Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 34, No. 3, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00261-2

One-Year Follow-up After Intravascular Ultrasound Assessment of Moderate Left Main Coronary Artery Disease in Patients With Ambiguous Angiograms

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OBJECTIVES The purpose of this study was to correlate angiographic and intravascular ultrasound (IVUS) findings in left main coronary artery (LMCA) disease and identify the predictors of coronary events at one year in patients with LMCA stenoses.

BACKGROUND Significant (≥50% diameter stenosis [DS]) LMCA disease has a poor long-term prognosis.

METHODS One hundred twenty-two patients who underwent angiographic and IVUS assessment of the severity of LMCA disease and who did not have subsequent catheter or surgical intervention were followed for one year. Standard clinical, angiographic and IVUS parameters were collected.

RESULTS The quantitative coronary angiography (QCA) reference diameter (3.91 ± 0.76 mm, mean ± 1 SD) correlated moderately with IVUS (4.25 ± 0.78 mm, $r = 0.492$, $p = 0.0001$). The lesion site minimum lumen diameter (MLD) (2.26 ± 0.82 mm) by QCA correlated less well with IVUS (2.8 ± 0.82 mm, $r = 0.364$, $p = 0.0005$). The QCA DS measured 42 ± 16%. During the follow-up period, 4 patients died, none had a myocardial infarction, 3 underwent catheter-based LMCA intervention and 11 underwent bypass surgery. Univariate predictors of events ($p < 0.05$) were diabetes, presence of another lesion whether treated with catheter-based intervention or untreated with DS > 50% and IVUS reference plaque burden and lesion lumen area, maximum lumen diameter, MLD, plaque area and area stenosis. Using logistic regression analysis diabetes mellitus, an untreated vessel (with a DS > 50%) and IVUS MLD were independent predictors of cardiac events.

CONCLUSIONS In selected patients assessed by IVUS, moderate LMCA disease had a one-year event rate of only 14%. Intravascular ultrasound MLD was the most important quantitative predictor of cardiac events. For any given MLD, the event rate was exaggerated in the presence of diabetes or another untreated lesion (>50% DS). (J Am Coll Cardiol 1999;34:707–15) © 1999 by the American College of Cardiology

Patients with significant (≥50% diameter stenosis [DS]) left main coronary artery (LMCA) disease are known to have a poor long-term prognosis (1–10). However, the prognosis of patients with mild to moderate (<50% DS) LMCA narrowing is still unknown. Although coronary angiography has been accepted as the gold standard for the quantification of coronary artery disease, necropsy studies have shown that the severity of coronary artery stenoses in angiographically "mildly diseased" arteries may be underestimated (11–14). Furthermore, lesions in specific locations (e.g., LMCA or proximal left anterior descending coronary artery) are often difficult to assess angiographically (15,16). Intravascular ultrasound (IVUS) permits detailed, high-quality, cross-sectional imaging of the coronary arteries in vivo. The normal coronary artery architecture, the major components of the atherosclerotic plaque and the changes that occur in coronary arterial dimensions and anatomy with the atherosclerotic disease process can be studied in vivo in a manner otherwise not possible (17–30). The purposes of this study were: 1) to correlate angiographic and IVUS findings in LMCA disease, and 2) to identify the

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Manuscript received June 8, 1998; revised manuscript received April 2, 1999, accepted May 14, 1999.

Abbreviations and Acronyms

AS	=	area stenosis
CABG	=	coronary artery bypass graft
CASS	=	Coronary Artery Surgery Study
CSA	=	cross-sectional area
CSN	=	cross-sectional narrowing
DS	=	diameter stenosis
ECSS	=	European Coronary Surgical Study
EEM	=	external elastic membrane
IVUS	=	intravascular ultrasound
LMCA	=	left main coronary artery
MI	=	myocardial infarction
MLD	=	minimum lumen diameter
PTCA	=	percutaneous transluminal coronary angioplasty
P&M	=	plaque & media
QCA	=	quantitative coronary angiography
VA	=	Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery

predictors of coronary events at one year in patients with LMCA stenoses.

METHODS

Patient population. From November 5, 1991 to December 31, 1997, 355 patients underwent angiographic and IVUS evaluation of the LMCA. These patients had ischemic symptoms before diagnostic angiography and were referred because the angiographic assessment of LMCA lesion severity was inconclusive. Of this group, 233 patients underwent LMCA-related revascularization procedures disease after IVUS evaluation, and 122 did not have catheter-based or surgical intervention. This represents our entire cohort of patients with suspected LMCA disease who were studied specifically to quantify its severity. Three of the 122 patients were advised to undergo bypass graft surgery, but refused; they were included in the current analysis. In the current study population there were 82 men and 40 women with a mean patient age of 63 ± 10 years (range 32 to 92).

