Journal of the American College of Cardiology
Vol. 45, No. 2, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.09.066

Intravascular Ultrasound-Guided Treatment for Angiographically Indeterminate Left Main Coronary Artery Disease

A Long-Term Follow-Up Study

Amir-Ali Fassa, MD, Kenji Wagatsuma, MD, Stuart T. Higano, MD, Verghese Mathew, MD, Gregory W. Barsness, MD, Ryan J. Lennon, MS, David R. Holmes, Jr, MD, Amir Lerman, MD
Rochester, Minnesota

OBJECTIVES The purpose of this study was to evaluate the efficacy of an intravascular ultrasound (IVUS)-guided strategy for patients with angiographically indeterminate left main coronary artery (LMCA) disease.

BACKGROUND The assessment of LMCA lesions using coronary angiography is often challenging; IVUS provides useful information for assessment of coronary disease.

METHODS Intravascular ultrasound was performed on 121 patients with angiographically normal LMCAs to determine the lower range of normal minimum lumen area (MLA), defined as the mean − 2 SD. We conducted IVUS studies on 214 patients with angiographically indeterminate LMCA lesions, and deferral of revascularization was recommended when the MLA was larger than this predetermined value.

RESULTS The lower range of normal LMCA MLA was 7.5 mm^2. Of the patients with angiographically indeterminate LMCAs, 83 (38.8%) had an MLA <7.5 mm^2, and 131 (61.2%) an MLA ≥7.5 mm^2. Left main coronary artery revascularization was performed in 85.5% (71 of 83) of patients with an MLA <7.5 mm^2 and deferred in 86.9% (114 of 131) of patients with an MLA ≥7.5 mm^2. Long-term follow-up (mean 3.3 ± 2.0 years) showed no significant difference in major adverse cardiac events (target vessel revascularization, acute myocardial infarction, and death) between patients with an MLA <7.5 mm^2 who underwent revascularization and those with an MLA ≥7.5 mm^2 deferred for revascularization ($p = 0.28$). Based on outcome, the best cut-off MLA by receiver operating characteristic was 9.6 mm^2. Multivariate predictors of cardiac events were age, smoking, and number of non-LMCA vessels diseased.

CONCLUSIONS Intravascular ultrasound is an accurate method to assess angiographically indeterminate lesions of the LMCA. Furthermore, deferring revascularization for patients with a minimum lumen area ≥7.5 mm^2 appears to be safe. (J Am Coll Cardiol 2005;45:204–11) © 2005 by the American College of Cardiology Foundation

Left main coronary artery (LMCA) disease is associated with a poor prognosis when treated medically, and its presence is an indication for coronary artery bypass surgery (CABG), which significantly improves long-term outcome (1–3). Although angiography is considered as the gold standard for coronary artery disease assessment, this technique may present limitations in accurately determining the significance of LMCA lesions (4–8).

Intravascular ultrasound (IVUS) is an accurate method to determine vessel dimensions and wall characteristics, and is more sensitive than angiography in detecting early atherosclerosis (9–12). Observations at our institution and others have shown that IVUS may be helpful in assessment and treatment guidance for angiographically indeterminate LMCA disease (13–19).

From the Center of Coronary Physiology and Imaging, Cardiac Catheterization Laboratory, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota. This work was supported by the National Institutes of Health (R01 HL63911, R01 HL69840) and the Miami Heart Research Institute. Dr. Fassa is the recipient of the Zahedi Family Visiting Clinician Scholarship at the Mayo Foundation.

Manuscript received May 27, 2004; revised manuscript received September 24, 2004, accepted September 28, 2004.

The purpose of this study is to evaluate the safety and efficacy of an IVUS-guided strategy for angiographically indeterminate LMCA disease, by defining a lower range of normal minimum lumen area (MLA), and deferring revascularization for patients who have an MLA larger than this value.

METHODS

Patient population. The following study protocol was approved by the Mayo Clinic Institutional Review Board. All patients included were seen from November 1994 to September 2002. A total of 121 patients who were found to have a normal or minimally diseased LMCA on angiography underwent IVUS examinations. The lower range of the normal MLA was defined as the mean MLA − 2 SDs. Based on this criterion, a recommendation was implemented that all patients with an angiographically indeterminate LMCA should undergo IVUS, and that revascularization be performed when the MLA was smaller than the predefined lower range of normal; IVUS studies were carried out at the discretion of the treating physician. All cases in which IVUS had been performed in order to clarify

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CSA = cross-sectional area
EEM = external elastic membrane
IVUS = intravascular ultrasound
LMCA = left main coronary artery
MACE = major adverse cardiac events
MLA = minimum lumen area
MLD = minimum lumen diameter
PCI = percutaneous coronary intervention
P+M = plaque plus media

ambiguous angiographic findings, and help determine acute therapy, were included. During the study period, 231 patients underwent an IVUS study for angiographically indeterminate lesions of the LMCA. Seventeen patients with the following criteria were excluded from the study: 1) research consent denied by the patient (one patient); 2) quantitative assessments of IVUS findings was difficult due to severe calcification or obscure IVUS imagery (two patients); 3) the IVUS catheter could not be maintained coaxial to the LMCA during pull-back (three patients); 4) stent had been previously placed in the LMCA (four patients); 5) proven spasm of the LMCA (four patients); and 6) LMCA revascularization therapy was unclear or unknown (three patients). Therefore, 214 patients were included in the present study.

