# The Usefulness of Intracoronary Ultrasound in the Treatment Decision-Making of Patients with Ambiguous Lesions in the Left Main Coronary Artery

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**Objective:** To evaluate the safety and efficacy of surgical treatment approach vs. conservative approach in patients with ambiguous lesions in the left main coronary artery (LMCA), based on intracoronary ultrasound (ICUS) findings.

**Methods:** Sixty-six consecutive patients with angiographically ambiguous lesions were included and submitted to ICUS assessment. They were divided in two groups, according to the ICUS findings. Group I was maintained under clinical treatment [minimal lumen area (MLA) $\geq$ 6.0 mm$^2$ and/or minimal lumen diameter (MLD) $\geq$ 2.5 mm] and Group II was submitted to revascularization (MLA < 6.0 mm$^2$ and/or MLD < 2.5 mm). The occurrence of major cardiac events (death, acute myocardial infarction and/or revascularization of the target lesion) was assessed during follow-up.

**Results:** Forty-one (62%) patients were allocated in Group I and 25 (38%) in Group II. Mean follow-up was 42.1 months. The coronary angiography did not differentiate the two groups regarding lesion severity (MLD 1.98 mm in Group I vs. 1.72 mm in Group II; p = 0.75) in opposition to ICUS (MLD 3.41 mm in Group I vs. 2.01 mm in Group II; p < 0.001). There was no death or myocardial infarction in Group I. The survival rate free of major cardiac events was 95% in Group I vs. 87.5% in Group II (p=ns).

**Conclusion:** Treatment decision-making of patients with ambiguous lesions in the LMCA guided by ICUS findings showed to be safe and effective.

**Key words:** Ultrasonography interventional, coronary vessels, myocardial revascularization.

Patients with severe left main coronary artery (LMCA) lesions are associated with a reserved long-term prognosis[1,2]. The coronary revascularization surgery (CRS) has shown to prolong survival in patients with significant LMCA lesions[3,4]. Referring patients with no significant LMCA lesions for coronary revascularization could lead, however, to the inappropriate use of available grafts, as well as to the premature occlusion of grafts or even of the native arteries. Angiography is considered the standard method of reference and it is most often utilized in the invasive diagnosis of coronary disease. Nevertheless, it can present limitations in some situations, such as when assessing the degree of severity of LMCA lesions. Furthermore, necropsy and intracoronary ultrasound (ICUS) studies have demonstrated several situations in which the LMCA presented significant lesions whereas, frequently, the angiography did not disclose important lesions[5,6].

ICUS is an invasive method that allows the identification of the real dimensions of the vessel and the components of the atherosclerotic plaque and the precise measurement of the arterial lumen, being a more sensitive method than angiography to assess the initial phase of atherosclerosis[7,8]. Several studies have demonstrated the usefulness of ICUS in the identification of LMCA lesions[9-11].

The aim of this study is to assess the safety and efficacy of the surgical vs. conservative treatment in patients with ambiguous lesions in the left main coronary artery (LMCA), based on intracoronary ultrasound (ICUS) findings.

## Methods

*Patients* - From December 1999 to June 2004, 66 consecutive patients who presented angiographically ambiguous LMCA lesions (moderate lesions, exclusively aortic-ostial lesions, short LMCA lesions, among others) and had been referred for ICUS assessment at the Invasive Cardiology Service of Dante Pazzanese Institute were enrolled in the study. To assess the degree of severity of the lesions, the following ultrasonographic variables were utilized: minimum lumen area (MLA) and minimum lumen diameter (MLD). Patients with MLA $\geq$ 6.0 mm$^2$ and/or MLD $\geq$ 2.5 mm did not meet the ultrasonographic criteria for severe lesions and

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were kept under clinical treatment and allocated to Group 1. Patients with MLA < 6.0 mm$^2$ and/or MLD < 2.5 were considered as having severe lesions and referred for coronary revascularization surgery (Group 2).

Information regarding the evolution of all patients was obtained through the analysis of hospital charts and completed by telephone contact. Two patients, whose clinical evolution data were not available, were excluded from the study. Major cardiac events, which were the primary study objective, included cardiac death (defined as death of cardiac origin or when a non-specific cause could not be determined), myocardial infarction (consensus of the European Society of Cardiology/American College of Cardiology)[12] and revascularization of the target vessel (defined as a surgical or percutaneous intervention related to the left coronary trunk).

