

# Prospective Application of Pre-Defined Intravascular Ultrasound Criteria for Assessment of Intermediate Left Main Coronary Artery Lesions

## Results From the Multicenter LITRO Study

Jose M. de la Torre Hernandez, MD, PhD,\* Felipe Hernández Hernandez, MD,†  
Fernando Alfonso, MD, PhD,‡ Jose R. Rumoroso, MD, PhD,§ Ramon Lopez-Palop, MD, PhD,||  
Mario Sadaba, MD,‡ Pilar Carrillo, MD, PhD,§ Juan Rondan, MD, PhD,¶ Iñigo Lozano, MD, PhD,¶  
Juan M. Ruiz Nodar, MD, PhD,# Jose A. Baz, MD,\*\* Eduard Fernandez Nofrerias, MD,††  
Fernando Pajin, MD,‡‡ Tamara Garcia Camarero, MD,\* Hipolito Gutierrez, MD,§§  
on behalf of the LITRO Study Group (Spanish Working Group on Interventional Cardiology)  
*Santander, Madrid, Bilbao, Alicante, Oviedo, Vigo, Badalona, Toledo, and Valladolid, Spain*

<b>Objectives</b>	This study is a prospective validation of 6 mm <sup>2</sup> as a minimum lumen area (MLA) cutoff value for revascularization of left main coronary artery (LMCA) lesions.
<b>Background</b>	Lesions involving the LMCA are prognostically relevant. Angiography has important limitations in the evaluation of LMCA lesions with intermediate severity. An MLA of 6 mm <sup>2</sup> assessed by intravascular ultrasound has been proposed as a cutoff value to determine lesion severity, but there are no large studies evaluating the prospective application and safety of this approach.
<b>Methods</b>	We have designed a multicenter, prospective study. Consecutive patients with intermediate lesions in unprotected LMCA were evaluated with intravascular ultrasound. An MLA <6 mm <sup>2</sup> was used as criterion for revascularization.
<b>Results</b>	A total of 354 patients were included in 22 centers. LMCA revascularization was performed in 90.5% (152 of 168) of patients with an MLA <6 mm <sup>2</sup> and was deferred in 96% (179 of 186) of patients with an MLA of 6 mm <sup>2</sup> or more. A large scatter was observed between both groups regarding angiographic parameters. In a 2-year follow-up period, cardiac death-free survival was 97.7% in the deferred group versus 94.5% in the revascularized group (p = 0.5), and event-free survival was 87.3% versus 80.6%, respectively (p = 0.3). In the 2-year period, only 8 (4.4%) patients in the deferred group required subsequent LMCA revascularization, none with an infarction.
<b>Conclusions</b>	Angiographic measurements are not reliable in the assessment of intermediate LMCA lesions. An MLA of 6 mm <sup>2</sup> or more is a safe value for deferring revascularization of the LMCA, given the application of the clinical and angiographic inclusion criteria used in this study. (J Am Coll Cardiol 2011;58:351-8) © 2011 by the American College of Cardiology Foundation

The limitations of angiographic assessment of left main coronary artery (LMCA) lesion severity are well established (1-3). Several studies have been published showing value of intravascular ultrasound (IVUS) in the assessment of intermediate LMCA lesions (4-11). A number of publications

have addressed the value of IVUS in deciding whether to treat an intermediate LMCA lesion (9-11). Some of these studies were not prospective, the number of patients included was limited, all were single-center, and different minimum lumen area (MLA) cutoff values were used (6 to 8 mm<sup>2</sup>).

From the \*Hospital Marques de Valdecilla, IFIMAV, Santander, Spain; †Hospital 12 de Octubre, Madrid, Spain; ‡Hospital Clinico San Carlos, Madrid, Spain; §Hospital de Galdakano, Bilbao, Spain; ||Hospital San Juan, Alicante, Spain; ¶Hospital Central de Asturias, Oviedo, Spain; #Hospital General, Alicante, Spain; \*\*H. Meixoeiro, Vigo, Spain; ††H. Germans Trias i Pujol, Badalona, Spain; ‡‡H. Virgen de la Salud,

Toledo, Spain; and the §§H. Clinico de Valladolid, Valladolid, Spain. This work was supported by Boston Scientific Corporation and GRIFOLS S.A. (distributor for Volcano Corporation in Spain). The authors have reported that they have no relationships to disclose.

