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Research paper

## Impact of Non-obstructive left main disease on the progression of coronary artery disease: A PARADIGM substudy

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## ABSTRACT

**Background:** The aim of the study is examine the impact of non-obstructive (< 50%stenosis) left main (LM) disease on the natural history of coronary artery disease using serial coronary computed tomography angiography (CTA).

**Methods:** CTAs from the PARADIGM (Progression of atherosclerotic plaque determined by computed tomographic angiography imaging) study, a prospective multinational registry of patients who underwent serial CTA at a  $\geq 2$  year interval were analyzed. Those without evidence of CAD on their baseline scan were excluded, as were those with obstructive left main disease. Coronary artery vessels and their branches underwent quantification of: plaque volume and composition; diameter stenosis; presence of high-risk plaque.

**Results:** Of 944 ( $62 \pm 9$  years, 60% male) who had evidence of CAD at baseline, 444 (47%) had LM disease. Those with LM disease had a higher baseline plaque volume ( $194.8 \pm 221\text{mm}^3$  versus  $72.9 \pm 84.3\text{mm}^3$ ,  $p < 0.001$ ) and a higher prevalence of high-risk plaque (17.5% versus 13%,  $p < 0.001$ ) than those without LM

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disease. On multivariable general linear model, patients with LM disease had greater annual rates of progression of total ( $26.5 \pm 31.4\text{mm}^3/\text{yr}$  versus  $14.9 \pm 20.1\text{mm}^3/\text{yr}$ ,  $p < 0.001$ ) and calcified plaque volume ( $17 \pm 24\text{mm}^3/\text{yr}$  versus  $7 \pm 11\text{mm}^3/\text{yr}$ ,  $p < 0.001$ ), with no difference in fibrous, fibrofatty or necrotic core plaque components.

**Conclusion:** The presence of non-obstructive LM disease is associated with greater rates of plaque progression and a higher prevalence of high-risk plaque throughout the entire coronary artery tree compared to CAD without LM involvement. Our data suggests that non-obstructive LM disease may be a marker for an aggressive phenotype of CAD that may benefit from more intensive treatment strategies.

## 1. Introduction

Left main (LM) coronary artery disease (CAD) is associated with high morbidity and mortality owing to the large mass of myocardium subtended by this vessel.<sup>1-3</sup> Due to this high-risk profile both European and American guidelines recommend coronary-artery bypass grafting for those with obstructive LM disease.<sup>4,5</sup> Non-obstructive LM disease is also associated with significantly increased risk of major adverse cardiovascular events.<sup>6-8</sup>

Previous studies utilizing intravascular ultrasound (IVUS) have demonstrated that LM plaque volume and rate of progression is predictive of major adverse coronary events.<sup>9</sup> These studies have also shown that longitudinal changes in LM plaque are associated with traditional risk factors and receptive to targeted medical therapy of these.<sup>10,11</sup> Whilst providing insight into the nature of LM plaque and stenosis, these prior studies have restricted their examination to either just the LM, or to include the proximal left anterior descending (LAD) and/or left circumflex (LCx) vessels, and did not contain a control group of those without LM disease.

While LM plaque rupture has an extremely poor prognosis, non-fatal myocardial infarctions (MI) is also more common in LM disease unrelated to LM plaque rupture.<sup>6</sup> This greater cardiovascular risk associated with LM disease is independent of baseline plaque burden suggesting that this cannot be the only factor determining downstream risk.<sup>6</sup> The longitudinal impact of the presence of LM disease on plaque volume and progression rates in the context of the entirety of the coronary artery circulation is currently unknown.

The purpose of the current study is to determine the long-term effects of LM disease on coronary atherosclerosis, using quantitative metrics in patients who underwent serial coronary computer tomographic angiography (CTA). We hypothesize that the presence of LM disease will be associated with more severe and extensive CAD at baseline, a greater prevalence of high-risk plaque (HRP), and accelerated plaque progression.

## 2. Methods

### 2.1. Study design

The current study is a substudy of the PARADIGM (Progression of atherosclerotic plaque determined by computed tomographic angiography imaging) study. The design of the study has been described in detail previously,<sup>12</sup> but in brief it is a prospective international multi-site observational registry in which clinical, procedural, and follow-up data was collected on patients undergoing clinically indicated serial CTA. The study protocol was approved by the institutional review boards at all participating sites.