*Procedure* - All ultrasonographic assessments were carried out in the same machine (ClearView - Boston Scientific). After the administration of 0.2 mg of intracoronary nitroglycerin and 100 IU/kg of intravenous heparin, the ICUS transducer was advanced until the intracoronary guide wire, up to approximately 10 mm distal to the LMCA, and then the transducer was backed from the distal part of the artery to the aorta, using an automatic traction equipment to a constant velocity of 0.5 mm/s, in order to acquire a sequence of images.

*Quantitative coronary angiography* - The MEDIS software version 5.1 (medical imaging system, QCA-CMS) was utilized to carry out the quantitative angiographies of the LMCA lesions. By means of automatic detection of borders and calibration through the coronary catheter, the following variables were analyzed: minimum lumen diameter (MLD), diameter stenosis (DS), reference diameter (RD) and LMCA extension. MLD was measured during diastole, at the site of greatest lumen severity. The reference diameters were measured in places considered to be angiographically normal, at 5 mm proximal and distal to the lesion, when possible. The distal reference was utilized only when the lesion was aortic-ostial. We discriminated the lesion site regarding its position, i.e., ostial, middle third or distal. The angiography was also utilized to assess the number of vessels, in addition to the LMCA, with lesions > 50%.

*Intracoronary ultrasound* - Data from the ICUS were evaluated by means of the TapeMeasure software (Indec System, Mountainview, California) for the analysis of ultrasonographic images previously recorded in VHS tapes. The MLA, the external elastic membrane area, corresponding to the vessel area (VA), the plaque area (PA), MLD and LMCA extension were measured at lesion site and proximal and distal reference points.

The percentage of plaque or plaque load (PL) = PA/VA; and stenosis area (SA) = [(reference MLA– lesion MLA) x 100]/reference MLA were also calculated.

*Statistical analysis* - Statistical analysis was carried out with the StatsDirect software version 1.617 and the data were analyzed as "intention to treat". The differences among the categorical variables were compared between the two groups through the Chi-square test or Fisher's exact test when appropriate. The comparisons among the continuous variables were carried out using Student's *t* test. The correlations between ICUS and QCA variables were performed through Pearson's correlation method. The probability curves of major cardiac events were carried out through Kaplan-Meier method.

## Results

According to the ultrasonographic criteria utilized, 41 (62%0) patients were kept under clinical supervision (Group 1) and 25 (38%) were referred for coronary revascularization surgery (Group 2). There was no statistically significant difference regarding the basal clinical and angiographic characteristics between the two groups (Table I). Only one patient from Group 2 did not undergo the revascularization surgery at the time of the ultrasonographic assessment at his own discretion. There were no complications during the ultrasonographic procedures. An example of the ICUS assessment can be observed in Figure 1.

At the coronary angiography assessment, most lesions were aortic-ostial (44%) followed by distal (34%) and middle third lesions (22%), with no significant differences between the two groups. When the lesion at the angiographic assessment was aortic-ostial or distal, only 31% and 30% of the patients, respectively, fulfilled the ultrasonographic criteria for severe lesions; when the lesions were located in the middle third of the LMCA at the angiographic assessment, 66% of them were considered severe at the ICUS. The quantitative coronary angiography was not able to differentiate between the two groups according to the severity of lesions. Mean MLD (1.77 ± 1.12 mm in group 1 *vs.* 1.68 ± 1.06 mm in group 2, p = 0.75) and DS (36.42 ± 15.1% group 1 *vs.* 35.22 ± 14.6% in group 2, p = ns) were similar in both groups. However, we observed lower MLD and MLA as well as higher PA and SA at the ICUS in Group 1, when compared to Group 2. The main ultrasonographic and angiographic variables are described in Table 2. There was no significant correlation between the quantitative angiography and the intracoronary ultrasound variables (MLD r = 0.152, p = 0.32 and RD r = 0.174, p = 0.26), even when comparing the two groups separately.

