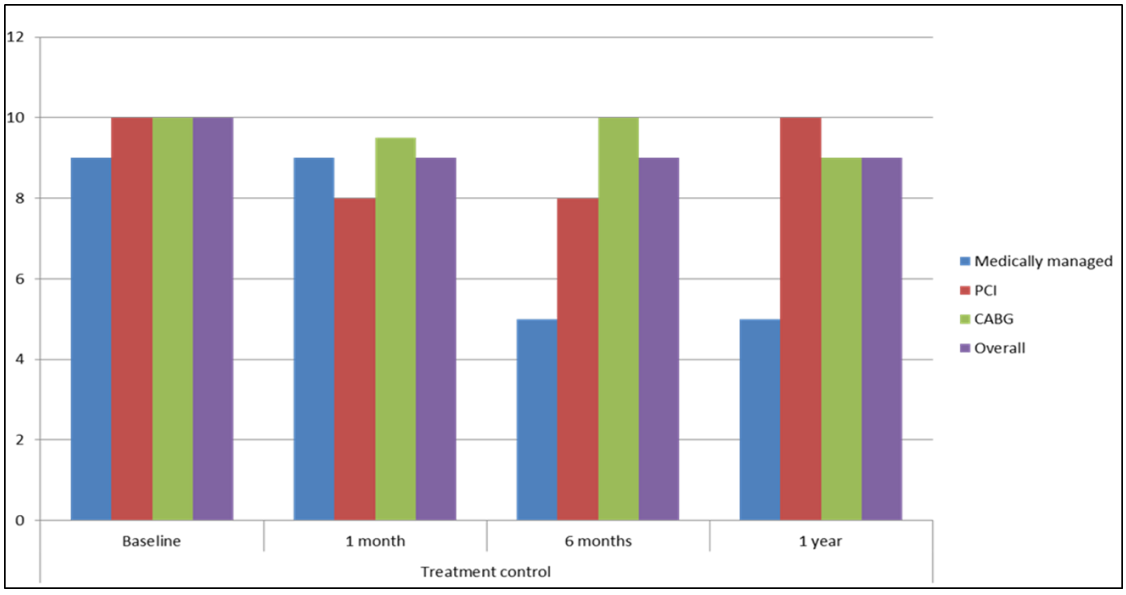

Figure 27: BIP treatment control score for the overall cohort for each treatment group over 1 year follow-up.

PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

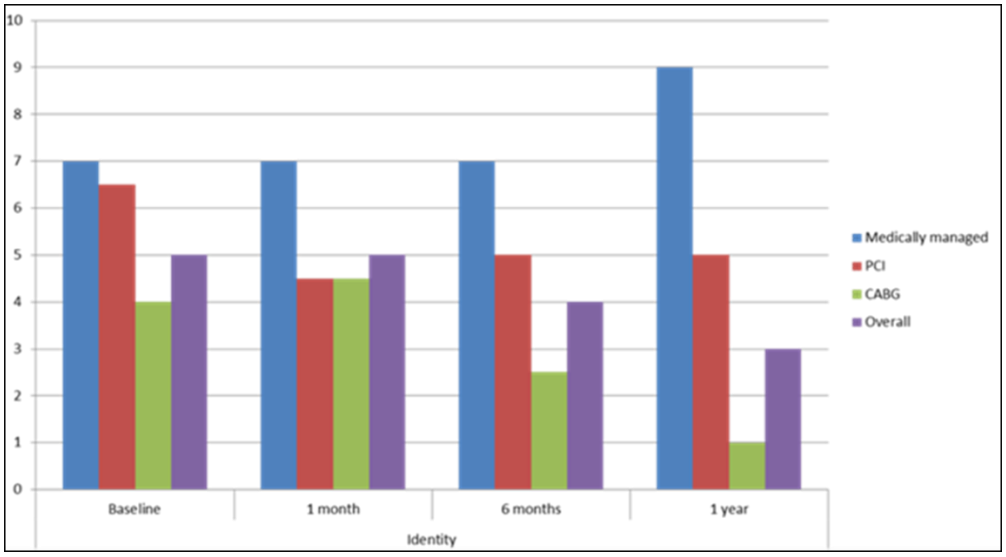

Figure 28: BIP identity for the overall cohort for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

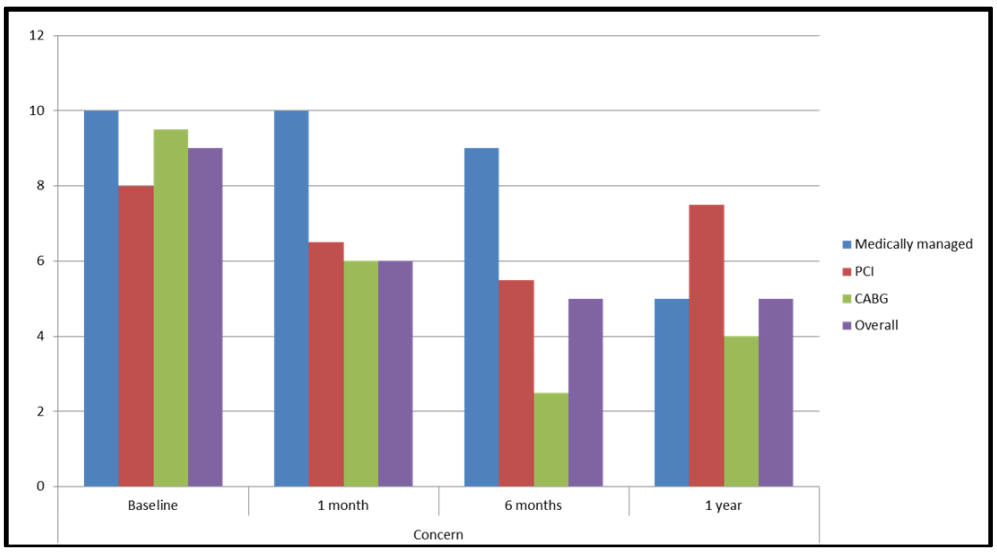

Figure 29: BIP illness concern for the overall cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

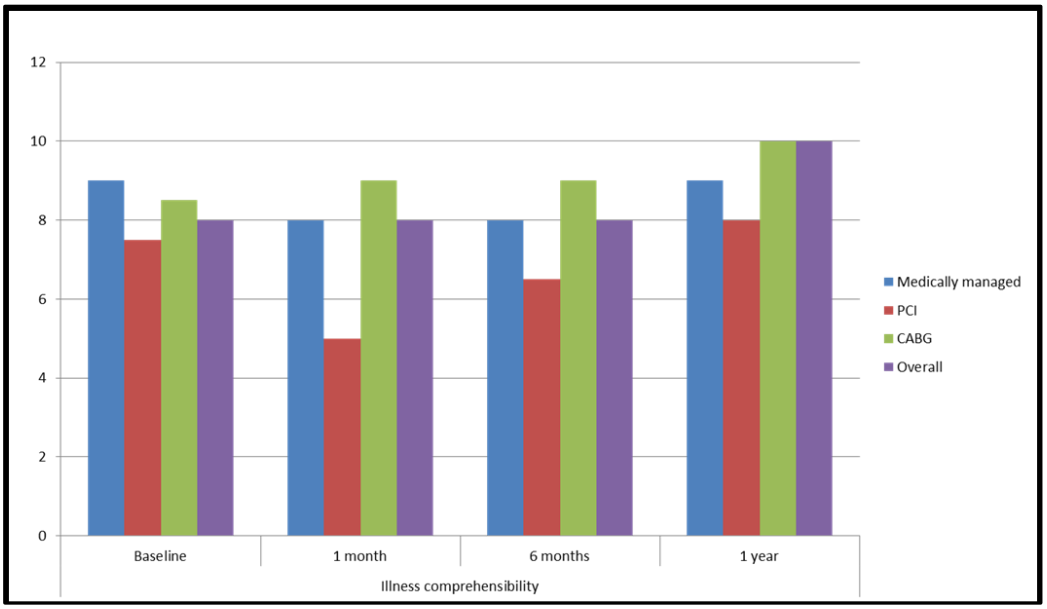

Figure 30: BIP illness comprehensibility for the overall cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

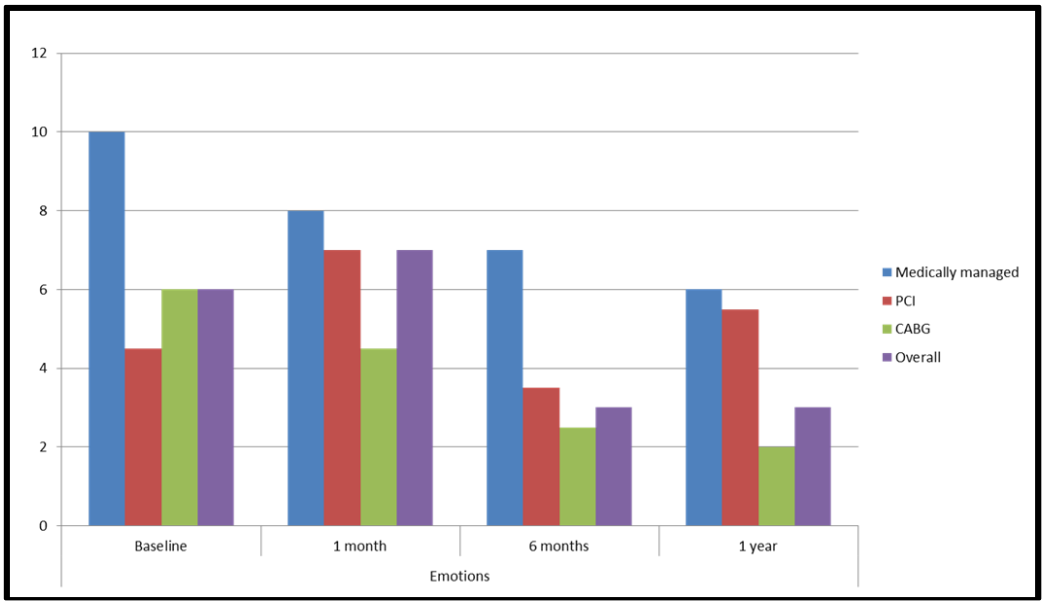

Figure 31: BIP emotions for the overall cohort and for each treatment group over 1 year follow-up. PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting.

Pearson product-moment correlation coefficient was computed to assess the relationship between the mean global MacNew scores and the 8 components of the brief illness perception questionnaire. There were negative correlations between global MacNew scores and patient illness perceptions of consequences (r = -0.7, n = 268, p <0.00), timeline (r = -0.22, n = 263, p <0.000), identity (r = -0.573, n = 270, p<0.000), illness concern (r = -0.572, n = 270, p <0.000) and emotional representation (r = -0.622, n = 267, p <0.000). Scatterplots summarise the results (**Figure 32-36**). Increase in scores for these five patient perceptions were correlated with lower global MacNew scores.

There were positive correlations between global MacNew scores and patient illness perceptions of personal control (r = 0.353, n = 266, p <0.000), treatment control (r = 0.177, n = 267, p <0.005), and coherence (r = 0.199, n = 270, p<0.005). Scatterplots summarise the results (**Figures 37-39**). Increase in scores for these three patient perceptions were correlated with higher global MacNew scores.

Pearson product-moment correlation coefficients were computed to assess the relationship between each of the three MacNew quality of life domains and the 8 components of the brief illness perception questionnaire. Positive correlations between the social MacNew domain and patients perception of personal control (r = 0.333, n = 264, p <0.000), treatment control (r = 0.147, n = 264,p <0.05) and illness coherence (r = 0.172, n = 267, p =0.005); while negative correlations were found with patients perception of consequences (r = -0.722 , n = 265 , p <0.000), timeline (r =-0.197, n = 263, p <0.005), identity (r = -.524 , n = 267, p <0.000), illness concern (r = -0.533, n = 267, p <0.000) and emotional representation (r = -0.507, n = 267, p <0.000).

Positive correlations between the physical MacNew domain and patients perception of personal control (r = 0.320,n = 260, p <0.000); while negative correlations were found with patients perception of consequences (r = -0.618, n = 261, p <0.000), identity (r = -0.431, n = 263, p <0.000), illness concern (r= -0.468,n = 263, p<0.000) and emotional representation (r = -0.379, n = 263, p <0.000).

Positive correlations between the emotional MacNew domain and patients perception of personal control (r = 0.299, n = 264, p <0.000), treatment control (r = 0.155, n = 264, p <0.05) and illness coherence ((r =0.198, n =267, p <0.005); while negative correlations were found with patients perception of consequences (r = -0.518, n = 265 , p <0.000), timeline (r = -0.127, n = 260, p <0.05), identity (r = -0.405, n = 267, p <0.000), illness concern (r = -0.510, n = 267, p <0.000) and emotional response (r = -0.685, n = 267, p <0.000).

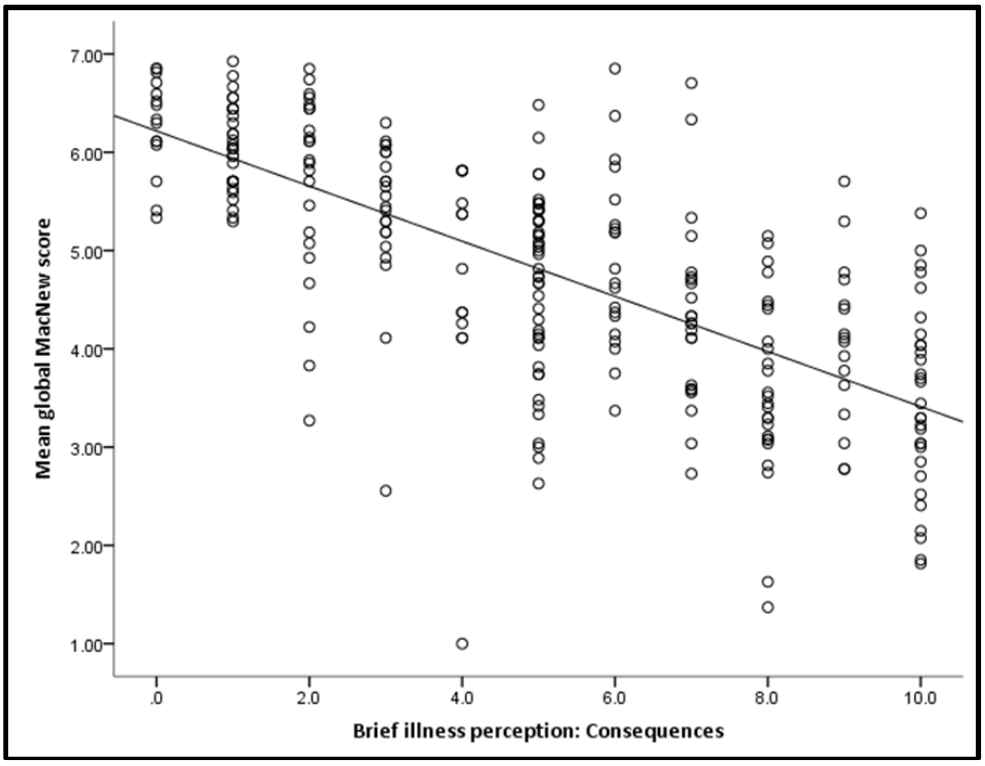

Figure 32: Correlation of global MacNew score with patient perception of illness consequences