The treatment strategy selection was left to the discretion of the treating physician and was generally based on the patients underlying clinical state, in light of the previous recommendation of performing revascularization when MLA was found to be smaller than the preestablished lower range of normal value.

Clinical demographics. Hospital records of all the patients with angiographically indeterminate LMCA were reviewed to obtain information on clinical demographics and medical history. Follow-up information was obtained through review of hospital charts, written questionnaires, telephone interviews, and the interventional database of the Mayo Clinic. Patients were considered to have follow-up only if information was available more than one year after the date of angiography, unless an adverse event had occurred during that period. Major adverse cardiac events (MACE) included target vessel revascularization (defined as a percutaneous coronary intervention [PCI] of the LMCA or CABG to the left coronary system due to progression of the LMCA disease), myocardial infarction (according to the definition stated by the European Society of Cardiology/American College of Cardiology consensus document [20]), and all-cause mortality.

Procedure. Coronary angiography was performed via the femoral artery approach, with insertion of a 6 to 8F sheath followed by an angiography catheter or guiding catheter of the same size. Patients received 2,500 U of intravenous heparin before the angiography procedure. An additional

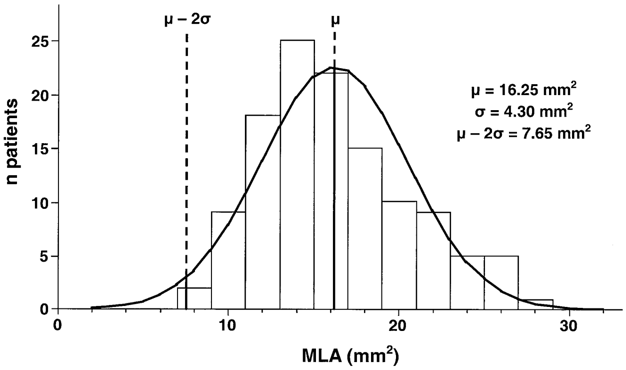

Figure 1. Distribution of 121 patients with an angiographically normal or minimally diseased left main coronary artery, according to minimum lumen artery (MLA). μ = mean; σ = standard deviation.

3,000 to 5,000 U of heparin, as well as 0.4 mg of sublingual nitroglycerin were administered before the IVUS examination. Angiographic assessments of the LMCA were made from a minimum of two angles. Two experienced angiographers reviewed the angiogram, and IVUS examinations were conducted to determine the most appropriate therapy.

IVUS examination. The IVUS imaging protocol was performed according to methods as described previously (21,22). After angiography, a 0.014-inch guidewire was passed through a 6-F to 8-F guiding catheter from the left main to the left anterior descending or circumflex artery. Intracoronary nitroglycerin 200 μg was administered to avoid coronary spasm. The IVUS transducer was inserted up to a point beyond the bifurcation from the left main to the left anterior descending or circumflex artery. Using manual pullback or a motorized pullback system, images were recorded on a VCR tape. Studies were performed using one of three commercially available systems. We used a 30-MHz, 3.5-F mechanical scanning IVUS catheter (Cardiovascular Imaging Systems Inc., Boston Scientific, Boston, Massachusetts, and Hewlett-Packard, Andover, Massachusetts), a 2.9-F or 3.2-F mechanical scanning IVUS catheter (Cardiovascular Imaging Systems Inc., Boston Scientific Corporation, Boston, Massachusetts), and a 3.5-F electronic scanning IVUS (Volcano, Endosonics, Rancho Cordova, California). The Volcano/Endosonics IVUS observations were recorded on a CD in addition to a VCR tape.

Quantitative coronary angiography analysis. Quantitative coronary angiography was performed off-line by an investigator unaware of the IVUS findings, using computer-assisted edge-detection methods (QCA-CMS version 5.0, MEDIS, Leiden, the Netherlands). The contrast-filled catheter was used for calibration. Minimal lumen diameter (MLD), reference diameter, and lesion length were measured in diastolic frames obtained by angiography before IVUS procedures. Percent diameter stenosis was calculated. The lesion segment was defined as the portion of the vessel where the lesion was located (ostial, middle of distal).