Sixty-four (96.9%) patients had a complete clinical follow-up. The mean follow up duration was 42.1 ± 15.6 months (range 6-70 months). Five patients (7.8%) presented major cardiac events during clinical evolution. In Group 1, two (5%) of the patients presented cardiac events. One patient was referred for surgery at another Service, for interatrial communication repair and coronary revascularization surgery five months after our evaluation. This patient probably presented an extrinsic compression of the LMCA by the pulmonary artery, as previously described in literature[13]. The second patient was also submitted to surgery, due to progression of the LMCA lesion, 34 months after the initial evaluation. In Group 2, three (12.5%) patients presented events during evolution. Two patients died, one during postoperative recovery and the other, seven months after the surgery, due to acute pulmonary edema. A third patient, who was diabetic and from Group 2, presented myocardial infarction 23 months after the surgery. The summarized descriptions of the events are shown in Table 3. At the univariate analysis, no clinical, angiographic or ultrasonographic variable was predictive of

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|  | Group 1 (n = 40) | Group 2 (n = 20) | p |
|---|---|---|---|
| Age (yrs±SD) | 55 ± 17.1 | 66 ± 11.4 | 0.15 |
| Male gender, n (%) | 20 (74%) | 11 (68%) | 0.72 |
| Arterial hypertension, n (%) | 9 (33%) | 6 (37%) | 0.99 |
| Diabetes, n (%) | 5 (18%) | 4 (25%) | 0.71 |
| Dyslipidemia, n (%) | 6 (22%) | 5 (31%) | 0.71 |
| Smoking, n (%) | 4 (14%) | 4 (25%) | 0.44 |
| Previous infarction, n (%) | 2 (7.4%) | 1 (6,2%) | 0.91 |
| Previous revascularization, n (%) | 1 (3.7%) | 2 (12,5%) | 0.50 |
| Presence of Angina, n (%) | 9 (33%) | 8 (29%) | 0.50 |
| Lesion >50% DS, n (%) | 6 (22%) | 6 (37%) | 0.32 |

DS- *diameter stenosis.*

**Table 1 - Clinical and angiographic characteristics**

major cardiac events.

The Kaplan-Meier curve showed that, at the end of a 70-month follow-up, 95% of the patients kept under clinical treatment were free of major cardiac events, as well as 87.5% of the patients in the surgical group (Fig. 2A). When the revascularization of any coronary lesion was included as a major cardiac event, the event-free survival was 87.5% in Group 1 and 75.0% in Group 2 (Fig. 2B).

## Discussion

The present study demonstrates the usefulness and safety of ICUS in the treatment decision-making in patients with angiographically ambiguous LMCA lesions. The LMCA constitutes the most relevant segment of the coronary trunk, for its prognostic and therapeutic implication. Patients with severe coronary LMCA lesions have their survival increased by undergoing myocardial revascularization. Nevertheless, patients with ambiguous LMCA lesions can be either referred for coronary revascularization (surgical or percutaneous intervention) or be kept under clinical treatment. If there is no definition regarding the lesion degree of severity, two important mistakes can be made. The first is to refer patients with non-significant lesions for surgery, which may result in (1) premature occlusion of the grafts or native coronary arteries; (2) the premature utilization of a graft and (3) submitting the patient to the inherent risks of surgery. The second would be to keep a patient who presents severe LMCA lesions under clinical treatment, with its well-known late reserved prognosis.

In the last decades, several necropsy and ICUS studies have shown that angiography can underestimate as well
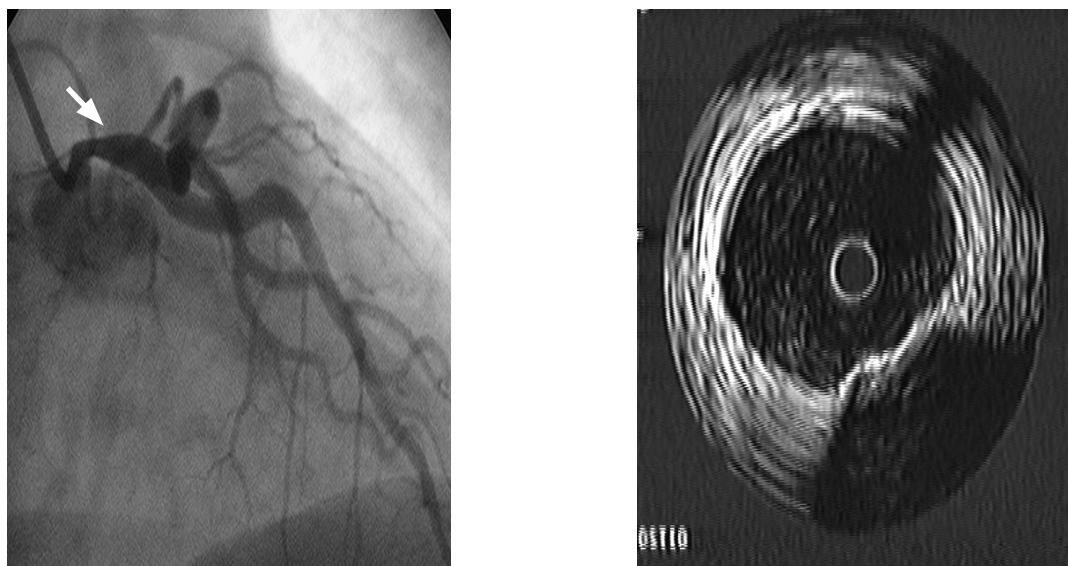