### 2.2. Study population

2252 patients at 13 sites in 7 countries were enrolled between 2003 and 2015. Those enrolled were consecutive patients with suspected or known CAD undergoing serial CTA at an inter-scan interval of  $\geq 2$  years. Inclusion and exclusion criteria of the PARADIGM study have been described in detail before.<sup>12</sup> As the current study was to examine

the effects of non-obstructive LM disease on progression of CAD those in whom coronary revascularization occurred prior to follow-up CTA were excluded from the study as were those with  $\geq 50\%$  stenosis within the LM on baseline CTA. Those without CAD at baseline were also excluded from the study so that the minimal segmental involvement score in both groups was 1.

### 2.3. Coronary computed tomography angiography

All CTAs were performed in accordance with Society of Cardiovascular Computed Tomography guidelines.<sup>13,14</sup> All datasets underwent blinded analysis at a single core laboratory. Coronary atherosclerosis evaluation by CTA was performed on multiplanar and cross-sectional images by Level III-experienced readers masked to clinical results using semi-automated plaque analysis software (QAn-gioCT Research Edition v2.1-9-1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction.<sup>15</sup>

Briefly, segments with a diameter  $\geq 2$  mm were evaluated using a modified 17-segment American Heart Association model for coronary segment classification.<sup>16</sup> For longitudinal comparisons of CTAs, coronary segments and lesions were co-registered between baseline and follow-up CTAs using anatomical landmarks such as distance from ostia or branch vessel takeoffs. Coronary segments not interpretable due to motion artifact were excluded from the analysis.

Quantitative atherosclerosis analysis of all coronary vessels  $\geq 2$  mm was performed at 1-mm cross-sectional intervals. Plaque volume (PV) and vessel volume (VV) of all coronary segments were obtained at baseline and follow-up CTAs, and then summated to generate total PV and VV on a per-patient and per vessel level. Change in plaque volume was calculated as annualized rate to account for the variability in time between baseline and follow-up CTA between participants.

Compositional analysis was performed of all atherosclerotic plaques, using Hounsfield units (HU) cutoff values of:  $-30$  to  $30$  HU for necrotic core;  $30$  to  $130$  HU for fibro-fatty plaque;  $131$  to  $350$  HU for fibrous plaque; and  $\geq 350$  HU for calcified plaque. These thresholds were determined based on prior validation studies compared against intravascular ultrasound.<sup>17,18</sup>

We evaluated atherosclerotic plaque features previously reported as being associated with incident major adverse cardiovascular events and ischemia, and which have been termed high-risk plaques (HRP).<sup>19,20</sup> HRP were defined as coronary lesions with  $\geq 2$  of the following features: positive remodeling (PR), low-attenuation plaque (LAP), napkin ring sign (NRS) or spotty calcification (SC).<sup>21</sup> LAP, previously correlated to necrotic core, was defined as any plaque containing  $\geq 1$  voxels with  $\leq 30$  HU.<sup>18,19</sup> SC was defined as presence of calcification  $< 3$  mm in any direction within a plaque.<sup>20,22</sup> PR was considered present when the maximal lesion vessel area divided by a reference cross sectional area 5-mm proximal to the beginning of the lesion was  $\geq 1.1$ . If a coronary lesion was present at the 5-mm cross-sectional mark, the reference cross sectional area was the 1-mm cross-section closest to this point without any atherosclerosis.

### 2.4. Study endpoints

The primary endpoint of the study was the difference in annualized

per-segment change in PV between CTA-1 and CTA-2 between patients with non-obstructive LM disease versus those with normal LM. Secondary endpoints included annualized change in PV by composition, prevalence of obstructive lesions and HRP at CTA-2.