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### Abbreviations and Acronyms

<b>FFR</b> = flow fractional reserve
<b>HBP</b> = high blood pressure
<b>IVUS</b> = intravascular ultrasound
<b>LMCA</b> = left main coronary artery
<b>LVEF</b> = left ventricular ejection fraction
<b>MI</b> = myocardial infarction
<b>MLA</b> = minimum lumen area
<b>MLD</b> = minimum lumen diameter
<b>PCI</b> = percutaneous coronary intervention

There is currently no agreement on what MLA value should be used to determine whether to treat an intermediate lesion. The most frequently recommended MLA value is 6 mm<sup>2</sup>; however, there are no large prospective validations of this cutoff value. The 6-mm<sup>2</sup> value was obtained from Murray's law (considering an MLA of 4 mm<sup>2</sup> as the ischemic threshold of the branches) (12–14) and has been supported by a study that used IVUS and pressure wire flow fractional reserve (FFR) (15). We previously published the results of a prospective application of a 6-mm<sup>2</sup> MLA cutoff value in 79 cases (10). This is the first prospective and multi-

center study that assessed the usefulness of an IVUS-related criterion to determine whether to revascularize intermediate LMCA lesions.

## Methods

The IVUS work team (from the Spanish Working Group of Interventional Cardiology) designed a prospective and multicenter study involving patients with moderate LMCA lesions by angiogram. We sought to assess the safety of a 6-mm<sup>2</sup> MLA as a cutoff value to decide whether LMCA lesions need to be revascularized or if the procedure can be deferred.

**Patients.** Throughout 2007, in 22 Spanish institutions, all consecutive patients undergoing an angiogram for suspected or confirmed coronary artery disease showing uncomplicated (no ulceration, dissection, or thrombus) intermediate (25% to 60% visual stenosis) unprotected LMCA lesions were included. Patients receiving primary percutaneous coronary intervention (PCI) also were included, provided the LMCA lesion was not the culprit. Exclusion criteria were: 1) cardiogenic shock; 2) left ventricular ejection fraction of <30%; 3) significant valvulopathy; and 4) any concomitant disease that could impair short-term survival.

All centers were strongly encouraged to adhere to the protocol-specified decision criteria for lesion treatment: Lesions with an MLA of 6 mm<sup>2</sup> or more were to remain untreated, whereas lesions with an MLA <6 mm<sup>2</sup> were to undergo revascularization (per operator choice, either coronary artery bypass graft or PCI).

**Imaging protocol and analysis.** IVUS examination was performed using the operator-preferred system. Ultrasound images were recorded starting at a point distal to the bifurcation of the left anterior descending and left circumflex arteries, and the entire LMCA was imaged to the aorto-ostial junction with the catheter disengaged, allowing

visualization of the ostium. Motorized pull-backs were performed at a speed of 0.5 mm/s after the administration of intracoronary nitroglycerin.

The clinical decision of whether to treat was based on online IVUS analysis. The studies were recorded in CD/DVD and were sent to a core laboratory for analysis (ICICOR, Hospital Clínico Universitario, Valladolid, Spain). The quantitative coronary angiography and IVUS analysis were performed by validated and automated edge-detection software (Medis QCA CMS 6.0/XA 7.2 and Medis QCU 1.0 [Medis Medical Imaging Systems Inc., Leiden, the Netherlands] and VIAS-Volcano Image Analysis Software [Volcano Inc., Rancho Cordova, California]).

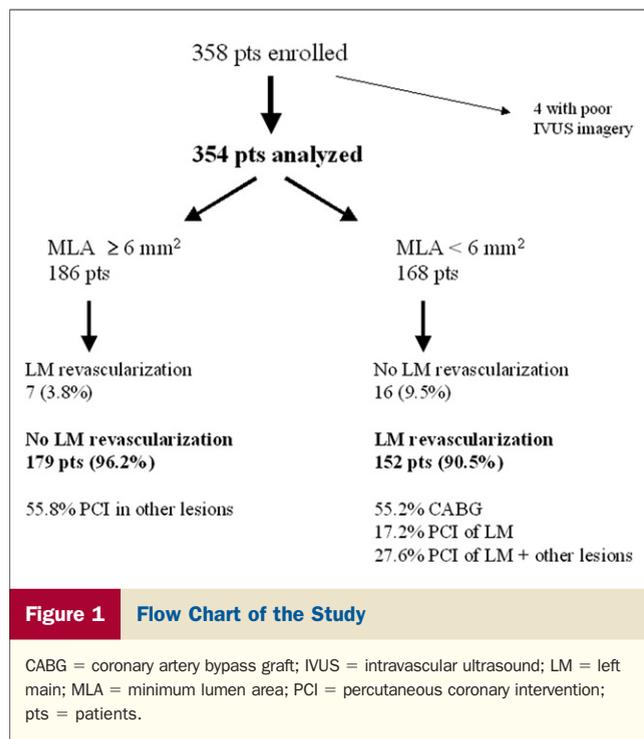
**Clinical follow-up.** Two- and 5-year follow-ups were planned. Follow-up information was collected by reviewing clinical reports and by telephone interview in all cases. The indication for repeated catheterization was driven clinically and was decided by the clinical cardiologists.

