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Authors: Andrew Ladwiniec, M.D; Simon J Walsh, M.D; Niels R Holm, M.D; Colm G Hanratty, M.D; Timo Makikallio, M.D; Thomas Kellerth, M.D; David Hildick-Smith, M.D; Lone JH Mogensen, MStat; Juha Hartikainen, M.D, PhD; Ian B A Menown, M.D, FRCP; Andrejs Erglis, M.D, PhD; Erlend Eriksen, M.D; Mark S Spence, M.D; Leif Thuesen, M.D, DMSc; Evald H Christiansen, M.D, PhD; For the NOBLE study group

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Intravascular ultrasound to guide left main stem intervention: a sub-study of the NOBLE trial

Andrew Ladwiniec MD¹, Simon J Walsh MD², Niels R Holm MD³, Colm G Hanratty MD², Timo Makikallio MD⁴, Thomas Kellerth⁵ MD David Hildick-Smith MD⁶, Lone JH Mogensen³ MStat, Juha Hartikainen⁷ MD PhD, Ian B A Menown MD FRCP⁸, Andrejs Erglis⁹ MD PhD, Erlend Eriksen¹⁰ MD, Mark S Spence MD², Leif Thuesen MD DMSc¹¹, Evald H Christiansen MD PhD³
For the NOBLE study group

1. Department of Cardiology, Glenfield Hospital, Leicester, UK.
2. Department of Cardiology, Royal Victoria Hospital, Belfast, Northern Ireland, UK.
3. Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark.
4. Department of Cardiology, Oulu University Hospital, Oulu, Finland.
5. Department of Cardiology, Örebro University Hospital Örebro, Sweden.
6. Sussex Cardiac Centre, Brighton and Sussex University Hospital, Brighton, UK.
7. Heart Center, Kuopio University Hospital, Kuopio, Finland.
8. Craigavon Cardiac Centre, Craigavon, Northern Ireland, UK.
9. Latvia Centre of Cardiology, Paul Stradins Clinical Hospital, Riga.
10. Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
11. Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Short running title: **The NOBLE intravascular ultrasound sub-study**

Corresponding author: Evald H Christiansen

Address: Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark

Tel: +45 78452028

E-mail: evald.christiansen@dadlnet.dk

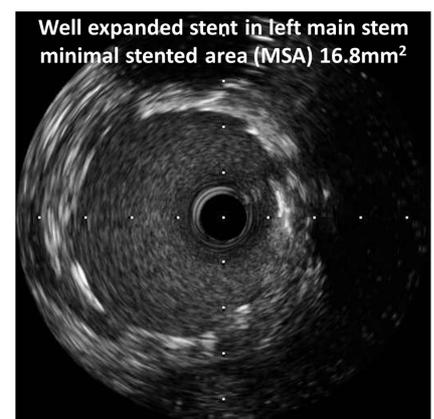
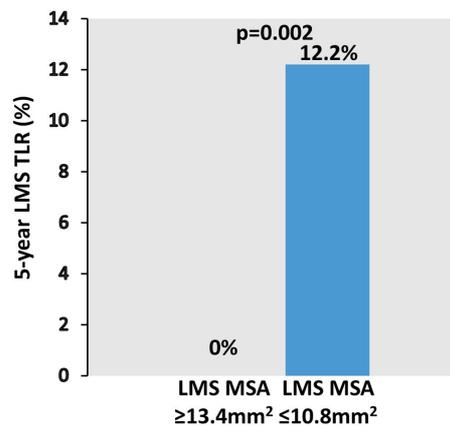
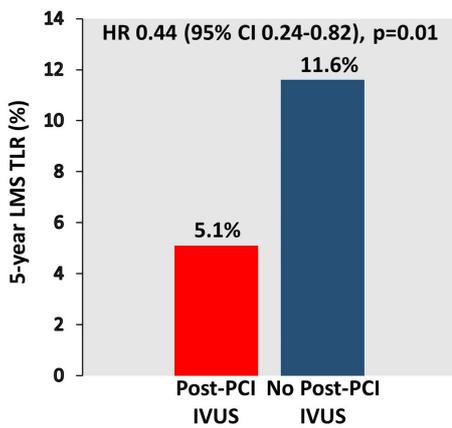
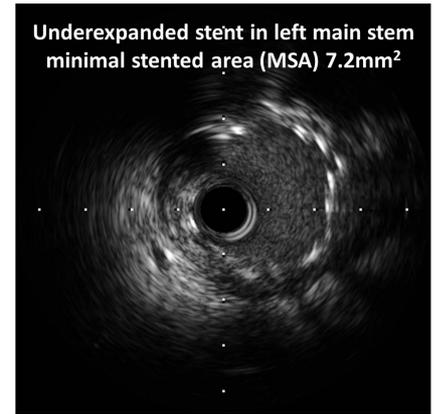
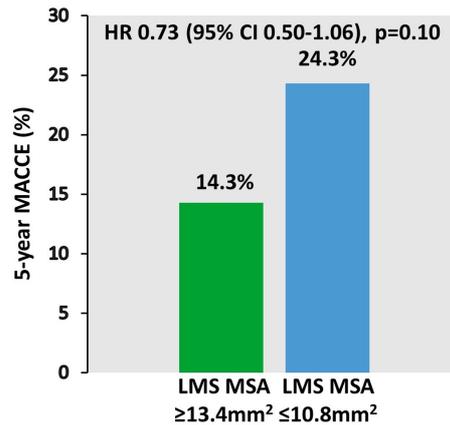
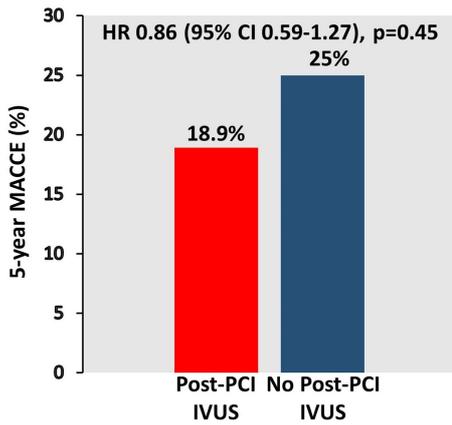
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Abstract

Aims—We investigated the association between the use and findings of IVUS with clinical outcomes in the PCI arm of a randomised trial of LMS PCI.

Methods and Results—The NOBLE trial randomised patients with LMS disease to treatment by PCI or CABG. Of 603 patients treated by PCI, 435(72%) underwent post-PCI IVUS assessment of which 224 were analysed in a core-laboratory. At 5 years, the composite of MACCE were 18.9% if post-PCI IVUS was performed vs. 25.0% if not ($p=0.45$, after adjustment). Overall repeat revascularization was not reduced (10.6% vs. 16.5%, $p=0.11$), however LMS TLR was (5.1% vs. 11.6%, $p=0.01$) if IVUS was used. For comparison of stent expansion, LMS MSA was split into tertiles. We found no significant difference in MACCE, death, myocardial infarction or stent thrombosis between tertiles. There was a significant difference between the lower and upper tertiles for repeat revascularisation (17.6% vs. 5.2%, $p=0.02$) and LMS TLR (12.2% vs. 0%, $p=0.002$).

Conclusions—Post PCI IVUS assessment and adequate stent expansion are not associated with reduced MACCE, however there is an association with reduced LMS TLR. Use of intra-coronary imaging to prevent stent under-expansion in LMS PCI is likely to improve outcomes.