*Fig. 1* - *Patient with angiographically severe lesion (white arrow) (MLD = 1.83 mm and SD = 56%). Not confirmed at ICUS, whereupon an excellent lumen was observed in the ostium of the left coronary artery [(minimum lumen area (MLA) = 16.4 mm2 and minimum lumen diameter (MLD) = 3.87 mm).*

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| | Group 1 (n = 40) | Group 2 (n = 20) | pACQ |
|---|---|---|---|
| **QCA** | | | |
| Reference diameter (mm) | 3.10 ± 0.86 | 2.92 ± 0.53 | ns |
| Minimum lumen diameter (mm) | 1.77 ± 1.12 | 1.68 ± 1.06 | ns |
| Diameter stenosis (%) | 35.22 ± 14.6 | 36.42 ± 15.1 | ns |
| **ICUS – Lesion site** | | | |
| Minimum lumen diameter (mm²) | 3.41 ± 0.8 | 2.10 ± 0.3 | < 0.001 |
| Vessel area (mm²) | 19.81 ± 6.6 | 14.15 ± 3.4 | 0.002 |
| Minimum lumen area (mm²) | 11.55 ± 5.7 | 5.05 ± 1.4 | < 0.001 |
| Plaque area (mm²) | 6.89 ± 4.1 | 10.81 ± 4.2 | 0.005 |
| Area of stenosis (%) | 23.2 ± 20.1 | 49.6 ± 15.3 | < 0.001 |

QCA - quantitative coronary angiography; ICUS - intracoronary ultrasound; ns - non-significant.

**Table 2 - QCA and ICUS Results**

| Patient/ Sex | Group | Age (yrs) | QCA-MLD (mm) | QCA-DS (%) | ICUS-MLD (mm) | MLA (mm²) | Event (months) | Event-Treatment |
|---|---|---|---|---|---|---|---|---|
| 1 / F | 1 | 39 | 1.83 | 56 | 3.87 | 16.4 | 5 | Surgery LMCA / IAC |
| 2 / M | 1 | 65 | 2.26 | 44 | 2.73 | 7.1 | 34 | Surgery Progression LMCA lesion |
| 3 / M | 2 | 68 | 1.74 | 41 | 2.11 | 4.1 | 0 | Postoperative death |
| 4 / F | 2 | 77 | 2.8 | 23 | 1.78 | 3.6 | 7 | Death/APE |
| 5 / M | 2 | 67 | 2.3 | 37 | 2.10 | 3.9 | 23 | AMI/Clinical |

QCA - Quantitative Coronary Angiography; MLD - minimum lumen diameter; DS - diameter stenosis; MLA - minimum lumen area; ICUS - intracoronary ultrasound; APE - acute pulmonary edema; AMI - acute myocardial infarction; MRS - myocardial revascularization surgery; IAC - interatrial communication; LMCA - left main coronary artery.