**Statistical analysis.** Continuous variables were expressed as mean ± SD and were compared by unpaired Student *t* tests. Categorical variables were expressed as percentages and were compared by chi-square statistics or the Fisher exact test, as indicated. A correlation test was used to evaluate the degree of association between angiographic and ultrasonographic measures. Kaplan–Meier analysis was used to obtain an event-free survival rate, and log-rank tests were applied to evaluate differences between groups. The level of significance for hypothesis testing was *p* < 0.05. SPSS Statistics software version 15.0 (SPSS, Inc., Chicago, Illinois) was used.

## Results

During the study period, 358 patients underwent an IVUS examination of intermediate LMCA lesions. Four patients were excluded from the study because of inadequate quantitative IVUS assessment. The analysis comprised 354 patients (Fig. 1). Of the 186 patients with an MLA of 6 mm<sup>2</sup> or more, 179 (96.2%) did not receive any revascularization procedure of the LMCA (deferred group). Of the 168 patients with an MLA of <6 mm<sup>2</sup>, 152 (90.5%) underwent LMCA revascularization (revascularized group).

There were no significant differences in clinical characteristics between the deferred and revascularized groups (Table 1). However, there were significant differences in baseline angiographic characteristics (Table 2). As shown in Figure 2, there was a wide overlap and scatter of angiographic stenosis and MLD relative to the MLA 6-mm<sup>2</sup> cutoff. We obtained correlation coefficients for angiographic stenosis and MLA, *r* = –0.18 (*p* = 0.0015), and for angiographic MLD and MLA, *r* = 0.34 (*p* < 0.0001). Seventeen percent of patients showed quantitative stenosis of <30%, which was comparable with that of other similar studies (16). Nevertheless, 33% of patients in this subgroup had an MLA of <6 mm<sup>2</sup>. On the other side, in 43% of



patients with angiographic stenosis over 50%, the MLA was larger than 6 mm<sup>2</sup>.

There were expected differences regarding ultrasonographic characteristics between the 2 groups (Table 3). Figure 3 illustrates the MLA and plaque burden of the lesions in both groups. In the deferred group, those with an MLA <9 mm<sup>2</sup> showed an angiographic stenosis of 35 ± 10%, whereas in those with an MLA of 6 to 9 mm<sup>2</sup> showed an angiographic stenosis of 37 ± 8% (p = 0.1).

A total of 351 patients (99%) completed 2-years follow up. In the deferred group, survival free from cardiac death to 2 years was 97.7%. A total of 12 deaths were reported,

8 noncardiac (3 cancer, 2 infectious diseases, 1 bleeding, and 2 accidents) and 4 cardiac deaths. Among the latter 3 were patients older than 75 years with left ventricular dysfunction and high clinical risk predictors. The MLA was <8 mm<sup>2</sup> in 3 of these patients and was 7 mm<sup>2</sup> in the remaining patient.

LMCA revascularization-free survival to 2 years in the deferred group was 96.5%. LMCA revascularization was required in 8 patients: in 7 because of stable angina and in 1 after unstable angina. Angiographic progression was observed in 4 cases; however, the stenosis was <75% in only 1 case. Revascularization therapy was PCI in 6 patients (75%) and surgical in the other 2 patients (25%). Survival free from cardiac death, MI, and LMCA revascularization to 2 years in the deferred group was 94.2%, whereas survival free from cardiac death, MI, and any revascularization was 87.3%. Table 4 compares the clinical characteristics of 8 deferred group patients who needed subsequent revascularization with those of the 171 patients who did not.

Figures 4 and 5 show comparative clinical outcomes from both the deferred and revascularized groups. Cardiac death-free survival was 97.7% in the deferred group versus 94.5% in the revascularized group (p = 0.5), and survival free from cardiac death, MI, and any revascularization was 87.3% versus 80.6%, respectively (p = 0.3).