Central Illustration: Rates of MACCE (top) and left main stem target lesion revascularization (bottom) for patients with and without post-PCI IVUS assessment (left) and lower and upper LMS minimal stented area tertiles (right).

Classifications

Drug-eluting stent; Intravascular ultrasound; Left main.

Abbreviations

IVUS: intravascular ultrasound

LMS: Left main stem

PCI: Percutaneous coronary intervention

CABG: Coronary artery bypass grafting

MACCE: Major adverse cardiac and cerebrovascular events

TLR: Target lesion revascularization

MSA: Minimal stented area

EEM: External elastic membrane

MI: Myocardial infarction

Condensed abstract

Of 603 patients treated by LMS PCI in the NOBLE trial, 72% underwent post-PCI IVUS assessment. At 5 years, the composite of MACCE were 18.9% if post-PCI IVUS was performed vs. 25.0% if not ($p=0.45$). LMS TLR was lower in the IVUS group (5.1% vs. 11.6%, $p=0.01$). We found no association between MACCE and stent expansion but did show an association between greater stent expansion and reduced repeat revascularisation (17.6% vs. 5.2%, $p=0.02$) and LMS TLR (12.2% vs. 0%, $p=0.002$). Post PCI IVUS assessment and adequate stent expansion are not associated with reduced MACCE overall, however there is an association with reduced LMS TLR.

Introduction

Percutaneous coronary intervention (PCI) of unprotected left main stem (LMS) coronary disease is now an acceptable treatment with comparable medium-term survival to coronary artery bypass graft surgery (CABG)^{1,2}. It is also frequently undertaken in patients in whom the risks of CABG are prohibitively high³. However, composites of major cardiovascular events, in particular repeat revascularization (the majority of which is TLR^{1,2}), are inferior in those treated by PCI relative to CABG^{1,2}. Intra-vascular ultrasound (IVUS) measurements of stent expansion are predictive of restenosis and target lesion revascularization (TLR)^{4,5}, a finding which appears to remain applicable in patients who have undergone LMS stenting⁶. The use of IVUS in LMS PCI is recommended, and its use in this setting has been associated with improved survival at long-term follow-up^{7,8}.

The Nordic-Baltic-British left main revascularisation study (NOBLE) is a prospective, randomised, open-label, non-inferiority trial. It enrolled 1201 patients with unprotected LMS disease and randomised them in a 1:1 fashion to PCI or CABG¹. Rates of major adverse cardiac or cerebrovascular events (MACCE) were higher in the PCI arm than in the CABG arm¹. IVUS was not used to guide all PCI procedures in NOBLE. This is a sub-study of NOBLE with the aim of investigating (1) whether the use of IVUS to guide optimization of the post-stenting result was associated with superior clinical outcomes compared with angiographic guidance alone and (2) the relationship between post-PCI IVUS findings, in-particular stent expansion, and clinical outcomes.

Methods

Study Design

The Nordic-Baltic-British left main revascularisation study (NOBLE) is a trial comparing PCI and CABG in the treatment of unprotected LMS coronary disease¹. The study protocol has been described in detail previously¹. Briefly, patients were eligible for study enrolment if they presented with stable angina, or an acute coronary syndrome and were found to have a stenosis of $\geq 50\%$ diameter or fractional flow reserve ≤ 0.80 in the LMS, with no more than three additional non-complex lesions (lesions not involving chronic total occlusions, bifurcations requiring two stent techniques or excessive calcification or tortuosity). Participants were excluded if they had suffered an ST-elevation infarction within 24 hours, were considered too high risk for CABG or PCI, or expected to survive for < 1 year. All enrolled patients provided written informed consent. The study complied with Good Clinical Practice and the Declaration of Helsinki. It was approved by The Central Denmark Region Committees on Health Research Ethics, and by national or local ethics committees for the individual sites as appropriate, and by the Danish Data Protection Agency. The trial was registered with ISRCTN87206264 and ClinicalTrials.gov identifier: NCT01496651.

Procedures

Patients were treated with the intention of achieving complete revascularisation of all vessels with significant stenoses. Ostial and mid-shaft lesions were treated with a single stent strategy. Distal bifurcation lesions could be treated with two-stent techniques at the

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discretion of the operator, with a preference for the culotte technique. Final kissing balloon dilation was mandatory when a two-stent technique was used. IVUS was strongly recommended pre and post-stent deployment, but was not mandatory. Suggested criteria for stent expansion were not included in the trial protocol. Use of drug-eluting stents was mandatory. After treatment of 73 patients with PCI, the Biolimus-eluting stent (Biomatrix Flex, Biosensors, Morges, Switzerland) became the recommended study stent.

Patients treated with PCI were eligible to be included in the IVUS core-lab analysis if they had post-PCI IVUS assessment of the LMS. Site investigators would send anonymised IVUS images to the core lab (Royal Victoria Hospital, Belfast). Once analysed, IVUS data was linked to adjudicated study follow-up data.

Outcomes

The primary endpoint was a composite of MACCE (death from any cause, non-procedural myocardial infarction⁹ (MI), repeat revascularisation, or stroke). Other clinical endpoints were the individual components of the primary MACCE endpoint and definite stent thrombosis. Procedural MIs were documented (post hoc). Repeat revascularisations were categorised as TLR, LMS TLR, or de-novo lesion revascularisation.

Intravascular ultrasound

Immediate post-stenting IVUS imaging was performed, using motorized transducer pullback (0.5 mm/s) and Atlantis SR Pro 40MHz rotating 3.2 French catheters (Boston Scientific, Natick, MA, USA) or a synthetic-aperture-array, 20-MHz, 3.2-French catheter (Eagle Eye, In-Vision Gold, Volcano). Off-line IVUS analysis was performed using DICOM analysis software for computerized planimetry (Rubo Medical Imaging, Netherlands).

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Minimal lumen area or MSA were measured in the LMS and when available, in the bifurcation core segment⁶, the ostial LAD (defined as ≤ 5 mm from the carina), and the ostial LCx (defined as ≤ 5 mm from the carina). An MSA < 8 mm² in the LMS, < 7 mm² in the bifurcation core segment, < 6 mm² in the ostial LAD and < 5 mm² in the ostial LCx has been previously associated with adverse events⁶. Those in whom IVUS had demonstrated a smaller MSA at any of these sites were identified, and outcomes compared with those in whom all MSA measurements exceeded these values. At the site of the MSA, the cross-sectional areas of external elastic membrane (EEM) and residual plaque were measured by 2D planimetry. Residual plaque burden was calculated as $plaque/EEM \times 100$ expressed as a percentage (**figure 1**). At each measured segment, calcification was noted to be present or absent in binary form; and the extent of calcification at the MSA was measured in degrees, the maximum being 360°. This was recorded as a summed total if not a continuous arc. Malapposition was defined as a separation of at least 1 metallic strut from the vessel wall in the absence of a side branch. We did not routinely record whether IVUS assessment resulted in further optimisation of the stenting result. All analysed IVUS images were of the final stenting result.

Statistical analysis

Continuous variables are reported as mean (SD) and were compared by *t*-test if they followed a Gaussian distribution. Continuous variables not following a Gaussian distribution are reported as their median value (IQR) and compared using the Mann-Whitney test.