Quantitative coronary angiography (QCA) analysis. Angiograms of the LMCA, all major epicardial vessels (left anterior descending, left circumflex and right coronary) and saphenous vein or arterial bypass grafts were reviewed by a core angiographic laboratory that had no knowledge of the IVUS or clinical findings. Quantitative coronary angiography analysis was performed by use of a computer-assisted, automated edge-detection algorithm (Cardiovascular Measurement System, CMS-GFT, MEDIS, Leiden, The Netherlands). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimum lumen diameter (MLD) in diastole was measured from orthogonal projections and the results from the "worst" view were recorded. The reference segment diameter was averaged from 5-mm long angiographically normal segments proximal to the lesion; when a normal proximal segment could not be identified (e.g., ostial lesion location), a distal angiographically normal segment was analyzed. Target lesion location was designated as ostial, proximal, mid or distal. Ostial lesions were those lesions that began within 3 mm of the LMCA ostium. Lesion location was proximal in 15%, mid in 10%, distal in 52% and ostial in 21%.

Angiograms were assessed to determine the number of untreated vessels and treated vessels that were present in addition to the LMCA stenosis. An untreated diseased vessel was defined as any major epicardial vessel or bypass graft with >50% DS narrowing that was not treated. Thirty-nine of the 122 study patients had 56 vessels containing an angiographic stenosis >50% DS that were not treated. A treated diseased vessel was defined as any major epicardial vessel or bypass graft with >50% DS narrowing that was treated. Sixty-two of the 122 study patients had an interventional procedure of 91 stenoses in a major epicardial vessels 24 left anterior descending, 26 left circumflex, 23 right coronary arteries and 18 bypass grafts.

IVUS imaging protocol. Operators were not blinded to the ultrasound images and used the information to make indication decisions regarding the necessity of in-hospital coronary artery bypass graft (CABG) or catheter-based intervention. Intravascular ultrasound imaging was performed after administration of 0.2 mg intracoronary nitroglycerin.

Studies were performed using one of three commercially available systems. The first (CVIS/InterTherapy Inc., San Jose, California) incorporated a single-element 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft that was rotated at 1,800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time; with this system, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. The second (Hewlett-Packard, Andover, Massachusetts, and Boston Scientific Corporation, Watertown, Massachusetts) incorporated a single-element 30-MHz beveled transducer rotated at 1,800 rpm within a 3.5F short monorail imaging catheter; with this system, the catheter was advanced or withdrawn manually with fluoroscopy guidance to perform the imaging sequence. The third (Cardiovascular Imaging Systems/Boston Scientific Corporation, San Jose, California) used a single-element beveled transducer mounted on the end of a flexible shaft and rotated at 1,800 rpm within either a 2.9F long monorail/common distal lumen imaging sheath or within a 3.2F short monorail imaging sheath. With this system, the transducer was also withdrawn automatically at 0.5 mm/s to perform the imaging sequence. The use of a motorized transducer pullback device and sheath-based imaging catheters permitted the transducer to move at the same speed as the proximal end of the imaging core. The IVUS catheter was advanced approximately 10 mm distal to the lesion, the video recorder turned on, the transducer pullback device activated or manual pullback initiated and

the entire artery imaged retrograde to the aorto-ostial junction. Intravascular ultrasound studies were recorded on 0.5 in. high-resolution super VHS tape for off-line analysis.

Qualitative and quantitative IVUS analysis. Validation of normal coronary anatomy, plaque composition and measurements of external elastic membrane (EEM) cross-sectional area (CSA), lumen CSA and plaque plus media (P&M) CSA by IVUS have been reported previously (31–35). The EEM CSA, the area encompassed by the ultrasonic media-adventitia border, is measured by tracing the leading edge of the adventitia; this has been shown to be a reproducible measure of total arterial CSA. The lesion site was the image slice with the smallest lumen CSA; among image slices with the same small lumen CSA, the one with the largest EEM and P&M CSA was selected. If the atherosclerotic plaque was "packed" around the catheter, then the lumen was assumed to be the physical (not acoustical) size of the catheter. Because IVUS cannot measure media thickness accurately, P&M was used as a measure of plaque. Cross-sectional narrowing (CSN) has also been called the plaque burden or the percent plaque area. The reference segments were the most visually normal LMCA cross sections within 5 mm proximal and distal to the lesion; a distal reference was used for ostial lesions.