Of the 168 patients with a baseline MLA <6 mm<sup>2</sup>, there were 16 patients who did not undergo revascularization because of operator or patient preferences, or both. The MLA was 5 to 6 mm<sup>2</sup>, and ejection fraction was preserved in all but 2 cases. The lesions frequently were complex for PCI (75% bifurcations and 37.5% heavily calcified), and 6 patients (37.5%) had problems for long-term dual antiplatelet therapy. In addition, the estimated surgical risk was high in 31% of patients (43.7% were older than age 75 years and 50% had lung or renal comorbidities), and 2 declined to

**Table 1 Clinical Characteristics of Both Groups**

	Deferred Group (n = 179)	Revascularized Group (n = 152)	p Value
Age, yrs	66.5 ± 11.0	65.2 ± 11.0	0.30
Female	24 (13.4)	33 (21.7)	0.06
Diabetes	64 (35.8)	57 (37.5)	0.80
HBP	113 (63.1)	91 (59.8)	0.60
Smoker	45 (25.1)	44 (28.9)	0.50
Hypercholesterolemia	118 (65.9)	101 (66.4)	0.90
LVEF, %	56.6 ± 10.0	58.1 ± 10.0	0.07
Previous MI	52 (29)	42 (27.6)	0.70
Previous PCI	53 (29.6)	41 (26.9)	0.70
Previous CABG	5 (2.8)	8 (5.3)	0.30
STEMI	21 (11.7)	13 (8.6)	0.40
Unstable angina	64 (35.8)	52 (34.2)	0.80
Stable angina	74 (41.3)	60 (39.5)	0.80
Silent ischemia	20 (11.5)	17 (11.2)	0.90

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; HBP = high blood pressure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

	Deferred Group (n = 179)	Revascularized Group (n = 152)	p Value
Visual stenosis, %	37.2 ± 8.0	47.4 ± 10.0	0.001
QCA stenosis, %	36.2 ± 9.0	40.4 ± 10.0	0.002
MLD, mm	2.5 ± 0.6	2.3 ± 0.7	0.005
RLD, mm	3.9 ± 0.8	3.6 ± 0.8	0.008
Ostial	75 (41.8)	33 (21.7)	0.002
Mid shaft	42 (23.4)	44 (28.9)	0.30
Bifurcation	62 (34.6)	75 (49.3)	0.01
Diffuse	25 (13.9)	47 (30.9)	0.001
Calcification	32 (17.8)	47 (30.9)	0.008
Isolated LMCA disease	35 (19.5)	18 (11.8)	0.07
Multivessel disease	68 (38)	74 (48.7)	0.06
No. of significant lesions*	1.53 ± 1.00	1.90 ± 1.00	0.0009
Complete revascularization	116 (64.8)	116 (76.3)	0.03

Values are mean ± SD or n (%). \*Lesions in other segments of the coronary tree (no LMCA included).  
 LMCA = left main coronary artery; MLD = minimum lumen diameter; QCA = quantitative coronary angiography; RLD = reference lumen diameter.