### 2.5. Statistical analysis

Continuous variables are expressed as means  $\pm$  standard deviation (SD), and categorical variables are presented as absolute counts and percentages. Between group differences were analyzed using the chi-square test or Fisher's exact test for categorical variables, as appropriate, and those between continuous variables using Student's t-test. Changes between CTA-1 and CTA-2 in categorical variables were analyzed using McNemar's test, and those between continuous variables using a paired Student's t-test. For comparison of total plaque volume at baseline, a general linear model (GLM) was performed using plaque volume as the dependent variable, LM status as the fixed factor, and age, sex, hypertension, diabetes mellitus (DM), smoking history, body mass index (BMI), and statin therapy as covariates. For comparison of per patient annualized plaque progression rates, A general linear model (GLM) was performed using plaque progression rate as the dependent variable, LM status as the fixed factor, and age, sex, hypertension, diabetes mellitus (DM), smoking history, body mass index (BMI), and statin therapy as covariates. A second GLM was performed using all the variables from the first model, with the addition of the baseline plaque volume as an additional covariate, with the component plaque volume of interest used as the baseline plaque volume. For example, when fibrous plaque volume rate of progression was the independent variable of interest, the model would include the baseline fibrous plaque volume as a covariate. A p value  $< 0.05$  was considered to indicate a statistically significant difference. All analyses were performed with SPSS (version 22, IBM SPSS, NY).

### 2.6. Role of the funding source

This study was supported by grants from the Dalio Foundation, Michael Wolk Foundation and the Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (Grant No. 2012027176). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## 3. Results

### 3.1. Study population

Of the 2252 enrolled in the PARADIGM registry, 944 (60% male,  $61.6 \pm 9.0$  years old) were included in the final analysis (See CONSORT diagram – Fig. 1). Of these, 500 (62% male,  $62.7 \pm 8.8$  years old) had evidence of non-obstructive LM disease while 444 had CAD without evidence of LM disease (57% male,  $60.4 \pm 9.2$  years old). Those with LM disease were older ( $p < 0.001$ ), more likely to have history of hypertension (LM +ve = 298 (60%) vs. LM -ve = 232 (52%),  $p = 0.02$ ) or cerebrovascular accident (LM +ve = 35 (7%) vs. LM -ve = 15 (3%),  $p = 0.006$ ), and to have presented with typical angina at baseline (LM +ve = 23 (5%) vs. LM -ve = 10 (2%),  $p = 0.02$ ). The populations were otherwise matched for baseline characteristics (see Table 1).

### 3.2. Subject based plaque analysis

At baseline those with LM disease had a higher total plaque volume (LM +ve =  $194.8 \pm 221$  vs. LM -ve =  $72.9 \pm 84.3$  mm<sup>3</sup>,  $p < 0.001$ ), with higher volumes of all constituent plaque types (calcified, fibrous, fibrous fatty and necrotic,  $p < 0.001$  for all.) These differences persisted after correcting for baseline age, sex, hypertension, DM, BMI, smoking, and statin therapy ( $p < 0.001$  for all - see Table 2). At follow-up those with LM disease had a greater annualized plaque progression rate for total plaque volume (LM +ve =  $26.5 \pm 31.4$  vs. LM -ve =  $14.9 \pm 20.1$  mm<sup>3</sup>/yr,  $p < 0.001$ ). This was driven by a greater annualized plaque progression rate for calcified plaque volume (LM +ve =  $17.4 \pm 24.0$  vs. LM -ve =  $7.2 \pm 10.7$  mm<sup>3</sup>/yr,  $p < 0.001$ ), but with no difference in rate of progression of fibrous, fibrous fatty or necrotic core components ( $p > 0.1$  for all). These differences persisted after correcting for baseline age, sex, hypertension, DM, BMI, smoking, and statin therapy ( $p < 0.001$ ) and after further correcting for these factors in addition to baseline plaque volume ( $p = 0.002$ ).

