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Outcomes of predefined optimisation criteria for intravascular ultrasound guidance of left main stenting

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KEYWORDS

- drug-eluting stent
- intravascular ultrasound
- left main

Abstract

Aims: This study sought to investigate the prognostic effect of a protocol with optimisation targets for intravascular ultrasound (IVUS)-guided left main (LM) revascularisation.

Methods and results: A protocol was prospectively applied for IVUS-guided LM revascularisation (IVUS-PRO group) including predefined optimisation targets. Using propensity score matching, we selected as control groups patients with angiography-guided PCI (ANGIO group) and IVUS-guided PCI (IVUS group) from a large multicentre registry. The primary endpoint was a composite of cardiac death, LM-related infarction and LM revascularisation at 12 months. In each group, 124 patients with comparable characteristics were included. The incidence of the primary outcome was significantly higher in the ANGIO group compared to the IVUS-PRO group (12.9% vs 4.8%, HR 0.35, 95% CI: 0.15 to 0.82, p=0.02), but not with respect to the IVUS group (12.9% vs 8%, HR 0.51, 95% CI: 0.20 to 1.22, p=0.1), driven by a lower rate of LM revascularisation (8% in the ANGIO group, 6.4% in the IVUS group and 3.2% in the IVUS-PRO group). IVUS-PRO resulted in being an independent risk predictor (HR 0.45, 95% CI: 0.15 to 0.98; p=0.041).

Conclusions: IVUS guidance of LM stenting provides prognostic benefit with respect to the use of angiography alone, particularly when following a protocol with these predefined optimisation criteria.

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Abbreviations

DES	drug-eluting stents
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LCx	left circumflex artery
LM	left main coronary artery
MI	myocardial infarction
MSA	minimum stent area
PCI	percutaneous coronary intervention
RLA	reference lumen area
TLR	target lesion revascularisation

Introduction

Percutaneous revascularisation of the left main coronary artery (LM) is already recommended by the clinical guidelines, especially in those cases without multivessel disease[1].

The use of intravascular ultrasound (IVUS) to guide PCI of the LM with drug-eluting stents (DES) has been associated with a better prognosis in several studies, though mostly retrospective registries[2-12]. In fact, the most recently released guidelines provide a class IIa recommendation for the use of IVUS in LM PCI; its use is also encouraged by recent consensus documents[1,13,14].

Nonetheless, in the abovementioned studies[2-12], what was evaluated was simply the use or non-use of IVUS to guide LM PCI, without evaluating specific protocols with predefined optimisation criteria. Thus, there is a remarkable knowledge gap in how best to utilise IVUS to guide the best outcomes in PCI of the LM.

Our group has carried out extensive research in the field of IVUS and LM. We prospectively validated a cut-off value for luminal area to defer safely the revascularisation of intermediate LM lesions[15,16] and subsequently reported a large registry comparing IVUS and angiography in the guidance of LM PCI[4].

In this study, we present a strategy for the use of IVUS to guide PCI of the LM, based on a protocol with clear recommendations and optimisation targets adapted to the different locations of the lesions and the morphological characteristics of the LM[17]. We analyse the clinical results derived from its prospective application.

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Methods

POPULATION

Since January 2014 we have systematically applied an IVUS protocol for the guidance of LM PCI, including predefined optimisation targets. Patients with a clinical indication for percutaneous revascularisation of the LM as determined by the local Heart Team were eligible. Patients with cardiogenic shock at the time of PCI were excluded from the analysis.

All interventional cardiologists in the institution were urged to follow the strategy of LM PCI guided by IVUS according to the protocol previously established by consensus. However, the decision to use IVUS was ultimately left to the operator. Patients treated according to this IVUS protocol constituted the IVUS-PRO group.

PROCEDURES AND IVUS PROTOCOL

The recommendations for the use of IVUS and the optimisation criteria applied **(Figure 1, Figure 2)** are described in detail in **Supplementary Appendix 1**.

A 12-month period of dual antiplatelet therapy was generally recommended during most of the study period; however, according to the more recently released clinical guidelines, the possibility of prescribing a six-month period became an alternative in the last period of the study, specifically in stable patients who did not require two stents and had a higher risk of bleeding.

There was no routine angiographic follow-up, unless clinically indicated by the referring cardiologist in the presence of