Continuous variables were compared amongst 3 or more groups using a one-way ANOVA test or Kruskal-Wallis test as appropriate. Binary variables are reported as counts and

percentages, and baseline and in-hospital differences between the two groups were

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assessed with the χ^2 or Fisher's exact test if a cell value was <5. Follow-up began at randomisation. In the analysis of individual endpoints, follow-up continued until the date of a clinical endpoint event, death, or 5 years after randomisation, whichever occurred first. All patients were followed for at least 1 year. Cumulative rates of MACCE were stratified into three tertile groups based on LMS MSA and presented by Kaplan-Meier curves. MACCE and its components are reported using 5-year Kaplan-Meier estimates and hazard ratio by unadjusted Cox-regression analysis with 95% confidence intervals. In addition, adjusted hazard ratios are stated, calculated using a multivariate Cox proportional hazard model. Only the significant variables were retained in the final model. A p-value of <0.05 was considered significant. All analyses were done using Stata 12.

Results

In the NOBLE trial, 603 patients received PCI, including 13 allocated to CABG and were included in the present analysis. Of those, 474 underwent IVUS guidance in some form (pre-PCI in 270 (45%) and post-PCI in 435 (72%). Characteristics of those who did and did not undergo post-PCI IVUS assessment are presented in **supplementary table 1**. Of the participants who underwent post-PCI IVUS, 224 (37% of the total PCI population and 52% of those in whom post-PCI IVUS was undertaken), had images submitted to the IVUS core-lab for analysis. Demographics and clinical characteristics for those included in the core-lab analysis and those who underwent post-PCI IVUS but were not analysed in the core-lab are listed in the supplementary appendix, **supplementary table 2**.

The use of IVUS to guide LMS PCI

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Table 1 and figure 2 summarise clinical event rates for those patients in the NOBLE trial who underwent LMS PCI and had post-PCI IVUS assessment, and for those that did not. There was a numerical reduction in MACCE, non-procedural MI and repeat revascularization in the IVUS group, however after adjustment none reached conventional statistical significance. There was however significantly reduced repeat revascularization of the LMS (LMS TLR) in favour of post-PCI IVUS. There was no difference in survival between groups.

Of the 435 patients that underwent post-PCI IVUS assessment, 243 had IVUS assessment both pre and post-stenting. There were an additional 29 patients who only had IVUS assessment prior to stenting. There was no difference in MACCE or LMS TLR between those with only post-stenting IVUS assessment and those with both pre and post (**supplementary figures 1 and 2**).

Post-PCI IVUS findings and clinical outcomes

Malapposition

Of the 224 patients with post-PCI IVUS images analysed in the core-lab, we identified malapposition in 12 (5.4%). We demonstrated no difference in MACCE at 5 years between those with and without malapposition: 33%(4) vs 21%(44), hazard-ratio 1.47(0.53-4.10), $p=0.47$. Individual components of the composite endpoint are detailed in **supplementary table 3**. None of the differences reached statistical significance.

Previously identified predictors of adverse events

Mean MSA measurements in the LMS, bifurcation core segment, ostial LAD and ostial LCx are detailed in the supplementary appendix, **supplementary table 4a**, including number of failures to achieve an MSA in each segment in excess of those previously associated with

adverse events⁶ (<8mm² in the left main stem, <7mm² in the bifurcation core segment, <6mm² in the ostial LAD and <5mm² in the LCx). Of the 224 patients analysed in the IVUS core-lab, 19 (8.5%) failed to achieve an MSA above these values in ≥1 vessel segments. Rates of adverse events for those with at least one 'failure to achieve MSA' compared with those without a failure are compared in **supplementary table 4b**. Numerically, event rates were higher in those in whom there was stent under-expansion in ≥1 vessel segment. However, there was no statistically significant difference in MACCE, death, non-procedural MI or repeat revascularisation between groups; although the number of events and failures to achieve MSA were both small.

IVUS and clinical predictors of events

Of the 224 patients with post-PCI IVUS images analysed in the core-lab, univariate predictors of MACCE were: age in years, logistic euroscore and hypertension. When incorporated into a multi-variable proportional hazards model, only age (HR 1.03, 95% CI 1.00-1.06, p=0.048) and hypertension (HR 2.23, 95% CI 1.07-4.65, p=0.03) remained significant predictors (**supplementary table 5**).

Univariate predictors of LMS TLR included LMS MSA and LMS maximal residual plaque burden. Residual plaque burden was removed from the model due to collinearity with LMS MSA, leaving LMS MSA as the only significant multivariable predictor of LMS TLR (HR 0.75, 95% CI 0.61-0.92, p=0.006) (**supplementary table 6**).

Stent expansion in the LMS

The mean MSA in the LMS measured $12.5 \pm 3.0 \text{ mm}^2$ with a mean maximal stented area of $15.6 \pm 3.8 \text{ mm}^2$. Mean maximal stented LMS luminal diameter was $4.8 \pm 0.6 \text{ mm}$, 151 of 224 patients (67.4%) included in the sub-study had a maximal stented LMS diameter of $\geq 4.5 \text{ mm}$. LMS stent brand and platform/diameter were known in 199/224 patients. Of those patients in whom the maximal LMS stented diameter was $\geq 4.5 \text{ mm}$ ($n=133$) and stent brand and platform/diameter were known, the largest stent platform with the greatest overexpansion capacity (3.5/4.0 for Biomatrix, 4.0 for Promus Element, >4.0 for Taxus Liberte, 3.0/3.5/4.0 for Resolute Integrity, 3.5/4.0 for Cypher¹⁰) was used in 119/133 (89.5%). In the 14 cases where this was not the case, there was no malapposition found by post-procedural IVUS imaging and no association with MACCE.

To further investigate the relationship between stent expansion and events at follow-up patients were split into tertiles according to the post-PCI LMS MSA. Details of the three tertile groups are shown in **supplementary table 7**. With respect to the IVUS characteristics, EEM area increased with each tertile and the residual plaque burden expressed as a percentage $(\text{EEM-MSA})/\text{EEM}$ was higher in the lower tertiles. The frequency and extent of visible calcification on IVUS at the MSA site was higher in the lower tertiles.

Outcomes at 30 days are presented in **supplementary table 8** and 5-year follow-up with a median follow-up of 4 years is detailed in **table 2** and **figure 3**. At 30 days, event rates were very low and there was no difference in outcomes between tertiles. At a median follow-up of 4 years, there was no significant difference in MACCE, death, MI or stent thrombosis between tertiles. However, there was a trend towards a difference in MACCE between the low and upper tertiles. There was a significant difference between the low and upper tertiles for repeat revascularisation and specifically LMS TLR.

Discussion

The main findings of this NOBLE sub-study were that 1) a final IVUS assessment was associated with a reduction in LMS TLR; 2) an association between better stent expansion and superior clinical outcomes was demonstrated, in particular for TLR at the site of IVUS assessment (the LMS); 3) Inferior stent expansion in the LMS was associated with a greater extent of calcification in the LMS; and 4) in what is a sample of convenience of those in the NOBLE trial who underwent IVUS guided PCI, overall stent expansion was good relative to other publications in the field^{6,11,12}.

Post-PCI IVUS assessment and improved outcomes

We have demonstrated an association between post-PCI IVUS examination and reduced LMS TLR. The data are not randomised and we did not record whether a post-PCI IVUS resulted in further optimisation. Nevertheless, the finding of increased LMS TLR if we don't assess for optimal stent expansion and the same increased TLR if we do assess it, but accept a smaller MSA provide a powerful message regarding the importance of optimising our PCI result in the LMS with intra-coronary imaging. The findings are consistent with what we know about predictors of restenosis whether the PCI involves the LMS⁶ or not^{4,13}. They also raise the question of whether we might have achieved better clinical outcomes in the PCI

arm of the NOBLE trial if all operators had followed the recommendation of pre and post-PCI IVUS assessment.