### 3.3. Segmental analysis

These observations of more rapid progression of total plaque volume and calcified plaque volume were observed at a segmental level. Irrespective of vascular territory, there was more rapid calcified plaque

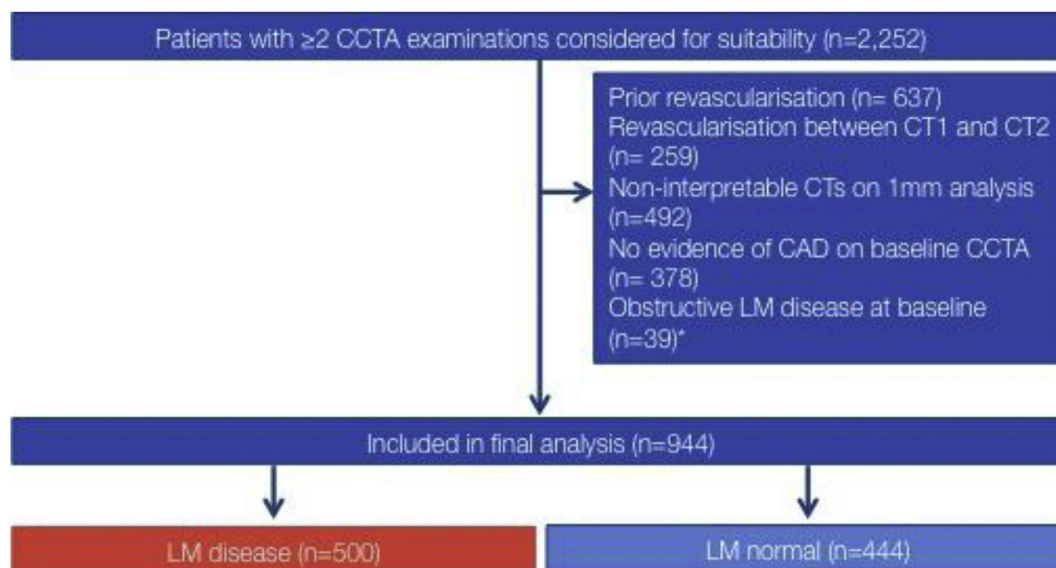


Fig. 1. CONSORT flow diagram of the PARADIGM study.

\*n add up to more than 1308 as participants can be excluded for more than one reason.

**Table 1**  
Baseline patient characteristics in the total population and by LM disease status.

	Total	LM -ve	LM +ve	p-value
N	944	444	500	
Age (years)	61.6 ± 9.0	60.4 ± 9.2	62.7 ± 8.8	< 0.001
Sex (male)	563 (60%)	255 (57%)	308 (62%)	0.19
BMI	25.4 ± 3.3	25.4 ± 3.4	25.5 ± 3.3	0.64
SBP	130 ± 17	130 ± 17	131 ± 17	0.26
DBP	78 ± 11	79 ± 11	78 ± 11	0.15
DM	221 (23%)	108 (24%)	113 (23%)	0.58
Hypertension	530 (56%)	232 (52%)	298 (60%)	0.02
Hyperlipidaemia	383 (41%)	173 (39%)	210 (42%)	0.29
Smoking Hx:				
Current	191 (20%)	96 (22%)	95 (19%)	0.35
Previous	187 (20%)	87 (20%)	100 (20%)	0.82
Never	510 (54%)	241 (54%)	269 (54%)	0.81
FHx CVD	268 (28%)	129 (29%)	139 (28%)	0.67
CAD	18 (2%)	9 (2%)	9 (2%)	0.80
CVA	50 (5%)	15 (3%)	35 (7%)	0.006
PAD	7 (0.7%)	2 (0.4%)	5 (1%)	0.29
HbA1c	6.37 ± 1.13	6.37 ± 1.18	6.38 ± 1.08	0.94
TC	188 ± 39	188 ± 37	189 ± 40	0.86
HDL	51 ± 14	51 ± 14	51 ± 14	0.86
TG	145 ± 87	145 ± 90	145 ± 85	0.99
LDL	114 ± 34	115 ± 34	114 ± 34	0.73
CRP	1.63 ± 4.75	1.33 ± 2.26	1.90 ± 6.19	0.29
Medications				
Aspirin	395 (43%)	175 (40%)	220 (45%)	0.14
Beta-blocker	256 (28%)	120 (28%)	136 (28%)	0.94
Calcium Channel blocker	227 (25%)	112 (26%)	115 (49%)	0.41
Diuretic	92 (10%)	43 (10%)	49 (10%)	0.96
Renin-angiotensin System inhibitor	294 (32%)	142 (33%)	152 (31%)	0.58
Statin Tx (baseline)	407 (46%)	179 (43%)	228 (48%)	0.12
Statin Tx (follow-up)	533 (62%)	243 (58%)	290 (65%)	0.07
Chest pain:				
Typical angina	33 (3%)	10 (2%)	23 (5%)	0.048
Atypical angina	662 (70%)	324 (73%)	338 (68%)	0.11
Non cardiac	93 (10%)	44 (10%)	49 (10%)	0.98
Interval between CT scans	3.7 ± 1.5	3.8 ± 1.5	3.7 ± 1.5	0.70