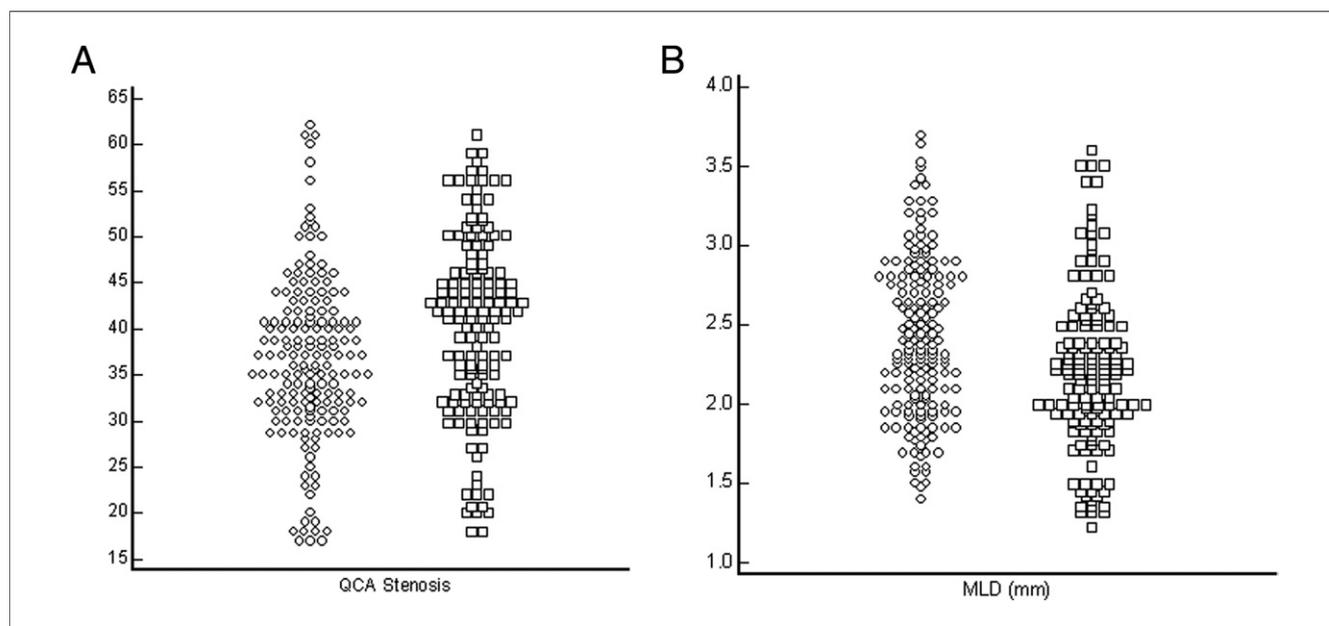
undergo surgical revascularization. During follow-up, there were 2 cardiac deaths, 3 patients had an MI, and 4 patients underwent LMCA revascularization (2 PCI and 2 coronary artery bypass graft). In this group of 16 patients, cardiac death-free survival to 2 years was 86% (97.7% in the deferred group; p = 0.04), and survival free of cardiac death, MI, and revascularization was 62.5% (87.3% in the deferred group; p = 0.02).

**Discussion**

This is the first multicenter, prospective study that assessed the safety of an invasive tool to assist in the decision making

regarding when to intervene in intermediate LMCA lesions. Our study supports the assertion that the IVUS-derived cutoff value of 6 mm<sup>2</sup> of MLA is safe in the context of the inclusion and exclusion criteria of the current study.

Our study also corroborates the crucial limitations of angiography, already revealed in previous studies, when trying to discriminate lesions with significant luminal narrowing. Moreover, the diffuse nature of the disease and the short length of the LMCA makes stenosis a less reliable parameter in this location compared with other locations in the coronary tree. The reference segments frequently are diseased (as is evident by IVUS), and angiographic stenosis



**Figure 2** Individual Data Comparison Graphs

(A) Individual data comparison graph for angiographic left main coronary artery stenosis in both intravascular ultrasound (IVUS)-derived groups. (B) Individual data comparison graph for angiographic left main coronary artery minimum lumen diameter in both IVUS-derived groups. Circles = deferred group; squares = revascularized group; MLD = minimum lumen diameter; QCA = quantitative coronary angiography.

**Table 3** Ultrasonographic Characteristics of Both Groups

	Deferred Group (n = 179)	Revascularized Group (n = 152)	p Value
<b>Lesion site</b>			
MLA, mm <sup>2</sup>	9.3 ± 3.0	4.8 ± 0.8	<0.001
Maximum LD, mm	4.2 ± 0.7	3.1 ± 0.7	<0.001
Minimum LD, mm	2.8 ± 0.6	2.2 ± 0.3	<0.001
EEM area, mm <sup>2</sup>	20.2 ± 5.5	16.1 ± 5.0	<0.001
Remodeling index	1.1 ± 0.2	1.2 ± 0.3	<0.001
Plaque burden, %	52.6 ± 12.0	67.5 ± 11.0	<0.001
Plaque burden >50%	109 (60.8)	149 (98)	0.001
Calcified	107 (59.7)	108 (71)	0.07
Circumference of CA <sup>++</sup> , °	80 ± 77	91 ± 76	0.08
<b>Reference site</b>			
LA, mm <sup>2</sup>	14.9 ± 5.0	11 ± 4.0	<0.001
EEM, mm <sup>2</sup>	22.8 ± 6.6	19.5 ± 5.0	<0.001
Plaque burden, %	37.2 ± 12.0	43.5 ± 16	<0.001