Plaque composition was assessed visually. Calcium was brighter than the reference adventitia with shadowing of deeper arterial structures; the arc of calcium was measured with a protractor centered on the lumen. Hyperechoic, noncalcified plaque was as bright or brighter than the adventitia without shadowing. Hypoechoic plaque was less bright compared with the adventitia.

Using computer planimetry (TapeMeasure, Indec Systems, Mountain View, California), the target lesion and references segments were analyzed quantitatively as follows: 1) EEM CSA (mm^2), 2) lumen CSA (mm^2), 3) maximum and minimum lumen diameters (mm), 4) P&M CSA (mm^2) equal to EEM CSA minus lumen CSA, 5) eccentricity index equal to maximum divided by minimum P&M thickness and 6) CSN equal to P&M CSA divided by the EEM CSA.

The target lesion was compared with the reference segment. The area stenosis (AS) was calculated as follows:

$$\frac{(\text{mean reference lumen CSA} - \text{lesion lumen CSA}) \times 100}{\text{mean reference lumen CSA}}$$

Clinical data and definitions. Baseline demographics and in-hospital complications were confirmed by hospital chart review. Prior myocardial infarction occurred >6 weeks before the study. A history of coronary artery bypass surgery and percutaneous transluminal coronary angioplasty (PTCA) were recorded. Risk factors for coronary artery disease included diabetes mellitus (oral agent or insulin treated), hypertension (medication treated only) and hypercholesterolemia (medication treated or a measured >240 mg/dl). Clinical demographics of the 122 patients were as follows: 45% had a history of myocardial infarction, 32% had previous bypass surgery, 46% had unstable angina, 34% had previous PTCA, 26% had diabetes mellitus, 58% had hypertension and 68% had hypercholesterolemia.

Follow-up information was obtained by serial telephone interviews 1, 3, 6 and 12 months following the diagnostic catheterization. All events during this one-year period were source documented. Cardiac events at follow-up interviews that were tabulated included cardiac death, myocardial infarction and PTCA or CABG related to the LMCA.

Statistical analysis. Statistical analysis was performed using StatView 4.5 (Abacus Concepts, Berkeley, California) or SAS (Statistical Analysis Systems, SAS Institute Inc., Cary, North Carolina). Continuous data were presented as mean value ± 1 SD; comparisons are performed using unpaired Student *t* test. Categorical data are presented as frequencies; comparisons were performed using chi-square statistics or Fisher's exact test. A p-value <0.05 was considered significant.

Logistic regression analysis was used to identify the independent predictors of late cardiac events. Univariate predictors of cardiac events at follow-up procedures with a p-value <0.05 were entered into the multivariate model.

RESULTS

Correlation of angiographic versus IVUS results. In the overall cohort, reference lumen diameter measured 3.91 ± 0.76 mm, MLD measured 2.26 ± 0.82 mm and the DS measured 42 ± 16%. Overall, the QCA reference diameter correlated moderately with IVUS reference diameter (4.25 ± 0.78 mm, $r = 0.492$, $p = 0.0001$). The lesion site MLD by QCA correlated less well with IVUS (2.81 ± 0.82 mm, $r = 0.364$, $p = 0.0005$). These results and a clinical example are shown in Figures 1 and 2. In addition, the DS (35 ± 15%) by IVUS did not correlate at all with QCA ($r = 0.106$).

One-year cardiac events. Follow-up data were available in 98% of the 122 patients, in a mean follow-up time of 11.7 months.

There were four (3%) cardiac deaths (mean time of 4.4 months). Two patients died after complications of bypass surgery, one patient had sudden cardiac death and one patient with severe LMCA and triple vessel disease refused bypass surgery and died one month after diagnostic catheterization. There were no patients with myocardial infarction at the time of follow-up procedures.

During the 12-month follow up period, three (2%) patients had PTCA of the LMCA (mean time of 5.8 months): three Palmaz-Schatz stents (two in a protected LMCA and one in an unprotected LMCA). Eleven (9%) patients had bypass surgery (mean time of 8.3 months).