IVUS analysis. Intravascular ultrasound analysis was performed according to the methods described in the consensus

JACC Vol. 45, No. 2, 2005
January 18, 2005:204–11

Table 1. Revascularization Therapy of LMCA

	MLA <7.5 mm^2 (n = 83)		MLA ≥7.5 mm^2 (n = 131)	
	A (Revascularization)	B (Deferral)	C (Revascularization)	D (Deferral)
n	71 (85.5)	12 (14.5)	17 (13.0)	114 (87.0)
CABG	69 (97.2)	—	17 (100)	—
PCI of LMCA	2 (2.8)	—	0	—
Medical therapy only	—	9 (75.0)	—	79 (69.3)
PCI of non-LMCA vessels	2 (2.8)	3 (25.0)	0	35 (30.7)

CABG = coronary artery bypass surgery; LMCA = left main coronary artery; MLA = minimum lumen area; PCI = percutaneous coronary intervention.

document on IVUS studies by the American College of Cardiology (23). The quantitative and qualitative analyses were conducted off-line by an investigator unaware of the clinical characteristics or the treatment of the patient, using the recorded VCR tapes and CD. Hewlett-Packard Sonos Intravascular, Volcano/Endosonics In-Vision, and CVIS ClearView, Boston Scientific, were used for analysis of IVUS observations. Standard calibration markers directly from the ultrasound images were used for calibration of absolute measurements. Based on images depicted during pullback of the transducer that had been inserted beyond the LMCA bifurcation into the left anterior descending or circumflex artery, the lesion was defined as the image slice with the smallest lumen cross-sectional area (CSA).

Quantitative assessment measured the following parameters through computer planimetry at the lesion site. Minimal lumen area: obtained by tracing the intimal leading edge. External elastic membrane (EEM) CSA: obtained by tracing the EEM CSA at the lesion site. Plaque plus media (P+M) CSA: the difference between EEM CSA and MLA. Minimum lumen diameter: the shortest diameter through the center point of the lumen. Maximum lumen diameter: the longest diameter through the center point of the lumen. In addition, plaque burden was calculated as the ratio of P+M CSA to EEM CSA (plaque burden [%] = P+M CSA × 100/EEM CSA).

Qualitative assessments classified plaque properties into the following four classes. Soft: plaque has less echogenicity than the adventitia. Calcified: plaque has higher echogenicity than the adventitia accompanied by acoustic shadowing. Fibrous: plaque has echogenicity that falls between that of calcified and soft plaque. Mixed: plaque composed of two or more of the above properties (soft, calcified, fibrous). Calcium score was studied to determine severity of calcification. Cross-sections to be assessed for calcium score were divided into quadrants, and classified into five stages according to calcium occupied area (0 to 4, 0 = no calcium, 4 = calcium in all four quadrants).

Statistical analysis. Continuous variables are presented as mean ± SD. Discrete variables are presented as absolute numbers (percentages). Group differences were compared with the unpaired two-sample *t* test, the one-way analysis of variance, Pearson's chi-square test, or the log-rank test, as appropriate; MACE curves were constructed according to Kaplan and Meier (24). All tests were two-tailed at the 0.05 significance level. The receiver operating characteristic method according to Contal and O'Quigley (25) was used to determine the best cut-off point for MLA based on the outcome. Logistic regression analysis was used to identify the independent predictors of MACE. Univariate predictors of MACE with a p value <0.05 were entered into the multivariate model.

RESULTS

Normal LMCA group. The mean MLA of the 121 patients with an angiographically normal or minimally diseased LMCA (control group) was 16.25 ± 4.30 mm^2 (Fig. 1). The lower range of normal value, calculated as the mean MLA − 2 SDs, was 7.65 mm^2. Therefore, we used the near equal value of 7.5 mm^2 to establish the threshold MLA for performing revascularization in the patients with angiographically indeterminate LMCA disease.

Treatment strategy. Among the 214 patients who underwent IVUS for angiographically indeterminate LMCA disease, 83 (38.8%) had an MLA <7.5 mm^2 and 131 (61.2%) had an MLA ≥7.5 mm^2 (Table 1). The majority (85.5%) of the patients with an MLA <7.5 mm^2 underwent revascularization of the LMCA (group A); most (97.2%) underwent CABG, and two patients (2.8%) had a stent implanted in a protected LMCA (the same two patients also underwent PCI of another vessel). There were 12 patients (14.5%) with an MLA <7.5 mm^2 who were treated conservatively (group B). The main reasons for deferring revascularization in these patients were normal fractional flow reserve of the LMCA (25.0%), patient's refusal of CABG (16.7%), advanced age or comorbidities (16.7%), prior CABG (16.7%), and surgeon's opinion (8.3%). Among the patients with an MLA ≥7.5 mm^2, a large proportion (87.0%) was deferred for revascularization (group D), while the remainder (13.0%) underwent CABG (group C). The main reasons for the latter to undergo revascularization despite an LMCA lesion considered nonsignificant by IVUS were three-vessel disease (35.3%), left anterior descending disease nonamenable to PCI (35.3%), and CABG to the left coronary system during a valve operation for a non-LMCA lesion (6.9%). The CABG procedures were performed within a few days from angio-