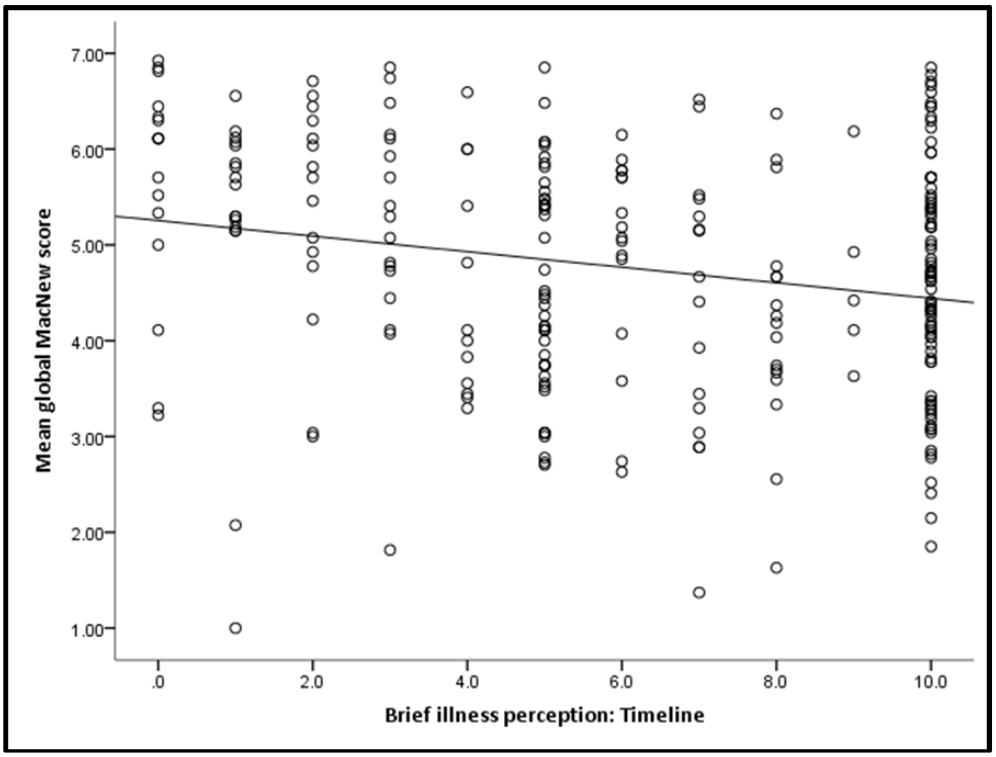

Figure 33: Correlation of global MacNew score with patient perception of disease timeline

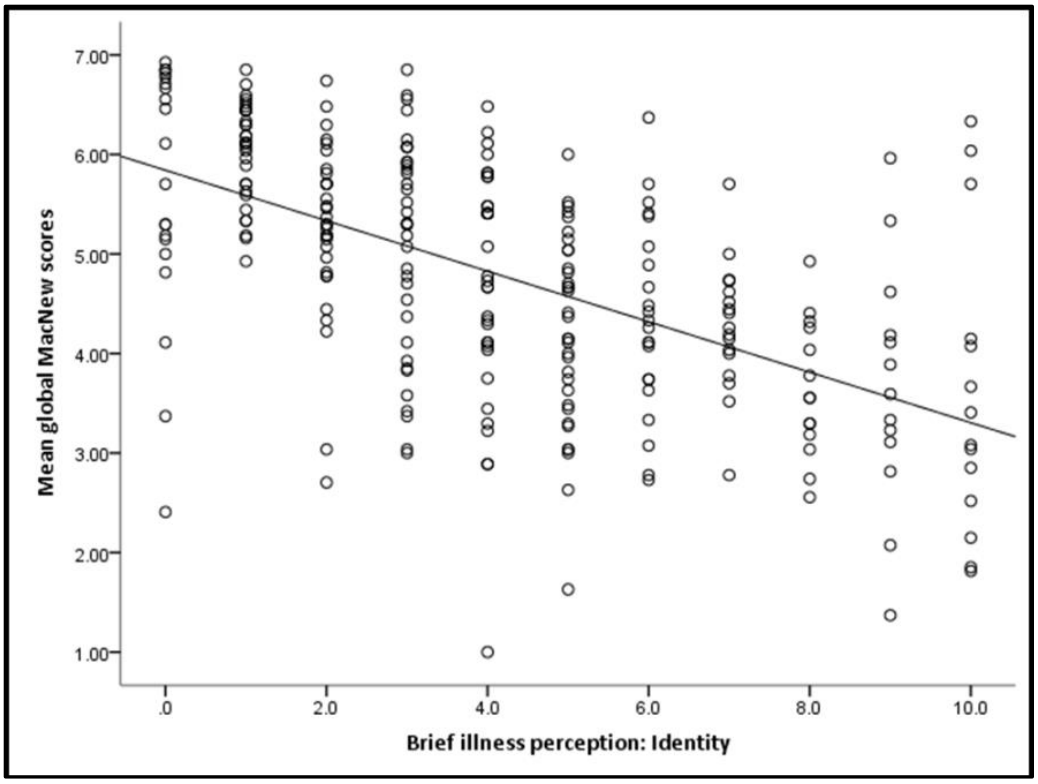

Figure 34: Correlation of global MacNew score with patient perception of increasing personal identity

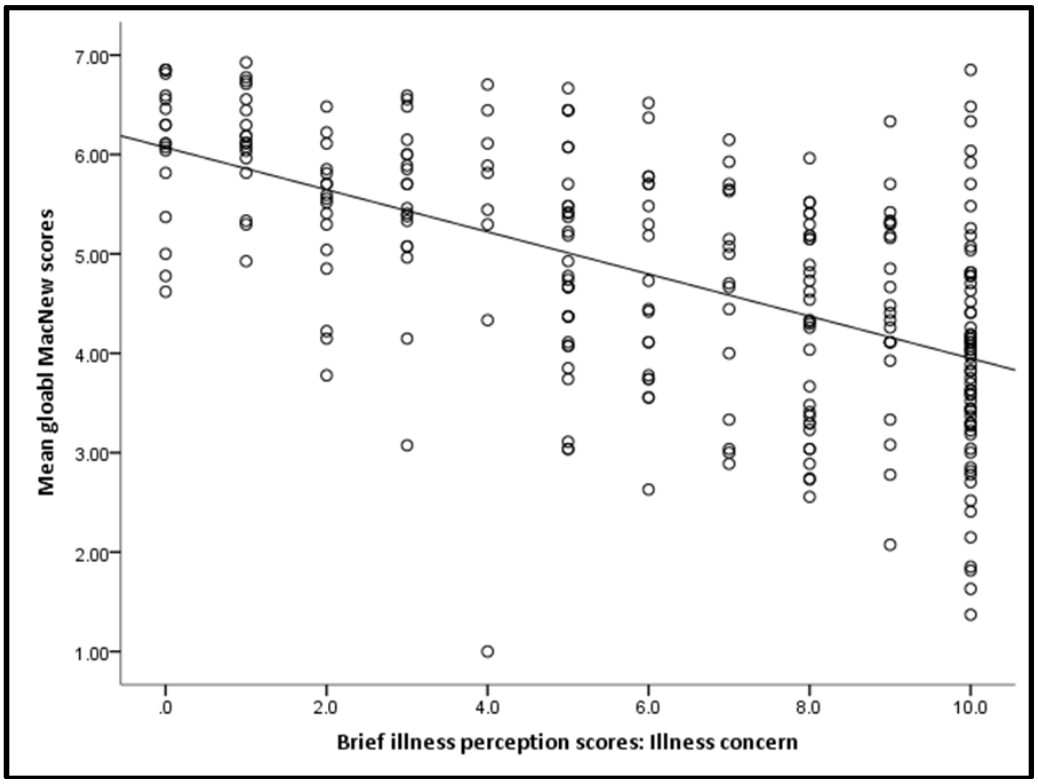

Figure 35: Correlation of global MacNew score with patient perception of illness concern

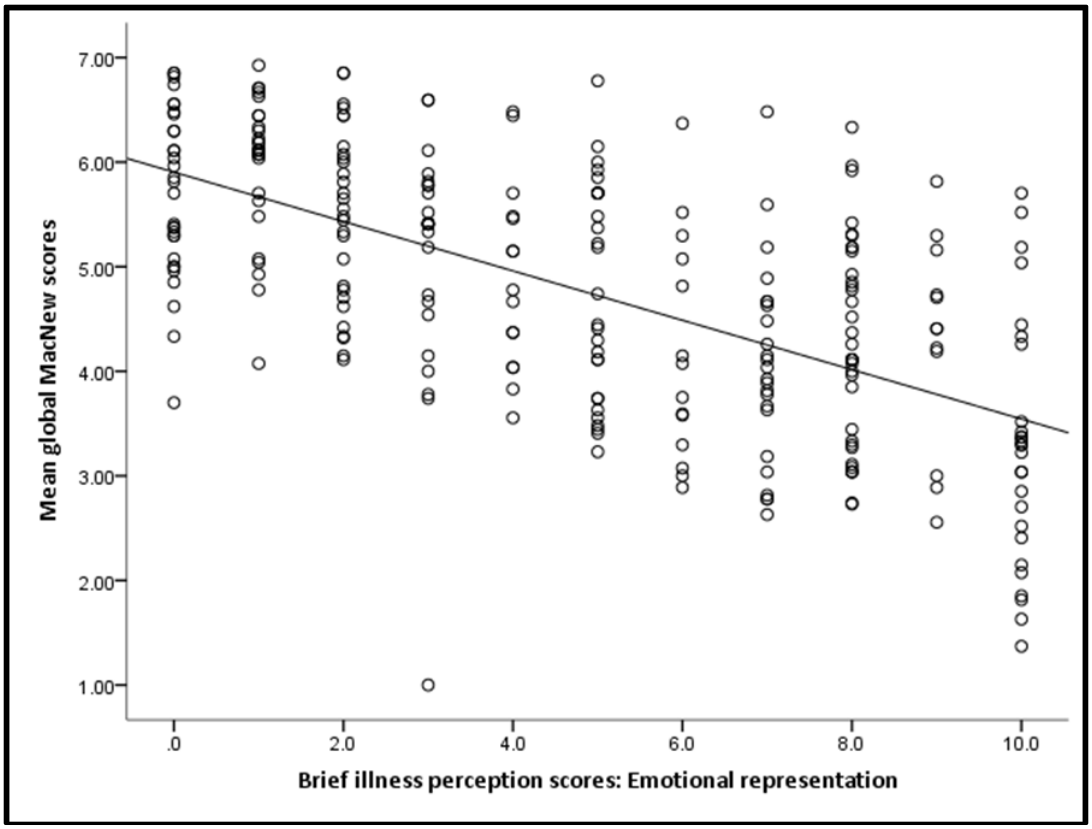

Figure 36: Correlation of global MacNew score with patient perception of emotional representation of illness

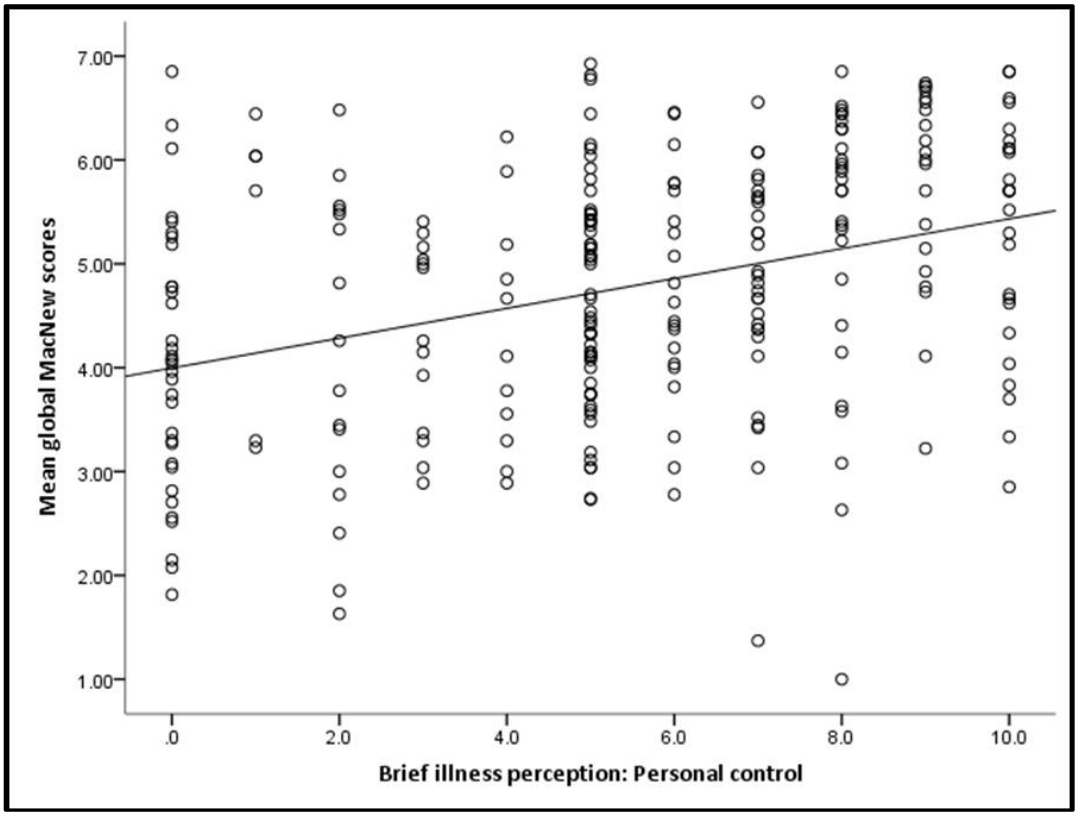

Figure 37: Correlation of global MacNew score with patient perception of personal control

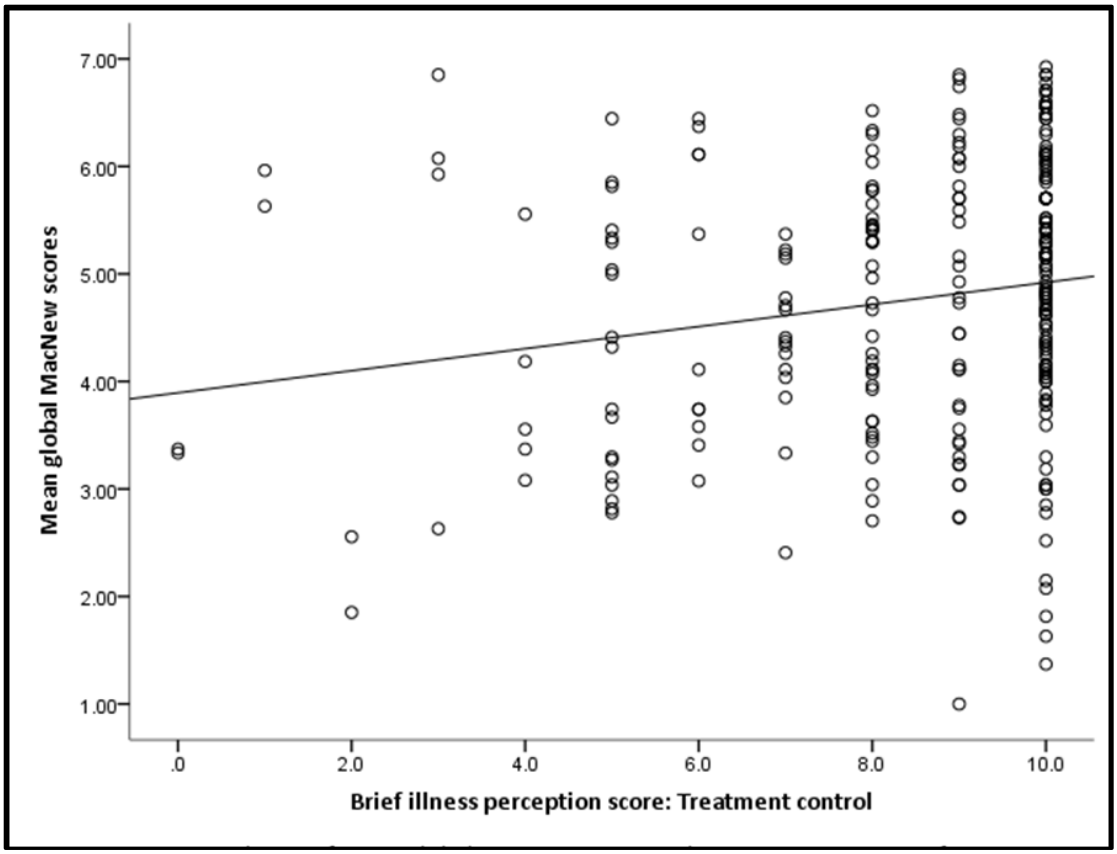

Figure 38: Correlation of global MacNew score with patient perception of treatment control