The association between stent expansion and clinical outcomes

Stent under-expansion has been shown to be associated with increased rates of restenosis and stent thrombosis¹⁴. We demonstrate an association between LMS MSA and repeat revascularisation, most notably repeat revascularisation at the site of under-expansion (LMS TLR). A lower MSA may reflect an anatomically smaller LMS rather than under-expansion, and indeed the lower LMS MSA tertiles do have correspondingly lower LMS EEM areas. However, the residual plaque burden expressed as a percentage $(EEM-MSA)/EEM$ is higher in the lower tertiles, suggesting that these are not just smaller LMS, but the stented segment was less well expanded. We did not identify a difference in overall MACCE or harder endpoints such as MI or stent thrombosis between tertiles. A similar analysis reported from the EXCEL trial¹² did show an excess in MACCE, and the individual endpoints of MI, stent thrombosis and all cause death in the lowest LMS MSA tertile, but no difference in TLR.

We also demonstrated a greater frequency and extent of calcification at the site of the LMS MSA in the lower MSA tertiles (**supplementary table 7**). This is a possible explanation for poorer stent expansion. Calcification in itself has been associated with restenosis and stent thrombosis¹⁴, as well as stent under-expansion¹⁵. Once a calcified stenosis is stented, it can be more challenging to address the under-expansion than it would have been to modify the calcific segment prior to stenting¹⁶; post-PCI IVUS assessment might highlight the problem

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too late. A lower threshold for calcification modification techniques such as rotablation, or intra-coronary lithotripsy¹⁷ may be important in achieving adequate stent expansion and reducing LMS stent failure. Alternatively, if good stent expansion cannot be achieved, favouring CABG in patients with a heavily calcified LMS might be appropriate.

Noble IVUS results in comparison with other studies

In any trial involving PCI, it is always possible to question the quality of the PCI procedure. A simple metric, given the established association between adequate stent expansion and clinical outcomes¹⁴, is a comparison of LMS MSA. Mean LMS MSA in this sub-study was 12.5mm², greater than the IVUS sub-study taken from the EXCEL trial¹¹, which measured <10mm². Similarly, compared with the study from which binary measurements of under-expansion in the LMS, bifurcation core segment, ostial LAD and ostial LCx associated with adverse events were derived⁶; under-expansion in this sub-study was much less frequent at 8.5%, compared with 33.8%⁶. The most vulnerable anatomical site for under-expansion is the ostium of the LCx and the frequency of IVUS assessment in the LCx in this sub-study was low. Nevertheless, measurements of stent expansion presented here compare favourably with similar studies^{6,11}. This could be explained by the patient population in NOBLE being from the United Kingdom or Scandinavia¹ and therefore larger than in Korea⁶, or even the population included in the EXCEL trial². However, the EEM measurements at the site of the LMS MSA presented here are very similar to those presented in the IVUS sub-study of the EXCEL trial¹².

It is interesting that we have demonstrated an association between stent under-expansion and TLR, but not the harder endpoints of MACCE, death, MI and stent thrombosis as have been described in the IVUS sub-study of the EXCEL trial¹². It is difficult to explain this

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discrepancy, although our results are in keeping with the results of other studies⁶. A possible explanation might be that the Xience stent platform used in EXCEL when ≤ 3.0 mm has an upper overexpansion limit (ca. 4.4 mm diameter) which is lower than most other stent platforms including those used in Noble¹⁰. This might have resulted in a greater risk of malapposition and underexpansion in EXCEL cases if 3.0mm Xience stents were brought back into the LMS.

Limitations

This study is limited by its small size and non-randomised nature. Interpretation of the association between stent malapposition and adverse events is limited by both the low rate of malapposition and the low event rate. In addition, not all segments were imaged in all patients (particularly the ostium of the circumflex artery), so the prevalence of stent-underexpansion may have been higher than reported. Whilst our findings of an association between LMS stent expansion, post-PCI IVUS assessment and repeat revascularisation are interesting and consistent with other similar studies^{12,14}, they can only be considered hypothesis generating. An assessment of the frequency in which post-PCI IVUS assessment resulted in further optimisation would have been valuable, but this data was not collected. Finally, this study does not provide a threshold LMS MSA above which we should strive to prevent TLR, the number of events is too small.

Conclusions

Undertaking post LMS PCI IVUS assessment is not associated with reduced MACCE, however it is associated with reduced TLR. If undertaken, LMS stent under-expansion is associated with both LMS calcification and increased TLR. Use of IVUS in addressing and preventing

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stent under-expansion in LMS PCI is likely to result in improved outcomes. Stent expansion in the NOBLE trial compares favourably with other studies of LMS PCI.

Impact on daily practice

This sub-study supports the suggestion that post-procedural intra-coronary imaging and optimal stent expansion improves long-term durability of LMS PCI. In order to attain optimal stent expansion and reduce TLR; patient selection, adequate lesion preparation and stent optimisation guided by intra-coronary imaging are all likely to be important.

Funding

Biosensors provided an institutional research grant for the trial.

Conflicts of Interest Statement

The authors report grant support from Biosensors and consulting fees from Boston Scientific, Abbott Vascular, Medtronic and Edwards, unrelated to the present study.

Tables

Event	No Post IVUS n=164	Post IVUS N=435	H R (9	p- v al	A dj u	A dj u
MACCE	41(25.0%)	82(18.9%)	0.	0.	0.	0.
Death	12(7.3%)	24(5.5%)	0.	0.	1.	0.
Non-procedural MI	12(7.3%)	17(3.9%)	0.	0.	0.	0.
Repeat Revascularization	27(16.5%)	46(10.6%)	0.	0.	0.	0.
LMS TLR	19(11.6%)	22(5.1%)	0.	0.	0.	0.
Stroke	3(2.1%)	13(3.0%)	1.	0.	1.	0.

Table 1. Rates of clinical events for those with and without post-PCI IVUS assessment. Unadjusted and adjusted HRs have been generated from univariate and multivariate Cox proportional hazards models, respectively. Adjusted co-variables for each outcome were as follows: MACCE: IVUS + Age + Smoking + Euroscore + Hypertension + Euroscore*Age + Hypertension*Age; Death: IVUS + Smoking + Age + BMI; Non-procedural MI: IVUS + Age; Repeat Revascularization: IVUS + Euroscore + Age + Smoking + Euroscore*Age + Smoking*Age; LMS TLR: IVUS + Age; Stroke: IVUS + Age

IVUS LMS MSA tertile (range)	Low 4.4-10.8mm ² n=74	Intermediate 10.9-13.4mm ² n=73	Upper 13.4-25.4mm ² n=77	p-value L vs I	p-value L vs H
MACCE	18 (24.3%)	19 (26.0%)	11 (14.3%)	0.92	0.10
All cause mortality	2 (2.7%)	6 (8.2%)	6 (7.8%)	0.14	0.19
Cardiac death	0 (0%)	1 (1.3%)	4 (5.3%)	0.33	0.19
Non-procedural MI	4 (5.4%)	5 (6.9%)	3 (3.9%)	0.69	0.68
Definite stent thrombosis	1 (1.4%)	2 (2.7%)	1 (1.3%)	0.62	0.75
Stroke	2 (2.7%)	2 (2.7%)	3 (3.9%)	0.99	0.72
Repeat revasc	13 (17.6%)	10 (13.7%)	4 (5.2%)	0.47	0.02
LMS TLR	9 (12.2%)	4 (5.5%)	0 (0%)	0.15	0.002

Table 2. Comparison of 5-year outcomes by LMS stent expansion tertile. L vs I denotes low tertile versus intermediate tertile; L vs H, low versus high tertile.