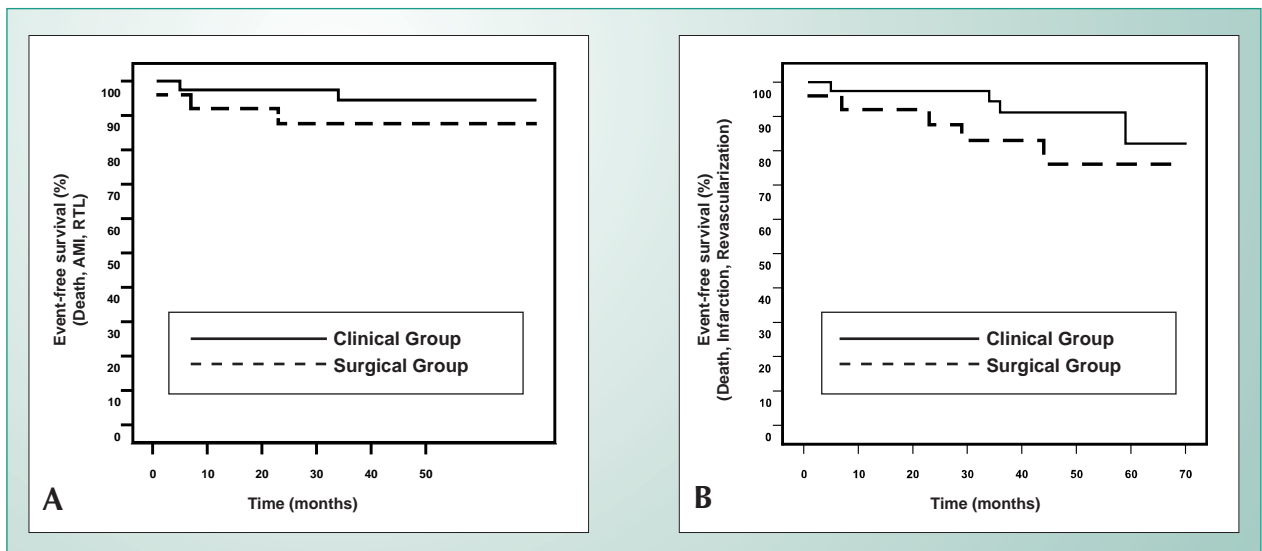**Table 3 - Summarized description of major cardiac events that occurred**

as overestimate LMCA lesions. Hermiller et al[14], evaluating 27 normal LMCA at the angiography, observed that 89% of them presented some degree of atherosclerotic plaque at the ICUS, with 27% of them being considered severe. Isner et al[15], in a necropsy study, observed that the assessment of LMCA lesions through angiography underestimated (39%) or overestimated (25%) the lesions in 64% of the times. In our study, the coronary angiography did not differentiate the two groups by the severity of the LMCA lesion, as observed by the similar results of MLD and DS in the two groups. Thus, in the last two years, other invasive methods, such as ICUS and coronary flow reserve have been considered for the assessment of angiographically ambiguous lesions[16-18].

The ICUS is a tomographic technique with direct visualization of the inner part of the vessel, which allows a unique *in vivo* visualization of the arterial layers. Recently, it has also been shown to be useful in the stratification of coronary lesions, including those located in the LMCA[19,20]. Corroborating the findings of previous studies, our study showed that, in opposition to the angiography, the ICUS allowed the differentiation of severe LMCA lesions from the non-severe ones. An important finding of the study was to show that more than half of the lesions were not considered to be severe at the ICUS, which is in accordance to literature[20]. It is noteworthy that, in lesions located elsewhere, i.e., not in the LMCA, the opposite is observed; thus, 60% of the lesions are considered severe at the ICUS[17].

Another important information is the fact that there was a worse concordance between the ICUS and the angiography when the lesions were ostial and distal, in opposition to the lesions located in the middle-third of the LMCA.

As the severity of lesions in the coronary angiography correlates with the occurrence of cardiac events, some longitudinal studies also demonstrated the same results with the ICUS, since the variables in such studies (MLA and MLD) were independent predictive factors of cardiovascular events[21,22]. Nevertheless, in opposition to the other segments of the coronary arteries, where there is a established cutoff value for lesion severity (MLA< 4.0 mm²), LMCA values are less consensual. Recently, the utilization of the fractional flow reserve and intracoronary Doppler in LMCA lesions was able to define MLA cut off values that were determinant of some

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*Fig. 2A - Kaplan-Meier Curve showing an event-free survival (death, infarction and trunk-related revascularization) after a 70-month follow-up according to the allocated group.*

*Fig. 2B - Kaplan-Meier Curve showing an event-free survival, including revascularization of any vessel, after a 70-month follow-up according to the allocated group.*

degree of myocardial ischemia[23]. Nonetheless, the appropriate MLA cutoff is yet to be defined, given that, depending on the study in question, the MLA varied from 5.0 to 8.0 mm$^2$ [20,23]. Other studies that utilized the invasive methods of coronary flow in the LMCA, also observed that the MLD at the ICUS was correlated to the myocardial ischemia, especially when the diameter was < 2.5 mm[21]. Although there was no consensual cutoff value of the ultrasonographic variables at the time when our study was designed, most of the patients from Group 2 had lower MLA and MLD values compared to the established ones (Figs. 3A and 3B).