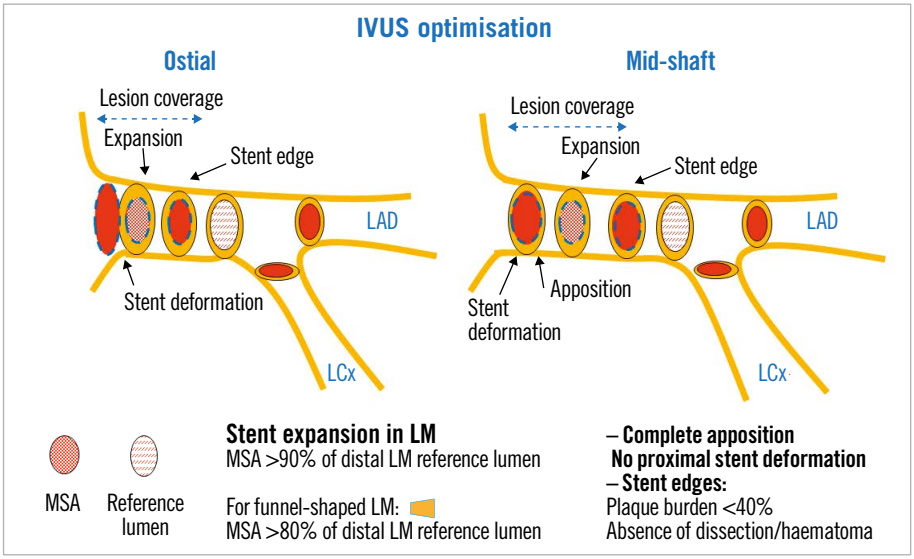

Figure 1. *Optimisation targets for ostial and mid-shaft LM lesions.*

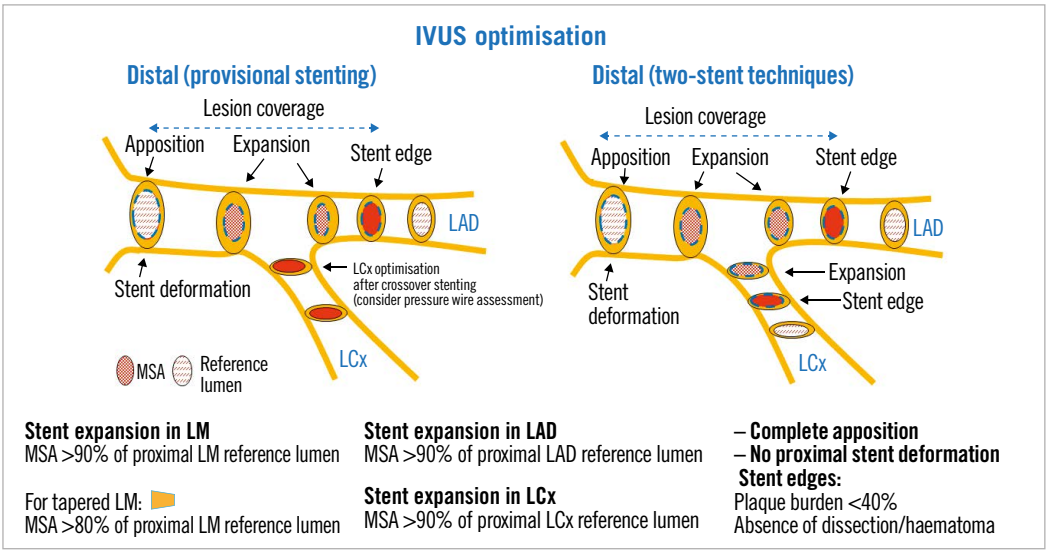

Figure 2. *Optimisation targets for distal LM lesions.*

symptomatic recurrence or the appearance of relevant ischaemia in non-invasive tests. For the clinical follow-up, telephone contact was made with all the patients and the data in the electronic health records for both in-hospital and out-of-hospital care were consulted.

The patients signed the specific informed consents for the procedures performed. The protocol was framed in healthcare practice and the approval of the institutional review board (IRB) was obtained for the execution of a prospective observational registry.

CONTROL GROUPS

Our multicentre research group has built a prospective database of patients with LM disease treated with DES which served as the basis for a previous publication that showed the association between IVUS guidance and better clinical outcomes[4].

From this multicentre LM database, we selected as control groups those patients treated with non-first-generation DES before implementation of our IVUS protocol, using either IVUS guidance (415 patients) or only angiography (603 patients) **(Figure 3)**. A propensity score-matching analysis was carried out to pair patients from these two groups with those of the IVUS-PRO group. With regard to the IVUS group from the multicentre database, a protocol with predefined optimisation criteria was not generally applied and in every single case all decisions were left to the operator's judgement.

ENDPOINTS

The primary endpoint was a composite of cardiac death, myocardial infarction (MI) (ST- or non-ST-elevation) related to the LM and target lesion revascularisation (TLR) in the LM.