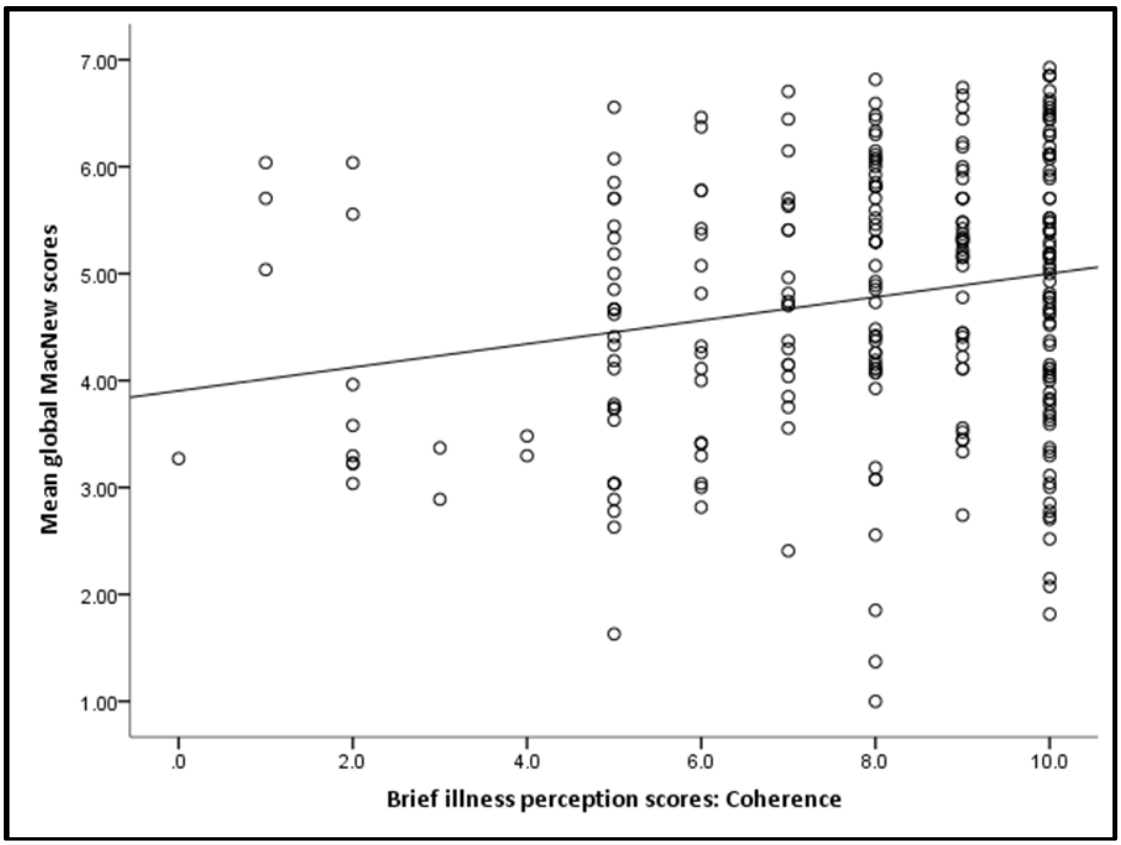

Figure 39: Correlation of global MacNew score with patient perception of illness coherence

MACCE outcomes

Over 1 year follow-up there was a total of 6 acute coronary syndromes, 3 patients required further revascularisation (**table 54**). The 1 year mortality rate for the entire cohort was 5.8%, including 3 deaths within the medically managed group, 2 patients treated with PCI and 1 patient who had CABG. Univariate linear regression analysis did not reveal a correlation of MACCE and mean global MacNew scores over 1 year follow-up [β =-0.16, p=0.19], nor was MACCE identified as a predictor variable in the best fitting growth model for global mean MacNew scores.

Follow-up continued for the entire cohort until completion of all 1 year questionnaires for all patients, the median follow-up was 502 (286) days (**table 55**). MACCE recorded for this period include 1 further ACS within the PCI patient cohort, 1 patient treated with PCI initially suffered a repeat revascularisation, while 1 patient failed medically management and converted to a revascularisation strategy. There was 1 additional CVA within the CABG managed group and no further deaths were recorded.

Table 54: MACCE over 1 year follow-up

MACCE	Medical Management (%)	PCI (%)	CABG (%)
ACS	2 (10.0%)	3 (8.6%)	1 (2.1%)
Repeat revascularisation	2 (10.0%)	0	1 (2.1%)
CVA	0	1 (2.9%)	0
Death	3 (15.0%)	2 (5.7%)	1 (2.1%)

CABG – coronary artery bypass surgery; PCI- percutaneous coronary intervention; MACCE – major adverse cardiac or cerebrovascular event; ACS – acute coronary syndrome; CVA – cerebrovascular accident

Table 55: MACCE over median follow-up 502 (IQR 286) days

MACCE	Medical Management, n(%)	PCI, n(%)	CABG, n(%)
ACS	2 (10.0%)	4 (11.4%)	1 (2.1%)
Repeat revascularisation	3 (15.0%)	1 (2.9%)	1 (2.1%)
CVA	0	1 (2.9%)	1 (2.1%)
Death	3 (15.0%)	2 (5.7%)	1 (2.1%)

CABG – coronary artery bypass surgery; PCI- percutaneous coronary intervention; MACCE – major adverse cardiac or cerebrovascular event; ACS – acute coronary syndrome; CVA – cerebrovascular accident

6.5. Discussion

Over 100 patients were recruited into the prospective Leeds left main stem registry. Whilst the aim was to follow-up all patients for 1 year completing 4 time point HRQOL questionnaires, we achieved a completion rate of 45% for all time points. The conventional general linear model therefore included data from only 45 patients and indicated serial improvements in quality of life from baseline up to 6 months, maintained up to 1 year, for the revascularisation treatment groups. The medically managed cohort did not show an improvement in quality of life scores. Independent predictors of poor quality of life at 1 year were a history of cardiac surgery, previous CVA and presentation with a STEMI. The best fitting linear growth model, 98 patients were included, indicated that quality of life improves significantly with time from baseline in patients treated with CABG. PCI was not identified as a predictor of improvement in QOL when compared with CABG. Recent MI, within 90 days, was identified as a significant predictor of improvement in QOL over 1 year.

Published data indicate that mixed model analysis using the linear growth models provides a better fitting model than one-way repeated measures analysis of variance (ANOVA) due: (a) to the inclusion of a larger number of cases, where missing data are estimated with maximum likelihood, and (b) by allowing the construction of a growth curve using data collected at unequal time points [416, 425]. These are the first published data on repeated measures quality of life data for patients with LMCA disease which include medically managed patients as a comparator [390]. The SYNTAX study compared QOL outcomes in patients with multivessel disease treated with PCI or CABG using the linear growth model; however only 39.2% of study patients had LMCA disease and they did not include a medically managed cohort [377]. We did not show a significant difference in HRQOL outcomes between PCI and CABG, which is consistent with other studies comparing HRQOL outcomes for CABG and PCI used to revascularise LMCA disease [388, 390]. However, as we used the linear growth model, as opposed to a single time-point measure, we found there was a non-significant trend for better outcomes from CABG over 1 year follow-up.

Quality of life is an important clinical measure of outcomes because of the increasing number of patients who could be treated with ULMCA PCI as a viable alternative to surgery

[299, 426]. In particular patients with low to intermediate burden coronary disease [59, 60, 215, 252] and those with high surgical risk patients may benefit from PCI [69, 299]. The first study to report quality of life outcomes in patients with LMCA disease found no significant difference in HRQOL scores for both CABG and PCI treatment arms at a single time-point, measured at 6 months [390]. While our results correlate with these findings and those from other studies of revascularisation [377], we analysed repeated measures of QOL. The repeated measures analysis of QOL is a more robust methodology employed in more recent studies comparing PCI to CABG [388, 391].

We did not show a significant difference in QOL scores comparing PCI to CABG; CABG was a predictor of better QOL in the linear growth model and PCI was not. Furthermore, mean QOL scores for CABG seem to improve to a greater degree than PCI within 6 months, which is in contrast to other studies which show larger early gains in QOL from PCI up to 6 months post-procedure [379], which may be reversed at 1 year. Possible explanations for this include the unmeasured differences in the disease burden between the cohorts, the significantly older PCI cohort and possibly larger burden of incomplete revascularisation in the PCI cohort.

Compared with our retrospective LMCA PCI cohort, this was a much younger overall cohort, where patients treated with PCI though were significantly older than the CABG and medically managed cohorts. Age was not identified as a predictor of poor QOL outcomes, which is consistent with other studies which show similar HRQOL outcomes amongst older and the younger patients up to 1 year [358, 390, 427, 428]. QOL scores did not improve significantly from 6 months to 1year following CABG, but were maintained, this too reflects a relatively younger study population compared with other studies which show a deterioration in QOL after 6 months in older patients following CABG [429]. The older PCI cohort similarly maintained the early gains in QOL up to 1 year. The early and sustained improvement in QOL becomes more relevant amongst those with relatively short life expectancy, while other outcomes measures, such as repeat revascularisation, may become less relevant in the elderly.

For the overall study cohort, all subgroup domains of the MacNew questionnaire significantly improved over time, with the largest improvement in the physical domain after

6 months. Previous studies have shown that amongst patients treated with CABG the physical domain lags behind the other QOL domains [376]. Indeed the 6 month physical domain QOL scores seem to lag behind the other QOL health domains for patients with LMCA treated with both PCI and CABG [390]. Elderly patients tend to have worse physical domain scores which do not improve as much as other domains [390, 430, 431]. CABG represents a significant physical trauma; despite this we did not show a significant difference in the physical domain scores between the PCI and CABG cohorts, this is more than likely a consequence of the older PCI cohort.

This is the first longitudinal study of brief illness perception questionnaires of patients with LMCA disease. All BIP questionnaire scores increased over time apart from treatment control, which showed a significant decline. Treatment control had a weak positive correlation with global MacNew scores. This knowledge has important practical implications for rehabilitation programmes and patient education; by improving the perception of treatment control one can potentially improve quality of life outcomes [432][407]. Strong negative correlations were found between the mean global MacNew scores and patients perceptions of consequences and emotional representations each accounting for 49.0% (r^2=0.49) and 38.6% (r^2=0.386) of the variability in the overall QOL scores respectively. While moderate negative correlations were found between the mean global MacNew scores and identity and illness concern. There was a weak positive correlation of the mean global MacNew score and perceptions of personal control, which accounted for only 12.4% of the variability in the score.

Across social and physical domains of the MacNew score, patients' perception of consequences had a strong negative correlation accounting for 52.1% of the variability in the social domain score and 38.1% in the physical domain score. MacNew physical and social domain scores had a moderate negative correlation with BIP emotional representations while in the emotional domain of the MacNew it had a strong negative correlation which accounted for 46.9% of the variability in these scores. Other BIP perception scores with a moderate negative correlation to the social and physical MacNew domain scores include identity and illness concern. The physical and social MacNew domains were both found to have a moderate positive correlation with BIP personal control, while there was only a weak correlation with the emotional MacNew domains. The

emotional domain of the MacNew had no strong or moderate positive correlations with BIP scores.

The perception of negative illness consequences was assessed with the first item in the questionnaire (see appendix), 'how much does your illness affect your life?' with higher scores indicating worse consequence. While the effect of BIP consequence on long term QOL outcomes has not been studied in LMCA disease, it was known that the immediate (<24hours) beliefs in unpleasant consequences following an MI are predictive of poor long term QOL [433]. However this study correlated only a single measure of illness beliefs with QOL while we have demonstrated significant improvements in the BIP consequence scores with longitudinal data analysis. Results from meta-analysis of all BIP published data have confirmed the strong negative correlation of QOL with BIP consequences [434]. It is known that in-hospital interventions which are designed to change patients' illness perceptions can improve long term QOL and angina scores following an MI [414]. So while BIP consequence scores were not included in the best fitting predictive linear growth model of QOL, it may have contributed to the overall improvement in QOL scores over time. It is worth noting that medically managed patients had some observable improvement in the mean BIP consequence scores.

Emotional representation was assessed with item 8 in the BIP questionnaire; 'how much does your illness affect you emotionally? (E.g. does it make you angry, scared, upset or depressed)' (see appendix). Strong correlation of BIP emotional representation with depression, QOL psychological and emotional domains have been demonstrated in meta-analysis of the published brief illness perception data [434]. Patient emotional representations can identify cardiac patients at high risk of depression [435], while depressed patients are more likely to have poor QOL scores [436]. Interventions, such as CBT, which target changes in illness perceptions, can improve depression in cardiac patients [437, 438].

While the angina scores were not directly assessed in this study, we were able to determine the change in anti-anginal therapy over the course of 1 year. There was no significant difference in anti-anginal therapy between groups, which probably reflects what is known from other studies comparing CABG to PCI in multivessel disease; there was no significant

difference in angina [377]. This is interesting as patients treated with CABG achieve significantly more complete revascularisation than those treated with PCI [155]. The benefits of complete revascularisation extend to generic QOL scores too; physical domain QOL scores show a greater improvement amongst patients with complete revascularisation compared to those with incomplete revascularisation [163]. It should however be noted that revascularisation was not guided by ischaemia testing in either treatment group [47]. However, it is not possible for us to interpret the burden of angina in our study, as drug therapy, acting as a surrogate, may not have been actively reviewed. Revascularisation is known to augment the relief of angina when added to medical therapy [439, 440], and may explain why none of the medically managed patients in this cohort had a reduced dose of anti-anginal medication.

Independent predictors of poor quality of life scores at 1 year include a history of previous CABG. While this is the first reported analysis to show this association, previous cardiac surgery is well known predictor of mortality from subsequent surgical revascularisation [137]. This has implications in decision making, probably tipping the scales further in favour of PCI for this subgroup of patients. Indeed if there were patent grafts to the left coronary tree, this could confer protection when undertaking LMCA PCI.

Previous CVA and presentation with STEMI were also identified as independent predictors of poor HRQOL outcomes. While a history of CVA has never been reported as a predictor of QOL in other revascularisation studies, the mechanism could simply be related to the level of baseline physical disability, depression, lack of social support [441] or even marital status [442]. While only 17.5% of patients presented with STEMI and almost half with NSTEMI, STEMI was a predictor of poor QOL; this is in contrast to known data which show worse QOL outcomes in patients with NSTEMI compare with STEMI following revascularisation [443]. Nevertheless, we are unable to confirm whether the mechanism for this poor QOL outcome post STEMI is related to known psychosocial factors, such as depression [444].

The MACCE rate for PCI was similar to that reported for randomised studies of LMCA revascularisation, while the MACCE rate we report for CABG was half that reported in other studies [45, 61]. Similarly the MACCE rate we report for the medically managed group was almost half that reported by other studies [5, 6, 8, 445] , however our medically managed

cohort was significantly younger than included in these studies. MACCE was not however an independent predictor of HQOL outcomes, yet it is known that there are measurable changes in QOL scores in patients suffering MACCE events post-revascularisation [195]. Significant change in QOL scores could therefore identify significant MACCE, which may allow a more appropriate censorship of MACCE. A 'weighted' MACCE if you like, where insignificant MACCE, determined by a minor reduction in QOL scores, are ignored. Thus, longitudinal change in HRQOL in combination with hard end-points, could inform patients and clinicians of the prognostic and symptomatic gains of various therapies. However, in order for this study to measure a change in QOL related to a specific MACCE event, the QOL questionnaires should be administered at the time of the new event, thus creating additional time-point measurements for these patients. The study design was therefore not capable of establishing a 'weighted' MACCE, which was one of the recommendations from the Patient and public consultation group. Another factor precluding this analysis would be the small numbers included in the study, with such a low MACCE rate; we would need a much larger study population.

Questionnaire completion rates varied across the treatment groups with the medically managed group having the lowest completion rates across the year of follow-up. Poor completion rates for questionnaires are similar to those found in other studies of QOL [446, 447], yet the factors related to this were not assessed. Death accounted for over a third of the missing questionnaires amongst the medically managed group. Indeed it is well documented in other studies that patient attrition due to the disease process results in a decline in completion rates over time [416, 446]. Other factors given are poor socio-economic status, older age and foreign or socially isolated groups [447]. However, other studies report higher questionnaire completion rates amongst older patients, 71.0% for those over 75 years old and only 66.7% for those under 75 years old [390]. In previous chapters we have demonstrated that the cohort of patients treated with LMCA PCI at our institution is older than the published data, however this prospective study cohort, median (IQR) age of 69.0 (14.0) years old, was younger than the retrospective cohort, median (IQR) age of 75.0 (18.0) years old. Furthermore, there was no difference in age between the missing and completed QOL questionnaire groups. Neither did we report a significant difference in socio-economic status between those with missing and completed

questionnaires. There were significantly more STEMI patients who did not complete the questionnaires. STEMI patients treated at our institution are recovered from a wide geographical area, and they are then repatriated to their respective district hospitals soon after treatment. This may account for the low completion rate despite posting questionnaires to these patients. Possible mechanisms may include the lack of routine clinical follow-up with the sponsored research site, such as routine outpatient clinic visits. We also found that patients with diabetes were less likely to complete all questionnaires; the mechanism for this is unclear.