Table 2. Baseline Characteristics

	MLA <7.5 mm² (n = 83)		MLA ≥7.5 mm² (n = 131)	
	A (Revascularization)	B (Deferral)	C (Revascularization)	D (Deferral)
n	71 (85.5)	12 (14.5)	17 (12.9)	114 (87.0)
Age (yrs)	65.1 ± 10.5	65.3 ± 8.9	62.4 ± 7.6	64.5 ± 10.9
Male gender	48 (67.6)	6 (50.0)	12 (70.6)	61 (53.5)
Hypertension	43 (60.6)	7 (58.3)	12 (70.6)	58 (50.9)
Diabetes	10 (14.1)	2 (16.7)	3 (17.7)	16 (14.0)
Hyperlipidemia	43 (60.6)	3 (25.0)	14 (82.4)	55 (48.3)§
Smoking*	14 (19.7)	2 (16.7)	4 (23.5)	21 (18.4)
Family history†	42 (59.2)	4 (33.3)	13 (76.5)	53 (47.6)§
Prior PCI	17 (23.9)	4 (33.3)	3 (17.7)	16 (14.0)
Prior CABG	5 (7.0)	2 (16.7)	1 (5.9)	5 (4.4)
Body mass index (kg/m²)	28.6 ± 4.9	31.0 ± 10.7	29.2 ± 4.7	30.0 ± 6.3
Body surface area (m²)	1.96 ± 0.23	1.91 ± 0.24	2.02 ± 0.23	1.95 ± 0.24
Ejection fraction (%)‡	54.7 ± 13.5	60.3 ± 10.9	54.1 ± 16.8	59.1 ± 14.5
Indication for angiography				
Angina pectoris	29 (40.9)	3 (25.0)	6 (35.3)	34 (29.8)
Unstable angina	11 (15.5)	1 (8.3)	4 (23.5)	12 (10.5)
Acute myocardial infarction	7 (9.9)	1 (8.3)	2 (11.8)	10 (8.8)
Silent ischemia	5 (7.0)	1 (8.3)	3 (17.7)	6 (5.3)
Other	19 (26.8)	6 (50.0)	2 (11.8)	52 (45.6)§

*Active smoking at time of or up to one year before angiography; †available for 211 of 214 patients; ‡available for 18 of 214 patients; §$p < 0.05$ across groups A, B, C, D.
Abbreviations as in Table 1.

graphy, and no complications occurred during that interval. No patient underwent PCI of an unprotected LMCA.

Baseline characteristics. The rate of hyperlipidemia and family history of coronary artery disease differed significantly among the groups, and was highest in group C (Table 2). "Other" indications for angiography, which included mainly atypical or noncardiac chest pain and shortness of breath, were more often encountered in patients who were deferred for revascularization (groups B and D). There were no other significant differences in baseline characteristics.

Angiography characteristics. There was a significant trend toward a higher number of non-LMCA vessels diseased among the patients who underwent revascularization (groups A and C) (Table 3). Minimum lumen diameter and the reference diameter were significantly lower in the patients who had an MLA <7.5 mm², in contrast with the lack of difference in the degree of stenosis and lesion length between the four groups. There were no significant differences in the location of the LMCA lesion.

IVUS characteristics. Patients in groups A and B had a significantly smaller EEM CSA, MLD, and maximum lumen diameter, as well as a higher plaque burden and calcium score than in groups C and D (Table 4). Furthermore, patients in the control group did have a limited degree of atherosclerosis. Additionally, during IVUS examination, two patients (0.9%) experienced transient chest pain with ST-segment change, which rapidly resolved after discontinuation of the examination; there was no associated myocardial injury.

Long-term outcome. Overall follow-up was obtained for 185 (86.4%) patients, for a mean period of 3.5 ± 2.1 years

Table 3. Angiographic Characteristics

	MLA <7.5 mm² (n = 83)		MLA ≥7.5 mm² (n = 131)	
	A (Revascularization)	B (Deferral)	C (Revascularization)	D (Deferral)
n	71	12	17	114
Vessels diseased*	2.0 ± 1.0	1.7 ± 1.2	2.2 ± 1.0	1.1 ± 0.9†
LMCA lesion location				
Ostium	35 (49.3)	7 (58.3)	9 (52.9)	73 (64.0)
Middle	14 (19.7)	1 (8.3)	2 (11.8)	18 (15.8)
Distal	22 (31.0)	4 (33.3)	6 (35.3)	23 (20.2)
MLD (mm)	2.3 ± 0.5	2.2 ± 0.4	2.7 ± 0.6	2.6 ± 0.6†
Reference diameter (mm)	3.6 ± 0.7	3.5 ± 0.6	4.1 ± 0.7	4.0 ± 0.8†
Diameter stenosis (%)	35.0 ± 10.7	37.0 ± 7.0	33.9 ± 9.3	34.0 ± 12.1
Lesion length (mm)	4.1 ± 2.2	4.2 ± 3.2	3.4 ± 2.0	3.6 ± 1.6

*Number of vessels diseased excluding the LMCA; †$p < 0.05$ across groups A, B, C, D.
MLD = minimum lumen diameter; other abbreviations as in Table 1.