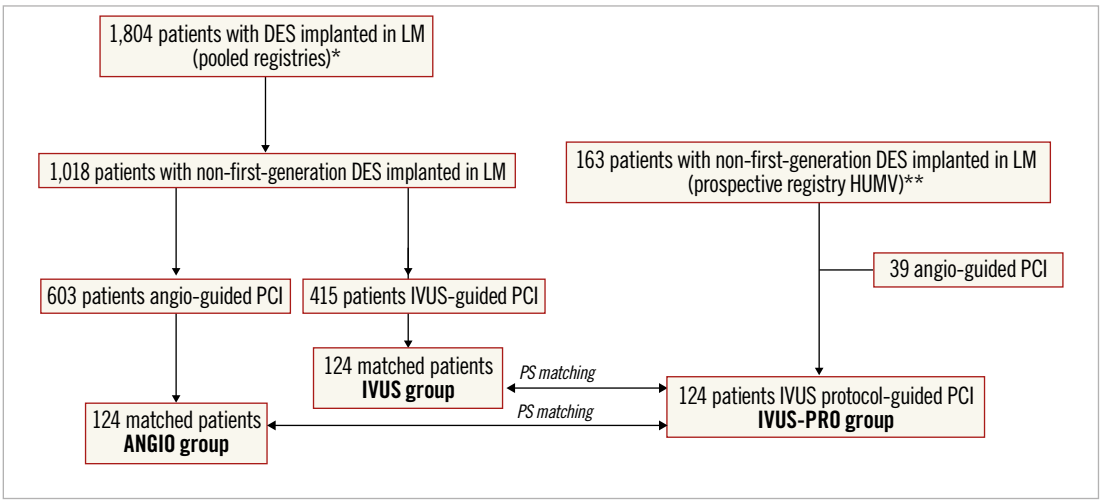

Figure 3. *Flow chart of the study. * Pooled registries of patients undergoing LM PCI with DES from 2002 to 2013. ** Prospective registry in the Hospital Universitario Marques de Valdecilla (HUMV) of patients undergoing LM PCI with DES (January 2014 to March 2018).*

MI was linked to the LM lesion in either of the following circumstances: 1) LM lesion identified as culprit on angiography, based on stenosis severity/lumen morphology or intravascular imaging assessment and always considering clinical data; 2) electrocardiographic and/or echocardiographic findings suggestive of LM involvement with no confirmatory angiography available. Periprocedural MI was defined as an increase in CK-MB >10x URL, or >5x URL plus either 1) new pathological Q-waves in ≥2 contiguous leads or new left bundle branch block (LBBB), or 2) angiographically documented coronary artery occlusion or new severe stenosis with thrombosis, or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. TLR was defined as revascularisation for LM restenosis (>50%), also including proximal or distal segments (5 mm) adjacent to the stent or stents used for treatment of the lesion, and including the first 5 mm distal to the ostial circumflex artery if not stented. Any surgical revascularisation as the result of LM restenosis as previously defined was also considered a TLR. Definite or probable stent thrombosis at the LM site was considered according to the Academic Research Consortium definitions.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation or median (interquartile range) and categorical variables as percentages. Distribution was assessed for each variable with the Kolmogorov-Smirnov test. Accordingly, continuous variables were compared with the Student's t-test if they followed a normal distribution and by Wilcoxon tests when this was not the case. The categorical variables were compared with the chi-square test or Fisher's exact test, as required. Kaplan-Meier curves for event-free survival were obtained for each group and compared using the log-rank test and hazard ratios with 95% confidence intervals. A Cox proportional hazards multiple regression analysis was used to determine independent predictors of the primary outcome. The model included all variables that showed an association with the primary outcome in univariate analysis with a p-value <0.1. A propensity score-matching analysis was conducted **(Supplementary Appendix 2)** pairing patients in the three groups. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, Version 24 (IBM Corp., Armonk, NY, USA).

Results

During the study period, from January 2014 to March 2018, a total of 124 patients underwent percutaneous revascularisation of the LM with DES guided by the IVUS protocol (IVUS-PRO group). The flow chart of the study is shown in **Figure 3**. These represented 76% of the patients undergoing PCI of the LM in that period, since in 39 patients IVUS was not used. These decisions were based on the operator's judgement in each particular case and were definitely more related to the preferences of the operator than to the characteristics of the case.

By means of a propensity score matching with the IVUS-PRO group, two groups of 124 patients each were selected from the multicentre registry, the ANGIO group and the IVUS group. These groups showed clinical and angiographic baseline characteristics comparable to the IVUS-PRO group, but also between themselves, without significant differences being observed **(Supplementary Table 1, Supplementary Table 2)**.

Regarding procedural aspects, pre-interventional IVUS was used in 87% of the cases in the IVUS-PRO group but only in 25% of the IVUS group. Among the former, in 12 cases IVUS examination was carried out after predilatation. The stents implanted were significantly larger in the two IVUS groups. Post-dilatation was more frequently used in the IVUS-PRO group and performed with larger balloons.

IVUS findings are shown in **Table 1**. At baseline in the IVUS group, the LM minimum lumen area (MLA) was larger and the plaque burden and the calcification arc smaller, which is explained by the fact that baseline IVUS examination was much less commonly performed in this group and mostly conducted in those cases with less angiographic severity (ambiguous stenosis). With regard to the procedural results, the LM minimum stent area (MSA) along with the LAD and LCx MSAs were significantly larger in the IVUS-PRO group. The IVUS-PRO optimisation targets were retrospectively applied in the IVUS group. All optimisation criteria,

Table 1. IVUS findings.

