

Title: The Application of Predefined Optimization Criteria for Intravascular Ultrasound Guidance of Left Main Stenting Improves Outcomes.

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The Application of Predefined Optimization Criteria for Intravascular Ultrasound Guidance of Left Main Stenting Improves Outcomes.

Brief title:

Optimization for IVUS guided left main revascularization

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Aims

This study sought to investigate the prognostic effect of a protocol with optimization targets for intravascular ultrasound (IVUS) guided left main (LM) revascularization.

Methods and results

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

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 optimization criteria.

Key Words: drug-eluting stent, intravascular ultrasound, left main

CONDENSED ASBTRACT

This study sought to investigate the prognostic value of a protocol with predefined optimization targets for IVUS guided left main coronary artery revascularization. A total of 124 patients were prospectively treated according to this protocol. This group was matched with patients undergoing angiography guided PCI (ANGIO group) and IVUS guided PCI (IVUS group) from a multicenter database. The incidence of primary outcome was significantly higher in ANGIO group compared to IVUS-PRO group (12.9% vs. 4.8%, HR 0.35 CI 95% 0.15 to 0.82, $p=0.02$), but not with respect to the IVUS group (12.9% vs. 8%, HR 0.51 CI 95% 0.20 to 1.22, $p=0.1$).

ABBREVIATIONS AND ACRONYMS

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 revascularization

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INTRODUCTION

Percutaneous revascularization 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 to 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 and its use is also encouraged by recent consensus documents. (1, 13, 14)

Nonetheless, in the mentioned 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 optimization criteria. Thus, there is a remarkable knowledge gap in how best to utilize IVUS to guide the best outcomes in PCI of LM.

Our group has developed extensive research in the field of IVUS and LM. We prospectively validated a cut off value for luminal area to defer safely the revascularization 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 optimization targets adapted to the different locations of the lesions and the morphological characteristics of the LM. (17) We analyze the clinical results derived from its prospective application.

METHODS

Population

Since January 2014 we systematically applied an IVUS protocol for the guidance of LM PCI including predefined optimization targets. Patients with a clinical indication by the local heart team of percutaneous revascularization of the LM 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 conformed the IVUS-PRO group.

Procedures and IVUS protocol

The recommendations for the use of IVUS and the optimization criteria applied ([Figures 1-2](#)) are described in detail in [Supplementary material](#).

A 12 months period of double antiplatelet therapy was generally recommended during most of the study period, but according to the more recently released clinical guidelines the possibility of prescribing a 6 months period became an alternative in the last period of the study, specifically in stable patients who did not required 2 stents and portending a higher risk of bleeding.

There was no routine angiographic follow-up, unless clinically indicated by the referring cardiologist in the presence of symptomatic recurrence or the appearance of relevant ischemia in non-invasive tests. For the clinical follow-up, telephone contact was made with all the patients and the data of the electronic health records for both in-hospital and out-hospital care were consulted.

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

Control groups

Our multicenter research group have 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)

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

Endpoints

The primary endpoint was a composite of cardiac death, myocardial infarction (ST or non-ST elevated) related with the LM and target lesion revascularization in LM. Myocardial infarction was linked to the LM lesion in any of the following circumstances: 1) LM lesion identified as culprit in 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 myocardial infarction 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 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 revascularization 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 revascularization 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 definitions by the Academic Research Consortium.

Statistical analysis

Continuous variables are presented as mean \pm 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 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 exact test, as required. Kaplan-Meier curves for event-free survival were obtained for each group and compared using the log-rank test and the hazard ratios with 95% confidence interval. A Cox proportional hazard multiple regression analysis was used to determine independent predictors of primary outcome. The model included all variables that showed association with primary outcome in univariate analysis with a p value <0.1 . A propensity score matching analysis was conducted ([Supplementary material](#)) pairing patients in the three groups. A p value <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 24 for windows.

RESULTS

During the study period, from January 2014 to March 2018, a total of 124 patients underwent percutaneous revascularization 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 criteria 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 multicenter registry, the ANGIO group and the IVUS group. These groups showed clinical and angiographic baseline characteristics comparable to IVUS-PRO group, but also between themselves, without significant differences being observed ([Supplementary tables 1-2](#)).