BMI – Body mass index; CAD – coronary artery disease; CRP – C-reactive protein; CVA – cerebrovascular accident; CVD – cardiovascular disease; DBP – Diastolic blood pressure; DM – Diabetes mellitus; FHx – Family history; HbA1c – Hemoglobin A1c; HDL – High density lipoprotein; LDL – Low density lipoprotein; PAD – peripheral arterial disease; TC – total cholesterol; SBP – Systolic blood pressure; TG – triglycerides.

Significant is defined as a p-value < 0.05.

**Table 2**  
Per patient CTA findings at baseline and follow-up by left main status.

	Total	LM -'ve	LM +'ve	Unadjusted	Model 1	Model 2
				F, p-value	F, p-value	F, p-value
Total PV at baseline (mm <sup>3</sup> )						
Total PV, mm <sup>3</sup>	137.3 ± 179.9	72.9 ± 84.3	194.8 ± 221	116.2, < 0.001	87.9, < 0.001	
Calcified PV, mm <sup>3</sup>	49.4 ± 101.1	22.4 ± 41.9	73.4 ± 128.7	62.0, < 0.001	43.6, < 0.001	
Fibrous PV, mm <sup>3</sup>	60.4 ± 80.0	32.4 ± 39.6	85.4 ± 97.0	112.6, < 0.001	87.8, < 0.001	
Fibrous fatty PV, mm <sup>3</sup>	24.5 ± 38.0	15.9 ± 27.8	32.1 ± 43.8	43.9, < 0.001	36.0, < 0.001	
Necrotic core PV, mm <sup>3</sup>	3.1 ± 7.5	2.3 ± 5.9	3.9 ± 8.6	11.4, 0.001	8.6, 0.003	
Annualized change in total PV (mm <sup>3</sup> /yr)						
Total PV, mm <sup>3</sup>	21.0 ± 27.3	14.9 ± 20.1	26.5 ± 31.4	43.1, < 0.001	32.5, < 0.001	9.5, 0.002
Calcified PV, mm <sup>3</sup>	12.6 ± 19.6	7.2 ± 10.7	17.4 ± 24.0	65.9, < 0.001	51.4, < 0.001	16.2, < 0.001
Fibrous PV, mm <sup>3</sup>	7.1 ± 15.8	6.3 ± 12.3	7.8 ± 18.3	112.6, 0.14	2.0, 0.16	2.78, 0.10
Fibrous fatty PV, mm <sup>3</sup>	1.2 ± 10.3	1.3 ± 8.9	1.1 ± 11.4	0.1, 0.77	0.001, 0.97	0.02, 0.88
Necrotic core PV, mm <sup>3</sup>	0.1 ± 2.4	0.06 ± 1.7	0.13 ± 2.8	0.2, 0.65	0.2, 0.64	1.8, 0.18

Model 1 – Accounts for baseline age, sex, hypertension, Diabetes, body mass index, smoking, and statin therapy.

Model 2 – Model 1, plus baseline constituent plaque volume.

LM = Left main; PV = Plaque volume.

Significant is defined as a p-value < 0.05.

**Table 3**  
Per segment annualized change (mm<sup>3</sup>/yr) within the proximal segments according to the presence or absence of left main disease.