	IVUS-PRO N=124	IVUS N=124	*p*-value
Baseline*			
LM minimum lumen area, mm²	4.3 (3.2-5.5)	4.7 (3.9-5.7)	<0.01
LM reference lumen area, mm²	12.5 (10.5-13.6)	12.7 (10.8-14)	0.4
LM maximal plaque burden, %	74 (67-82)	68.5 (62-79)	<0.01
LM maximal arc of calcification, °	109 (71-166)	98 (66-149)	<0.01
Final result			
LM minimum stent area, mm²	11.8 (10.2-12.6)	10 (8.1-11.2)	<0.01
**LAD minimum stent area, mm²	8.5 (7.4-9.2)	7.4 (6.6-8.2)	<0.01
**LCx minimum stent area, mm²	7 (6.3-7.6)	6.1 (5.4-6.5)	<0.01
IVUS-PRO criteria			
Expansion criteria met	109 (88%)	80 (64.5%)	<0.01
Complete apposition	118 (95.2%)	108 (87%)	0.04
Plaque burden <40% at stent edges	114 (92%)	101 (81.4%)	0.02
No dissection/haematoma at stent edge	123 (99.2%)	120 (96.7%)	0.4
No proximal stent deformation	124 (100%)	116/116 (100%)***	1.000

Values presented as median (interquartile range) or n (%). * Data reported for cases undergoing baseline IVUS examination, 108 (87%) in the IVUS-PRO group and 31 (25%) in the IVUS group. However, the LM reference lumen area could be estimated during intraprocedural examinations. ** Data corresponding to cases with stent implanted in that vessel. *** In 8 cases the final IVUS run was not adequate to assess properly the presence of proximal stent edge deformation. LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main

except for dissection/haematoma at the stent edges and longitudinal deformation, were more frequently met in the IVUS-PRO group.

In the IVUS-PRO group, the optimisation criteria were fulfilled in the majority of patients, with the expansion having a certain lower compliance (88%), mainly due to the presence of heavily fibro-calcified lesions that limited the capacity of stent expansion either in the distal LM or in the ostium of branches. In a few cases, minor degrees of incomplete apposition were left, corresponding to distal LM lesions with a proximal landing site lumen >5.5 mm and a stent implanted from the LAD to the LM with a nominal diameter <4 mm. Overexpansion of these stents >2 mm over the nominal size was considered inappropriate. Only one case was left with a short (<2 mm) intimal dissection extending <45º. Stent deformation was detected during intraprocedural IVUS examinations in seven cases (5.6%) and was finally solved in all cases.

No patients were lost to follow-up. Survival curves for the composite primary endpoint are shown in **Figure 4**. There were significant differences between the IVUS-PRO and ANGIO groups but not between the IVUS and ANGIO groups. Survival free of TLR is shown in **Figure 5**, demonstrating a strong but not significant trend favouring the IVUS-PRO group. The reported adverse cardiovascular events are listed in **Table 2**. None of the periprocedural myocardial infarctions was related to the LM lesion but to lesions in other locations; these were caused by transient or permanent side branch occlusion, non-reflow phenomenon or distal thrombus embolisation.

Among the four cases requiring TLR in the IVUS-PRO group, two were reported in the subgroup of 15 patients with suboptimal expansion (13.3%) and the other two in the optimal expansion subgroup (1.8%). LM revascularisation was performed in the ANGIO group in 10 cases and, among these, 6 presented effort angina (3 positive stress echo, 2 positive treadmill test and 1 no test conducted) and 4 an ACS. In the IVUS group, TLR was carried out in 8 cases and, among these, 5 presented effort angina (3 positive stress echo, 1 positive treadmill test, 1 nuclear stress test) and 3 an ACS. Finally, in the IVUS-PRO group, TLR was required in 4 cases and, among these, 3 presented effort angina (3 positive stress echo) and 1 an ACS.

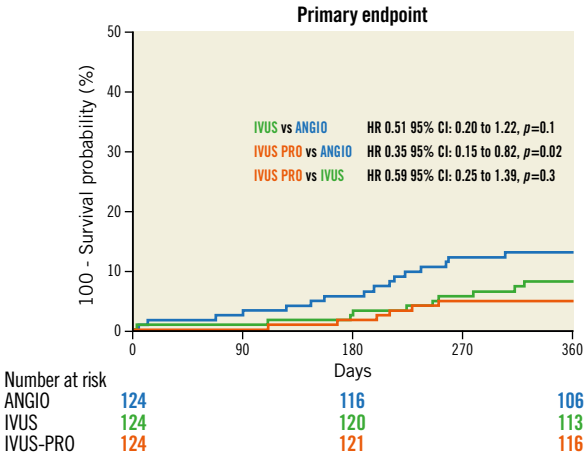

Figure 4. *Outcomes of the study groups. Primary endpoint-free survival curves (composite of cardiac death, ST- or non-ST-elevation myocardial infarction related to the LM lesion and target lesion revascularisation in the LM).*