Figure legends

Figure 1. IVUS image taken post LMS PCI. Both MSA and EEM areas are highlighted. The residual plaque burden is the area outside the MSA, but within the EEM, expressed as a proportion of the total EEM area.

Figure 2. Kaplan-Meier curves showing 5-year MACCE (top left), LMS TLR (top right), non-procedural MI (bottom left) and repeat revascularisation (bottom right) comparing those who underwent post-PCI IVUS assessment with those that did not.

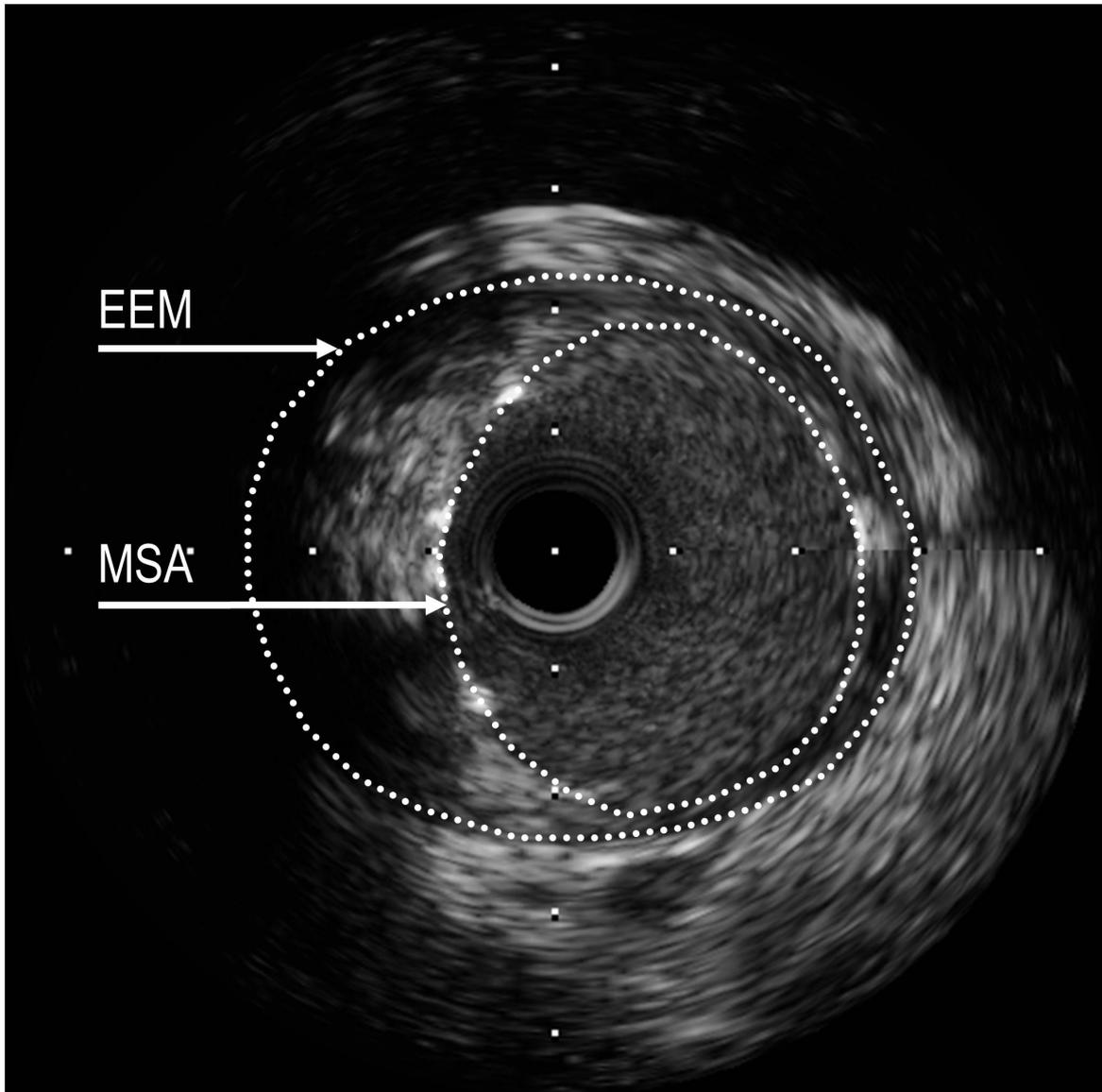
Figure 3. Kaplan-Meier curves showing 5-year MACCE (top), repeat revascularisation (middle) and LMS TLR (bottom) for lower, intermediate and upper LMS MSA tertiles.