Clinical predictors of cardiac events (Table 1). In this patient cohort, age, male gender, prior myocardial infarc-

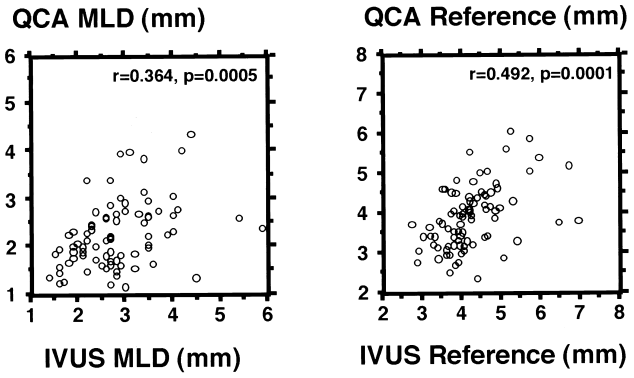

Figure 1. The correlation between the lesion site MLD by QCA (2.26 ± 0.82 mm) and IVUS (2.81 ± 0.82 mm was r = 0.364, p = 0.0005 **[Panel A]**). The correlation between the QCA reference diameter (3.91 ± 0.76 mm) and IVUS (4.25 ± 0.78 mm) was r = 0.492, p = 0.0001 **(Panel B).** IVUS = intravascular ultrasound; MLD = minimum lumen diameter; QCA = quantitative coronary angiography.

tion, previous CABG, previous PTCA, hypertension and hypercholesterolemia were not significant univariate predictors of cardiac events at follow-up. The only clinical predictor of cardiac events was the presence of diabetes mellitus; 25% of the diabetic patients versus 11% of the non-diabetics had an event (p = 0.029).

Angiographic predictors of cardiac events (Table 2). There was a strong trend toward smaller reference segment LMCA diameters in patients with cardiac events (3.63 ± 0.81 mm vs. 3.98 ± 0.74 mm with no events, p = 0.059). It is important to note that the QCA MLD and DS were not univariate predictors of events; 10% of patients with DS < 50%, 18% of patients with DS 50% to 70%, and 8% of patients with DS > 70% had events. The presence of any untreated or treated vessel was a predictor of cardiac events at follow-up.

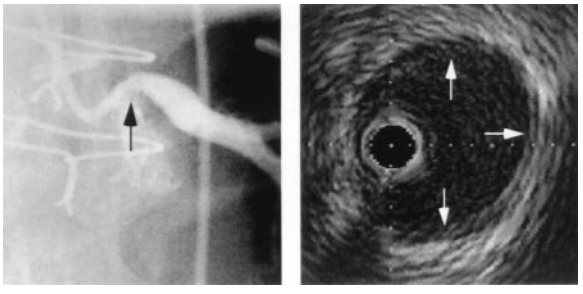

Figure 2. This case example illustrates the discrepancy between angiographic and IVUS evaluation of LMCA disease. This patient underwent bypass surgery for ostial LMCA disease **(black arrow).** After the bypass grafts closed, he was referred for IVUS study. By QCA, the ostial LMCA stenosis MLD measured 1.32 mm. By IVUS, there was mild diffuse atherosclerosis **(white arrows),** no significant plaque burden and an MLD of 3.5 mm. LMCA = left main coronary artery. Other abbreviations as in Figure 1.

IVUS predictors of cardiac events (Table 3). Plaque composition did not predict events at follow up. Plaque composition was as follows: 42% dominantly hyperechoic, 38% dominantly hypoechoic and 20% a combination of both. None of the plaques was dominantly calcific; the arc of calcium measured 66° ± 107°.

Patients with events had smaller lesion site lumen CSA (6.8 ± 4.4 vs. 10 ± 5.3 mm^2), maximum lumen diameter (3.07 ± 0.77 vs. 3.85 ± 0.86 mm) and MLD (2.30 ± 0.69 vs. 2.94 ± 0.81 mm); larger lesion site P&M CSA (15.7 ± 5.2 vs. 11.9 ± 5.9 mm^2) and CSN (70 ± 14 vs. 53 ± 18%); larger reference segment CSN (42 ± 13 vs. 35 ± 12%); and larger AS (52 ± 21 vs. 34 ± 20%). For the entire cohort, the event rate was 60% for an IVUS MLD < 2.0 mm, 24% for an MLD 2.0 to 2.5, 16% for an MLD 2.5 to 3.0 mm and 3% for an MLD > 3.0 mm.

Multivariate predictors of cardiac events (Table 4). All clinical, angiographic and IVUS parameters with p < 0.05 were tested in the multivariate model. These included the following: diabetes mellitus, presence of untreated or treated vessels, IVUS reference CSN, IVUS lesion site lumen CSA, maximum lumen diameter, MLD, P&M CSA, CSA and IVUS AS. Using multivariate logistic regression analysis, the presence of diabetes mellitus, the presence of an untreated vessel and IVUS MLD were found to be the independent predictors of cardiac events at follow up. The probability curves of any cardiac event are shown in Figure 3.