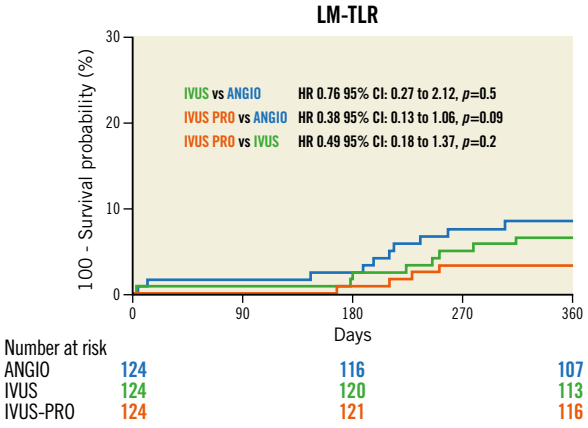

Figure 5. *Outcomes of the study groups. LM lesion revascularisation-free survival curves.*

Independent predictors for the primary outcome are listed in **Table 3**. The IVUS-PRO group resulted in being an independent predictor for a lower risk.

Table 2. Clinical outcomes at 12-month follow-up.

	ANGIO N=124	IVUS N=124	*p*(1)	IVUS-PRO N=124	*p*(2)	*p*(3)
Primary outcome	16 (12.9%)	10 (8%)	0.1	6 (4.8%)	0.02	0.3
Cardiac death	5 (4%)	3 (2.4%)	0.4	2 (1.6%)	0.2	0.6
LM-related MI	4 (3.2%)	3 (2.4%)	0.6	1 (0.8%)	0.1	0.3
LM revascularisation	10 (8%)	8 (6.4%)	0.5	4 (3.2%)	0.09	0.2
LM stent thrombosis*	2 (1.6%)	1 (0.8%)	0.6	1 (0.8%)	0.6	0.9
All-cause death	7 (5.6%)	4 (3.2%)	0.3	4 (3.2%)	0.3	0.9
Spontaneous MI	6 (4.8%)	5 (4%)	0.7	4 (3.2%)	0.5	0.7
Periprocedural MI	5 (4%)	4 (3.2%)	0.8	4 (3.2%)	0.8	0.9

Values are n (%). *Definite or probable thrombosis. *p*-values: *p*(1) for the comparison ANGIO versus IVUS; *p*(2) for the comparison ANGIO versus IVUS-PRO; *p*(3) for the comparison IVUS-PRO versus IVUS (log-rank test). LM: left main; MI: myocardial infarction (ST-elevation and non-ST-elevation)

Table 3. Independent predictors of the primary outcome.

	HR (95% CI)	*p*-value
Age	1.05 (1.01–1.10)	0.006
Insulin-treated diabetes	3.25 (1.08–9.82)	0.036
Distal LM treated with 2 stents	5.50 (2.26–13.38)	0.0002
IVUS-PRO group	0.45 (0.15–0.98)	0.041
LM: left main		

Discussion

The main findings of this study can be summarised as follows. 1) The application of a detailed protocol for the use of IVUS with predefined optimisation targets to guide PCI of the LM with new-generation DES is associated with better outcomes compared to the use of angiography alone. 2) The systematic use of a protocol with well-defined targets seems to provide an additional clinical benefit with respect to a non-protocolised use of IVUS.

Differences in the primary endpoint were primarily driven by differences in the TLR. This finding makes sense, since IVUS guidance is associated with better stent sizing and subsequent higher expansion rates, providing a larger in-stent lumen. Thus, the clinical event most sensitive to the procedural advantage linked to IVUS guidance is TLR, with infarction or death rates being affected to a lesser degree.

The use of IVUS to guide DES implantation in the LM provides a significant clinical advantage according to the multiple studies (mostly registries) conducted so far[2-12]. However, none of these previous studies prospectively evaluated a specific IVUS protocol with a set of PCI optimisation criteria.

Our protocol recommended the use of IVUS before PCI, so the planning of the optimal PCI strategy was facilitated, starting with adequate plaque modification techniques and correct stent sizing. Targets for stent expansion were established in the protocol. Stent underexpansion is a well-known major predictor of stent failure but there are no uniform criteria regarding recommended targets for PCI optimisation in clinical practice for the LM. The optimal IVUS MSA values for preventing in-stent restenosis in the LM were retrospectively assessed in 403 patients undergoing DES implantation[18]. These values were 5.0 mm^2 for the LCx ostium, 6.3 mm^2 for the LAD ostium, 7.2 mm^2 for the distal LM, and 8.2 mm^2 for the proximal LM. However, these cut-off values for the MSA, derived from studies carried out in an Asian population, are conditioned by the size of the coronary vasculature which, in turn, has ethnic and anthropomorphic determinants[19,20]. Therefore, the absolute values of MSA have a limited value as optimisation targets. With respect to the relative values of stent expansion, different targets for stent optimisation in overall coronary lesions have been proposed[13]. In the particular case of the LM, given its short length and clinical relevance, we thought it would be appropriate to choose a 90% expansion cut-off, which was modified (80%) according to the particular anatomy of the LM in each case[17].