6.6. Limitations

Issues with recruitment are a source of potential bias in this study. This prospective study intends to describe the QOL outcomes amongst all patients with LMCA disease; however we were unable to recruit all patients diagnosed at our institution. From the conception of this study we anticipated issues relating to recruitment and attempted to negate these using various strategies. Patients admitted as emergencies overnight were often repatriated to the district hospitals prior to recruitment. Our strategy involved communicating actively with clinical staff which would alert the research team to potential patients within the department prior to their discharge. To enhance inclusion of all patients diagnosed with LMCA disease, we invited referrals to the Leeds MDT. We presented an outline of the study at the regional commissioning group meeting in September 2012. Furthermore, the study design and ethics application made possible the recruitment from multiple centres. Despite this we were unable to recruit additional centres to the study due to concerns raised by the research committee about loss of Comprehensive Local Research Network (CLRN) funding and the already stretched technical support staff. Direct referrals from the district hospitals to a named surgeon continued which therefore bypassed discussion at the MDT and led to missed recruitment. A further source of potential bias includes the unknown numbers of patients diagnosed at the district general hospitals who were medically managed. Despite encouraging referral, without a multicentre study design a number of medically managed would have been missed. Due to small numbers of medically managed patients we are unable to assess factors associated with poor QOL.

A major limitation of this study is that we did not provide comparative coronary disease burdens for each treatment group. There were obvious differences between groups with an older PCI cohort compared to the CABG group. This introduces potential confounding, disease burden and indeed the residual disease burden significantly affects the QOL outcomes [155].

While we included recognised predictor variables in developing the linear growth model, possible confounding factors not measured include: emotional/mood status [442], educational level [417], cognitive impairment [448-450], living environment [451], ischaemic burden [452], the requirement for social support[431]. All these are known predictors of poor QOL, and thus contribute to the overall causative psychological model.

At most this study provides a snapshot in terms of QOL outcomes. It is known that over longer term follow-up, up to 3 years, QOL scores seem to deteriorate amongst the elderly [453]. Older patients though are underrepresented in HRQOL studies [358]. Yet for these elderly patients, HRQOL is particularly relevant given their relatively short life expectancy. For the elderly, traditional measures of outcome, such as MACCE, becomes less relevant. We should consider extending the use of QOL questionnaires up to 3 years following revascularisation with appropriate strategies to deal with the with poor questionnaire completion rates found amongst the elderly [447].

'Missingness' is correlated with outcomes and missing questionnaires introduce extreme bias to the data, cautious interpretation of the available data is warranted [446]. The bias is proportional to (a) the difference in mean QOL scores between those who have completed the questionnaires and those who have not (one assumes they have completed the questionnaire), and to (b) the proportion of non-responders. If we compare two treatments, A and B, in a randomised clinical trial using overall QOL scores; the proportion of patients who completed all questionnaires, in treatment arm A would be given by 'A', while those who did not would be '1-A'. The mean scores for patients who completed the questionnaires, the A 'comp' group, is given by $\bar{u}^{A}$*comp*; while the mean scores for those who did not complete the questionnaires, the A 'incomp' group is given by, $\bar{u}^{A}$*incomp*; assuming they had responded. Thus the mean score for all patients in treatment group A

would be $\bar{u}^A = A.\bar{u}^A comp + (1-A).\bar{u}^A incomp$ [454]. Yet while we only have the mean scores for the A 'comp' group, the bias in the scores for treatment group A is given by:

$$\begin{aligned} Bias_A &= \bar{u}^A - \bar{u}^A comp \\ &= A.\bar{u}^A comp + (1-A).\bar{u}^A incomp - \bar{u}^A comp \\ &= (1-A).(\bar{u}^A incomp - \bar{u}^A comp) \end{aligned} \quad [446]$$

Thus, we cannot reduce the bias by increasing the study size; rather we should achieve this by reducing the proportion of those with incomplete questionnaires. While it is tempting to deal with the missing data using statistical methods, such as multiple imputation, these methods do not account for confounding. Statistical methods assume that those who have not completed the questionnaires are similar to those who did complete the questionnaires. However, where it is not possible to account for all variables associated with incomplete questionnaires this assumption will be erroneous. Our study design did not account for reasons why patients did not respond to the baseline questionnaire; however this was a small proportion of patients, fewer than 15.0%. Furthermore, we failed to record factors which led to incomplete questionnaires over the course of 1 year follow-up. In order to ameliorate this we included a linear mixed model which led to the inclusion of over 97/106 patients. By increasing the number of time points included, the mixed model improved the reliability of HRQOL parameters by reducing the standard error of the within-patient change in the HRQOL parameter estimates [455][456]. Despite this our study compares favourably with other studies where the missing questionnaires or non-responder rates were up to 30.0% for a single time-point questionnaire [457].

While we were able to demonstrate longitudinal trends for generic HRQOL measures, we did not include a disease specific QOL measure, such as an angina score. Disease specific measures assess the progression and modification by treatment of the organ specific pathology [458]. One such widely used measure is the Seattle Angina Questionnaire [459]. Disease specific QOL have disadvantages though, while the treatment may improve disease specific QOL measures it may lead to a decline in other QOL measures. Take for example a scenario where CABG improves the angina score but due to the severe trauma of the

surgery it leads to a worsening in musculoskeletal pain or limitation in mobility as a result. It is recommended to include both disease specific and generic HRQOL measures [460]. Correlation between angina and repeat revascularisation has been demonstrated in trials comparing PCI to CABG [461, 462]. While it is known that CABG offers greater freedom from angina than PCI for multivessel disease [463], other studies have shown no difference in angina scores between these two treatments [377].

There seems a large dispersion of baseline global MacNew scores which become more bunched up towards the 1 year follow-up period. Firstly, this indicates the large variability in baseline characteristics; secondly, it may indicate learning as patients become more accustomed to the questionnaires. Other confounding variables may account for the wide dispersion in baseline scores such as including patients presenting with both stable and acute coronary syndromes and timing of recruitment, e.g. soon after a CABG or STEMI versus an elective admission. In the case of clinical syndrome, baseline scores may be 'abnormally low' amongst patients recruited immediately following PPCI for STEMI. Furthermore, where some patients were recruited in the first few days following their CABG, they too may have 'abnormally low' baseline scores. These 'abnormally low' baseline scores may thus result in a 'significant' increase over 1 year as it is the rate of change in scores over time which we describe with growth curves [377]. The acuity of presentation itself and indeed the trauma of the management is a confounding factor in these baseline scores. In order to negate this confounding, patients were asked to relate their baseline answers to the premorbid, 2 weeks prior to presentation, life. Moving forward it would be important to address when the baseline questionnaires were administered. In the SYNTAX trial this was prior to randomisation [377] . It may be prudent to exclude STEMI patients and those we are unable to recruit prior to surgery or PCI.

6.7. Conclusions

Serial global and sub-domain QOL scores improve over 1 year for both revascularisation groups but not for medically managed patients, while CABG and not PCI is a predictor of significantly improved QOL outcomes. Medically managed patients did not have any improvement in QOL compared with those who had revascularisation, yet it should be noted that there may be a significant placebo effect. A recent study of revascularisation in less severe stable coronary disease has shown that revascularisation with PCI offers no symptomatic benefit over medical management when employing a sham procedure for randomisation [359]. While this study informs the risk benefit analysis of whether a limited or targeted revascularisation strategy may be appropriate in medically managed patients, it is not powered to draw any conclusions. The current study design limits the exploration of a causative model for all known predictors of poor QOL and does not exclude the significant confounding from the placebo effect. Ongoing recruitment would allow a meaningful insight into the medically managed cohort which has hitherto not been studied in published data. However, future studies should be designed as randomised controlled trials using sham procedures to study PCI versus medical management for symptom control in severe LMCA disease.

Chapter 7: Discussion

7.1 Retrospective study

Current recommendations for revascularisation of LMCA disease are based on randomised controlled trials comparing CABG and PCI for patients with LMCA disease [69, 299]. Patients randomised in these trials were considered appropriate for either CABG or PCI as the revascularisation strategy; indeed they have low surgical risk [464]. The SYNTAX trial was designed to investigate patients with extensive coronary disease, including LMCA disease and patients with three vessel coronary disease [47]. Thus, the left main cohort of all-comers had a wide range of coronary disease severity which could be treated with either PCI or CABG [61]. The results indicated worse outcomes from PCI in patients with the greatest burden of atheroma, including patients with LMCA disease and extensive atheroma, SS >32 [215], for these patients CABG offered superior results. Later studies were designed to focus on patients with less complex and less extensive coronary atheromatous disease [59, 60]. After a recent meta-analysis of these randomised studies, one can conclude that the study populations are more restricted by risk profile and extent of coronary disease [465, 466] than a large proportion of the actual population treated with LMCA PCI in the UK [154]. Indeed recent randomised trials have excluded just over half of all patients screened [59, 465, 467].

Current revascularisation guidelines encourage weighing the risk of surgery and the clinical presentation, as in LMCA culprit acute STEMI, against the complexity of coronary disease using the SS and the anatomical location of LMCA disease when deciding on the optimal revascularisation strategy [468]. While for decades CABG has remained the accepted best practice for LMCA revascularisation, previous published national PCI registries have demonstrated that PCI was offered to patients considered high surgical risk [154]. It is amongst these high surgical risk patients for whom predictors of poor outcomes from LMCA PCI are unknown. While published registries provide large patient cohorts [154], they fail to provide the depth of data required to examine all anatomical and demographic factors which more recent studies have shown are predictors of poor outcomes in randomised samples [47, 82, 155]. In order to further examine the clinical and anatomical factors which are associated with poor outcomes following revascularisation with PCI, we chose to study a retrospective cohort of consecutive unselected patients presenting to a cardiac surgery unit and who had LMCA revascularisation with PCI.

Notwithstanding these patients may be considered high surgical risk, they may also have coronary anatomy which would otherwise be considered unfavourable for PCI [299, 469]. Examples of unfavourable coronary anatomy include distal LMCA disease and SS>32. Outcomes from LMCA bifurcation PCI is associated with poor outcomes [271] and while there is evidence suggesting a provisional single stent for coronary bifurcation disease is the preferred option [82], there are no randomised studies of two versus single stent strategies for the treatment of LMCA bifurcation disease [106, 271]. Current published non-randomised studies comparing single and two stent strategies for LMCA bifurcation PCI suffer from bias, with groups unmatched for atheroma burden at the LMCA bifurcation [77, 113, 114]. Current evidence suggests a greater the burden of atheroma at the LMCA bifurcation predicts poor outcomes from PCI, particularly involvement of the side branch in 'True' bifurcation disease [96, 113]. Indeed, current guidelines suggest a two stent strategy for 'True' left main bifurcation disease [119]. Thus, we assessed the factors associated with poor outcomes from revascularisation in a subgroup of patients with 'True' LMCA bifurcation disease.

Furthermore, while a previous analysis of ULMCA PCI in a national registry revealed that age >80 years old is a predictor of poor outcomes [154], it is not known which factors are associated with these poor outcomes, nor if it is simply a consequence of a long lived patient group. However, this age group has seen a great increase in life expectancy over the last 10 years [470], with the proportion of octogenarians in the population expected to rise from 5% currently up to 20% by 2050 [134]). Coronary revascularisation offers greater absolute gains in survival in the elderly in comparison to the young [130, 142]. However, octogenarians are more likely to have more complex coronary lesion including multivessel disease and left main disease compared to younger patients [1, 126, 130, 141, 146, 152]. Indeed with greater complexity of coronary disease one finds incremental levels of incomplete revascularisation [47, 155], yet the merits of complete revascularisation has only been demonstrated in younger cohorts [155].

While rSS has been shown to be a reliable quantification of residual coronary disease [155], there is conflict in the data assessing the association of rSS with poor outcomes in

octogenarians. A recent study of less than 100 patients suggested that residual coronary disease was associated with poor outcomes in octogenarians presenting with ACS [170]. However, a much larger retrospective study, including the largest ever analysis of angiograms calculating the SS and rSS, found no association between rSS and poor outcomes in the octogenarians [171]. Both of these studies included relatively small cohorts of patients with LMCA disease, with fewer than 10.0% of patients in the larger study and fewer than a third of patients in the smaller study with LMCA disease. Furthermore, while rSS was validated in patients with extensive coronary disease [155], in relatively low risk populations with a narrow delta SS, such as in the larger UK study, where the median SS was only 18.3 and the median rSS 10.1 [171], it may be less discriminative.

Greater coronary artery lesion severity and complexity as well as the presence of multi-morbidity may introduce challenges in achieving complete revascularisation in elderly patients with ULMCA disease. Indeed while it is known that incomplete revascularisation following CABG in the elderly leads to worse survival compared with complete revascularisation [169]; it is uncertain whether the residual coronary disease burden, as measured by the rSS, is associated with poor long term outcomes among octogenarians treated with ULMCA PCI. Given the sparsity of data for outcomes in octogenarians with LMCA disease, we sought to determine whether the residual coronary artery disease burden, as measured by the rSS, was associated with mortality in the elderly treated with ULMCA PCI.

7.1.1 Principal findings

Overall cohort

In this retrospective study, 366 unselected patients with ULMCA disease were treated with PCI between March 2005 up to March 2013. Over a median (IQR) follow-up of 584 (1036) days, cardiogenic shock on presentation contributed more than fivefold hazard to the risk of MACCE, [aHR 5.88, 95% CI 3.81-9.06, p<0.05], when compared to other significant covariates. Other independent covariates associated with MACCE include the burden of coronary disease, as measured with the SS [aHR 1.01, 95% CI 1.00-1.02, p<0.05], previous MI [aHR 1.94, 95% CI 1.37-2.75, p<0.05] and a history of diabetes [aHR 1.61, 95% CI 1.12-2.31, p<0.05]. In view of up to a third missing LV function assessments, we conducted multiple imputation which confirmed the association of these covariates with MACCE. However, the multiple imputation datasets further identified that moderate to severe LV dysfunction was associated with poor outcomes.

We identified cardiogenic shock on presentation as a predictor of early death, in patients presenting with cardiogenic shock, cardiac death accounted for 85.0% of all MACCE at 30 days. By including patients presenting with cardiogenic shock, the regression analysis was less discriminatory of long term outcomes [180]. A separate analysis of patients who did not present with cardiogenic shock prior to the admission, found that the SS [aHR 1.02, 95% CI 1.00-1.04, p<0.05], previous MI [aHR 1.89, 95% CI 1.28-2.80, p<0.05] , peripheral vascular disease [aHR 1.68, 95% CI 1.09-2.61, p<0.05] and renal impairment [aHR 1.89, 95% CI 1.05-3.43, p<0.05] were significantly associated with MACCE.

Furthermore, when one assesses the components of MACCE, we report a repeat revascularisation rate of only 2.8% in the first year. Death therefore makes up the largest component of MACCE. Considering that all-cause death contributed over 80.0% of all the MACCE in this relatively long-lived cohort, median(IQR) age was 76.0(18.0) years old, we assessed the separate composite end-point of: cardiac death, MI, stroke and repeat revascularisation. For this composite end-point we found that SS [aHR 1.02, 95% CI 1.02-1.04, p<0.05], previous MI [aHR 1.82, 95% CI 1.15-2.88, p<0.05] and diabetes [aHR 1.81, 95% CI 1.13-2.91, p<0.05] were associated with poor outcomes.

Bifurcation study

We conducted a subgroup analysis of 262 patients with LMCA bifurcation disease with a median (IQR) follow-up of all patients of 642 (1069) days. Unadjusted Kaplan-Meier survival analysis showed a significantly worse outcome for patients with 'True' left main bifurcation disease compared with 'Non-True' LMCA bifurcation disease. After adjustment we found that 'True' left main bifurcation disease was associated with a two-fold increase in the risk of MACCE over long-term follow-up, [aHR 2.0; 95% CI, 1.1-3.6; $p<0.05$]. In addition we found that the presence of significant right coronary artery disease [aHR 1.8; 95% CI, 1.1-2.9; $p<0.05$], diabetes [aHR 1.7; 95% CI, 1.1-2.7; $p<0.05$] and peripheral vascular disease [aHR 1.7; 95% CI, 1.0-2.8; $p<0.05$] were independently associated with MACCE. A separate analysis of 162 patients with 'True' left main bifurcation disease identified peripheral vascular disease [aHR 1.9; 95% CI, 1.1-3.3; $p<0.05$] and diabetes [aHR 1.7; 95% CI, 1.0-2.9; $p<0.05$] as independently predictors of MACCE over long-term follow-up. Unadjusted survival analysis showed that there was no significant difference in outcomes when comparing patients treated with a single or two-stent strategy.