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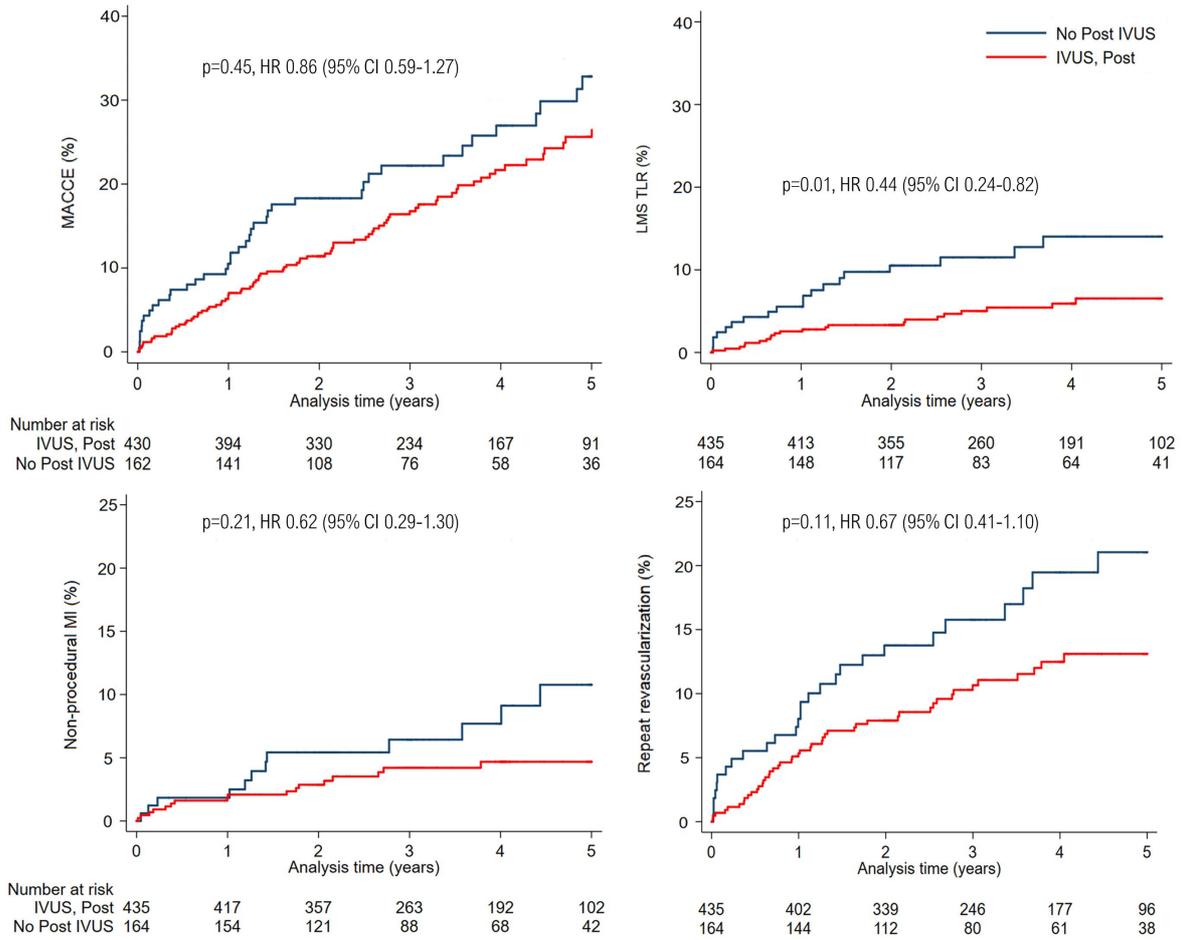
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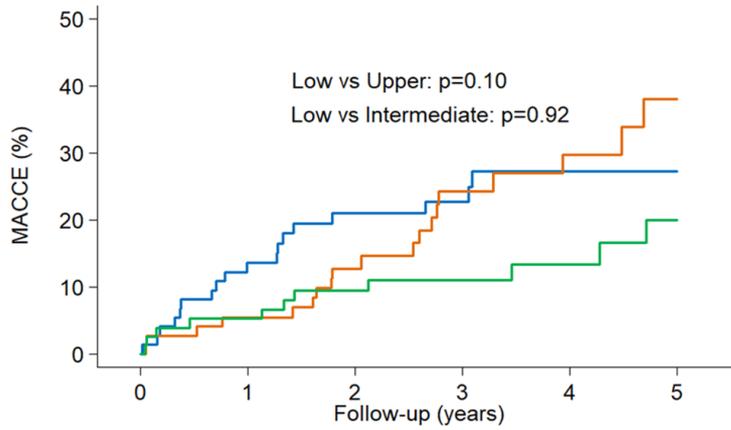
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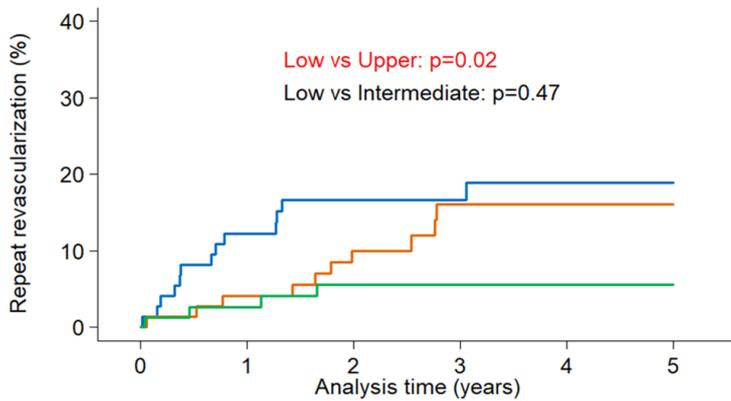
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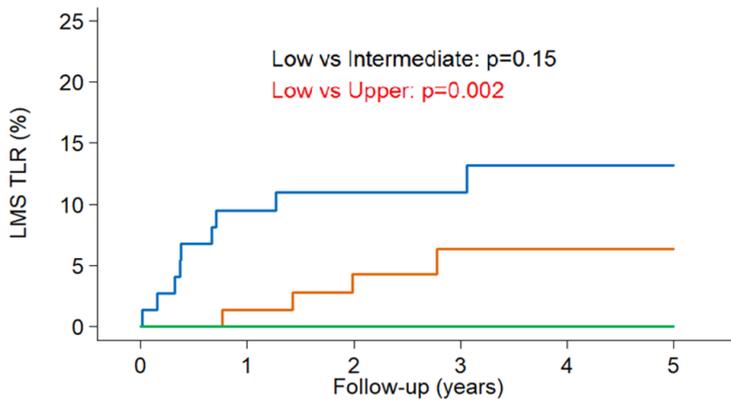
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Number at risk						
Lower tertile	74	63	50	41	29	13
Intermediate tertile	73	68	57	36	26	10
Upper tertile	77	72	62	53	37	19



Number at risk						
Lower tertile	74	64	52	44	32	13
Intermediate tertile	73	69	58	38	28	11
Upper tertile	77	72	63	54	38	21



Number at risk						
Lower tertile	74	66	56	47	34	13
Intermediate tertile	73	71	62	43	32	13
Upper tertile	77	73	66	56	39	22

Tertiles: — Lower — Intermediate — Upper

Supplementary appendix

	No Post IVUS (n=164)	Post IVUS (n=435)
Female gender (%)	39 (23.8)	79 (18.2)
Body-mass index (kg/m ²)	27.5±4.2	28.1±4.6
Diabetes type 1 or type 2 (%)	23 (14.0)	67 (15.4)
Family history of ischaemic heart disease (%)	79 (52.3)	243 (59.6)
Statin treatment (%)	127 (77.4)	360 (83.0)
Hypertension (%)	118 (72.0)*	273 (63.1)*
Age (years)	68.3±9.7*	65.6±9.8*
Active smoking (%)	33 (20.4)	76 (17.8)
Previous PCI (%)	29 (17.7)	88 (20.3)
Previous CABG (%)	3 (1.8)	2 (0.5)
Ejection fraction	57.8±9.9	58.6±9.5
NYHA class (%)		
I	71 (53.8)	176 (53.2)
II	38 (28.8)	98 (29.6)
III	16 (12.1)	41 (12.4)
IV	7 (5.3)	16 (4.8)
EUROSCORE	2 (IQR 1-4)*	2 (IQR 1-3)*
SYNTAX score	22.3±7.8	22.5±7.3
Stable angina pectoris (%)	133 (81.1)	358 (82.3)
LMS lesion location (%)		
Ostial	38 (25.7)	112 (26.7)
Shaft	50 (33.6)	164 (38.6)
Distal	139 (84.8)	345 (79.3)
Two stent strategy (%)	46 (33.8)	136 (35.6)
Biomatrix stent use (%)	83 (55.7)*	342 (78.8)*
First generation DES (%)	23 (15.4)*	24 (5.5)*
Newer generation DES (%)	122 (81.9)*	406 (93.6)*

Supplementary table 1. Baseline characteristics, NOBLE study patients allocated to PCI (added 6 patients allocated to CABG included in the core-lab analysis), by Post IVUS/No Post IVUS group. *=statistical significance between groups.