In our study 88% of cases met the expansion criteria. Accordingly, the LM MSA in the IVUS-PRO group was significantly larger than in the IVUS group. It is noteworthy that the average MSA values achieved in our study were higher than those reported in the aforementioned study[18].

No clear link exists between acute malapposition (in the absence of underexpansion) and subsequent stent failure; however, in the case of the LM there are aspects that encouraged us to recommend correcting as far as possible the incomplete strut apposition. In our registry, very few cases were left with minor incomplete apposition. These were limited to those with a large disproportion of size between the implanted stent from the LAD to the LM and the size of the proximal LM (notable tapering). However, the magnitude of incomplete apposition was minor (<0.5 mm axial distance and <2 mm long) and considered to be benign[21].

Regarding stent edges, avoidance of stent landing sites with plaque burden >40% appears to be clinically important, as this has been linked to subsequent stent edge restenosis following new-generation DES implantation[22]. Large edge dissections by IVUS have been reported as correlates of early stent thrombosis[23], whereas minor edge dissections (only intimal, <45º and <2 mm in length) are unlikely to be clinically significant and possibly do not require correction[24]. Finally, the longitudinal deformation of the stent could be more frequent in LM procedures and may increase the risk of events and hinder future reinterventions on the left coronary artery[25,26]. Therefore, we took great care to recognise and, when required, tackle this phenomenon.

Limitations

This is an observational comparative registry with baseline differences between groups. Notwithstanding the use of a propensity score matching, it still remains possible that some unmeasured confounders could have had an effect on clinical outcome.

It is clear that a randomised trial would be the most appropriate design, but the optimisation criteria to apply in such an eventual trial (really complex and expensive to carry out) should be based on a previous prospective experience such as the one described here. In the meantime, the use of a protocol like this could be very helpful to the community of interventional cardiologists.

The sample size was limited and the study was underpowered for certain clinical outcomes. Nonetheless, significant prognostic differences emerged in favour of the IVUS-PRO group with the remarkable differences in post-procedural IVUS findings providing a rationale for these clinical differences.

The registry from which the IVUS group was extracted was not originally designed to assess the influence of different IVUS optimisation criteria on final clinical outcomes. Therefore, the IVUS criteria for stent sizing or identification and treatment of malapposition or underexpansion were mostly unknown. The decisions taken after IVUS examination in this control group were left to the operator's judgement. Data regarding procedure duration, contrast medium volume and radiation were not available in all groups.

Conclusions

IVUS guidance of LM stenting provides a prognostic benefit with respect to the use of angiography alone, particularly when using a detailed IVUS protocol comprising a set of predefined optimisation criteria such as those considered in this study. These findings should be evaluated further in randomised controlled trials.

Impact on daily practice

The use of IVUS may improve the prognosis of patients undergoing left main percutaneous revascularisation but there are no well-established criteria for optimisation. The application of an IVUS protocol with the predefined optimisation targets considered in this study for left main coronary artery revascularisation appears to improve outcomes with respect to the use of angiography alone or even with respect to the use of IVUS outside this protocol.

Conflict of interest statement

J.M. de la Torre Hernandez reports receipt of grants/research support from Abbott, Biosensors, Bristol Myers Squibb, and Amgen, and receipt of honoraria or consultation fees from Boston Scientific, Medtronic, Biotronik, AstraZeneca, and Daiichi Sankyo. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. Statistics: propensity score matching.

Supplementary Table 1. Clinical characteristics.

Supplementary Table 2. Angiographic and procedural characteristics.

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Supplementary data

Supplementary Appendix 1. Methods

IVUS protocol

The recommendations for IVUS assessment of the LM were the following: a) perform a baseline study of the LM, not only in ambiguous but also in significant lesions; b) in case of a distal LM lesion, always try to conduct two IVUS runs, from both the LAD and the LCx, aimed at assessing accurately the involvement of the ostium of both branches; c) in cases presenting backward leap of the IVUS catheter during pullback, usually because of a marked angulation at the LM bifurcation, acquire imaging during a gentle push forward of the IVUS catheter to obtain a complete study; d) in cases with an ostial lesion, try to achieve coaxiality of the catheter and keep the guiding catheter disengaged from the LM during IVUS pullback.

Regarding lesion preparation prior to stenting, IVUS provides morphological characterisation of plaques, specifically the location and extension of calcification. According to these findings, the operator should choose and size the most appropriate device, including a non-compliant balloon, scoring/cutting balloon or rotational ablation (coronary lithotripsy not available during study period).

Stent sizing should be based on IVUS findings (always considering only the lumen) with the stent diameter being equivalent to the lumen diameter in the selected distal landing site, rounding it up (adding up to 0.4 mm). Try to choose landing sites showing plaque burden <40%. In cases with distal LM lesions requiring a <4 mm in diameter DES from the LAD to the LM showing a very large proximal LM lumen (>5.5 mm) due to observed tapering, the stent length should be fitted just to land in a proximal site up to 5-5.5 mm in size, in order to facilitate further complete stent apposition.