DISCUSSION

The current study of LMCA disease showed the following: 1) there was a poor correlation between QCA and IVUS in the assessment of reference segment and lesion site lumen dimensions, 2) the one year event (death, myocardial infarction or need for revascularization) rate in patients with IVUS-guided deferred treatment of LMCA stenoses was 14% with <2% having procedure unrelated deaths and 3) there were three distinct predictors of these cardiac events: diabetes, a major epicardial vessel or bypass graft with a QCA DS ≥50% that was left untreated and LMCA lesion site MLD measured by IVUS.

Limitations of angiography in assessing LMCA disease. The angiographic assessment of LMCA stenoses has been compared with necropsy or IVUS. Coronary angiography underestimates stenosis severity most markedly in vessels with 50% to 75% arterial area narrowing at necropsy (13,15,16,36). Hermiller et al. showed that a very high percentage (89%) of patients with angiographically normal LMCA had disease by IVUS (27). These findings were confirmed in studies by Yamagishi, Gerber and Ge (25,28,30).

Hermiller also reported no correlation between IVUS and QCA lumen dimensions in patients with angiographically detectable LMCA disease (27). In the current study, there

Table 1. Clinical Variables

	Total (n = 122)	No Event (n = 104)	Any Event (n = 18)	p
Age (yr)	63 ± 10	62 ± 10	63 ± 11	0.76
Male gender, n (%)	82 (67)	68 (65)	14 (78)	0.19
Prior MI, n (%)	55 (45)	45 (43)	10 (58)	0.24
Prior bypass surgery, n (%)	39 (32)	33 (32)	6 (33)	0.74
Prior intervention, n (%)	41 (34)	36 (35)	5 (28)	0.37
Unstable angina, n (%)	54 (46)	44 (42)	10 (58)	0.26
Diabetes, n (%)	32 (26)	24 (23)	8 (44)	0.029
Hypertension, n (%)	71 (58)	60 (58)	11 (61)	0.87
Hypercholesterolemia, n (%)	83 (68)	71 (68)	12 (66)	0.74
Body surface area (M^2)	1.93 ± 0.21	1.93 ± 0.23	1.91 ± 0.16	0.74

was a poor correlation in measurement of MLD by IVUS and QCA and QCA overestimated the degree of LMCA narrowing in some patients. Ultimately, the clinical value of any quantitative assessment is its ability to predict patient outcomes and its reproducibility. The QCA MLD and DS were similar in patients with and without cardiac events at one year. Conversely, numerous IVUS parameters were significantly different in patients with and without events, and the IVUS MLD was the only independent quantitative predictor of late events.

The main reasons for the discrepancy between angiography and necropsy or IVUS appear to be the following: 1) diffuse atherosclerotic involvement affects the DS calculation because of the lack of a normal reference segment, 2) a short LMCA also makes identification of a normal reference segment difficult, 3) there is compensatory enlargement (positive remodeling) of the vessel as plaque burden increases to preserve lumen size as shown by Glagov et al. (37), 4) there may be unique geometric issues in LMCA disease because the correlation between angiography and necropsy or IVUS appears to be somewhat better in non-LMCA stenoses (19,20) and 5) there is significant inter- and intraobserver variability in the angiographic assessment of LMCA disease (14,38–40). Interpretations of a single lesion have varied from 0% to 80% stenosis, and interobserver disagreement has been as high as 20% (41,42). Fisher et al. (14) reported on 810 arteriograms from the Coronary Artery Surgery Study (CASS) that were independently read by two angiographers; measurements of the LMCA were the least reproducible of any coronary arterial segment. When one angiographer reported a stenosis of >50%, a second angiographer reported no lesion 19% of the time. Cameron et al. (43) tested the reliability of the angiographic assessment of the LMCA using 106 coronary cineangiograms also from CASS; in three separate readings, there was only a 41% to 59% agreement on stenosis severity although there was an 80% agreement on whether the lesion was greater or less than 50% . These studies have all shown that the discrepancy between angiography and necropsy or IVUS and the interobserver variability in angiographic assessment of LMCA stenoses have been most significant in patients with moderate stenoses (13,15,16,36,44). The patients in the current study had a mean QCA DS of 42% and a mean IVUS CSN of 57%, indicative of moderate disease.