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 done after predilatation. The stents implanted were significantly larger in the two IVUS groups. Postdilatation was more frequently used in the IVUS-PRO group and performed with larger balloons.

IVUS findings are shown in [Table 1](#). At baseline in IVUS group the LM MLA was larger and the plaque burden and the calcification arc smaller, which is explained because baseline IVUS examination was much less commonly done in this group and mostly conducted in those cases with less angiographic severity (ambiguous stenosis). With

regards to the procedural results, the LM minimum stent area along with LAD and LCx minimum stent areas were significantly larger in the IVUS-PRO group. The IVUS-PRO optimization targets were retrospectively applied in IVUS group. All optimization criteria, except for dissection/hematoma at stent edges and longitudinal deformation, were more frequently met in IVUS-PRO group.

In IVUS-PRO group the optimization 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 distal LM or in 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 LAD to LM with a nominal diameter <4 mm. Overexpansion of these stents > 2 mm over nominal size was considered inappropriate. Only one case was left with a short (<2 mm) intimal dissection extending <45°. Stent deformation was detected during intra-procedural IVUS examinations in 7 cases (5.6%) and was finally solved in all cases.

No patients were lost in 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. The survival free of TLR is shown in **Figure 5**, demonstrating a strong but not significant trend favoring the IVUS-PRO group. The reported adverse cardiovascular events are listed in **Table 2**. None of the periprocedural myocardial infarctions were related with the LM lesion but with lesions in other locations, and were caused by transient or permanent side branch occlusion, non-reflow phenomenon or distal thrombus embolization.

Among the 4 cases requiring TLR in the IVUS-PRO group, 2 were reported in the subgroup of 15 patients with suboptimal expansion (13.3%) and the other 2 in the optimal expansion subgroup (1.8%). LM revascularization was performed in 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 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 IVUS PRO group TLR was required in 4 cases and among these, 3 presented effort angina (3 positive stress echo) and 1 an ACS.

Independent predictors for primary outcome are listed in [Table 3](#). IVUS-PRO group resulted an independent predictor for a lower risk.

DISCUSSION

The main findings of this study can be summarized as follows: 1) The application of a detailed protocol for the use of IVUS with predefined optimization targets to guide the PCI of the LM with new generation DES, is associated to a 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-protocolized use of IVUS.

Differences in primary endpoint were primarily driven by differences the TLR. This finding makes sense, since IVUS guidance is associated with better stent sizing and subsequent higher expansion rates, providing 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 in less degree.

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

Our protocol recommended the use of IVUS before PCI, so the planning of the most optimal PCI strategy is 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 optimization in clinical practice for the LM. The optimal IVUS minimum stent area (MSA) values for preventing in-stent restenosis in LM were retrospectively assessed in 403 patients undergoing DES implantation. (18) These values were 5.0 mm² for the LCx ostium, 6.3 mm² for the LAD ostium, 7.2 mm² for the distal LM and 8.2 mm² for the proximal LM. However, these cut-off values for the MSA, derived from studies carried out in 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 optimization targets. With respect to the relative values of stent expansion, different targets for stent optimization 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 cutoff, 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 IVUS-PRO group was significantly larger than in the IVUS group. It is noteworthy that the

average MSA values achieved in our study were notably 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 struts apposition. In our registry, very few cases were left with minor incomplete apposition and were limited to those with a large disproportion of size between the implanted stent from LAD to LM and the size of the proximal LM (notable tapering). However, the magnitude of incomplete apposition was of minor degree (<0.5 mm axial distance and <2 mm long) 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, $<45^\circ$ 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 major care to recognize, and when require 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 an effect on clinical outcome.

It is clear that a randomized trial would be the most appropriate design, but the optimization 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 is limited and the study is underpowered for certain clinical outcomes. Nonetheless, significant prognostic differences emerged in favor 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 optimization 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 up to the operator's criteria. 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 optimization criteria like those considered in this study. These findings should be further evaluated through randomized controlled trials.

Impact on daily practice:

The use of IVUS may improve the prognosis of patients undergoing left main percutaneous revascularization but there are not well established criteria for optimization.

The application of an IVUS protocol with the predefined optimization targets considered in this study for left main coronary artery revascularization appears to improve outcomes with respect to the use of angiography alone or even with respect to the use of IVUS out of this protocol.