IVUS optimisation criteria

1. Complete LM stent apposition.

As described above, in cases with distal LM lesions requiring a 4 mm in diameter DES from the LAD to the LM and showing a very large proximal LM lumen (>5.5 mm), the intention was to select a proximal landing site with a lumen diameter no larger than 5-5.5 mm. However, in those cases in which this approach was neither feasible nor successful, it was considered acceptable to leave minor residual degrees of incomplete apposition (axial distance <0.5 mm and <2 mm in length) if overexpansion of the stent 2 mm or more over the nominal stent size was not considered adequate.

2. Optimal LM stent expansion defined as follows:

a) Ostial and mid-shaft LM lesions: expansion >90% of the distal reference lumen in the LM (>80% if funnel-shaped LM).

b) Distal LM lesions: expansion >90% of the proximal reference lumen in the LM (>80% if markedly tapered LM).

c) In cases showing diffuse LM disease, the estimated hypothetical reference lumen was equivalent to 90% of the smallest vessel area in the LM. The goal was to attain at least 90% of the expansion according to the selected hypothetical reference lumen.

The morphological shape of the LM was estimated visually and no quantitative metrics were used to categorise an LM as funnel-shaped or tapered, though an angiographic difference >0.5 mm between the proximal and distal LM was generally the threshold for this visual classification.

3. Optimal stent expansion at ostial LAD and LCx sites aiming at >90% of the reference lumen in the proximal LAD and LCx, respectively.

4. Stent edges with residual plaque burden <40%, absence of dissection or haematoma and no proximal stent deformation. Longitudinal stent deformation was defined as distortion or shortening of the stent in the longitudinal axis following deployment.

Dissections limited to the intima, with arc <45º and <2 mm in length, could be left untreated if considered so by the operator.

IVUS assessment was in all cases performed using solid-state or phased array catheters (Philips Volcano). Non-first-generation DES were used, taking into account the different workhorse designs and their maximal achievable diameter with overexpansion, given that LM PCI often involves deployment of a single stent across vessels with marked disparity in diameters.

In patients showing distal LM lesions, the provisional stent strategy was the most common approach, supported by the observation of a minimum luminal area in the ostium of the LCx >3.5 mm^2 with plaque burden <50%. In patients requiring a crossover stenting from the LM to the LAD, it was not uncommon to open struts towards the LCx, particularly in cases showing more closed angulation between branches. This was done with a 1:1 vessel to artery ratio balloon at nominal pressure followed by a kissing balloon inflation and finally a new proximal post-dilatation. However, this was left to the judgement of the operator. In cases with suspected flow compromise to the LCx, a pressure wire assessment was carried out and action was taken accordingly.

The type of two-stent technique when required was decided according to the anatomy of the bifurcation (angle and size of LM/LAD/LCx) and the preference of the operators, but only the T, TAP and culotte techniques were used. Once both stents were implanted, a kissing balloon inflation was accomplished followed by a final proximal optimisation in the LM aimed at correcting the asymmetry.

In relation to the longitudinal stent deformation, this was evaluated in the last IVUS pullback after the optimisation of the implanted stent(s), disengaging the guiding catheter from the LM and thus allowing imaging of the entire stent length. In case of any deformation being present, a balloon dilatation of the proximal edge of the stent was performed.

Supplementary Appendix 2. Statistics: propensity score matching

The propensity score matching was aimed at pairing each patient in the IVUS-PRO group with a patient in the IVUS group and a patient in the ANGIO group. This procedure involved two stages. 1) The propensity scores were estimated using logistic regression in which IVUS-PRO-guided PCI was used as the outcome variable and all the covariates as predictors (age, gender, smoker, diabetes, hypertension, hypercholesterolaemia, chronic renal failure, left ventricular ejection fraction, previous MI, previous PCI, previous CABG, clinical presentation, number of diseased vessels, number of lesions treated, distal LM lesion, diffuse LM disease, LM ulceration or dissection, LM visual stenosis and use of IIb/IIIa inhibitors). 2) Patients were matched using simple 1:1 nearest neighbour matching based on a "greedy" matching algorithm that sorts the observations in the IVUS-PRO group by their estimated propensity score. It then matches each unit sequentially to a unit in the ANGIO group and to a unit in the IVUS group that has the closest propensity score. All standardised mean differences after matching were below 10%. Calibration was tested using the Hosmer-Lemeshow test and accuracy was assessed using the area under the ROC curve. The "psmatching" custom dialogue was used in conjunction with SPSS version 19 (IBM Corp., Armonk, NY, USA). The psmatching program performs all analyses in R through the SPSS R-Plugin.

Supplementary Table 1. Clinical characteristics.