	LM -'ve	LM +'ve	p-value
LM			
Total PV, mm <sup>3</sup> /year	0.48 ± 2.4	2.10 ± 5.0	< 0.001
Calcified PV, mm <sup>3</sup> /year	0.16 ± 1.6	1.67 ± 3.4	< 0.001
Fibrous PV, mm <sup>3</sup> /year	0.23 ± 1.0	0.60 ± 3.2	0.025
Fibrous fatty PV, mm <sup>3</sup> /year	0.08 ± 0.48	-0.11 ± 2.1	0.07
Necrotic core PV, mm <sup>3</sup> /year	0.01 ± 0.07	-0.04 ± 0.63	0.16
pLAD			
Total PV, mm <sup>3</sup> /year	2.26 ± 6.1	2.23 ± 6.1	0.94
Calcified PV, mm <sup>3</sup> /year	0.94 ± 2.0	1.84 ± 4.0	< 0.001
Fibrous PV, mm <sup>3</sup> /year	1.07 ± 3.5	0.79 ± 4.1	0.28
Fibrous fatty PV, mm <sup>3</sup> /year	0.29 ± 3.5	-0.32 ± 3.4	0.009
Necrotic core PV, mm <sup>3</sup> /year	0.00 ± 0.79	-0.08 ± 0.96	0.17
pLCx			
Total PV, mm <sup>3</sup> /year	0.65 ± 2.2	1.36 ± 3.9	0.001
Calcified PV, mm <sup>3</sup> /year	0.45 ± 1.5	0.90 ± 2.8	0.003
Fibrous PV, mm <sup>3</sup> /year	0.22 ± 1.2	0.44 ± 2.1	0.06
Fibrous fatty PV, mm <sup>3</sup> /year	-0.02 ± 0.6	0.01 ± 1.4	0.66
Necrotic core PV, mm <sup>3</sup> /year	-0.00 ± 0.2	0.00 ± 0.2	0.73
pRCA			
Total PV, mm <sup>3</sup> /year	2.17 ± 5.7	3.77 ± 9.0	0.002
Calcified PV, mm <sup>3</sup> /year	0.97 ± 2.8	2.00 ± 5.3	< 0.001
Fibrous PV, mm <sup>3</sup> /year	1.07 ± 3.8	1.49 ± 5.0	0.17
Fibrous fatty PV, mm <sup>3</sup> /year	0.13 ± 2.2	0.27 ± 3.7	0.51
Necrotic core PV, mm <sup>3</sup> /year	0.01 ± 0.6	0.01 ± 0.7	0.94

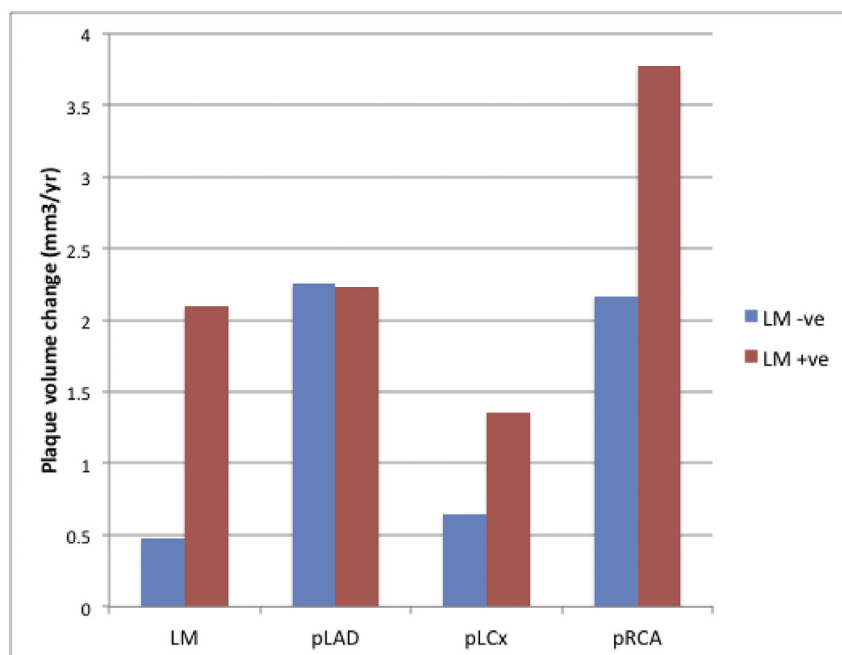
LM = Left main; pLAD = proximal left anterior descending; pLCx = proximal left circumflex; pRCA = proximal right coronary artery; PV = Plaque volume. Significant is defined as a p-value < 0.05.

progression in those with LM CAD proximal LAD, proximal LCx, and the proximal right coronary artery (RCA) (p < 0.005 for all - see Table 3 and Fig. 2). Similar observations were also present at a per lesion level with greater total plaque progression (LM +ve = 6.46 ± 12.18 vs. LM -ve = 4.75 ± 10.24 mm<sup>3</sup>/yr, p < 0.001), and calcified plaque progression (LM +ve = 4.64 ± 8.36 vs. LM -ve = 2.72 ± 4.51 mm<sup>3</sup>/yr, p < 0.001) in those with LM disease compared to those without (See Table 4).