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Conflicts of interest:

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FIGURE LEGENDS

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

Figure 2. Optimization targets for distal LM lesions

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

Figure 4. Outcomes for study groups. Primary endpoint free survival curves (composite of cardiac death, ST or non-ST elevated myocardial infarction related with the LM lesion and target lesion revascularization in LM).

Figure 5. Outcomes for study groups. LM lesion revascularization free survival curves.

Table 1. IVUS findings.

| | IVUS-PRO | IVUS | |
|---|--------------------|-----------------|-------|
| | N=124 | N=124 | |
| <i><u>Baseline*</u></i> | | | |
| LM minimum lumen area, mm ² | 4.3 (3.2-5.5) | 4.7 (3.9-5.7) | <0.01 |
| LM reference lumen area, mm ² | 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 |
| <i><u>Final result</u></i> | | | |
| LM minimum stent area, mm ² | 11.8 (10.2 - 12.6) | 10 (8.1-11.2) | <0.01 |
| **LAD minimum stent area, mm ² | 8.5 (7.4 – 9.2) | 7.4 (6.6-8.2) | <0.01 |
| **LCx minimum stent area, mm ² | 7 (6.3 – 7.6) | 6.1 (5.4-6.5) | <0.01 |
| <i><u>IVUS-PRO criteria</u></i> | | | |
| 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/hematoma at stent edge | 123 (99.2%) | 120 (96.7%) | 0.4 |
| No proximal stent deformation | 124 (100%) | 116/116 (100%)* | 1 |

Values presented as median (interquartile range) or n (%). *Data reported for cases undergoing baseline IVUS examination, 108 (87%) in IVUS PRO group and 31 (25%) in IVUS group. However, the LM reference lumen area could be estimated during intraprocedural examinations.

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****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.**

LM = left main; LAD = left anterior descending artery; LCx = left circumflex artery

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Table 2. Clinical outcomes at 12 months follow up.

| | ANGIO | IVUS | p(1) | IVUS-PRO | p(2) | p(3) |
|-----------------------|------------|----------|------|----------|------|------|
| | N=124 | N=124 | | N=124 | | |
| 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 revascularization | 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(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 (Logrank test).

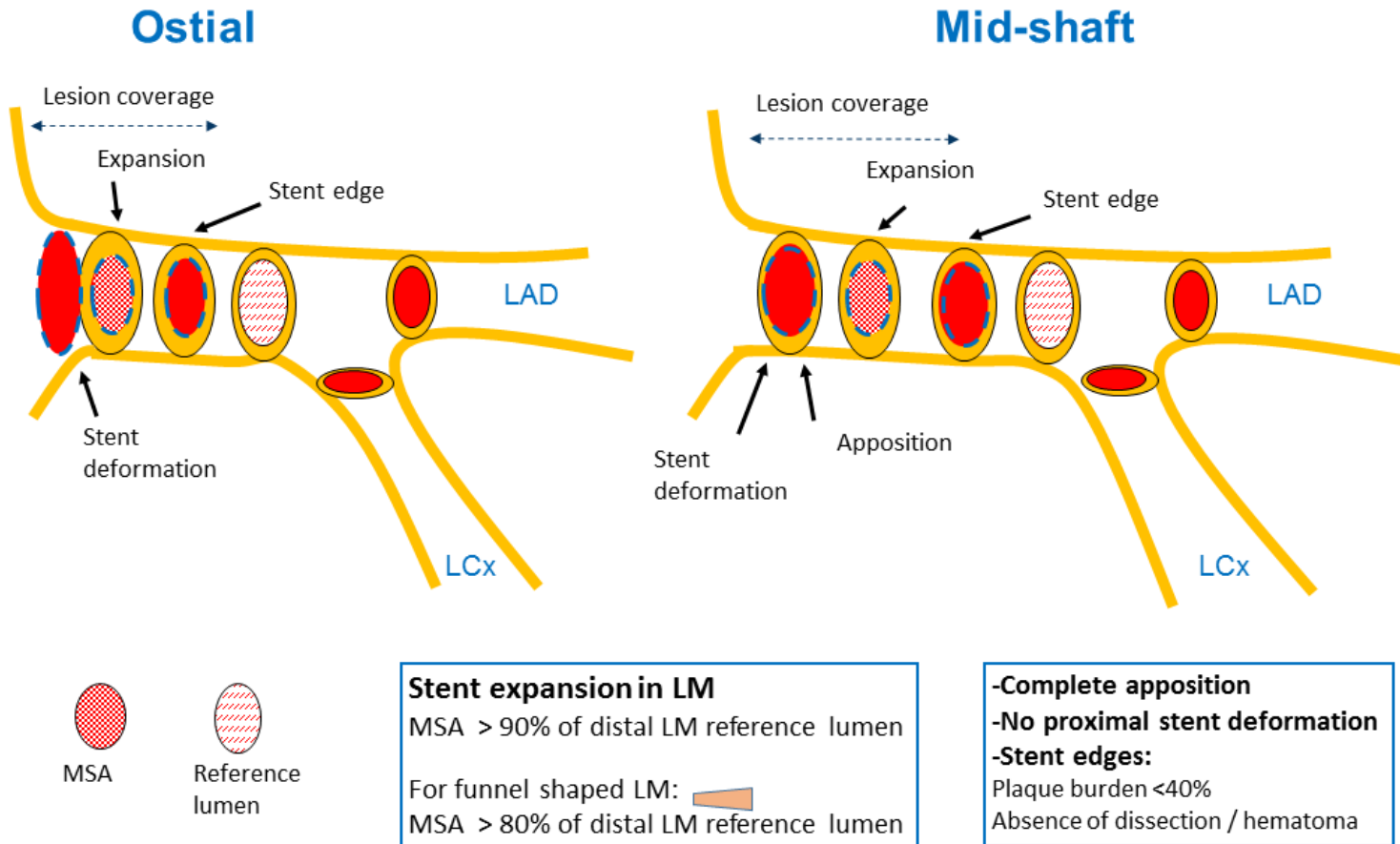
LM = left main; MI = myocardial infarction (ST elevated and non ST elevated)