	ANGIO	**IVUS**	***p*(1)**	**IVUS-PRO**	***p*(2)**	***p*(3)**
	N=124	**N=124**		**N=124**		
Age, yrs	66.9±12	66.2±11.8	0.6	66.5±11.6	0.8	0.7
Women	26 (20.1)	27 (21.8)	0.8	30 (24.2)	0.5	0.7
Current smoker	37 (29.8)	35 (28.2)	0.8	33 (26.6)	0.6	0.8
Diabetes	44 (35.4)	41 (33)	0.7	40 (32.2)	0.6	0.9
Hypertension	84 (67.7)	79 (63.7)	0.5	81 (65.3)	0.7	0.8
Hypercholesterolaemia	77 (62)	70 (56.4)	0.4	73 (58.8)	0.7	0.7
Chronic renal failure	7 (5.6)	8 (6.4)	0.9	10 (8)	0.6	0.8
LVEF, %	55.2±12.6	55.5±13	0.8	55.9±13	0.6	0.8
Previous MI	32 (25.8)	30 (24.2)	0.8	28 (22.5)	0.6	0.8
Previous PCI	25 (20.1)	29 (23.3)	0.6	27 (21.8)	0.8	0.8
Previous CABG	4 (3.2)	3 (3.5)	0.8	2 (1.6)	0.6	0.5
ACS	76 (61.2)	77 (62)	0.9	80 (64.5)	0.6	0.7
MI	29 (23.3)	27 (21.8)	0.8	25 (20)	0.6	0.8

Values are mean±SD or n (%).

p-values: *p*(1) for the comparison ANGIO vs IVUS; *p*(2) for the comparison ANGIO vs IVUS-PRO; *p*(3) for the comparison IVUS-PRO vs IVUS.

ACS: acute coronary syndrome; CABG: coronary artery bypass graft; IVUS: intravascular ultrasound; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 2. Angiographic and procedural characteristics.

	ANGIO N=124	IVUS N=124	*p*(1)	IVUS-PRO N=124	*p*(2)	*p*(3)
2-vessel disease	37 (29.8)	40 (32)	0.8	41 (33)	0.6	0.9
3-vessel disease	32 (25.8)	29 (23.3)	0.7	27 (21.7)	0.5	0.8
Lesions treated	1.45±1.2	1.42±1.1	0.8	1.4±1.1	0.7	0.8
Ostial LM lesion	30 (24.2)	26 (21)	0.6	24 (19.3)	0.4	0.8
Mid-shaft LM lesion	20 (16.1)	21 (17)	0.9	19 (15.3)	0.9	0.8
Distal LM lesion	74 (60)	77 (62)	0.8	81 (65.3)	0.4	0.6
Diffuse LM disease	21 (16.9)	18 (14.5)	0.7	19 (15.3)	0.8	0.9
LM ulceration or dissection	18 (14.5)	20 (16.1)	0.8	22 (17.7)	0.6	0.8
LM visual stenosis, %	70±15.3	69.8±15.8	0.9	69.4±16	0.7	0.8
LM stent length, mm	16.1±5.5	16.6±5.4	0.4	17.9±5.9	0.01	0.07
LM stent diameter, mm	3.6±0.4	3.78±0.38	<0.001	3.85±0.4	<0.001	0.1
Post-dilatation	55 (44.3)	81 (65.3)	0.002	102 (82.2)	<0.001	0.004
Post-dilatation balloon, mm	3.8±0.42	4.05±0.38	<0.001	4.2±0.4	<0.001	0.003
2-stent technique	20 (16)	19 (15.3)	0.9	18 (14.5)	0.8	0.9
- 2 stents/distal lesion	27%	24.6%	0.8	22.2%	0.5	0.8
- SB stent length, mm	16.4±4	17.1±5	0.2	18±5.1	0.006	0.2
- SB stent diameter, mm	2.94±0.38	3.04±0.4	0.04	3.1±0.46	0.001	0.1
Rotational ablation	5 (4)	5 (4)	0.9	4 (3.2)	0.8	0.8
IIb/IIIa inhibitors	19 (15.3)	17 (13.7)	0.8	15 (12)	0.5	0.8
Angiographic success	122 (98.4)	122 (98.4)	0.9	123 (99.2)	0.9	0.9
DAPT for at least 12 mo.	124 (100)	124 (100)	0.9	110 (88.7)	0.001	<0.001

Values are mean±SD or n (%).

p-values: *p*(1) for the comparison ANGIO vs IVUS; *p*(2) for the comparison ANGIO vs IVUS-PRO; *p*(3) for the comparison IVUS-PRO vs IVUS.

Diseased vessel was defined as a vessel with angiographic stenosis ≥50% in a segment with reference lumen diameter >2 mm. Lesion location in the LM could be ostial (at the aorto-ostial junction), mid-shaft (at the mid portion, not affecting ostium or bifurcation) or distal (lesion located at the bifurcational level of the LM). Post-dilatation was defined as the dilatation of the stent with a non-compliant balloon, either larger in size or at higher pressure or both. Angiographic success was defined as a residual stenosis <25% and TIMI 3 flow.

DAPT: dual antiplatelet therapy; IVUS: intravascular ultrasound; LM: left main; PCI: percutaneous coronary intervention; SB: side branch