Despite the observation of a positive correlation between myocardial ischemia detected by invasive or non-invasive methods, and the MLA and the MLD at the ICUS, few clinical prospective studies evaluated LMCA lesions. Abizaid et al[21], in a retrospective analysis of ambiguous LMCA lesions assessed by ICUS, demonstrated an event-free survival of 86% in patients kept under clinical treatment for a year. Furthermore, they observed that the MLD at the ICUS was an independent

predictor of cardiac events, especially when it was < 2.5 mm. Recently, Fassa et al[20], prospectively assessing 214 patients with ambiguous LMCA lesions, also utilizing a treatment strategy guided by ICUS, found an event-free survival of 88.4% in patients kept under clinical treatment, during a mean follow-up period of 3.5 ± 2.1 yrs[20]. In the present study, the decision to refer patients with angiographically ambiguous LMCA lesions for coronary revascularization surgery or not was based exclusively on ICUS results. This treatment strategy guided by the ICUS resulted in a survival free of major cardiac events, during a 42-month follow-up. In addition, the group of patients kept under clinical treatment showed an event-free survival similar to that of patients referred for surgery, with no death or infarction observed in patients kept under clinical treatment. It is noteworthy that, in the pioneering study by Fassa et al[20], a LMCA lesion with MLA < 7.5 mm$^2$ was considered severe. On the other hand, 10 (15.5%) of the patients in the present study had MLA between 6.0 and 7.5 mm$^2$, and two of them were kept under clinical treatment with no occurrence of
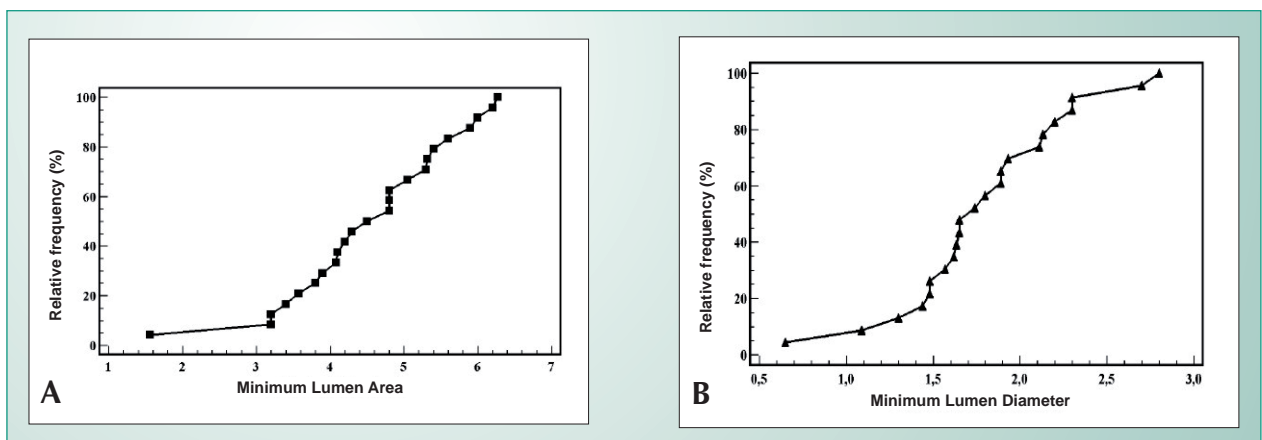


*Fig. 3A - Relative cumulative frequency curve of MLA (minimum lumen area) of the surgical group.*

*Fig. 3B - Relative cumulative frequency curve of MLD (minimum lumen diameter) of the surgical group.*

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cardiac events during the clinical evolution.

*Limitations* - This study was designed in a non-randomized fashion, and therefore presents limitations that are innate to such method. Therefore, we cannot affirm that patients with MLA < 6 mm$^2$ or MLD < 2.5 mm (lesions considered severe at the ICUS) would benefit from an exclusively clinical treatment in opposition to revascularization surgery. Nevertheless, as there is a consensus that the area size of the myocardial ischemia is an important predictor of cardiac events, and considering the numerous studies that demonstrated some degree of ischemia in LMCA lesions with MLA < 8 mm$^2$, it would be likely unethical to keep such patients solely under clinical treatment. The patients from the surgical group were treated exclusively by revascularization surgery, which did not incorporate the percutaneous interventions with pharmacological stents.

## Conclusion

This study shows that a treatment approach established by the ICUS findings in patients with angiographically ambiguous lesions of the LMCA is effective and safe. We suggest that patients with LMCA lesions with MLA > 6.0 mm$^2$ and MLD > 2.5 mm at the ICUS be kept under clinical supervision, with excellent major cardiac event-free survival.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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