Table 2. Angiographic Findings

	Total (n = 122)	No Event (n = 104)	Any Event (n = 18)	p
Reference (mm)	3.91 ± 0.76	3.98 ± 0.74	3.63 ± 0.81	0.0594
Minimum lumen diameter (mm)	2.26 ± 0.82	2.32 ± 0.83	2.00 ± 0.72	0.1086
Diameter stenosis (%)	42 ± 16	42 ± 17	44 ± 16	0.47
Ostial lesion location (%)	21	20	22	0.90
Left ventricular ejection fraction (%)	48 ± 11	48 ± 12	50 ± 7	0.58
Any untreated vessel, n (%)	39 (32)	27 (26)	12 (67)	0.007
1 untreated vessel	24 (62)	17 (63)	7 (59)	
2 untreated vessels	13 (33)	9 (33)	4 (33)	
3 untreated vessels	2 (5)	1 (4)	1 (8)	
Any treated vessel, n (%)	63 (52)	48 (46)	15 (83)	0.014
1 treated vessel	40 (64)	34 (71)	6 (40)	
2 treated vessels	15 (25)	10 (22)	5 (33)	
3 treated vessels	7 (11)	3 (7)	4 (27)	
Any treated or untreated vessel, n (%)	83 (68)	69 (66)	14 (78)	0.051

Table 3. IVUS Findings

	Total (n = 122)	No Event (n = 104)	Any Event (n = 18)	p
Reference				
EEM CSA (mm^2)	23.3 ± 6.9	23.3 ± 7.1	23.2 ± 6.3	0.96
Lumen CSA (mm^2)	14.7 ± 5.7	15.0 ± 5.6	13.4 ± 6.0	0.31
P&M CSA (mm^2)	8.6 ± 4.1	8.3 ± 4.1	9.7 ± 3.9	0.18
CSN (%)	37 ± 13	35 ± 12	42 ± 13	0.0418
Lesion site				
EEM CSA (mm^2)	22.0 ± 6.9	21.9 ± 7.0	22.5 ± 7.0	0.72
Lumen CSA (mm^2)	9.3 ± 5.3	10.0 ± 5.3	6.8 ± 4.4	0.0127
Maximum lumen diameter (mm)	3.70 ± 0.90	3.85 ± 0.86	3.07 ± 0.77	0.0003
MLD (mm)	2.81 ± 0.82	2.94 ± 0.81	2.30 ± 0.69	0.0012
P&M CSA (mm^2)	12.7 ± 5.9	11.9 ± 5.9	15.7 ± 5.2	0.0077
Arc of calcium (°)	66 ± 107	62 ± 108	82 ± 103	0.47
Eccentricity index	12.7 ± 15.1	13.1 ± 15.4	11.5 ± 14.8	0.69
CSN (%)	57 ± 18	53 ± 18	70 ± 14	0.0002
AS (%)	38 ± 22	34 ± 20	52 ± 21	0.0007

AS = area stenosis; CSA = cross-sectional area; CSN = cross-sectional narrowing; EEM = external elastic membrane; P&M = plaque & media; MLD = minimum lumen diameter.

Natural history of LMCA disease. The presence of LMCA disease has important prognostic and therapeutic implications (1–10). In general, surgical treatment improves survival significantly (2,3,5,8,9,45–48). Recently, the CASS Registry reported the longest follow-up period of the largest cohort of patients (n = 1484) with >50% LMCA angiographic DS (49). The 15-year cumulative survival estimates were 37% for surgery compared with 27% for medical therapy. Median survival in the surgical group was 13.3 years, compared with only 6.6 years in the medical group ($p < 0.0001$). However, subgroup analysis showed that the prognosis of medically treated patients was not always poor. Median survival was not prolonged by surgery in patients with: 1) LMCA stenoses <60%, 2) normal left ventricular function and 3) a nonstenotic (<70%) right coronary artery.

Two other randomized trials comparing surgical versus medical therapy in patients with significant LMCA stenosis were the Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery (VA) and the European Coronary Surgical Study (ECSS) (50,51,52). The VA Cooperative Study showed that most of the mortality in medically treated patients occurred within the first year of diagnosis. However, these findings were contradicted by ECSS, which reported one-, two- and three-year survival rates of 95%, 88% and 82% in patients treated medically.