Octogenarian study

In this retrospective analysis of 139 octogenarians treated with ULMCA PCI, we found that patients with incremental levels of residual coronary disease after PCI, as calculated from the residual Syntax score (rSS), were at greater risk of mortality over long-term follow-up. Each 10 unit increase in rSS was associated with a 3% increase in all-cause mortality. Whilst one year survival amongst this aged population approached 90% and at about 2 years, was 77%, we found that, in addition, the SS was significantly associated with poor long term outcomes. Furthermore, the presence of 'True' LMCA bifurcation disease was associated with a three-fold increase in risk of death after a median follow-up of 645 (IQR 1041) days. While 'True' LMCA bifurcation was independently associated with MACCE, no other covariates were associated with MACCE after adjustment.

7.1.2 Context of findings

7.1.2.1 Overall cohort

We identified an overall registry cohort with significantly higher surgical risk than published randomised trials examining outcomes from LMCA revascularisation [25, 45, 46, 59, 60, 211, 215]. Indeed, the median age was close to 10 years greater than in other studies published on LMCA revascularisation[25, 30, 31, 33, 59-61, 209, 210], with nearly twice the proportion of octogenarians than that reported for LMCA PCI in the UK national PCI registry [147, 154]. In addition the study population had more comorbidity than these other published studies, with a greater prevalence of previous MI, CKD and peripheral vascular disease reported for the study population [25, 33, 210]. International guidelines on LMCA revascularisation draw on randomised trials to inform best practice. PCI is a Class IIb recommendation for patients at high surgical risk, where risk of mortality is >2%, and modest coronary complexity (SS<33, not distal LMCA disease), while it is a Class IIa recommendation for those with a mortality risk of >5% [69]. In our study the median (IQR)risk of mortality, estimated using EuroSCORE II (IQR), was 8.4% (13.7), with only 34 (9.3%) of patients with a EuroSCORE of less than 2% [211]. Of these 34 patients, 26 (7.1%) had a SS of under <32 while 22(6.0%), had distal LMCA disease. It could therefore be argued that at least 34 (9.3%) patients in this cohort should have had CABG. While we were unable to determine the reason for PCI in our patient cohort, this study represents the typical high surgical risk patients who have LMCA PCI in a tertiary UK centre.

This unselected cohort includes over an eighth of patients with cardiogenic shock, yet cardiac death amongst these patients accounts for close to two-thirds of all MACCE at 30 days. While it is known that patients presenting with cardiogenic shock have poor outcomes despite revascularisation [202, 203, 471], in our cohort the 30 day and one-year survival was worse still compared with the SHOCK trial and the SHOCK trial registry where less than a quarter of patients had a significant LMCA stenosis. This comparison taken together with other data seem to suggest that increasing severity of coronary disease results in worse

outcomes for patients presenting with cardiogenic shock [204]. Indeed, the mortality rate for patients with cardiogenic shock and LMCA disease was close to two thirds at 1 year, similar to nationally reported outcomes [154].

Despite a similar incidence of subsequent MI compared with other studies, we reported a considerably lower repeat revascularisation rate [18, 73, 205]. This may indicate a tendency to manage subsequent cardiac events more conservatively in this older cohort [18, 73, 170, 206, 207]. All-cause death was another significant component of MACCE. While death may be the earlier event in this older population, it may not be a disease-specific or device-specific measure of long term outcomes from LMCA revascularisation. It could be argued that all-cause death represents a better overall measure of outcomes in randomised samples, where we are comparing the overall treatment efficacy; while in a non-randomised sample, with no treatment comparator, the use of a more disease-specific measure may further illuminate our understanding of the disease process in long-lived individuals, in this case we are measuring the effectiveness of treatment [472]. Considering that all-cause death contributed over 80.0% of all the MACCE in this relatively long-lived cohort, we assessed the separate composite end-point of: cardiac death, MI, stroke and repeat revascularisation. For this composite end-point we found that SS, previous MI and diabetes were associated with worse outcomes.

In agreement with other studies, for the overall cohort we found that the SS was significantly associated with MACCE [47, 63] such that for every 10 point increase in the SS there was a 2.0% increase in risk of MACCE. Similar to other studies, patients in the high SS tertile, SS>32, had the worst survival compared with the lower two tertiles [215]. The SS is predictive of death and MACCE following PCI in multivessel revascularisation [47, 212] as well as LM revascularisation [61-64, 213]. However, the interaction between SS and outcomes has not always been found to be consistent across studies and some may argue that the SS is not predictive of MACCE in more recent studies [59, 60]. These inconsistencies are mainly explained by the significant differences in median SS between studies which results in differing tertile cut points [62-64, 212]. In more selective study populations with a

narrower range of SS, it becomes less discriminatory, such as the recent randomised trial comparing PCI and CABG [59, 60]. What is evident is that event rates vary with the extent of coronary disease which represents an interplay between disease-specific and treatment-specific end-points. Other factors which could account for an apparent lack of sensitivity of the SS include the different DES used to validate the SS in the SYNTAX trial, first generation DES, compared with second and third generation DES used in more recent studies [59, 60, 473]. While in our cohort close to two thirds of patients received a second generation DES, over a quarter were treated with a BMS.

Diabetic patients have an increased risk of cardiac death [217-219]. They have an earlier onset of more extensive coronary disease [220, 221], including LMCA disease [125]. However, there is some conflict in the published data on outcomes from ULMCA revascularisation in diabetic patients. While some observational studies have not shown an association between diabetic status and MACCE [18, 224], these studies were not designed to examine outcomes from LMCA revascularisation in diabetic patients. Larger non-randomised studies of LMCA revascularisation have shown diabetes was a predictor of MACCE [36, 223, 225, 226], while diabetes is not a predictor of early mortality following PCI [24] or CABG [465]. Early results from the SYNTAX trial and left main subgroup identified diabetes as a predictor of worse outcomes [61, 227]; however in a later analysis at 4 years the association was no longer evident [228]. Indeed diabetes was not included in the SYNTAX II model of predictors of long term outcomes [43, 229]. Other randomised studies of left main revascularisation, comparing CABG and PCI, found no excess hazard with diabetes [62, 216]. These last two studies can be criticised for significant differences in the burden of coronary disease between diabetic and non-diabetic groups, and between the two treatment arms. Patients with the worst coronary disease burden were treated with CABG in both groups, so it seems that when accounting for coronary disease severity and adjusting treatment decisions accordingly, there is no excess effect from diabetes on outcomes.

It is suggested that the end-organ consequences, rather than the presence of diabetes are strongly predictive of poor outcomes [229-231]. The burden of coronary disease can be viewed as an end-organ effect of diabetes. This is evident in the BARI registry where patients received physician-led choice of treatment strategy; they found no difference in outcome between CABG and PCI for diabetic patients [232]. As the majority of patients screened ended up in the registry, the choice of revascularisation strategies were based on the merits of treating the specific pattern of coronary disease burden. Similarly in the LMCA, where the choice of revascularisation strategy was based on the burden of disease, we find no interaction between diabetes and poor outcomes [216]. However, randomised studies of ULMCA revascularisation comparing groups with similar burdens of coronary disease have found significantly worse outcomes in diabetic patients [233]. While there is a lack of data for outcomes amongst diabetic patients with ULMCA disease, after correction for SS and other comorbidities, we found a significant association between diabetes and adverse outcomes. Our study indicates diabetes may be an important factor with respect to MACCE in ULMCA revascularisation independent of SS.

Despite significant differences in comorbidity but a similar burden of coronary disease between deprivation groups, we did not demonstrate a statistically significant difference in survival after PCI between the quintiles of deprivation. Other studies have found worse outcomes amongst the more deprived following PCI; however they failed to quantify the coronary disease between groups [178, 240, 241]. In our study cohort the more deprived patients had more comorbidity, diabetes and renal impairment compared with the least deprived, which is consistent with other PCI study populations [178, 238]. There is an earlier onset of subclinical coronary disease amongst the more deprived [239], and while we found no difference in the burden of coronary disease amongst the quintiles of deprivation, measured with the SS, the more deprived patients were younger. This may reflect the earlier development of worse categories of coronary artery disease, such as left main coronary artery disease, amongst the more deprived [175, 239]. Hence the younger more deprived with severe disease.

We report a large number of complications, over 25.1%. While one may accept this high complication rate is due to the significantly older cohort of patients it is five times higher than the complication rate reported for elderly patients in other studies [133]. Over half of all our reported complications include coronary dissections. Untreated coronary dissections post-angioplasty may result in acute complications [244, 245], poor long term outcomes [242-244], additional stenting [246, 247]. Nevertheless, we did not demonstrate an association between poor long term outcomes and angiographic LMCA dissection during angioplasty.

Access site complications were reported in 5.7% of all patients; over 90.0% of these complications were reported in patients where larger sheaths (7-8Fr) were used via femoral access. Over three quarters of these patients had LMCA bifurcation disease. Arterial sheaths greater than 7 Fr in size were used in almost 70.0% of our total cohort which is ten times the proportion reported in other studies [250, 251]. The combination of larger sheaths and a greater burden of PVD in our patients may account for the increased rate of access site complications compared with these studies [250, 251]. We report a large burden of LMCA bifurcation disease, and while this may require a two stent strategy to treat, it may account for the need to use larger sheaths and catheters. Further analysis is required to determine the mechanisms and decision making leading to the use of large catheters in a population with higher than reported rates of peripheral vascular disease.

We report a definite and probable stent thrombosis ST rate of 1.9% in the first year, rising to 2.2% over the course of the follow-up. While this is similar to that reported for other LMCA PCI cohorts [31, 252], it is twice the number reported in a large multi-centre registry of ULMCA PCI [253]. There could be a few of reasons for this increased ST rate in our study compared to this registry, including: 1) significantly longer median stent length used in our study [253]; 2) our patients have significantly more comorbidity [254]. While LMCA bifurcation requiring a two stent strategy may be a risk of ST [31, 77], we had a similar burden of distal LMCA disease and similar usage of the two stent approach compared to this registry [253]. Despite less DES use in our cohort compared to the multi-centre registry, we

reported very late ST (VLST), while they reported none. Unfortunately, we were unable to exclude premature cessation of DAPT in our patients. One other factor which may explain the significantly lower ST in this multi-centre registry is that the study authors may have under-reported ST in unexplained deaths [253]

7.1.2.2 LMCA bifurcations

In order to study long-term outcomes from ULMCA bifurcation disease, and given the known association of cardiogenic shock with early mortality [256-259], we did not include patients with cardiogenic shock in this analysis. This methodology is in keeping with the study design of prospective left main bifurcation studies and other bifurcation studies where they excluded patients with cardiogenic shock [106, 110]. We included all Medina classes of LMCA bifurcation disease, both 'True' and 'Non-true' [84, 104].

The MACCE rate in this study population was 13.1% at 30 days and 26.2% at 1 year, which is similar to that reported in registries of LMCA PCI with 1st generation DES [21], while it is almost twice the MACCE found in other LMCA PCI registries of 1st generation DES which include close to 80.0% distal LMCA disease [22, 23, 26, 77]. However, the burden of coronary disease may not be comparable as these studies do not specify the Medina class of LMCA bifurcation disease, nor do they use the SYNTAX score to quantify associated coronary involvement. Our MACCE rate seems to be comparable with the treatment of complex LMCA bifurcations [73].

This is the first study reporting outcomes in 'True' versus 'Non-true' left main bifurcation disease, we found a significant association between 'True' left main bifurcation disease and MACCE. While significant distal LMCA disease and poor long-term outcomes [78] and 'True' coronary bifurcations have worse outcomes when compared to 'Non-true' [260], no study has demonstrated this within the LMCA bifurcation. While it is known that the greater the burden of atheroma at the bifurcation, the worse the long-term outcomes [78, 96], this is

the first study reporting outcomes in ‘True’ versus ‘Non-true’ left main bifurcation disease using the Medina classification of bifurcation disease [104, 107, 114].

Distal left main disease is associated with a greater burden of multivessel disease [62, 300-302] and indeed this is the case for ‘True’ left main bifurcation disease, more so than ‘Non-true’ bifurcation disease. We report significantly more multivessel disease, LM +2VD and LM+3VD, amongst the ‘True’ bifurcation cohort compared with the ‘Non-true’ cohort. However, other studies of PCI for unselected distal LMCA disease have reported associated multivessel coronary disease in up to four-fifths of patients [113, 115], twice the proportion in our study. They show no difference in the burden of coronary disease between the 'True’ and 'Non-true' groups [72]. Despite this association with multivessel disease, after multivariate analysis including the SS, we can conclude that the association of 'True' LMCA bifurcation disease with poor outcomes were independent of the greater coronary disease burden.

In the separate analysis of patients with ‘True’ left main bifurcations, we showed no statistically significant difference in outcomes for single and two stent strategies. There are no randomised trials comparing single to two stent strategies for ‘True’ LMCA bifurcation PCI and there is contradiction in the available data for the use of either a single or two stent strategies in the treatment of LMCA bifurcation disease. While some studies report better outcomes from a single-stent strategy [90, 112, 115, 127], they have compared unmatched samples. Due to the nature of observational data the groups compared are unmatched with regards to ‘True’ vs ‘Non-true’ LMCA bifurcation disease [90, 112], and in other cases due to comorbidity [115]. Furthermore, there is often a lack of reporting atheroma burden in the left main bifurcation [115, 127]. Similarly, studies reporting no difference in outcomes between the single and two stent strategies for LMCA bifurcation PCI [113, 114, 261, 266] suffer from the inherent issues with observational data. These issues include a mismatch between the treatment groups with more ‘true’ bifurcation disease in the two stent group [113, 114, 266], while only a third of patients may have ‘true’ bifurcation disease [113, 114, 266]. There may also be significant differences in accepted practice between the treatment

groups, such as significantly fewer final kissing inflations in the single stent group compared with the two stent group [114]. This is the first study reporting outcomes from a two stent versus single-stent strategy in 'True' left main bifurcation disease, while other studies have compared two stent strategies to one another [111, 267].

PCI of the distal LMCA carries a higher risk of ST compared with other LMCA lesions [127]. While we report a greater number of definite and probable ST in the 'True' bifurcation group compared with the 'Non-true' LMCA group, 3.1% vs 0.0, this was not statistically significant. The ST rate for 'True' left main bifurcation disease in our study was similar to that reported in other left main bifurcation PCI studies [114, 127]. However, while other studies report a greater risk of ST amongst patients treated with a two stent strategy compared with a single stent strategy [127, 261], we found no difference between the single and two stent treatment groups with respect to ST rates. Other studies confirm our findings that the ST rate is similar for single and two stent groups, however these studies include patients with both 'True' and 'Non-true' LMCA disease [113, 114].

Side branch occlusion rates in our study were numerically higher amongst patients with 'True' left main bifurcations; while amongst the patients with 'True' bifurcation disease those treated with a single stent suffered more SB occlusions than the two stent group, 5.4% vs. 1.1%. However, this was not statistically significant. Sixteen patients treated with rotational atherectomy and a single stent in the 'True' bifurcation disease group did not suffer side branch occlusions. While this was not statistically significant in our study, other studies confirm that debulking of bifurcation lesions results in less SB occlusion especially when employing a single stent procedure [274, 283]. SB occlusion is a recognised complication of bifurcation PCI and may occur in up to 8.0% of all cases [80, 291-293]. It is commonly due to carina shift after main across side branch stenting [103]. While some studies suggest that 'True' bifurcations are at risk of side branch occlusion [260, 291, 294], our study suggests that using a single-stent strategy in 'True' LMCA bifurcation disease increases this risk but not after rotational atherectomy.