	Core-lab, Post IVUS (n=224)	Not in Core-lab, Post IVUS (n=221)
Female gender (%)	50 (22.3)	34 (15.4)
Body-mass index (kg/m ²)	28.2±4.4	28.0±4.8
Diabetes type 1 or type 2 (%)	35 (15.6)	35 (15.8)
Family history of ischaemic heart disease (%)	138 (64.8)*	112 (55.2)*
Statin treatment (%)	200 (89.3)*	169 (76.8)*
Hypertension (%)	152 (67.9)	129 (58.9)
Age (years)	66.7±8.7*	64.5±10.7*
Active smoking (%)	32 (14.4)	45 (20.8)
Previous PCI (%)	41 (18.4)	49 (22.3)
Previous CABG (%)	2 (0.9)	1 (0.5)
Ejection fraction	58.5±9.2	58.8±9.7
NYHA class (%)		
I	87 (52.4)	97 (56.1)
II	48 (28.9)	50 (28.9)
III	26 (15.7)	15 (8.7)
IV	5 (3.0)	11 (6.4)
EUROSCORE	2 (IQR 1-4)*	2 (IQR 1-3)*
SYNTAX score	23.4±7.2*	21.5±7.2*
Stable angina pectoris (%)	191 (85.3)	175 (79.2)
Lesions treated	2 (IQR 1-3)*	2 (IQR 1-2)*
Distal LMCA lesion (%)	189 (84.4)*	164 (74.2)*
LMS lesion location		
Ostial	53 (23.7)	61 (28.5)
Shaft	69 (30.8)	96 (44.7)*
Distal	203 (90.6)	164 (74.2)*
Two stent strategy	73 (32.6)	61 (33.3)
Biomatrix Flex stent use	184 (82.1)	165 (75.0)
First generation DES	16 (7.1)	12 (5.5)
Newer generation DES	206 (92.0)	204 (92.7)

Supplementary table 2. Baseline characteristics, NOBLE study patients allocated to PCI and underwent post IVUS (added 6 patients allocated to CABG included in the core-lab analysis), by core-lab/no core-lab group. *=statistical significance between groups.

N=224	Malapposition	No Malapposition	HR (95% CI)	p-value
MACCE	33.3%(4)	20.8%(44)	1.47 (0.53-4.10)	0.46
Death	8.3%(1)	6.1%(13)	0.99 (0.13-7.63)	1.0
Non-procedural MI	0%(0)	5.7%(12)		0.38
Stent thrombosis*	0%(0)	1.4%(3)		0.68
Repeat Revascularization	25%(3)	11.3%(24)	2.16 (0.65-7.18)	0.26

Supplementary table 3. Rates of clinical events for those with and without stent malapposition identified on IVUS. *relates to definite stent thrombosis.

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Vessel segment	MSA (mm ²)	Failures to achieve MSA
Left main stem n=224	12.5±3.0	8 (3.6%)
Bifurcation core segment n=223	16.9±4.2	1 (0.5%)
Ostial LAD n=213	10.1±2.9	11(5.2%)
Ostial LCx n=53	9.6±3.4	4 (7.6%)

Supplementary table 4a. Mean minimal stented areas (MSA) for each vessel segment, and number of failures to achieve an MSA of ≥8mm² in the LMS, ≥7mm² in the POC, ≥6mm² in the ostial LAD and ≥5mm² in the ostial LCx.

	Failure to achieve MSA	No failure to achieve MSA	HR (95% CI)	p-value
MACCE	7 (36.8%)	41 (20%)	1.8 (0.81-4.82)	0.15
Death	3 (15.8%)	11 (5.4%)	2.8 (0.79-10.14)	0.11
Non-procedural MI	3 (15.8%)	9 (4.4%)	3.6 (0.97-13.26)	0.06
Repeat revascularisation	3 (15.8%)	24 (11.7%)	1.3 (0.38-4.18)	0.71

Supplementary table 4b. Event rates for those in whom on post-procedure IVUS examination, one or more vessel segments failed to achieve an MSA of ≥8mm² in the LMS, ≥7mm² in the POC, ≥6mm² in the ostial LAD and ≥5mm² in the ostial LCx. CI represents confidence interval; MI, myocardial infarction.

	HR	95% CI	p-value
Age	1.04	1.01-1.08	0.01
Female gender	0.86	0.42-1.78	0.61
Diabetes	1.29	0.60-2.76	0.51
Treated hypercholesterolemia	0.55	0.25-1.24	0.15
Hypertension	2.33	1.13-4.81	0.02
Current smoker	1.33	0.65-2.75	0.44
Prior PCI	1.45	0.72-2.93	0.30
Ejection fraction (%)	0.99	0.96-1.03	0.60
Ostial LMS	0.67	0.32-1.39	0.28
Distal bifurcation	2.39	0.58-9.85	0.23
LMS treated alone	0.51	0.16-1.65	0.26
Syntax Score	1.04	1.00-1.08	0.06
Logistic Euroscore	1.06	1.02-1.10	0.003
LMS MSA(mm ²)	0.93	0.84-1.03	0.19
Maximum residual plaque burden (%)	1.02	0.99-1.05	0.19
Calcification arc >90° at MSA	1.46	0.82-2.61	0.20
Malapposition on IVUS	1.47	0.53-4.10	0.46

Supplementary table 5: Univariate predictors of MACCE in 224 patients with post-procedural IVUS assessment. Multi-variable predictors of MACCE: age (HR 1.03, 95% CI 1.00-1.06, p=0.048) and hypertension (HR 2.23, 95% CI 1.07-4.65, p=0.03)

	HR	95% CI	p-value
Age	1.04	0.97-1.10	0.26
Female gender	0.44	0.14-1.35	0.15
Diabetes	2.69	0.83-8.75	0.10
Treated hypercholesterolemia	1.23	0.16-9.46	0.84
Hypertension	2.81	0.62-12.7	0.18
Current smoker	-	-	-
Prior PCI	1.46	0.40-5.34	0.56
Ejection fraction (%)	1.02	0.94-1.10	0.66
Ostial LMS	0.30	0.04-2.33	0.25
Distal bifurcation	-	-	-
LMS treated alone	-	-	-
Syntax Score	1.03	0.96-1.11	0.41
LMS MSA(mm ²)	0.73	0.59-0.90	0.004
EEM at LMS MSA (mm ²)	0.91	0.78-1.05	0.21
Maximum residual plaque burden (%)	1.06	1.01-1.11	0.01
Calcification arc >90° at MSA	1.55	0.51-4.75	0.44
Malapposition on IVUS	1.35	0.18-10.42	0.77
Logistic Euroscore	1.02	0.92-1.12	0.73

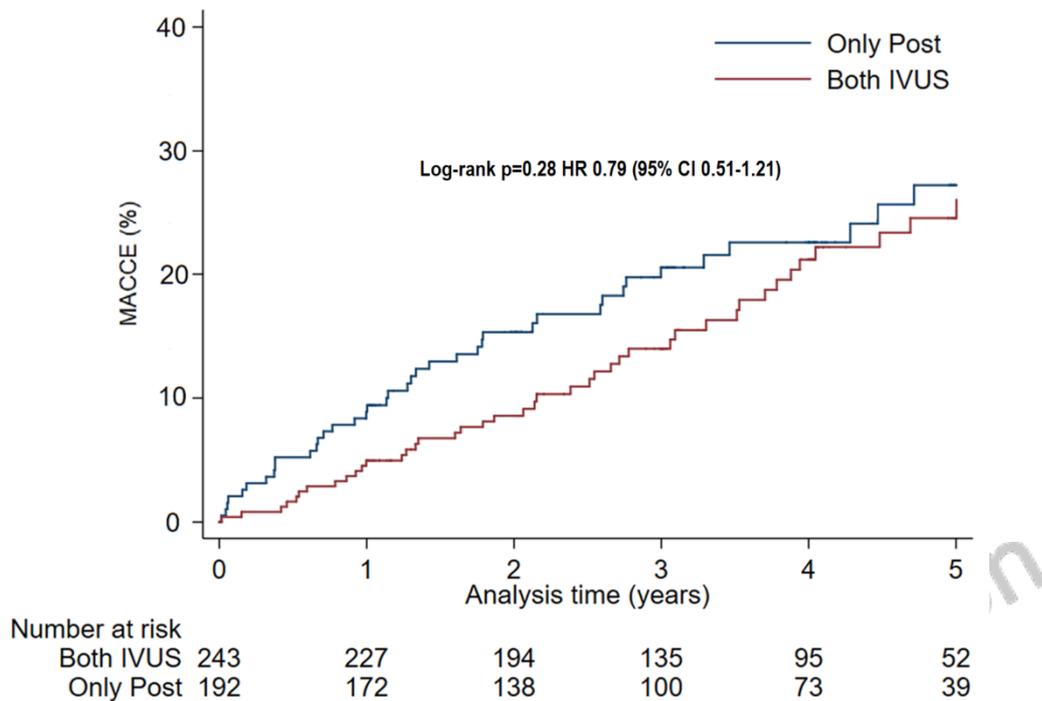
Supplementary table 6: Univariate predictors of LMS TLR in 224 patients with post-procedural IVUS assessment. Multi-variable predictors of LMS TLR: LMS MSA (HR 0.75, 95% CI 0.61-0.92, p=0.006.