Table 4. Multivariate Predictors of Cardiac Events at Follow-up Procedures

	OR	95% CI	p
Diabetes mellitus	6.32	1.82–22.04	0.004
Any untreated vessel	3.80	1.08–13.39	0.037
IVUS lesion site minimum lumen diameter	0.17	0.05–0.59	0.005

IVUS = intravascular ultrasound.

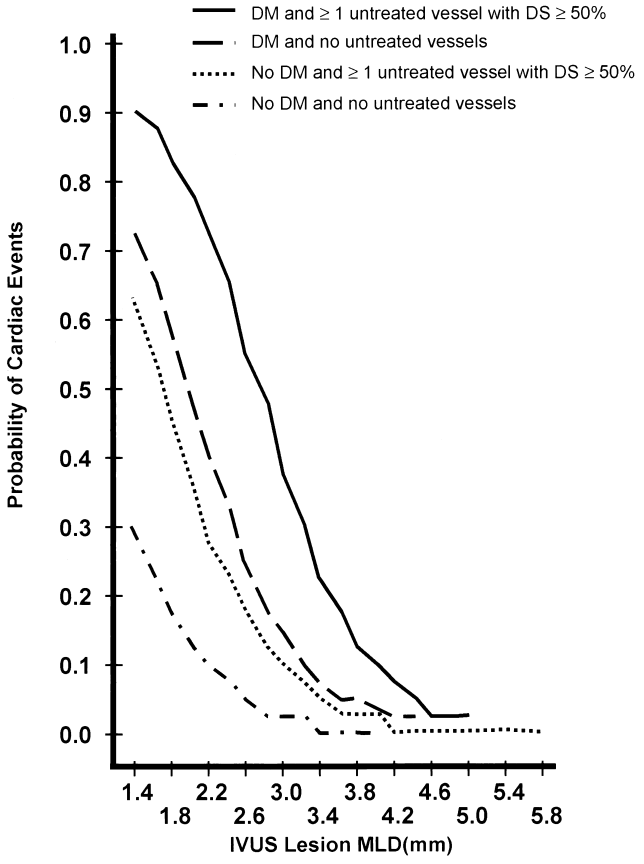

Figure 3. The probability of cardiac events at one year was quantitatively related to the IVUS MLD (mm). At the same MLD, the frequency of events was highest in patients with diabetes and at least one untreated vessel with a DS > 50%; intermediate in patients with diabetes or at least one untreated vessel with a DS > 50%, but not both; and lowest in patients with neither diabetes nor an untreated vessel with a DS > 50%. DS = diameter stenosis. All other abbreviations as in Figure 1.

Patients in the ECSS differed from those in the VA study because all patients were <65-years-old with good left ventricular function. Findings similar to ECSS were seen in a study by Lim et al. (53).

The severity of the LMCA stenosis may have prognostic importance. Conley et al. (3) reported that patients with an LMCA stenosis of 50% to 70% had a three-year survival of 66%, whereas patients with a stenosis >70% had only a 41% three-year survival rate. In the current study, patients with mild LMCA disease had a survival rate of 97% and an event-free survival rate of 86% at one year. Although these were patients with moderate disease, the IVUS MLD was an independent predictor of cardiac events confirming the prognostic importance of LMCA disease severity. It is important to note that the QCA MLD and DS were similar in patients with and without events, indicating the limitations of angiography in prognosticating LMCA disease.

The presence of a significant stenoses in an untreated vessel, a predictor of cardiac events in the current study, has also been shown by others to be important. Yamagishi et al. (25) reported that the LMCA plaque burden was greater in the presence of a significant stenosis (>50% DS) in at least one of the three major coronary arteries. Shimazu et al. (54) also reported indirect evidence for increased severity of LMCA disease in multivessel coronary artery disease by showing decreased LMCA compliance with the development of stenoses in another vessels. Bruschke et al. (4), Campeau et al. (5) and DeMots et al. (55) demonstrated that the poor prognosis of patients with LMCA disease is largely related to the high frequency of coexisting coronary artery disease.

Diabetes mellitus as a predictor of cardiac events. In the current study, diabetes mellitus was an independent predictor of cardiac events. For every given LMCA lumen diameter, the risk of events was higher if the patient was diabetic.

Clinical and epidemiologic studies have shown that coronary artery disease is more aggressive in patients with diabetes. Diabetic patients are thought to have more diffuse disease, four to five times the mortality rate and worse outcomes after coronary interventions (56–60). Several factors have been found to promote accelerated atherosclerosis in diabetics. These factors include increased oxidation level of low density lipoproteins, non-enzymatic glycation of vessel wall proteins, accelerated smooth muscle cell proliferation and migration, hyperinsulinemia, impaired fibrinolysis and increase in platelet aggregation (61–67). These processes together may cause an increase in cholesterol synthesis, endothelial dysfunction, hyperplastic vasculopathy, microvascular disease and a prothrombotic state, hallmarks of diabetic vascular disease (61–67).