7.1.2.3 Residual Coronary disease

Our findings suggest that residual coronary disease, as measured with the rSS, may be predictive of poor outcomes in octogenarians with severe coronary disease. While other studies agree with these findings [155, 474, 475], we demonstrated these findings in a patient with limited life expectancy. There is some disagreement with the impact of rSS on PCI outcomes in octogenarians [171], however in this study there may a few reasons why the rSS was not associated with mortality. In this study, the largest study to assess SS and rSS in over 8000 angiograms, the cohort of patients had less severe baseline coronary disease, median SS of 18.7 compared with 32.0 in our study or 28.4 in the SYNTAX trial. While they included less than 10.0% of patients with LMCA disease the findings are therefore not comparable to our study. Furthermore, while we excluded patients with cardiogenic shock in their study over a fifth of all patients who died had cardiogenic shock. They report an 8 fold increase in hazard of death with cardiogenic shock, which may blunt the sensitivity of the multivariate analysis to determine factors associated with longer term outcomes.

We reported almost twice the burden of residual coronary disease compared with other randomised studies [155, 167] but similar to other observational studies [474]. In our study rSS and SS were strongly correlated: we observed greater residual coronary disease in patients with higher baseline SS. Indeed patients with more complex coronary disease are at greater risk of residual coronary disease. While other studies report no correlation between rSS and SS [155, 474], they achieved complete revascularisation in over 49% of patients, whereas only 4.3% of our patients had complete revascularisation. Accordingly, the median delta SS did not differ across the rSS tertiles confirming a tendency for selective rather than complete revascularisation in our cohort and this explains the significant collinearity of the SS with other measures of coronary disease, such as the rSS and distal LMCA involvement. There can be a number of reasons for selective revascularisation, which we will explore.

While the elderly are more likely to present with complex, multivessel coronary disease [304, 309, 310] including distal LMCA disease and multivessel disease [39, 146, 307], we report a significantly higher median baseline SS than that reported in other randomised trials of LMCA PCI [47, 61]. In agreement with other observational studies, we found that LMCA bifurcation disease was associated with poor outcomes [78], indeed using the Medina classification, we can report worse outcomes for 'True' LMCA bifurcation disease amongst octogenarians receiving PCI. Compared with younger patients our patients with 'True' LMCA bifurcation disease tended to have a provisional single stent rather than complex two stent strategy [31, 61]. It is not certain if the provisional single stent is inferior to the two stent strategies for treatment of the LMCA bifurcation disease [77, 113, 115].

Our analysis was limited to octogenarians, yet other all-comer studies of residual coronary disease found that incremental levels of rSS were correlated with increasing age of the patients [155, 474]. Selective revascularisation in the elderly has been reported in other studies [170, 206]. Over two thirds of our patients presented with an ACS compared with only 50-55% in other registries of octogenarians with ULMCA PCI [143, 144, 308] , while it is similar to UK national revascularisation trends [476]. Elderly patients are less likely to have access to revascularisation compared with younger patients [206, 207]. Octogenarians are more likely to receive treatment for unstable syndromes than stable angina when compared with younger patients [126, 130, 133, 146], indicating a possible preference to manage stable symptoms conservatively for this age group. While haemodynamic compromise has been implicated in poor outcomes from revascularisation of ACS in the elderly [131] we excluded patients presenting with cardiogenic shock. Less extensive revascularisation and increasing rSS following the treatment of ACS in octogenarians has been associated with poor outcomes [170]. Nevertheless, ACS on presentation was not associated with poor outcomes.

The presence of a chronic total coronary occlusion is a major factor in failing to achieve complete revascularisation by PCI [312]. CTOs were more prevalent and tended to be left untreated in our patients when compared with a younger LMCA study cohort [61]. However,

we were unable to assess whether CTO revascularisation was appropriately deferred due to lack of myocardial viability or ischaemia testing.

Octogenarians suffer more complex coronary disease than younger patients, including more bifurcation disease [477] and more calcified lesions [278-280, 321]. Calcified lesions are identified as a major factor leading to selective revascularisation [322], and are markers of poor prognosis following revascularisation [323]. Rotational atherectomy was required to treat the LMCA in almost a fifth of our patients, while it is used in less than half the proportion of younger patients with LMCA disease [32, 43]. In this context octogenarians are more likely to suffer complications following PCI [1, 133], making clinicians less likely to consider complex revascularisation strategies [206].

This study cohort had a large burden of peripheral vascular disease, similar to the levels reported in other observational studies of coronary revascularisation in the elderly [39, 126, 141] and more than twice the prevalence in younger patients [126, 129, 133, 141, 142, 332]. While the presence of peripheral vascular disease indicates widespread macrovascular disease, it has implications for the management of coronary disease in the elderly due to and increased risk of access site complications [133].

Our study population had a similar prevalence of comorbidities and burden of coronary disease compared with other reported registries of octogenarians treated with ULMCA PCI [126, 141, 143, 144, 308]. While the elderly undergoing revascularisation have a large burden of distal LMCA disease [39, 146, 307], poor outcomes from LMCA bifurcation revascularisation are driven by repeat revascularisation [115, 117]. Yet only 5.8% of our patients suffered repeat revascularisation compared with over 10.0% in other LMCA PCI studies [29, 60, 61, 464]. The 1 year mortality of 11.5% made up almost two thirds of all MACCE, rising to over 30.9% or four fifths of all MACCE for the median follow-up. However we reported a repeat revascularisation rate of only 2.8% at 1 year and 5.8% over the median

follow-up. When compared with other observational studies of DES revascularisation in octogenarians, our repeat revascularisation rate is similar or slightly higher [39, 303, 340].

In this older cohort, with more baseline and residual coronary disease compared with the SYNTAX trial patients [155], we did not observe a difference in the risk of repeat revascularisation across the rSS groups. It should be noted that in our cohort all repeat revascularisation was performed in the context of subsequent acute coronary events rather than stable angina. The younger cohorts studied in randomised trials seem to be at greater risk of repeat revascularisation [47, 59, 60]. This greater risk may in part be due to the difference in the pathology of the atheroma. Despite a greater burden of coronary disease in older age, the plaque morphology is more stable than in younger patients [321], and thus the older patient is less likely to present with further acute coronary events. In this way, while it is known that coronary revascularisation offers greater gains in survival for the elderly than the young [130], revascularisation also seems to offer a more robust form of treatment for the elderly. However, a more plausible explanation may be the greater likelihood of these patients suffering death prior to further coronary events.

7.1.3 Study implications

Firstly, the results of this observational study reflect the outcomes from LMCA PCI within the high surgical risk population treated in most cardiac centres in the UK [154]. We have demonstrated that this population differs considerably from those typically included in randomised trials in terms of baseline characteristics and outcomes. While our study findings are not generalizable due to the non-randomised nature of the data, it provides insight into the factors affecting outcomes from LMCA PCI in high surgical risk populations. This population of patients now represent a large proportion of those who are treated with LMCA PCI in the UK [154].

We have demonstrated that, due to specific characteristics of this study population, current accepted end-point measures may not allow meaningful interpretation of study outcomes.

Meta-analyses of randomised LMCA revascularisation studies show that while mortality is similar for CABG and PCI, differences are driven by MI and repeat revascularisation [57, 58, 478] even amongst older patient cohorts [479]. However, in our relatively high risk and long lived study population, mortality was the main contributor to MACCE where the 1 year mortality was nearly three times higher compared with these selected study populations. Amongst our study population the repeat revascularisation rate was only 2.8%, which is significantly less than reported in these randomised studies, even compared with older randomised cohorts [479]. While the high mortality rate is a reflection of the greater comorbidity in our population, after adjusting for covariates, SS remained a significant predictor of outcomes. Recent studies have demonstrated that amongst patients with low to intermediate burden of coronary disease the risk of repeat revascularisation is similar for PCI and CABG [59, 215, 478, 480]. CABG is the preferred option for those with more extensive burdens of coronary disease. So while it is relevant that further studies examine PCI outcomes in this high surgical risk population with large atheromatous burden, we should explore the possible reasons for this low repeat revascularisation rate.

This study cohort is older and has more extensive coronary disease than patients recruited to published studies from which the LMCA bifurcation PCI guidelines have been drawn [119]. Our study is the first to show that 'True' LMCA bifurcation disease, using the Medina classification, is associated with worse outcomes following PCI. While we demonstrated equal survival from two and single stent strategies for LMCA bifurcation PCI, this was unadjusted survival. While our data support the notion that a single or two-stent strategy is acceptable for the treatment of 'True' LMCA bifurcation disease, given the lack of lesion-level outcomes, including TLR, this is hypothesis generating rather than conclusive. Even now, the EBC is working to address this issue by recruiting to the EBC MAIN study, where they aim to exclude patients with extensive coronary three vessel disease [106].

Diabetes is associated with a two-fold increase in the risk of poor outcomes in patients with LMCA bifurcation disease, albeit patient-level rather than lesion-level outcomes. Our study sample is representative of current clinical practice, which include high risk patients with

complex coronary lesions. These data highlight the challenges facing both clinicians and researchers. Future research to assess single vs. two stent strategies for 'True' LMCA bifurcation disease should include a more specific outcome measure and the selection of patients with limited associated coronary disease to minimise confounding. The challenge, therefore, would be to design a study which can answer the narrow question of how to treat the LMCA bifurcation while acknowledging that the typical patient presenting with LMCA bifurcation disease would usually have extensive coronary disease and may well be older with more comorbidity. These patients, therefore, may not be appropriately managed with CABG. While we await the results of the EBC MAIN study, our findings seem consistent with the EBC recommendations for treating LMCA bifurcations.

While several recently published studies have attempted to identify a cohort of patients with LMCA disease who could appropriately be treated with PCI, the proportion of octogenarians included in these studies is low. Nevertheless, we have demonstrated that amongst a high surgical risk cohort of octogenarians with LMCA disease, survival can be similar if not better than other reported studies of revascularisation in octogenarians [307].

Baseline coronary disease burden, measured by the SS, is associated with poor outcomes in octogenarians with ULMCA disease. While octogenarians suffer from selective revascularisation, octogenarians in our real-world series had levels of residual disease more than twice those reported in randomised studies of ULMCA revascularisation [155, 167]. Incremental residual coronary disease among octogenarians who received ULMCA PCI was significantly associated with mortality. Currently, we are unable accurately determine the benefit octogenarians would receive from more complete revascularisation, however further studies designed to quantify this are warranted. While we have applied an anatomical quantification of incomplete revascularisation, future studies should be designed with functional classification of completeness of revascularisation.

Furthermore, while repeat revascularisation remains a significant factor limiting the use of PCI for LMCA disease, we have found a very low repeat revascularisation rate amongst elderly patients despite the large burden of residual disease; this is probably related to the more stable nature of plaque disease in the elderly [321]. The main discriminator of outcomes in our study is mortality, rather than repeat revascularisation as we find in the younger trial populations. Thus in future consideration needs to be given to assessing outcomes including measures of quality of life given the high burden of comorbidity in this population.

While this study indicates improvement in prognosis with increasing levels of revascularisation in octogenarians, the obvious selection bias would indicate that clinicians applied clinical judgement in assessing individuals. Thus a risk-benefit analysis, balancing the increased risks of revascularisation against prognostic gains and quality of life gains, should be analysed in future studies. Quality of life is an important outcome measure in the success of revascularisation in patients with limited life spans [358].

7.1.4 Strengths

Non-randomised data retains the strength of describing a population which remains clinically relevant to current practice. While randomised studies have allowed us to describe a narrower spectrum of patients for whom PCI is equal to CABG, those with less complex coronary disease, there is a lack of data describing the outcomes in patients for whom PCI is the only alternative. This makes our study relevant to current practice, as these patients represent a majority, when one considers the large numbers of patients excluded from recent randomised LMCA studies [59, 60].

7.1.5 Limitations

Selection bias was inherent in this retrospective study of a group of individuals for whom one can only presume CABG was not an option. Whether it is due to the acuteness of their presentation or high surgical risk, this heterogeneous study population would not be included in a randomised trial of ULMCA revascularisation. Considering the mode of presentation, this alone would bias the results in favour of those presenting free of cardiogenic shock. This is reflected in the significant differences between patients with and without cardiogenic shock. Therefore it was appropriate to consider these two groups separately for further analysis.

Limited access to patient data due to patients, as in the case of STEMI, being treated at one hospital and then repatriated to another with no access to their subsequent data at the district general hospital. We did attempt to negate this by applying to each hospital for data, however there was difficulty due to missing data at district hospital as this was retrospective data collection. In some cases physical files were no longer available and no electronic records existed. All this led to a large number of missing data points.

Missing data present a specific confounding on the analysis of outcomes, in particular when considering that poor LV function is accepted as a significant factor predicting poor outcomes from revascularisation. While accepting this was unavoidable given the retrospective nature of the study, missing LV function has been observed in nationally audited coronary interventional datasets [154]. Furthermore, other randomised trials report similarly high missing LV functions, up to a quarter in some instances [110]. Our sensitivity analysis seems to suggest that the data may be missing not at random, however taking into account plausible predictor variables, we performed multiple imputation. While this imputed data cannot be used to provide conclusions, we were able to confirm the findings from the initial analysis. The regression model for the imputed datasets was in agreement with the findings of our incomplete dataset. While these findings may confirm the model as predictive of poor outcomes, there may indeed be significant bias due to the missing data.

In addition to clinically relevant data, we were unable to locate relevant multidisciplinary discussions prior to the decision to revascularise these patients. While we may infer based on EuroSCORE and clinical presentation that over 90.0% of patients had PCI due to high surgical risk, there are 34 (9.3%) patients who one may reasonably argue could have had CABG. While this probably does not impact on the outcomes of the study, it does represent a potential governance issue. This does not imply a serious ethical issue with our study, but allows us the chance to design a future prospective registry with the appropriate checks and balances.

While we report a large amount of complications, these complications represent a combination of operator-reported complications, recorded on Cardiobase® at the time of the procedure, and those identified at the time of angiographic review for this analysis. The interventionalist who reviewed the angiograms was blinded to the procedural notes; complications were imported directly into the database and were not allocated separately by the reviewer or operator. Due to this method of data collection and coding, we were unable to discriminate those reported by the operator from those reported at the time of angiographic review. Complications are divided into procedural or access site related complications. Due to the way in which our data was collected, on a bespoke database, we were unable to elucidate whether the reported coronary dissections were edge dissections post-stenting and whether these resulted in unplanned additional stenting. In addition there was lack of information concerning the angiographic grades of dissection being reported.

There may be significant inaccuracy with respect to the outcomes employed to analyse the bifurcation dataset. Given that all cause death makes up three quarters of the MACCE, age may be considered a confounder as patients treated with a two stent strategy were significantly older than those treated with a single stent strategy. However, older patients treated with a single stent have been shown to do better than a younger patients treated with a two stent approach, where MACE was driven by TLR [115]. While we report MACCE, including death, MI, repeat revascularisation and stroke, we did not report on TLR due to a lack of lesion-level outcome data. TLR in the stented left main bifurcation is reported in up

to a fifth of patients over long term follow-up [127]. So, while it is considered an important determinant of outcomes, restenosis can be asymptomatic and is often diagnosed after routine angiographic follow-up [190]. Only a small number of our patients suffered repeat revascularisation, while MACCE was mainly driven by death. In this older cohort it could be suggested that a lack of access to revascularisation procedures may have led to an underreporting of TLR [207]. The choice of composite outcomes may therefore lack specificity, due to the lack of reported TLR. This could indicate a certain amount of inaccuracy in the outcome data. The inaccuracy relates to the clinical follow-up, as the data was collected retrospectively and a proportion of the patients were followed up at district hospitals. However, every effort was made, to ameliorate this by confirming patient reported events with information gathered from each hospital using PAS and GP summary care records.

Furthermore, the lack of specificity in the outcome data may be related to selection bias, e.g. measuring all cause death in older patients doesn't examine the long term treatment effect of revascularisation. There are two solutions to this problem, while the outcomes may be less specific by including more variables in the regression model, in particular unmeasured confounders, for example a frailty and dementia. The most glaring omission is the missing LV function. Due to the nature of this retrospective sample, we are unable to include these variables in our model. While for this older cohort, we used cardiac death in our composite end-points, which we argue would improve the disease-specific outcome measures. Unmeasured confounders could be addressed by constructing a prospective registry including known predictors of death in the elderly. This would be essential, given the context of current guidelines for LMCA PCI, it seems probable that any future prospective registry would continue to recruit a predominantly long-lived population.