IVUS LMS MSA tertile (range)	Low 4.4-10.8mm² n=74	Intermediate 10.9-13.4mm² n=73	Upper 13.4- 25.4mm² n=77	p-value
Age (years)	66.8±7.4	66.5±9.9	66.8±8.9	0.95
Female	10 (13.5%)	22 (30.1%)	18 (23.4%)	0.05
Diabetes	11 (14.9%)	7 (9.6%)	16 (20.8%)	0.15
Insulin treated diabetes	1 (1.4%)	0 (0%)	2 (2.6%)	0.78
Treated hyperlipidaemia	69 (93.2%)	61 (83.6%)	70 (90.9%)	0.14
Hypertension	52 (70.3%)	51 (69.9%)	49 (63.6%)	0.62
Current smoker	14 (18.9%)	8 (11.0%)	10 (13.0%)	0.35
Prior PCI	12 (16.2%)	14 (19.2%)	15 (19.5%)	0.84
Ejection Fraction (%)	58.4±10.1	59.4±8.2	57.9±9.4	0.64
LMS lesion involvement				
Ostial LMS	12 (16.2%)	22 (30.1%)	19 (24.7%)	0.14
Distal bifurcation	69(93.2%)	61 (83.6%)	73 (94.8%)	0.04
LMS treated alone*	9 (12.0%)	10 (13.7%)	5 (6.5%)	0.32
Two stent strategy	23 (31%)	17 (23.3%)	33 (42.9%)	0.04
SYNTAX score	23.1±7.1	22.4±7.5	24.7±7.0	0.15
MSA (mm ²)	9.4±1.3	12.3±0.8	15.7±2.1	<0.0001
EEM at MSA (mm ²)	17.9±2.9	20.7±2.8	23.9±3.7	<0.0001
Maximum residual plaque burden (%)	46.6±9.4	39.6±7.8	33.8±9.0	<0.0001
Calcification on IVUS at MSA	53 (71.6%)	41 (56.2%)	37 (48.1%)	0.01
Median arc of calcification (25 th -75 th centile)	135 (0-200)	90 (0-150)	0 (0-100)	0.001

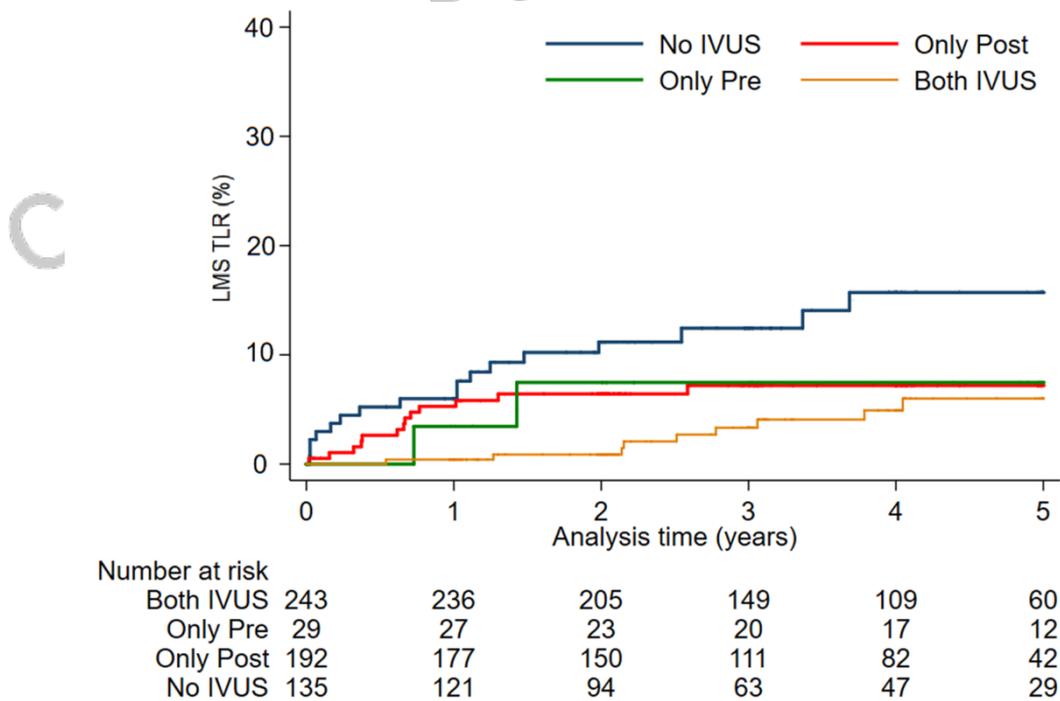
Supplementary table 7. Demographic, angiographic and IVUS characteristics for the three tertiles of LMS MSA.

IVUS LMS MSA tertile (range)	Low 4.4-10.8mm ² n=74	Intermediate 10.9-13.4mm ² n=73	Upper 13.4-25.4mm ² n=77	p-value L vs I	p-value L vs H
MACCE	1 (1.4%)	2 (2.7%)	2 (2.6%)	0.62	0.52
All cause mortality	0 (0%)	0 (0%)	2 (2.6%)	1.0	0.50
Cardiac death	0 (0%)	0 (0%)	2 (2.6%)	1.0	0.50
Non-procedural MI	1 (1.4%)	1 (1.4%)	1 (1.3%)	1.0	1.0
Definite Stent Thrombosis	0 (0%)	1 (1.4%)	0 (0%)	0.50	1.0
Stroke	0 (0%)	0 (0%)	0 (0%)	1.0	1.0
Rpt Revasc	0 (1.4%)	2 (2.7%)	1 (1.3%)	0.62	1.0

Supplementary table 8. Comparison of 30 day outcomes by left main stem MSA tertile. L vs I denotes low tertile versus intermediate tertile; L vs H, low versus high tertile



Supplementary figure 1. Comparison of MACCE outcomes by whether IVUS was performed both pre and post stenting of the left main stem, or only post-stenting.



Supplementary figure 2. Comparison of Left main stem target lesion revascularization (TLR) by whether IVUS was performed both pre and post stenting of the left main stem, only post-stenting, only pre-stenting, or not at all.

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