Table 3. Independent predictors for the primary outcome

| | HR (95% CI) | p |
|---------------------------------|---------------------|----------|
| Age | 1.05 (1.01 – 1.10) | 0.006 |
| Diabetes insulin-treated | 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 |

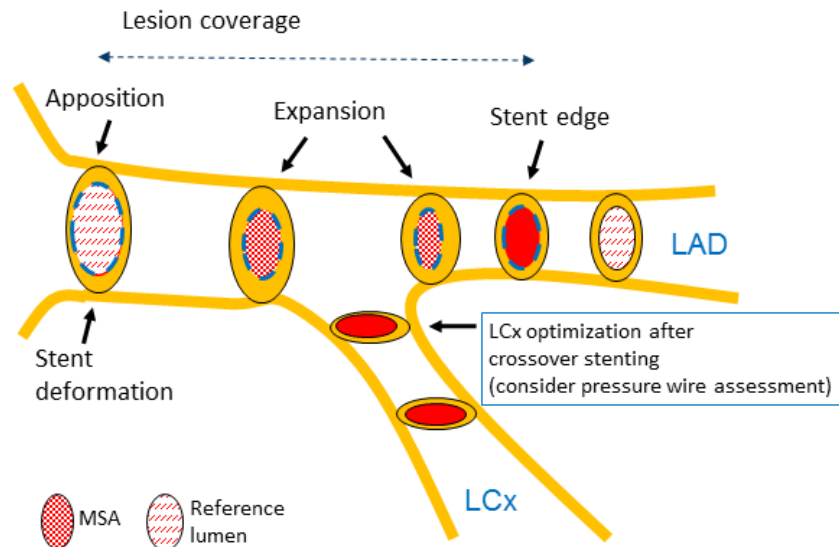
LM = left main

IVUS optimization

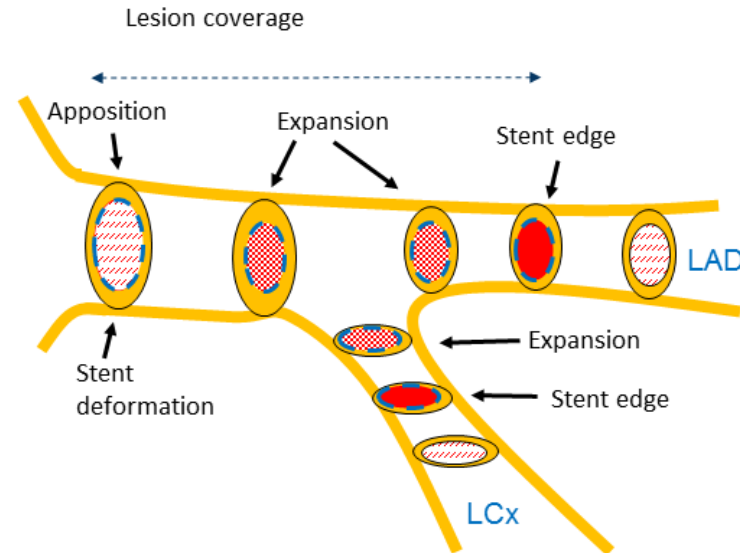


IVUS optimization

Distal (provisional stenting)




Distal (two stents techniques)



Stent expansion in LM

MSA > 90% of proximal LM reference lumen

For tapered LM: 