### 3.4. Lesion based analysis

Lesions present in those with LM disease were associated with a greater average degree of stenosis (LM +ve = 19.6 ± 13.2 vs. LM -ve = 16.2 ± 10.9%, p < 0.001) and more likely to be obstructive (greater than 50% severity) (LM +ve = 39 (2.3%) vs. LM -ve = 9





**Fig. 2.** Annualized change in total plaque volume within the proximal segments according to presence or absence of left main disease. LM = Left main; pLAD = proximal left anterior descending; pLCx = proximal left circumflex; pRCA = proximal right coronary artery.

**Table 4**

Per lesion comparison of plaque characteristics between those with and without left main disease.

	Lesions in LM +ve (n = 1713)		p-value between baseline vs follow-up	Lesions in LM -ve (n = 1089)		p-value between baseline vs follow-up	p-value between groups	
	Baseline	Follow-up		Baseline	Follow-up		Baseline	Follow-up
Stenosis severity								
Diameter stenosis ≥ 50%	39 (2.3%)	72 (4.2%)	< 0.001	9 (0.8%)	21 (1.9%)	0.02*	0.001	< 0.001
Stenosis severity, %	19.6 ± 13.2	22.3 ± 13.8	< 0.001	16.2 ± 10.9	19.6 ± 12.1	< 0.001	< 0.001	< 0.001
High-risk plaque characteristics								
High-risk plaque*	300 (17.5%)	336 (19.6%)	0.014	142 (13.0%)	179 (16.4%)	0.001	0.001	0.004
Positive remodeling	1187 (69.3%)	1301 (76.0)	< 0.001	774 (71.1%)	847 (77.8%)	< 0.001	0.28	0.64
Low attenuation plaque	202 (11.8%)	194 (11.3%)	0.46	112 (10.3%)	109 (10.0%)	0.80	0.30	0.26
Spotty calcification	236 (13.8%)	259 (15.1%)	0.06	83 (7.6%)	126 (11.6%)	< 0.001	0.001	< 0.001
Napkin ring sign	8 (0.5%)	5 (0.3%)	1^	4 (0.4%)	3 (0.3%)	1^	1	0.75
Annualized change in PV								
Total PV, mm³/yr	6.46 ± 12.18			4.75 ± 10.24			< 0.001	
Calcified PV, mm³/yr	4.64 ± 8.36			2.72 ± 4.51			< 0.001	
Fibrous PV, mm³/yr	1.70 ± 7.67			1.75 ± 5.97			0.83	
Fibrous fatty PV, mm³/ yr	0.11 ± 4.81			0.31 ± 5.15			0.32	
Necrotic core PV, mm³/ yr	0.02 ± 1.30			-0.02 ± 0.95			0.39	

Data are n (%) or mean (SD). CTA = coronary computed tomography angiography; DS = diameter stenosis; PV = plaque volume.

\*High-risk plaque is defined as lesions with ≥ 2 of low attenuation plaque, spotty calcium, napkin ring sign, or positive remodeling. ^McNemar Exact p-value.

LM = Left main; PV = Plaque volume.

(0.8%),  $p < 0.001$  – see Table 4). HRP made up a higher proportion of plaques in those with left main disease (LM +ve = 300/1713 (17.5%) vs. LM -ve = 142/1089 (13%),  $p = 0.001$ ). This was driven by a higher frequency of spotty calcification (LM +ve = 236/1713 (13.8%) vs. LM -ve = 83/1089 (7.6%),  $p = 0.001$ ), with no difference in the frequency of positive remodeling, low attenuation plaque or the napkin ring sign ( $p > 0.2$  for all – see Table 4).