While, we found 'True' LMCA bifurcation disease was associated with greater MACCE, this may reflect considerable confounding from the total burden of atheroma, we found significant collinearity with the SS. While we demonstrated equal survival from two and single stent strategies for LMCA bifurcation PCI, this was unadjusted survival. In the analysis

of ‘True’ bifurcation disease, patients treated with a single stent had a significantly greater median SS compared with patients in the two stent group. The greater SS is mainly accounted for by the associated coronary vessel disease, LM+2VD and LM+3VD, where half of patients in the single stent group had associated coronary disease as opposed to only a third of those in the two stent group. In contemporary registries up to 80% of patients with LMCA bifurcation disease are reported to have LM+2VD and LM+3VD [112, 113]. Other studies have failed to account for this confounding when demonstrating worse outcomes from a two stent strategy compared to a single stent, despite significantly more mulitvessel disease in the two stent group [112].

Patients with a greater SYNTAX score generally do worse [55]. The higher SYNTAX score for patients with ‘True’ bifurcation disease in our study is not accounted for alone by the burden of atheroma around the LMCA bifurcation. A ‘True’ left main bifurcation stenosis contributes only 2 points to the SYNTAX score when compared with a 'Non-true' lesion [35, 299]. When treatment groups are matched for SS, outcomes seem to be comparable; however these patients have SS in the low-intermediate tertile range compared to the high median SS in our study population [114]. After adjustment, SS was not an independent predictor of poor outcomes, yet there may be significant confounding from the coronary disease burden. Future studies examining the PCI strategy for distal LMCA disease should be designed to reduce the confounding created by this associated multivessel disease. Indeed the EBC MAIN study excludes patients with a SS of greater than 32 [106]. However, bearing in mind that we treated significantly older patients with more extensive coronary disease, the data from this study should be applied cautiously to the ‘real world’ patient cohorts.

Prospective trials, such as the BBC ONE and Nordic trials, include clear study treatment protocols which allow the identification of treatment crossover due to an unsuccessful stent strategy [83]. In this respect, while our retrospective study reports equal outcomes from a two stent vs single stent treatment for the LMCA, for those patients treated with ‘T-stent’/’Culotte’/’TAP’ strategies, there may have been considerable crossover from a provisional single stent to a T-stent strategy. In the EBC II trial the crossover was up to 16% [110]. Other confounders of an ‘intention-to-treat’ analysis would include the lack of QCA

data to confirm the size of the SB, while the viability of the subtended myocardial bed was unknown for a number of patients.

While our data support the notion that a single or two-stent strategy is acceptable for the treatment of 'True' LMCA bifurcation disease, given the lack of lesion-level outcomes, including TLR, this is hypothesis generating rather than conclusive. As this was a retrospective study we were unable to determine the revascularisation strategy on a per-patient level. This creates significant confounding when considering the reasons for failure to achieve complete revascularisation in our patients. While the elderly patients are at greater risk of selective revascularisation [171], our data lacks functional lesion assessment. While the rSS is an anatomical assessment of untreated coronary disease and does not necessarily imply functionally incomplete revascularisation Clinicians are more inclined to demonstrate lesion ischaemia, using fractional flow reserve (FFR), to assess appropriate revascularisation in multivessel disease [352, 353]. Functional lesion classification could change the SS for up to a third of patients and thus lead to a change in management decisions, from CABG to PCI and vice versa [354]. While this would result in a change in SS and rSS, no study has demonstrated an advantage of functional complete revascularisation over anatomical complete revascularisation in multivessel disease [355]. Indeed, while we await the results of the SYNTAX II and FAME 3 studies which will assess the FFR guided revascularisation of multivessel disease, these studies will not include patients with left main disease [356, 357]. Similarly, as information on myocardial viability was unavailable we are unable to exclude the possibility that stenoses in vessels subtending non-viable myocardial segments may have been appropriately left untreated. Chronic total occlusions were present in 15.0% of all octogenarians, while these significantly contribute to the SS and rSS, it is not certain if these lesions would have met the criteria for revascularisation with PCI due to a lack of data on viability and ischaemia assessments.

More so amongst elderly patients, selection bias may play a huge impact on outcomes from observational studies of revascularisation [206]. The elderly patients who eventually have revascularisation represent those most likely to benefit from the procedure. Indeed, there

are also a number of unmeasured confounders which were not accounted for in our analysis, such as dementia and frailty.

Overall the study size is small and thus with a modest number of MACCE events, it could be argued that we are unable to draw conclusions due to an underpowered study. Furthermore, while this is a long lived sample in which death predominates the MACCE, the associations could be considered confounded while they may even be inaccurate for the analysis of LMCA revascularisation.

7.2 Prospective Quality of life study

Recent analysis of LMCA revascularisation has revealed that TVR is the main discriminator between PCI and CABG. Yet it is suggested that the lesser impact of TVR events on quality of life compared with other MACCE events would result in equipoise [481]. It seems reasonable therefore to assume that these effects can be measured through quality of life assessments.

Physician-oriented measures of revascularisation include traditional outcomes, such as MACCE and mortality, describe the natural history of the pathophysiological processes as well as treatment effects [180]. These outcome measures inform treatment decisions of perceived prognostic benefit [69, 299]. Mortality correlates well with prognostic improvement; however the composite outcome, MACCE, does not. Due to binary censorship of MACCE, one may ascribe a minor MI as an equal outcome to a disabling stroke. In this way, for the treatment of LMCA disease, while PCI may be considered non-inferior to CABG on the basis of mortality [59, 60], for more extensive coronary disease, PCI is considered inferior to CABG on the basis of excess repeat revascularisations despite a higher risk of stroke with CABG [47, 215]. Of note, there is only one recently published study which found a greater risk of stroke with PCI compared to CABG for the treatment of LMCA disease [60]. These outcome measures inform the risk-benefit analysis for each patient when deciding between either PCI or CABG [47, 229]. In the case of high risk patients, where

revascularisation may offer no prognostic benefit, these outcome measures do not inform us of symptomatic benefit to the patient.

Increasing proportions of patients are having PCI rather than CABG for coronary disease [360], including those considered high surgical risk, such as the elderly [360, 361] and others with more complex coronary disease [362], such as LMCA disease [2]. Revascularisation decisions are therefore not solely based on improving traditional outcome measures, such as mortality, but rather symptomatic improvement. There is a need for data which informs this management approach.

Patient-oriented outcome measure or quality of life outcome measures may nuance the risk-benefit analysis. Quality of life outcomes amongst patients with coronary disease are predictive of poor outcomes, such as death [363, 364], repeat revascularisation [365, 366] and hospitalisation [367]. Poor quality of life outcomes within the first year predicts mortality up to a decade following revascularisation [368], including the long lived [369-371]. Several studies have compared quality of life outcomes in patients treated with coronary revascularisation using PCI or CABG [372-385], however the results are conflicting with some reporting no difference [377, 383, 386, 387], while other studies report greater benefit from CABG [376, 380-385, 388]. While these observational studies compare patients with varying degrees of severity of coronary disease only the SYNTAX trial and EXCEL trial compared large cohorts with LMCA disease [388, 391].

While it is known that CABG improves angina compared to medical management in patients with LMCA disease [389], the data from this study may be considered outdated given the changes that have occurred in treatments offered. A previous study comparing QOL outcomes from CABG or PCI in patients with LMCA disease failed to assess the known longitudinal changes in QOL by using only a single time point measure [390]. HRQOL outcomes in patients with LMCA disease has never been described over a 1 year longitudinal study in patients with left main coronary artery disease comparing patients who

are medically managed to those undergoing revascularisation with CABG or PCI [377, 388, 390, 391]. While other studies are designed to investigate prognostic outcomes in patients considered appropriate for prognostic improvement, our study will include those revascularised as well as those conservatively managed.

7.2.1 Principal findings

We undertook the analysis of the first 103 patients were recruited into the prospective Leeds left main stem registry, they had all completed 1 year clinical follow-up in May 2015. Whilst the aim was to follow-up all patients for 1 year completing 4 time point HRQOL questionnaires, we achieved a completion rate of 45% for all time points. The conventional general linear model therefore included data from only 45 patients and indicated serial improvements in quality of life from baseline up to 6 months, maintained up to 1 year, for the revascularisation treatment groups. The medically managed cohort did not show an improvement in quality of life scores over the course of 1 year. Independent predictors of poor quality of life at 1 year were a history of cardiac surgery, previous CVA and presentation with a STEMI, while predictors of good quality of life at 1 year included elective procedures, previous MI, good baseline quality of life scores and CABG. The best fitting linear growth model, 98 patients were included, indicated that quality of life improves significantly with time from baseline in patients treated with CABG. PCI was not identified as a predictor of improvement in QOL when compared with CABG. Recent MI, within 90 days, was identified as a significant predictor of improvement in QOL over 1 year.

For HRQOL domain scores, derived from MacNEW questionnaire, the overall cohort showed improvement in emotional, physical and social domain scores. Both revascularisation groups showed an increase in emotional and social domain scores, while medically managed patients did not experience an increase over 1 year. All treatment groups showed an increase in the physical domain scores.

Over 1 year follow-up there was a total of 6 acute coronary syndromes, 3 patients required further revascularisation. The 1 year mortality rate for the entire cohort was 5.8%, including 3 deaths within the medically managed group, 2 patients treated with PCI and 1 patient who

had CABG. MACCE identified as a predictor variable in the best fitting growth model for global mean MacNew scores.

Follow-up continued for the entire cohort until completion of all 1 year questionnaires for all patients, the median follow-up was 502 (286) days (table 6.9). MACCE recorded for this period include 1 further ACS within the PCI patient cohort, 1 patient treated with PCI initially suffered a repeat revascularisation, while 1 patient failed medically management and converted to a revascularisation strategy. There was 1 additional CVA within the CABG managed group and no further deaths were recorded.

In summary, while there is no significant difference in HRQOL outcomes between CABG and PCI for LMCA revascularisation, there was a trend for a quantitatively larger improvement in QOL with CABG than with PCI. PCI however achieves an earlier improvement in QOL than CABG. Medical management showed no improvement in HRQOL outcomes.

7.2.2 Context of findings

These are the first published data on repeated measures quality of life data for patients with LMCA disease which includes medically managed patients as a comparator [388, 390, 391]. The SYNTAX study compared QOL outcomes in patients with multivessel disease treated with PCI or CABG using the linear growth model; however only 39.2% of study patients had LMCA disease and they did not include a medically managed cohort [377]. We did not show a significant difference in HRQOL outcomes between PCI and CABG, which is consistent with other studies comparing HRQOL outcomes for CABG and PCI used to revascularise LMCA disease [388, 390]. However, as we used the linear growth model, as opposed to a single time-point measure, we found there was a non-significant trend for better outcomes from CABG over 1 year follow-up.

7.2.3 Strengths

Published data indicate that mixed model analysis using the linear growth models provides a better fitting model due: (a) to the inclusion of a larger number of cases, where missing data are estimated with maximum likelihood, and (b) by allowing the construction of a growth curve using data collected at unequal time points [416, 425]. These are the first published data on repeated measures quality of life data for patients with LMCA disease which include medically managed patients as a comparator [388, 390, 391].

While the study design allows us to assess outcomes in medically managed patients, if this study were suitably powered we could assess if medically managed patients could benefit from limited low risk revascularisation with PCI.

7.2.4 Limitations

This is not a randomised cohort, so outcomes may not be comparative between the three treatment groups. In this way there is probable confounding of the QOL outcomes. This exists due to the study design and limitations which exist in the inherent inclusion of a medically managed group. Nevertheless, while we cannot draw conclusions from the sample due to the size of the sample we can accept that the medically managed group, however small, did not have any improvement in QOL outcomes whatever the severity of their disease. So the confounding of disease severity will mainly affect our comparison of CABG and PCI samples.

The most obvious and glaring limitation in this study was the omission of an angina score. While other studies have reported angina scores, we did not measure this. However, while angina is a principle symptom of patients with coronary disease, due to placebo effect associated with coronary revascularisation [359], it may be beneficial to use a cumulative muti-modal measure of symptom improvement such as the MacNew. Nevertheless, future studies should always include an angina score in addition to other validated QOL scores,

while recent studies suggest an objective measure of exercise tolerance may also be required [359].

While the placebo effect may over-estimate the benefit from revascularisation, in a similar way medically managed patients, who may be aware of the severity of their condition, may interpret their HRQOL as being worse off, due to the awareness of a 'lack of treatment'. This is acknowledged as the mechanism in the way patients education may alter HRQOL outcomes [482]. This could be reflected in BIP consequence scores, however this was not included in the best fitting final model and medically managed patients seemed to have an observable improvement in BIP consequence over time.

Due to slow recruitment of the medically managed cohort, we cannot draw conclusions from the analysis of this sample. The principle reason for poor recruitment was down to where patients received their ultimate management. While stable and semi-urgent patients for revascularisation would be referred to the recruiting centre, medically managed patients would be managed in the periphery soon after diagnosis. In order to overcome this issue we designed the study with the capability of multicentre recruitment. However, due to poor regional uptake, in part due to the lack of a study co-ordinator for a large duration of the study, we did not have any uptake from other centres. Another reason for the poor recruitment of medically managed patients was the poor utilisation of clinicians of the 'heart team'. Indeed the MDT at the LGI was probably under-utilised for the purposes of decision making for patients with LMCA disease despite the recommendations by the ESC [299].

7.3 Study implications

Prognostic outcomes are similar from PCI or CABG for LMCA disease for patients with intermediate severity of coronary disease [59, 60, 215]. In these patients HRQOL outcomes may be an important factor in deciding between the two strategies as this will inform not only physicians but patients during the decision-making process [426]. Serial global and sub-domain QOL scores improve over 1 year for both revascularisation groups but not for medically managed patients, while CABG and not PCI is a predictor of significantly improved QOL outcomes. Furthermore, we found no improvement in HRQOL scores for those who had medical management, which is consistent with previous studies [389]. This study informs the risk benefit analysis, while revascularisation may not be considered appropriate on prognostic grounds, for these patients who would normally be considered for conservative management, it may be reasonable to consider a limited or targeted revascularisation strategy to improve QOL [426].

7.4 Future considerations

While selection bias is unavoidable for an all-comer registry type of study, by dividing the patients into subgroups, e.g. excluding cardiogenic shocked patients; it is possible to explore some research questions. A prospective registry may include exclusion and inclusion criteria, which would allow more conclusive outcomes research. Yet, given the context of current guidelines for LMCA PCI [299], it seems probable that any future prospective LMCA PCI registry would continue to recruit a predominantly long-lived population. So while exclusion criteria would usually provide a study population which allows the analysis of long term outcomes the nature of this population would continue to limit the applicability of the data.

Current data suggest patients with limited atheromatous burden have equal outcomes from PCI and CABG for LMCA revascularisation. While recent randomised trials have sought to examine these restricted population samples [60], for the majority of patients treated with LMCA PCI in the UK, CABG may not be an option [154]. Due to comorbidity these patients

would not usually be included in randomised trials, however no study thus far has examined outcomes from this high surgical risk patient cohort who suffer from extensive atheroma.

While the current study design limits the exploration of a causative model for all known predictors of poor QOL, ongoing recruitment would allow a meaningful insight into the medically managed cohort which has hitherto not been studied in published data. This would allow the study of interventions which could improve patient illness beliefs which we have demonstrated are correlated with QOL outcomes.

7.5 Thesis conclusions

For patients who may be considered high surgical risk, this study indicates that the burden of coronary disease is associated with poor outcomes, even amongst a long-lived sample. While there appears to be an association with residual coronary disease and poor outcomes for octogenarians, we cannot predict the benefit from more complete revascularisation to this population. 'True' left main bifurcation disease is associated with poor outcomes, yet there is no obvious benefit from a two strategy, however this conclusion is significantly biased by the lack of 'intention-to-treat' analysis.

Patients managed conservatively for LMCA disease have no improvement in HRQOL scores over 1 year follow-up. While patients who have received any revascularisation had improvement in HRQOL scores, only CABG was included in the final model as a predictor of improvement in HRQOL scores over 1 year.

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Appendices

Appendix 1: Patient information sheet

Version 1.6 23 16/12/2013 Leeds Central REC number 12/YH/0484

The Leeds Teaching Hospitals NHS
NHS Trust

Left Main Stem Study

Patient Information Sheet

Title: **Prospective study of outcomes following revascularisation for left main stem coronary artery disease**

We would like to invite you to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 5 minutes. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 of the information sheet

What is the purpose of the study?