Table 4. IVUS Characteristics

	MLA <7.5 mm^2		MLA ≥7.5 mm^2		
	A (Revascularization)	B (Deferral)	C (Revascularization)	D (Deferral)	Control
n	71	12	17	114	122
MLA (mm^2)	5.8 ± 1.1	6.1 ± 1.0	11.2 ± 3.1	11.7 ± 3.6*	16.3 ± 4.3
Range (mm^2)	(3.4–7.4)	(4.3–7.1)	(7.6–19.3)	(7.5–25.6)	(8.3–28.5)
EEM CSA (mm^2)	18.9 ± 4.9	19.6 ± 5.3	24.4 ± 5.6	21.4 ± 6.6*	21.5 ± 6.0
P+M CSA (mm^2)	13.1 ± 4.7	13.5 ± 4.7	13.2 ± 5.5	9.7 ± 5.7*	5.3 ± 3.0
Plaque burden (%)	67.7 ± 9.0	67.4 ± 7.7	53.4 ± 13.1	42.7 ± 16.2*	23.6 ± 8.3
MLD (mm)	2.3 ± 0.3	2.4 ± 0.2	3.2 ± 0.5	3.3 ± 0.7*	4.2 ± 0.6
Maximum lumen diameter (mm)	3.1 ± 0.5	3.1 ± 0.4	4.3 ± 0.7	4.3 ± 0.7*	4.8 ± 0.7
Plaque composition					
Soft	11 (15.5)	3 (25.0)	3 (17.7)	53 (46.5)*	—
Fibrous	12 (16.9)	3 (25.0)	4 (23.5)	22 (19.3)	—
Mixed	8 (11.3)	0	2 (11.8)	7 (6.1)	—
Calcified	40 (56.3)	6 (50.0)	8 (47.1)	32 (28.1)*	—
Calcium score (mean)	1.3 ± 1.3	1.3 ± 1.6	0.8 ± 1.0	0.6 ± 1.1*	

*$p < 0.05$ across groups A, B, C, D.
CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; P+M = plaque + media; other abbreviations as in Tables 1 and 3.

(range 0 to 8.2 years) (Table 5, Fig. 2). There was no difference in three-year and long-term freedom from MACE between the patients who were treated according to the IVUS-guided strategy (groups A and D). Patients in group C also had an outcome similar to the patients in groups A and D, while those in group B had an extremely high rate of events. The best cut-off for performing or deferring revascularization based on the outcome of the patients deferred for revascularization (groups B and D) by receiver operating characteristic was 9.6 mm^2 ($p = 0.062$). Univariate predictors of adverse events among the patients who underwent the IVUS-guided strategy (groups A and D) were age, smoking status, number of diseased vessels (excluding the LMCA), left ventricular ejection fraction, calcium score, and the presence of calcified plaques (Table 6). When performing multivariate analysis, age, smoking status, and the number of diseased non-LMCA vessels remained the only significant predictors of adverse events (Table 7).

DISCUSSION

The current study demonstrates that IVUS is a safe and useful tool for therapy guidance in patients with angiographically indeterminate LMCA disease. Moreover, deferral of revascularization for patients with an MLA ≥7.5 mm^2 appears to be safe.

Limitation of angiography and the role of IVUS in assessment of LMCA disease. Although it is the method of choice for coronary disease assessment, angiography presents several limitations in the evaluation of LMCA disease (4–8). Apart from interobserver and intraobserver differences in interpretation, the variable anatomy of the LMCA can make assessment difficult because of vessel overlap, ostial angulation and deformity, foreshortening, and streaming of contrast medium from the catheter tip. In addition, the two-dimensional silhouette method of angiography depicting contrast-filled lumen cannot detect diffuse, concentric plaque because of the lack of an undiseased reference segment for comparison.

Table 5. Long-Term Follow-Up

	MLA <7.5 mm^2		MLA ≥7.5 mm^2	
	A (Revascularization)	B (Deferral)	C (Revascularization)	D (Deferral)
n	71	12	17	114
n with follow-up	61 (85.9)	11 (91.7)	16 (94.1)	97 (85.1)
Follow-up period (yrs)	3.2 ± 2.2	3.0 ± 2.2	3.8 ± 1.7	3.6 ± 2.1*
Range (yrs)	(0–7.7)	(0.1–7.1)	(1.1–7.3)	(0.1–8.4)
Target vessel revascularization	1	4	2	8
Myocardial infarction	7	1	0	2
All-cause death	9	2	1	11
Three-year freedom from MACE (%)	79.2	49.9	93.8	88.4*†

*$p < 0.05$ across groups A, B, C, D; †$p = 0.48$ across groups A, C/$p = 0.28$ across groups A, D/$p = 0.86$ across groups C, D.
MACE = major adverse cardiac events; MLA = minimum lumen area.