#### 4. Discussion

In the current study we have shown that LM disease is associated with a higher plaque volume, greater plaque rate progression, more

severe stenosis and a higher prevalence of HRP features.

The finding that LM disease is associated with a greater global plaque burden within the coronary arterial tree is consistent with previous studies showing a high prevalence of single, double and triple vessel CAD and a higher segment involvement score with LM disease.<sup>6,23,24</sup> This is important as multiple studies have consistently demonstrated an increasing mortality with increasing burden of both obstructive and non-obstructive plaque.<sup>25–27</sup>

Plaque progression has previously been demonstrated to be the strongest imaging feature associated with later development of acute coronary syndrome, with the presence of HRP providing additive prognostic value.<sup>19</sup> In the current study we observed both these risk

factors with a higher rate of progression of plaque and a greater frequency of HRP features in those with LM disease. The higher frequency of HRP features was driven by a higher incidence of spotty calcification in the LM group. This HRP feature is associated with unstable plaque morphology, culprit lesions in acute coronary syndromes, and accelerated plaque progression despite the use of medical therapy.<sup>28-31</sup> The combination of a greater plaque volume and higher prevalence of spotty calcification in patients with LM disease suggest a more aggressive atherosclerosis process which may be driving LM disease rather than a result of it. In support of this is that the greater rate of plaque progression was present independent of coronary artery site, with equally advanced rates of plaque progression occurring in the right coronary artery as in the proximal LAD and LCx suggesting a systemic rather than localized process. This is a useful observation as it provides some insight into the results of the recent EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British left main revascularisation) trials, where increased revascularization rates were observed in patients undergoing LM percutaneous coronary intervention compared with coronary artery bypass graft surgery.<sup>27,32</sup> However, in these studies it was not the LM itself needing repeat revascularization, rather, it was revascularization of de novo lesions that drives this signal.<sup>32</sup> These results have also been borne out in substudy analysis of several other studies comparing percutaneous coronary intervention with coronary artery bypass surgery in those with LM disease.<sup>33-36</sup> Thus, it may be that the presence of LM disease is a marker of a need for more aggressive therapeutic intervention.

Both the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study using IVUS and a study by Motoyama et al. using CTA have described plaque volume, HRP, plaque progression and severe stenosis to be independent markers of an increased risk of cardiovascular events.<sup>19,37</sup> That all four of these markers are more prevalent in patients with LM disease provides further insights into the reported higher rates of cardiovascular mortality in this cohort and a need for more aggressive risk factor modification.

There are several limitations to the current analysis. Both the first and second CTA were performed for clinical indications. Thus, while all participants who underwent revascularization were excluded, the current observations cannot be considered a true representation of the 'natural history' of CAD. Instead, they are the natural history in the presence of persistent symptomatology or ongoing clinical concern. However, given that this is the population faced clinically, and of particular challenge to clinicians, this is perhaps a more relevant natural history to daily practice. Secondly, the current study is an observational study without protocolled guidance on management strategy. As such, it is entirely possible that management may differ between the two groups. While baseline therapy was available and equal between the groups, downstream medications at follow-up were not. However, given the presence of both LM disease and a higher baseline plaque burden, one would expect that if either group were to be the recipients of a more intensive treatment regime, it would be the LM disease group. As statin use causes a reduction in total plaque volume, and a fall in the prevalence of HRP,<sup>38,39</sup> this would cause a resultant reduction in the magnitude of between group differences. Finally, as the study focused on those with non-obstructive LM disease it is possible that as the stenosis becomes more severe, local hemodynamic effects and flow destabilization may occur resulting in a regional pattern of plaque progression secondary to this over and above the globalized pattern observed in the current study. Further work in this field for better understanding however is unlikely to occur due to the morbidity and mortality implications of leaving severe LM stenosis untreated in order to observe for these longitudinal effects.

## 5. Conclusion

Those with non-obstructive LM disease have greater plaque burden,

greater rates of plaque progression and a higher prevalence of high-risk plaque throughout the entire coronary artery tree. This suggests that LM disease is a marker for an aggressive phenotype of CAD that may benefit from more intensive treatment strategies.

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