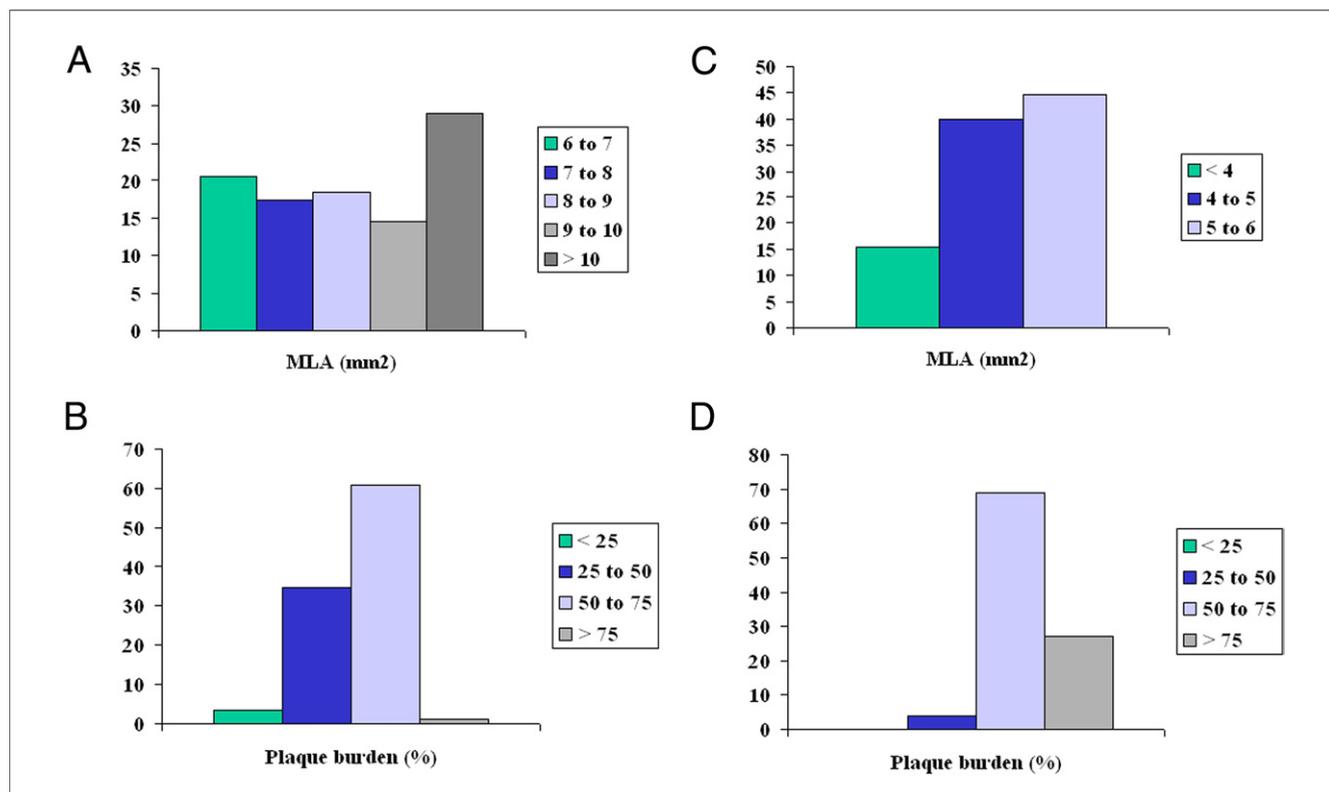
Values are mean ± SD or n (%).

EEM = external elastic membrane; LA = lumen area; LD = lumen diameter; MLA = minimum lumen area.

underestimates the real lesion severity. This explains why IVUS revealed significant luminal compromise even in lesions with mild stenosis. Thus, in this study, we allowed broad angiographic limits to be able to accommodate most cases in which the operator believed that IVUS could potentially help assess lesion severity. Obviously, lesions of 25% in several projections that caused no doubts regarding

severity were not included in the current study. The same rationale was applied for the inclusion of lesions in the borderline range of 50% to 60% stenosis.

Abizaid et al. (8) verified the value of the IVUS-derived MLD as an independent predictor of clinical events at 1 year in untreated LMCA lesions. The same research group has published the results at 5 years demonstrating plaque



**Figure 3** Minimum Lumen Area and Plaque Burden Distribution in Both Groups

Minimum lumen area (MLA) and plaque burden distribution in (A, B) deferred group and (C, D) revascularized group.