MSA > 80% of proximal LM reference lumen

Stent expansion in LAD

MSA > 90% of proximal LAD reference lumen

Stent expansion in LCx

MSA > 90% of proximal LCx reference lumen

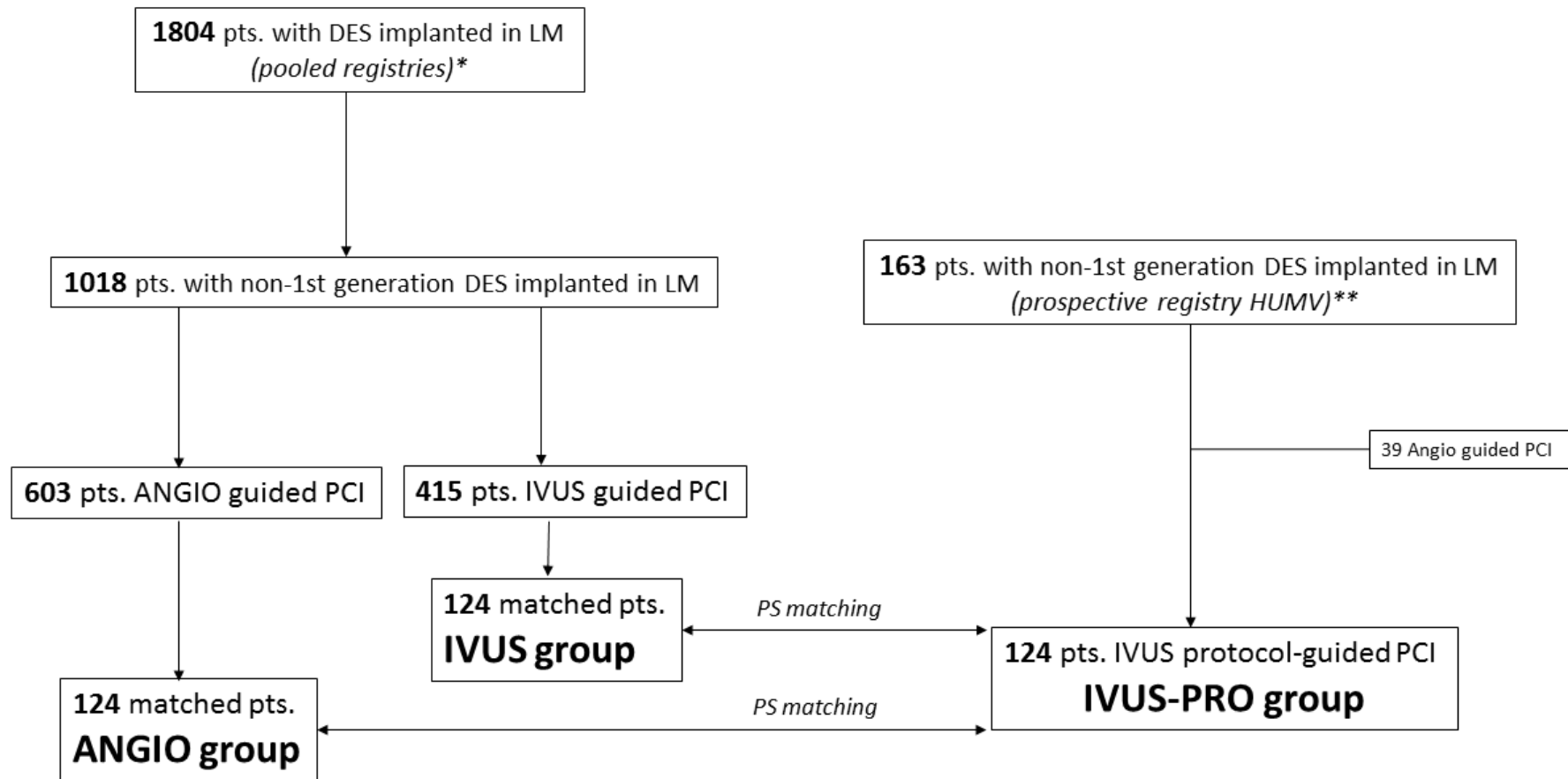
-Complete stent apposition

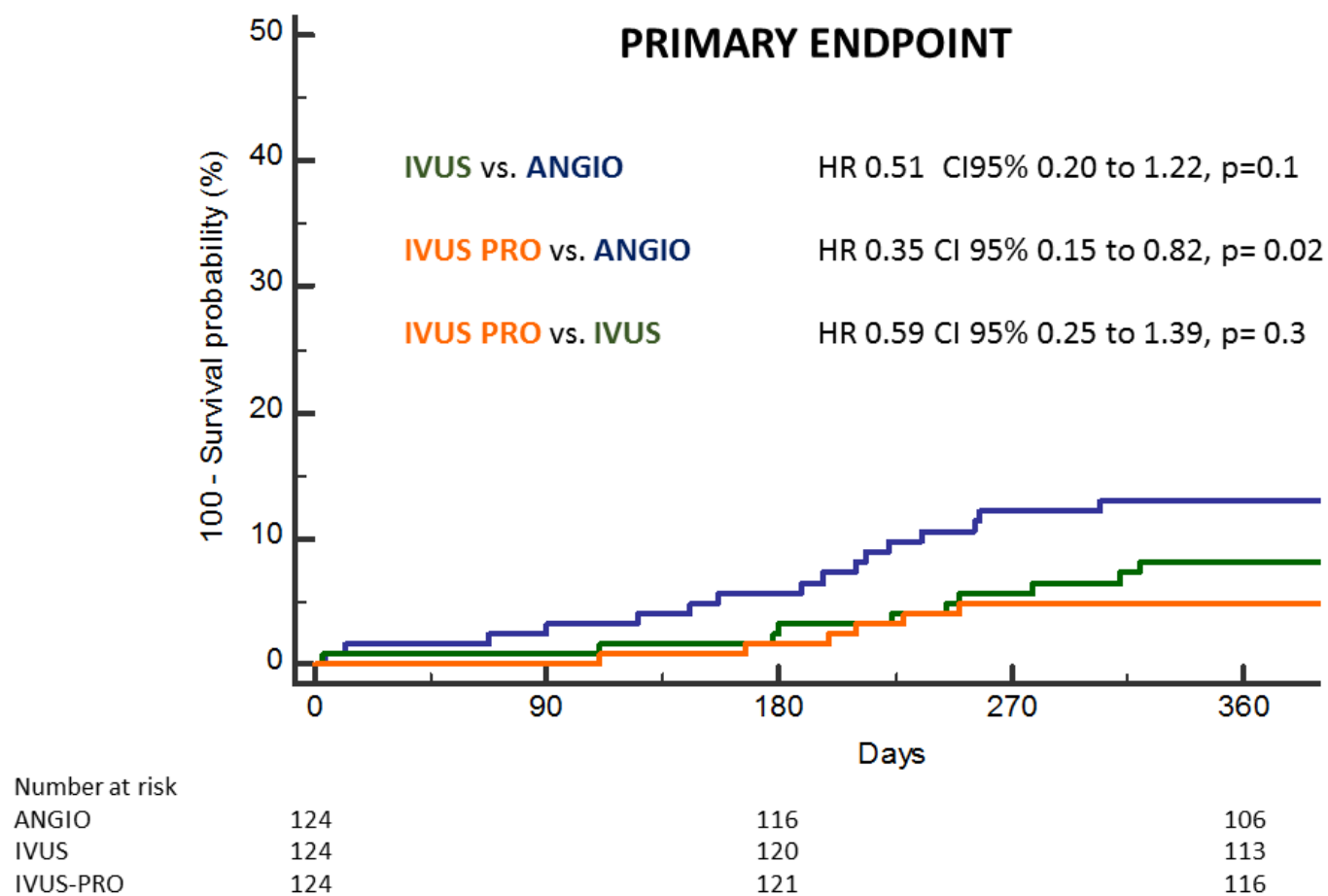
-No proximal stent deformation

-Stent edges:

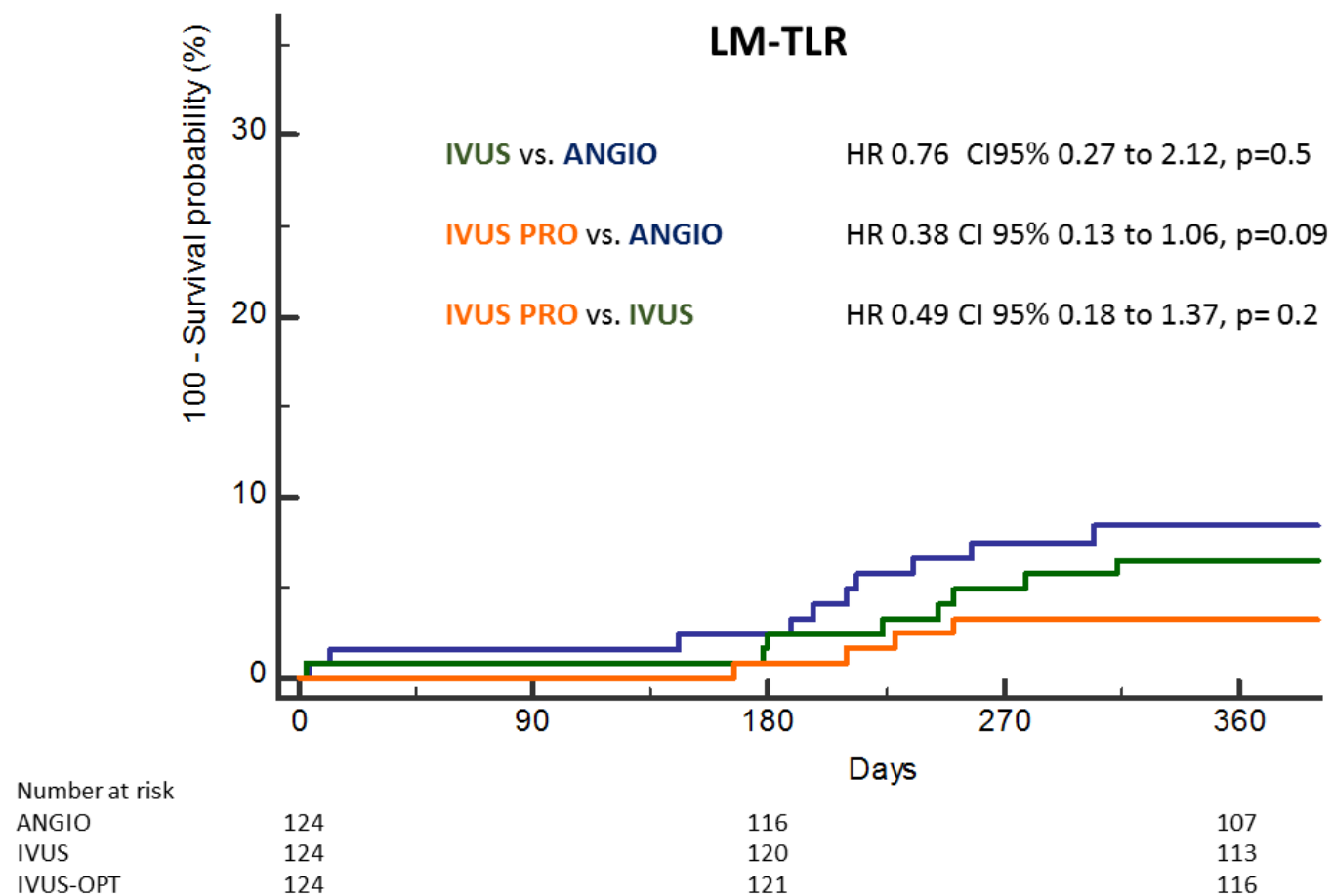
Plaque burden <40%

Absence of dissection / hematoma





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SUPPLEMENTARY MATERIAL

METHODS

IVUS protocol

The recommendations for IVUS assessment of LM were the following: a) Perform a baseline study of LM, not only in ambiguous but in significant lesions as well; b) In case of distal LM lesion always try to conduct two IVUS runs, from both LAD and LCx, aimed to assess accurately the involvement of the ostium of both branches; c) In cases presenting backward leap of the IVUS catheter during pull back, usually because 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 ostial lesion, try to achieve coaxiality of the catheter and keep the guiding catheter disengaged from the LM during IVUS pull back.

Regarding lesion preparation prior to stenting, IVUS provides morphological characterization of plaques, specifically the location and extension of calcification. According to these findings the operator should choose and size the most appropriate device, including 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 LAD to LM showing a very large proximal LM lumen (> 5.5 mm) due to remarked

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 optimization criteria

1-Complete LM stent apposition.

As described above, in cases with distal LM lesions requiring a < 4 mm in diameter DES from LAD to 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 as 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 a 90% of the smallest vessel area in 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 categorize a LM as funnel shaped or tapered, though an angiographic

difference > 0.5 mm between proximal and distal LM was generally the threshold for this visual classification.

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

4- Stent edges with residual plaque burden $< 40\%$, absence of dissection or hematoma 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 $< 45^\circ$ 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 (Volcano Corp., Philips Healthcare). Non-first generation DES were used, taken 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 ostium of LCx $> 3.5 \text{ mm}^2$ with plaque burden $< 50\%$. In patients requiring a crossover stenting from LM to LAD, it was not uncommon to open struts towards LCx, particularly in the 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 criteria of the operator. In cases with suspected flow compromise to LCx, a pressure wire assessment was done and actions were taken accordingly.

The type of 2-stents technique when required was decided upon 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 optimization in LM aimed to correct the asymmetry.