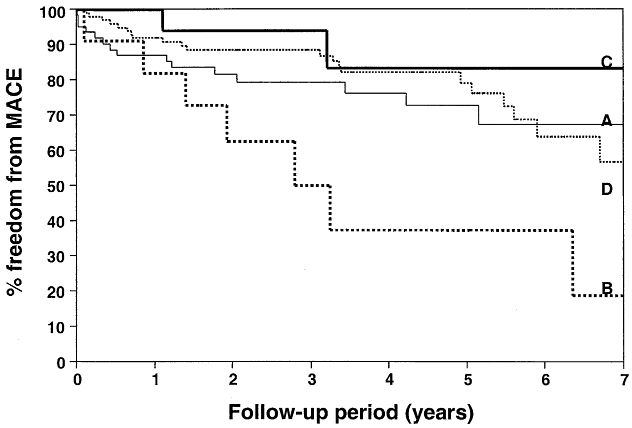

Figure 2. Kaplan-Meier freedom from major adverse cardiac events (MACE). **Thin solid line** = patients with an minimum lumen artery (MLA) <7.5 mm^2 who underwent revascularization (group **A**); **thick dashed line** = patients with an MLA <7.5 mm^2 who were deferred for revascularization (group **B**); **thick solid line** = patients with an MLA ≥7.5 mm^2 who underwent revascularization (group **C**); **thin dashed line** = patients with an MLA ≥7.5 mm^2 who were deferred for revascularization (group **D**); $p < 0.05$ groups **A, B, C, D**; $p = 0.28$ across groups **A, D**; $p = 0.48$ across groups **A, C**; $p = 0.86$ across groups **C, D**.

By providing a cross-sectional, real-time, tomographic perspective with direct visualization of the vessel wall, IVUS can overcome the limitations of angiography. This technique, which allows accurate assessment of lumen size, plaque area, and intimal composition, has demonstrated excellent results for the analysis of coronary artery disease (9–12). Several studies have demonstrated that it is more sensitive than angiography in detecting early atherosclerosis, and shown that it may be helpful for evaluation and treatment guidance of LMCA lesions that are angiographically indeterminate (13–19).

Rationale for using MLA as the criterion for decision-making. There is presently no strict IVUS criterion defining significant lesions of the LMCA that require revascularization. One approach would be to use the degree of area stenosis, by analogy to the degree of diameter stenosis used in angiography, which is obtained by dividing the lumen area at the lesion site by the lumen area at a normal reference site. A 50% diameter stenosis, which is the angiographic criterion for defining significant lesions, would be equivalent to a 75% area stenosis. However, the LMCA, being generally a short vessel, may be diffusely diseased, therefore leaving little opportunity for a normal reference segment (4,8). Complicating this assessment, LMCA atherosclerosis can be accompanied by arterial remodeling, which can be either inward (or "negative") or outward (or "positive"), and may affect the whole LMCA, even in the early stages of atherosclerosis (26,27).

Hence, absolute measurements such as MLA or MLD (as opposed to relative measurements such as lumen area stenosis and plaque burden) may be more representative of flow impairment, and, therefore, of long-term outcome. Indeed, in a study of patients with angiographically ambiguous LMCA disease in whom revascularization was deferred based on IVUS assessment, Abizaid et al. (15) found MLD to be a predictor of cardiac events at one year. Ricciardi et al. (28) showed that in patients with angiographically normal or mild LMCA disease assessed by IVUS, MLA was an independent predictor of clinical events. Finally, in another study of patients where PCI was deferred based on IVUS in non-LMCA coronary arteries, Abizaid et al. (29) also showed event rate to be correlated with MLA.

In the present study, we conducted IVUS examinations on patients who had an angiographically normal or minimally diseased LMCA. The distribution of these patients shows that there were more patients with a larger MLA who were included, with the curve slightly skewed to the right. This may be explained by the fact that patients with a smaller MLA were probably less likely to be considered having a normal LMCA by visual assessment of the angiogram than patients with a larger MLA, leading to a reduced inclusion of the former. Based on this series of patients, the lower range of normal MLA was defined as 7.5 mm^2. This result concurs with the finding of Legutko et al. (30), who determined the cut-off for MLA of the LMCA by correlation with fractional flow reserve to be 8.0 mm^2, but is somewhat higher than the one from a similar study that found a cut-off value of 5.9 mm^2 (31). In a recent study, Russo et al. (18) also proposed a 60% area stenosis or an MLA of 5.0 mm^2 when no distal reference vessel could be identified as a criterion for performing revascularization.

Benefit of the IVUS-guided strategy. We prospectively applied an IVUS-guided strategy to perform or defer revascularization of angiographically indeterminate lesions of the LMCA, based on MLA. This approach was followed in a majority (86.4%) of the cases. The main reasons for not following this strategy were the results from fractional flow reserve assessments of the LMCA lesion, as well as the general condition, comorbidities, and desire of the patients. The higher extent of coronary disease also influenced the revascularization of patients with an LMCA lesion considered nonsignificant (group C), and probably influenced the operators' decision for revascularization in the patients with an MLA <7.5 mm^2 (group A) as well. In addition, the higher rate of typical symptoms among these two groups of patients probably also influenced the decision for revascularization.