Table 4

Clinical, Angiographic, and Ultrasonographic Characteristics  
in Patients With and Without Left Main Coronary Artery  
Revascularization at Follow-Up in the Deferred Group

	No Revascularization (n = 171)	Revascularization (n = 8)	p Value
<b>Clinical</b>			
Age, yrs	66.7 ± 11.0	62 ± 11.0	0.20
Female	22 (12.8)	2 (25)	0.60
Diabetes	61 (35.6)	3 (37.5)	0.80
HBP	108 (63.1)	5 (62.5)	0.70
Smoker	44 (25.7)	1 (12.5)	0.70
Hypercholesterolemia	113 (66)	5 (62.5)	0.80
LVEF %	56.3 ± 10.0	52.2 ± 14.0	0.30
STEMI	19 (11.1)	2 (25)	0.60
Stable angina	70 (40.9)	4 (50)	0.90
PCI other vessels	96 (56.1)	4 (50)	0.90
<b>Angiography</b>			
Stenosis, %	36.3 ± 8.0	40.2 ± 10.0	0.20
MLD, mm	2.5 ± 0.6	2.6 ± 0.5	0.60
Ostial	73 (42.6)	2 (25)	0.50
Mid shaft	39 (22.8)	3 (37.5)	0.60
Bifurcation	59 (34.6)	3 (37.5)	0.80
Diffuse	24 (14)	1 (12.5)	0.70
Calcification	30 (17.5)	2 (25)	0.90
<b>IVUS</b>			
MLD, mm	2.9 ± 0.5	2.5 ± 0.7	0.07
MLA, mm <sup>2</sup>	9.4 ± 3.0	8.4 ± 2.1	0.40
MLA 6–7 mm <sup>2</sup>	35 (20.4)	2 (25)	0.90
MLA 7–8 mm <sup>2</sup>	29 (16.9)	2 (25)	0.90
MLA 8–9 mm <sup>2</sup>	32 (18.7)	1 (12.5)	0.90
MLA >9 mm <sup>2</sup>	75 (43.8)	3 (37.5)	0.90
Plaque burden, %	52.2 ± 13.0	59.1 ± 14.0	0.10
Plaque burden >50%	105 (61.4)	6 (75)	0.70

Values are mean ± SD or n (%).

IVUS = intravascular ultrasound; other abbreviations as in Tables 1, 2, and 3.

burden to be the only independent predictor of cardiac events (11).

The Mayo Clinic group reported a series of 214 patients recruited in an 8-year period in which the cutoff value for MLA was 7.5 mm<sup>2</sup> (9). This value was derived from a cohort of 121 patients with angiographically normal or minimally diseased LMCA. The decision regarding whether to revascularize was made following this criterion in 86% of patients, and the clinical outcomes at a mean follow-up of 3 years were similar in the patients with and without revascularization.

Several studies also have been published that used pressure wire to determine FFR, a more physiologically relevant assessment tool. One of these studies compared FFR with IVUS in a series of 55 patients. A close correlation was found between FFR <0.75 and MLA <5.9 mm<sup>2</sup> (15). Hamilos *et al.* (16) recruited 213 patients over 8 years from a single institution. Surgical revascularization was indicated whenever FFR was <0.8. This study pointed out the safety of this approach and the poor correlation between FFR and angiography. Taken together, the Mayo Clinic and Hamilos *et al.* (9,16)

MACE incidence at 2 years in the nonrevascularized group are quite similar to that found in our study.

IVUS and FFR each have benefits and drawbacks as assessment tools. The main limitations of IVUS reside in the potential lack of coaxiality and subsequent lumen distortion, as well as in the negative impact of irregular calcifications. Regarding FFR, the frequent concomitant presence of lesions in the descending anterior coronary artery, circumflex, or both interferes with a proper evaluation of the LMCA lesion. One advantage of IVUS over pressure wire is that this tool can help both in the diagnosis and the treatment of lesions. A potential survival impact derived from the use of IVUS already has been proven (17).

**Study limitations.** The main limitation of this study is that it was not randomized. Therefore, the value of the comparison between deferred and revascularized groups is limited by population differences between both strategies. Only a randomized trial can validate the value of revascularization according to pre-defined MLA cutoff points. However, considering the large body of evidence suggesting the clinical value of this cutoff criterion, we

selected a pragmatic strategy in which this single criterion was selected to guide revascularization decisions. This was considered to be the only viable study (ethical issues were raised in the initial discussions on study design).