The main artery to the heart is called the left main stem, and this artery can be affected by cholesterol plaque narrowing. The two main treatment options for this condition are surgery and the insertion of stents. We are undertaking this study to see if we can determine which option provides the best and safest treatment for the patient.

Why have I been invited?

You have been invited to take part because you have a narrowing in the left main stem artery which may require treatment.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive, the decision about which treatment option you would receive will not be affected.

1

The Leeds Teaching Hospitals NHS
NHS Trust

What will happen to me if I take part?

We will look through your medical records and identify data that may include results from routine tests and personal information from hospital appointments. We will follow up this data for up to 20 years. We will register your data with the Office of National Statistics so that we can track your progress over the study time period.

If you presented as an emergency, the decision about the best treatment will be made by your treating physician. If you have already received treatment (either a stent or surgery) we would still like to include you in our study as we would like to follow-up all patients with this condition.

If you are not referred as an emergency, the physician looking after you has referred you for a review in a multi-disciplinary (MDT) meeting involving cardiologists and surgeons. At the MDT we discuss the options of treatment which would include, either placing a stent in the artery or surgery to bypass the narrowing or in some cases just medical treatment.

Some patients are deemed only suitable for surgery and others only suitable for stents. However there are patients who could have both treatment options. These patients will have the opportunity of discussing these options in a clinic or on the ward with the surgeon and cardiologist who will perform the relevant treatments.

If you have a stent fitted you will return for this as a day procedure. Subsequent clinic follow up will be arranged at the discretion of your physician. If required a repeat day case angiogram in about 6 months to 1 year may be performed to ensure the stent is still working.

If you have surgery, this will be arranged for you. Further follow up will be arranged at the discretion of your physician.

You will be given questionnaires to complete relating to your care and monitoring your progress. These will be given to you at these time points: prior to your scheduled procedure and then posted to you at 1 month, 6 months and then 1 year after the procedure.

A member of the research team will contact you **by telephone/letter/e-mail at 6 months and then yearly for up to 10 years, in order to determine the status of your health.** You can choose how you would prefer to be followed up **if you prefer** (by letter, online, or by telephone). Your data will be identifiable to us.

You will not need to attend the hospital any more (or less) frequently than would normally be requested by your specialist.

We will store your contact details on a secure database. This is so that we can contact you to see if you would like to participate in future research studies.

The data that we collect on you may be enhanced through linkage with other clinical and administrative databases.

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Expenses and payments

There are no expenses available for this study.

What will I have to do?

You will need to sign the consent form. You will be asked to choose your preferred method of questionnaire follow-up which will occur at 1 month, 6months and 1 year after the procedure, either sent to you in the post, provided online, or telephone.

What is the drug, device or procedure that is being tested?

We are looking at whether a different approach, by implementing international guidelines, relating to planning treatment for patients improves outcomes. Specifically, the way we decide on treatment, by increasing patient involvement through a multi-disciplinary clinic with the cardiologist and surgeons in attendance. Your participation in the study will not affect the decision about your treatment as all cases will be decided upon in this way.

What are the possible disadvantages and risks of taking part?

There is no risk to your health from this study as it is an observational study looking at recognised treatment strategies for narrowing in the heart arteries. The data that we collect will be stored securely on our computers.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with a left main stem artery narrowing in the future.

What happens when the research study stops?

Your access to healthcare and the treatment you receive will be no different during or after the study.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes part I. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2 of the information sheet

What will happen if I don't want to carry on with the study?

You can withdraw from the study if you wish, but we will need to use the data collected up to your withdrawal.

What if there is a problem?

Complaints and harm

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

NHS based research

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

Any personal data that is stored on anything other than the research database will be linked anonymised and will not contain any primary identifiers. Only those in the research team, employed by the cardiovascular research department working within the Leeds TH trusts data protection policies, will have access to the data. Your data will be managed within the confines of the trusts policies. We will forward identifiable data to the Office of National Statistics.

What will happen to any samples I give?

The samples that you give will have been requested by your specialist as part of your standard care. We will have access to results from previous samples that have been taken as part of your routine care. Data from blood tests and heart scans are normally stored on computers and will we access these computers to look at your results. Samples will not be transferred outside the UK.

Involvement of the General Practitioner

We will inform your General Practitioner of your participation in this study, if you consent to this.

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NHS Trust

What will happen to the results of the research study?

The results of the study will be presented at local and international cardiology meetings, and published in medical journals. The results will also be made available to local Cardiologists and to Nurses who routinely work with patients with artery narrowing's in the heart. You will not be identified in any report/publication.

Who is organising and funding the research?

There are a number of funders of this research including:

1) The Take Heart charity

2) Abbott Vascular Ltd.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Yorkshire and Humber Research Ethics Committee.

Further information and contact details

If you require further information about the study, then please contact Professor UM Sivananthan, Leeds General Infirmary, LS1 3EX, telephone number 0113 3925735. Alternatively, Research Nurse Rebecca Dickinson, Cardiology Research, Leeds General Infirmary, LS1 3EX, telephone number 0113 3925393.

Appendix 2: Consent form

The Leeds Teaching Hospitals NHS
NHS Trust

REC number: 12/YH/0484
Centre Number: LGI
Study Number: 1
Patient study ID: _____

Chief investigator:
Prof. UM Sivananthan
University of Leeds
Version 1.2; 04 November 2013

CONSENT FORM

Title of Project: Left Main Stem Revascularisation Study
Prospective study of outcomes following revascularisation of the left main stem coronary artery

Name of Researcher: Dr C Maart

Please initial box

1. I confirm that I have read and understand the information sheet (Version 1.5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that my details will be registered with the Office of National Statistics ☐
5. I understand that information held by the NHS and records maintained by the NHS Information Centre, the NHS Central Register and by my General Practitioner may be used to help contact me and provide information about my health status. I give permission for this information to be obtained from the NHS Information Centre, the NHS Central Register and/or my GP if necessary. ☐
6. I understand that my clinical data may be linked with other clinical or administrative databases. ☐
7. I understand that my data may be used in future research studies and that appropriate researchers from other research and academic groups may have access to my data after my personal details have been ☐

removed, upon application and at the discretion of the Chief Investigator.

8. I understand that my GP will be informed of my participation in this study and that you may contact my GP, if required, to confirm any medical data relevant to the study. ☐

9. I consent to having my name and contact details stored so that I may be contacted in the future regarding other research projects ☐

10. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 to be kept in medical notes

Appendix 3: Health related quality of life questionnaires

LMS Study REC: 12/YH/0484

Patient ID:

The Leeds Teaching Hospitals NHS
NHS Trust

Rebecca Maindonald
Cardiology Research Nurse
G Floor, Jubilee Wing
Leeds General Infirmary
Leeds, LS1 3EX

Tel: 0113 392 5393
Fax: 0113 392 8611

Patient Name & Address
Automatically Imported from
Database

Dear Mr./Mrs. Patient,

Prospective study of outcomes following left main coronary artery revascularisation

Please find enclosed the first/second/third questionnaire for you to complete and return to me in the envelope provided.

We have sent you the following questionnaires to help us to understand more about the way you think about your quality of life and your heart health. There are no right or wrong answers as the information we seek is about your own personal view. Please could you be kind enough to complete all of the questions and return it to us in the enclosed stamped addressed envelope. We really appreciate your help and time. Feel free to call me if you have any questions.

Yours Sincerely,

RMcM

Rebecca Maindonald
Cardiology Research Nurse

macnew.org
HEALTH-RELATED QUALITY OF LIFE INSTRUMENT

Patient ID:

We would now like to ask you some questions about how you have been feeling DURING THE LAST 2 WEEKS

1. In general, how much of the time during the last 2 weeks have you felt frustrated, impatient or angry?
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ A good bit of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ Hardly any of the time
   - ☐ None of the time

2. How often during the last 2 weeks have you felt worthless or inadequate?
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ A good bit of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ Hardly any of the time
   - ☐ None of the time

3. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your heart problem?
   - ☐ None of the time
   - ☐ A little of the time
   - ☐ Some of the time
   - ☐ A good bit of the time
   - ☐ Most of the time
   - ☐ Almost all of the time
   - ☐ All of the time

4. In general, how much of the time did you feel discouraged or down in the dumps during the last 2 weeks?
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ A good bit of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ Hardly any of the time
   - ☐ None of the time

5. How much of the time during the past 2 weeks did you feel relaxed and free of tension?
   - ☐ None of the time
   - ☐ A little of the time
   - ☐ Some of the time
   - ☐ A good bit of the time
   - ☐ Most of the time

- ☐ Almost all of the time
- ☐ All of the time

6. How often during the last 2 weeks have you felt worn out or low in energy?
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ A good bit of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ Hardly any of the time
   - ☐ None of the time

7. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks?
   - ☐ Very dissatisfied, unhappy most of the time
   - ☐ Generally dissatisfied, unhappy
   - ☐ Somewhat dissatisfied, unhappy
   - ☐ Generally satisfied, pleased
   - ☐ Happy most of the time
   - ☐ Very happy most of the time
   - ☐ Extremely happy, could not have been more satisfied or pleased

8. In general, how often during the last 2 weeks have you felt restless, or as if you were having difficulty trying to calm down?
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ A good bit of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ Hardly any of the time
   - ☐ None of the time

9. How much shortness of breath have you experienced during the last 2 weeks while doing your day-to-day physical activities?
   - ☐ Extreme shortness of breath
   - ☐ Very short of breath
   - ☐ Quite a bit of shortness of breath
   - ☐ Moderate shortness of breath
   - ☐ Some shortness of breath
   - ☐ A little shortness of breath
   - ☐ No shortness of breath

10. How often during the last 2 weeks have you felt tearful or like crying?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

11. How often during the last 2 weeks have you felt as if you are more dependent than you were before your heart problem?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

12. How often during the last 2 weeks have you felt you were unable to do your usual social activities or social activities with your family?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

13. How often during the last 2 weeks have you felt as if others no longer have the same confidence in you as they did before your heart problem?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

14. How often during the last 2 weeks have you experienced chest pain while doing your day-to-day activities?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

15. How often during the last 2 weeks have you felt unsure of yourself or lacking in self-confidence?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

16. How often during the last 2 weeks have you been bothered by aching or tired legs?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

17. During the last 2 weeks, how much have you been limited in doing sports or exercise as a results of your heart problem?
- ☐ Extremely limited
- ☐ Very limited
- ☐ Limited quite a bit
- ☐ Moderately limited
- ☐ Somewhat limited
- ☐ Limited a little
- ☐ Not limited at all

18. How often during the last 2 weeks have you felt apprehensive or frightened?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

19. How often during the last 2 weeks have you felt dizzy or lightheaded?
- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

20. In general, during the last 2 weeks how much have you been restricted or limited as a result of your heart problem?
- ☐ Extremely limited
- ☐ Very limited
- ☐ Limited quite a bit
- ☐ Moderately limited
- ☐ Somewhat limited
- ☐ Limited a little
- ☐ Not limited at all

21. How often during the last 2 weeks have you felt unsure as to how much exercise or physical activity you should be doing?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

22. How often during the last 2 weeks have you felt as if your family is being over-protective toward you?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

23. How often during the past 2 weeks have you felt as if you were a burden on others?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

24. How often during the past 2 weeks have you felt excluded from doing things with other people because of your heart problem?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

25. How often during the past 2 weeks have you felt unable to socialize because of your heart problem?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time

26. In general, during the last 2 weeks how much have you been physically restricted or limited as a result of your heart problem?
    - ☐ Extremely limited
    - ☐ Very limited
    - ☐ Limited quite a bit
    - ☐ Moderately limited
    - ☐ Somewhat limited
    - ☐ Limited a little
    - ☐ Not limited at all

27. How often during the last 2 weeks have you felt your heart problem limited or interfered with sexual intercourse?
    - ☐ All of the time
    - ☐ Most of the time
    - ☐ A good bit of the time
    - ☐ Some of the time
    - ☐ A little of the time
    - ☐ Hardly any of the time
    - ☐ None of the time
    - ☐ Not applicable

The questionnaire continues on the following page...

Patient ID:

The Brief Illness Perception Questionnaire

For the following questions, please write an 'X' under the number that best corresponds to your views about your heart health

28. How much does your illness affect your life?

No affect at all	0	1	2	3	4	5	6	7	8	9	10	Severely affects my life
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

29. How long do you think your illness will continue?

A very short time	0	1	2	3	4	5	6	7	8	9	10	Forever
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

30. How much control do you have over your illness?

Absolutely no control	0	1	2	3	4	5	6	7	8	9	10	Extreme amount of control
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

31. How much do you think your treatment can help your illness?

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely helpful
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

32. How much do you experience symptoms from your illness?

No symptoms at all	0	1	2	3	4	5	6	7	8	9	10	Many severe symptoms
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

33. How concerned are you about your illness?

Not at all concerned	0	1	2	3	4	5	6	7	8	9	10	Extremely concerned
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Patient ID:

34. How well do you feel you understand your illness?

Don't understand at all	0	1	2	3	4	5	6	7	8	9	10	Understand very clearly
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

35. How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

Not at all affected emotionally	0	1	2	3	4	5	6	7	8	9	10	Extremely affected emotionally
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

36. Please list in rank-order the three most important factors that you believe caused your illness.

The most important causes for me:-

1. _____
2. _____
3. _____

This completes the end of the questionnaire. Please return your completed questionnaire in the envelope provided. Thank you very much for your time.

Appendix 4: West Yorkshire Cardiac Patient and Public Involvement Group consultation

NHS National Institute for Health Research
The NIHR Research Design Service for Yorkshire & the Humber

NHS England
Yorkshire and the Humber
Strategic Clinical Networks

MACE Weighting for the Left Main Stem Study
Dr. Clint Maart

Presented to the West Yorkshire Cardiac Patient and Public Involvement Group 6th September 2013

Dear Dr. Maart-

Thank you for your recent presentation to the group about weighting the importance of MACE events in the follow up and analysis of the Left Main Stem outcomes study.

The feedback from the group is summarised below:

- We feel that quality of life is the single most important indicator for patients who are still alive
- The group feels a distinction should be made in acute vs. elective patients as patients who are fit have more to lose and patients who are poorly have more to gain.
- The majority of the patients feel stroke should be weighted more heavily than MI or revascularisation.
- Members of the group who have personally experienced ACS feel that revascularisation is a somewhat expected outcome from stenting procedures.
- The severity of each MACE event is also important i.e. a simple TIA or stroke from which the patient completely recovers should be less serious than an MI which then requires bypass surgery.

The group would be happy to advise on further work with this matter.

NHS Chair
Dr. Chris Gale

Appendix 5: Ethics approvals

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds Central
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050127
Facsimile: 0113 8556191

30 November 2012

Dr Clint Maart
Cardiology Research Fellow
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Dear Dr Maart

Study title: **Prospective study of outcomes following left main coronary artery revascularisation**
REC reference: **12/YH/0484**

Thank you for your email received on 30 November 2012. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 14 November 2012

Documents received

The documents received were as follows:

Document	*Version*	*Date*
GP/Consultant Information Sheets	1.1	01 November 2012
Participant Information Sheet	1.4	23 November 2012

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering Letter		05 October 2012
GP/Consultant Information Sheets	1.1	01 November 2012

Investigator CV	Professor Mohan U Sivananthan	31 August 2012
Letter of invitation to participant		
Other: Clint Anthony Maart CV		28 September 2012
Participant Consent Form	1.1	01 November 2012
Participant Information Sheet	1.4	23 November 2012
Protocol	1.4	25 September 2012
Questionnaire: Picker Patient Experience Questionnaire (PPE-15)	1.0	05 October 2012
Questionnaire: Health Survey (SF-36)	1.0	05 October 2012
Questionnaire: The Brief Illness Perception Questionnaire	1.0	05 October 2012
REC application		
Referees or other scientific critique report		
Response to Request for Further Information		01 November 2012
Summary/Synopsis	Study Flow Diagram v1.0	05 October 2012

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

12/YH/0484 **Please quote this number on all correspondence**

Yours sincerely

Mrs Nicola Mallender-Ward
Committee Co-ordinator

E-mail: nrescommittee.yorkandhumber-humberbridge@nhs.net

Copy to: *Professor U.M. Sivananthan, Leeds Teaching Hospitals*
Mrs Anne Gowing, Leeds Teaching Hospitals NHS Trust