Table 6. Univariate Predictors of MACE

	Risk Ratio	95% Confidence Interval	p Value
Age	1.05	1.01–1.08	0.009
Smoking*	2.13	1.03–4.42	0.043
Ejection fraction (%)	0.98	0.95–1.00	0.031
Vessels diseased†	1.48	1.07–2.03	0.016
Calcified plaque	2.52	1.29–4.90	0.007
Calcium score	1.33	1.02–1.72	0.035

*Active smoking at time of or up to one year before angiography; †number of vessels diseased excluding the left main coronary artery.
MACE = major adverse cardiac events.

Table 7. Multivariate Predictors of MACE

	Hazard Ratio	95% Confidence Interval	p Value
Age	1.05	1.02–1.09	0.004
Smoking*	2.42	1.13–5.14	0.022
Vessels diseased†	1.39	1.01–1.90	0.044

*Active smoking at time of or up to one year before angiography; †number of vessels diseased excluding the left main coronary artery.
MACE = major adverse cardiac events.

The rate of diabetes was low among all groups compared with the results usually seen in studies of patients undergoing angiography. This is probably due to the fact that patients with diabetes are at higher risk of having concomitant multivessel disease with an angiographically indeterminate LMCA lesion and would, therefore, have a clear indication for CABG, thus making them less likely of undergoing an additional IVUS examination to determine the severity of an LMCA lesion.

On angiographic examination, the degree of stenosis, which is the main criterion for performing revascularization, was not significantly different between the four groups, while there were significant differences in IVUS quantitative characteristics among the different groups. These results confirm the findings from earlier studies that demonstrate the limitations of angiography for the assessment of LMCA disease, and the usefulness of IVUS for accurately evaluating lesion severity. Moreover, the fact that the patients with an MLA <7.5 mm^2 had a smaller EEM CSA as well as a higher calcium score than the patients with an MLA ≥7.5 mm^2 suggests that inward remodeling and coronary calcification may interfere with the accuracy of assessment of LMCA disease by coronary angiography.

There was no significant difference in the rate of adverse events on long-term follow-up between the patients who were treated according to the IVUS-guided strategy (groups A and D). Furthermore, revascularization of the patients with an MLA ≥7.5 mm^2 (group C) did not result in any significant benefit compared with those with an MLA ≥7.5 mm^2 who were deferred for revascularization. This, therefore, suggests that deferral of revascularization for patients with an MLA ≥7.5 mm^2 is safe. In addition, deferral of revascularization for patients with an MLA <7.5 mm^2 is associated with a very poor outcome and should, therefore, be avoided.

The MLA cut-off for performing revascularization based on the outcome of the patients deferred for revascularization (groups B and D) was 9.6 mm^2, which is higher than the value of 7.5 mm^2 that was prospectively used in this study. This gap suggests that other factors in addition to MLA should probably be taken into account for decision-making on the appropriate treatment for patients with an MLA in the "gray zone" between 7.5 and 9.6 mm^2, such as the multivariate predictors of events, which were the extent of coronary disease, the smoking status, and the age.

The predictors of events by mutlivariate analysis differed from the ones in the study by Abizaid et al. (15), who found diabetes, untreated vessel, and MLD by IVUS to be associated with outcome. This can probably be explained by the differences in baseline characteristics (lower rates of diabetes, prior CABG, and PCI in the present study) and design between the two studies.

Finally, it is important to mention the usefulness of a fractional flow-reserve-guided strategy for patients with angiographically intermediate LMCA lesions, as reported by Bech et al. (32). Fractional flow reserve is certainly a reliable alternative for the assessment of indeterminate LMCA lesions in instances where IVUS is technically problematic (cases where the IVUS catheter cannot be maintained coaxial to the LMCA during pull-back, and where quantitative assessments of IVUS findings is difficult due to severe calcification or obscure IVUS imagery). Furthermore, a combination of physiologic assessment of LMCA disease by fractional flow reserve together with IVUS could provide more complete guidance for revascularization than any of the methods alone, as reported by recent studies (30,31,33).

Study limitations. The purpose of this study was to assess a given treatment strategy in clinical practice. It was conducted in a nonrandomized fashion and, therefore, suffers from the limitations associated with its design. Nevertheless, the IVUS-guided strategy was implemented in a prospective way, and was carried out in a majority of the cases.

In the present study, acute revascularization was performed mainly through CABG (there were only two cases of PCI of a protected LMCA, and no PCI of an unprotected LMCA). At the present time, PCI of LMCA performed by experienced operators in several centers is increasing (34,35). Therefore our study may not entirely reflect the current reality of LMCA revascularization. Nevertheless, revascularization was carried out in all cases respectful of the current guidelines.

Conclusions. Our study shows that IVUS is a safe method to accurately assess the degree of disease in the LMCA that appears indeterminate by angiography. It also suggests that an IVUS-guided treatment strategy based on deferral of revascularization in patients with MLA ≥7.5 mm^2 is safe.

Acknowledgment

The authors thank LaVon N. Hammes for her assistance.

Reprint requests and correspondence: Dr. Amir Lerman, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: lerman.amir@mayo.edu.