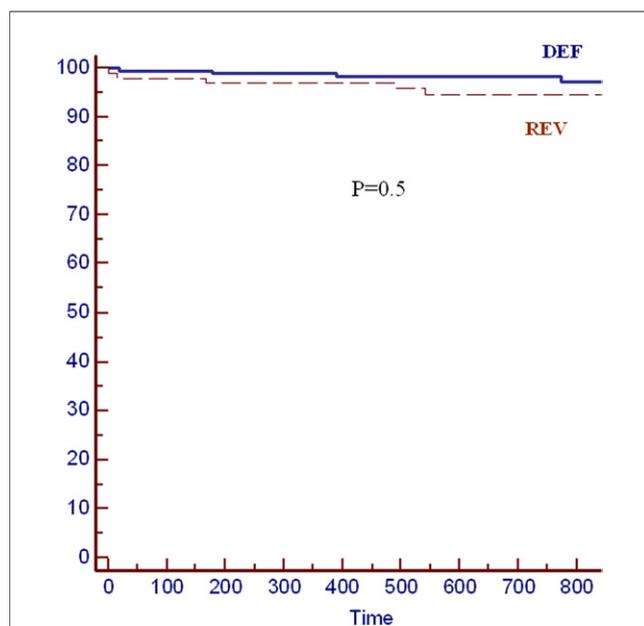
Another limitation is the lack of complete adherence to protocol, although protocol adherence was high and greater than in previous similar studies. A third limitation is the selection of patients based on the subjective operator criteria for intermediate lesions. However, this potential bias is reduced by the multicenter design. Finally, the follow-up period is only 2 years. However, the goal of this study resides in studying the ischemic potential of intermediate lesions, and not in assessing the progression of atherosclerotic lesions.

### Conclusions

Angiographic measurements are not reliable in the assessment of intermediate LMCA lesions. Ultrasonographic evaluation of intermediate LMCA lesions allows precise assessment of lesion severity, as well as lesion characteristics useful in cases where PCI is used to revascularize. An MLA of 6 mm<sup>2</sup> or more seems to be a safe value for deferring revascularization of the LMCA, provided the application of the clinical and angiographic criteria used in this study.

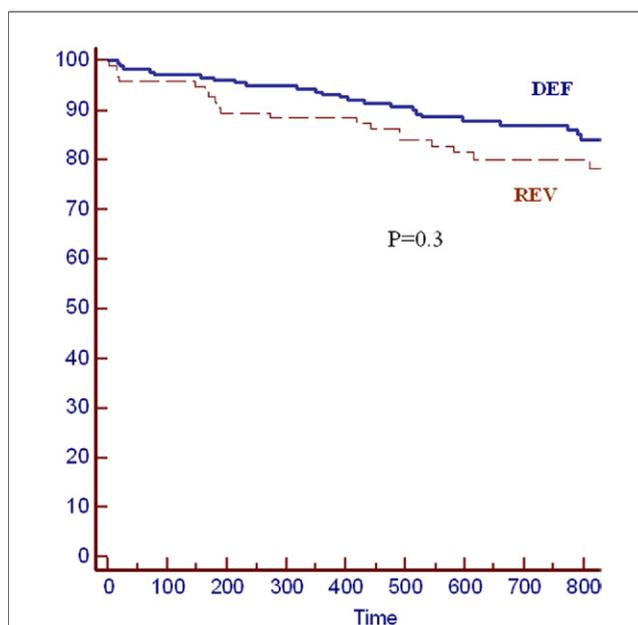
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**Figure 4** Survival Free of Cardiac Death in Both Groups

Survival free of cardiac death in the deferred (DEF) and revascularized (REV) groups.



**Figure 5** Survival Free of Cardiac Death, Myocardial Infarction, and Any Revascularization in Both Groups

Survival free of cardiac death, myocardial infarction, and any revascularization in the DEF and REV groups. Abbreviations as in Figure 4.

**Reprints requests and correspondence:** Dr. Jose M. de la Torre Hernández, Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Universitario Marques de Valdecilla, Valdecilla Sur., 39012 Santander, Spain. E-mail: he1thj@humv.es.

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**Key Words:** coronary artery disease ■ intravascular ultrasound ■ ischemia ■ left main coronary artery ■ stenosis.

#### APPENDIX

##### **Other participating centers and corresponding investigators:**

Antonio Domínguez (H. Virgen de la Victoria, Malaga), Jose G. Galache (H. Miguel Servet, Zaragoza), Victoria Martín (H. Sant Pau, Barcelona), Ramon Calviño (C. Hospitalario de la Coruña), Francisco Bosa (H. Clínico de Tenerife), Jose A. Fernández Diaz (H. Puerta de Hierro, Madrid), Armando Perez de Prado (H. de Leon), Jesus Jiménez Mazuecos (H. General de Albacete), Javier Botas (F. Alcorcon), Cristóbal Urbano Carrillo (H. Carlos Haya, Malaga), and Fernando Rivero (H. de la Princesa, Madrid).