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

Statistics: propensity score matching

The propensity score matching was aimed to pair each patient in IVUS-PRO group with a patient in IVUS group and a patient in ANGIO group. This procedure involved two stages: 1) The propensity scores were estimated using logistic regression in which IVUS-PRO guided PCI used as the outcome variable and all the covariates as predictors (age, gender, smoker, diabetes, hypertension, hypercholesterolemia, 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 neighbor matching that is 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 standardized mean differences after matching were below 10%. Calibration was tested using the Hosmer-Lermeshow 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, Armonk, New York). 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 |
| Hypercholesterolemia | 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(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.

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ACS = acute coronary syndrome; CABG = coronary artery by-pass graft; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

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Supplementary table 2. Angiographic and procedural characteristics.

| | ANGIO | IVUS | p (1) | IVUS-PRO | p (2) | p (3) |
|-----------------------------|------------|------------|--------|------------|--------|-------|
| | N=124 | N=124 | | N=124 | | |
| 2-vessels disease | 37 (29.8) | 40 (32) | 0.8 | 41 (33) | 0.6 | 0.9 |
| 3-vessels 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 |
| Postdilatation | 55 (44.3) | 81 (65.3) | 0.002 | 102 (82.2) | <0.001 | 0.004 |
| Postdilatation balloon, mm | 3.8 ±0.42 | 4.05 ±0.38 | <0.001 | 4.2 ± 0.4 | <0.001 | 0.003 |
| 2-stents 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 |

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| | | | | | | |
|-------------------------|------------|------------|-----|------------|-------|--------|
| Angiographic success | 122 (98.4) | 122 (98.4) | 0.9 | 123 (99.2) | 0.9 | 0.9 |
| DAPT at least for 12 m. | 124 (100) | 124 (100) | 0.9 | 110 (88.7) | 0.001 | <0.001 |

Values are mean \pm SD or n (%). 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 $\geq 50\%$ in a segment with reference lumen diameter > 2 mm. Lesion location in LM could be ostial (at the aorto-ostial junction), mid shaft (at the mid portion, not affecting ostium or bifurcation) and distal (lesion located at the bifurcational level of the LM). Postdilatation 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 III flow.

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