REFERENCES

1. Conley MJ, Ely RL, Kisslo J, Lee KL, McNeer JF, Rosati RA. The prognostic spectrum of left main stenosis. Circulation 1978;57:947–52.
2. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563–70.

3. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. Circulation 1995;91:2325–34.
4. Isner JM, Kishel J, Kent KM, Ronan JA Jr., Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing. Angiographic-histologic correlative analysis in 28 patients. Circulation 1981;63:1056–64.
5. Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). Catheter Cardiovasc Diagn 1982;8:565–75.
6. Cameron A, Kemp HG Jr., Fisher LD, et al. Left main coronary artery stenosis: angiographic determination. Circulation 1983;68:484–9.
7. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995;92:2333–42.
8. Bergelson BA, Tommaso CL. Left main coronary artery disease: assessment, diagnosis, and therapy. Am Heart J 1995;129:350–9.
9. Nishimura RA, Edwards WD, Warnes CA, et al. Intravascular ultrasound imaging: in vitro validation and pathologic correlation. J Am Coll Cardiol 1990;16:145–54.
10. St Goar FG, Pinto FJ, Alderman EL, Fitzgerald PJ, Stadius ML, Popp RL. Intravascular ultrasound imaging of angiographically normal coronary arteries: an in vivo comparison with quantitative angiography. J Am Coll Cardiol 1991;18:952–8.
11. Nissen SE, Gurley JC, Grines CL, et al. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. Circulation 1991;84:1087–99.
12. Porter TR, Sears T, Xie F, et al. Intravascular ultrasound study of angiographically mildly diseased coronary arteries. J Am Coll Cardiol 1993;22:1858–65.
13. Nishimura RA, Higano ST, Holmes DR Jr. Use of intracoronary ultrasound imaging for assessing left main coronary artery disease. Mayo Clin Proc 1993;68:134–40.
14. Pirolo JS, Fredi JL, Shuman TA. Intracoronary ultrasound-guided CABG in patients with angiographically noncritical lesions. Cardiovascular Surgery Associates. Ann Thorac Surg 1997;64:375–9.
15. Abizaid AS, Mintz G, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. J Am Coll Cardiol 1999;34:707–15.
16. Park SJ, Hong MK, Lee CW, et al. Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. J Am Coll Cardiol 2001;38:1054–60.
17. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. Circulation 2001;103:604–16.
18. Russo R, Wong SC, Marchant D, et al. Intravascular ultrasound-directed clinical decision making in the setting of an inconclusive left main coronary angiogram: final results from the Left Main IVUS registry (abstr). Circulation 2003;108 Suppl IV:462.
19. Doenges K, Schiele R, Taubert G, et al. Intracoronary ultrasound of angiographically ambiguous left main coronary artery stenoses. Safety and effect on further clinical decision making (abstr). Eur Heart J 2002;23 Suppl:130.
20. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959–69.
21. Hamasaki S, Higano ST, Al Suwaidi J, et al. Cholesterol-lowering treatment is associated with improvement in coronary vascular remodeling and endothelial function in patients with normal or mildly diseased coronary arteries. Arterioscler Thromb Vasc Biol 2000;20:737–43.
22. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
23. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology task force on clinical expert consensus documents. J Am Coll Cardiol 2001;37:1478–92.
24. Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. J Am Stat Assoc 1958;53:457–81.
25. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. Computational Statistics and Data Analysis 1999;30:253–70.
26. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5
27. Ward M, Pasterkamp G, Yeung A, Borst C. Arterial remodeling. Mechanisms and clinical implications. Circulation 2000;102:1186–91.
28. Ricciardi MJ, Meyers S, Choi K, Pang JL, Goodreau L, Davidson CJ. Angiographically silent left main disease detected by intravascular ultrasound: a marker for future adverse cardiac events. Am Heart J 2003;146:507–12.
29. Abizaid AS, Mintz GS, Mehran R. Long-term follow-up after percutaneous transluminal coronary angioplasty was not performed based on intravascular ultrasound findings: importance of lumen dimensions. Circulation 1999;100:256–61.
30. Legutko J, Dudek D, Rzeszutko L, Hubalewska A, Wizimirski M, Dubiel J. Invasive assessment of the borderline left main coronary artery stenosis—comparison with ^{99}Tc-MIBI SPET (abstr). Eur Heart J 2004;25 Suppl:429.
31. Jasti V, Yalamanchili V, Ivan E, Merrill B, Chandra M, Leesar MA. Fractional flow reserve versus intravascular ultrasound for decision-making in equivocal left main coronary stenosis (abstr). J Am Coll Cardiol 2004;Suppl 1:92A.
32. Bech GJ, Droste H, Pijls N, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery. Heart 2001;86:547–52.
33. Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. Catheter Cardiovasc Intervent 2004;62:349–57.
34. Tan WA, Tamai H, Park SJ, et al., for the ULTIMA Investigators. Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. Circulation 2001;104:1609–14.
35. Arampatzis CA, Lemos PA, Tanabe K, et al. Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease. Am J Cardiol 2003;92:327–9.