Other predictors of cardiac events. In the CASS study, left ventricular systolic function was found to be a predictor of 15-year survival in both surgically and medically treated patients (49). However, advanced age and severe angina pectoris were predictors of survival only in the medical group.

In a study of 163 medically treated patients with 50% or greater LMCA stenosis, Conley et al. (3) found that the following predicted one-year survival: history of congestive heart failure, angina at rest, cardiomegaly on chest X-ray, ST-T wave changes on the resting electrocardiogram and abnormal left ventricular contraction pattern. Other studies have substantiated the importance of left ventricular function, electrocardiograph abnormalities and concomitant multivessel disease, especially in medically treated patients (9,10,53).

Study limitations. Unlike most angiographic studies of the natural history of coronary artery disease (e.g., CASS), the current report was primarily a study of patients referred for diagnostic evaluation of LMCA disease. These patients typically had ambiguous angiograms, potentially leading to both the exaggerated discrepancy between QCA and IVUS and the lack of the independent predictive power of QCA measurements. This may have introduced a bias into the results. Furthermore, this patient population appears to be very stable which may limit the generalizability of these findings.

Plaque composition by IVUS was not a predictor of cardiac events. Current IVUS morphologic analysis was not able to determine lipid content of the atherosclerotic disease, and the propensity of plaques to become unstable and cause coronary events is directly related to the amount of extracellular lipid. In the future, raw radiofrequency signal analysis may help identify stable versus unstable lesions. However, the nonsignificant trend for larger arcs of calcium and smaller eccentricity indexes in LMCA lesions with subsequent events suggests that they contained more mature plaques.

The IVUS report, itself, could have biased the patients' decisions concerning revascularization, especially in patients with smaller lumen areas, diabetes and disease in other epicardial vessels. However, the nonprocedure-related mortality in this cohort of patients with IVUS-guided deferred treatment of LMCA stenoses was <2%, too low to identify specific predictors.

Although these patients all had symptoms indicating significant coronary artery disease, few had noninvasive testing.

Conclusions and clinical implications. In selected patients as assessed by IVUS, the natural history of moderate LMCA disease has a one-year event rate of only 14% (3% death and 11% need of any revascularization). Intravascular ultrasound measurement of MLD was the most important quantitative predictor of cardiac events. For any given MLD, the event rate was exaggerated in the presence of diabetes mellitus or an untreated lesion in a major vessel >50% DS. Intravascular ultrasound should be considered in the assessment of patients with angiographically ambiguous or inconclusive LMCA disease.

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REFERENCES

1. Takaro T, Pifarre R, Fish R. Left main coronary artery disease. Prog Cardiovasc Dis 1985;28:229–34.
2. Conti CR, Selby JH, Christie LG, et al. Left main coronary artery stenosis: clinical spectrum pathophysiology and management. Prog Cardiovasc Dis 1979;22:73–106.
3. Conley MJ, Ely RL, Kisslo J, Lee KL, McNeer JF, Rosati RA. The prognostic spectrum of left main stenosis. Circulation 1978;57:947–52.
4. Bruschke AVG, Proudfit WL, Sones FM, Jr. Progress study of 590 nonsurgical cases of coronary artery disease followed 5–9 years. I: arteriographic correlations. Circulation 1973;47:1147–53.
5. Campeau L, Corbara F, Crochet D, Petitclerc R. Left main coronary artery stenosis: the influence of aortocoronary bypass surgery on survival. Circulation 1978;57:1111–5.
6. Zeft JH, Manley JC, Huston JH, Tector AJ, Auer JE, Johnson WD. Left main coronary artery stenosis: results of coronary bypass surgery. Circulation 1974;49:68–76.
7. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1989;79:1171–9.
8. Oberman A, Kouchoukos NT, Harrell RR, Holt JR, Russell RO, Jr, Rackley CE. Surgical versus medical treatment in disease of the left main coronary artery. Lancet 1976;2:591–4.
9. Talano JV, Scanlon PJ, Meadows WR, Kahn M, Pifarre R, Gunnar RM. Influence of surgery on survival in 145 patients with left main coronary artery disease. Circulation 1975;51 Suppl I:I105–11.
10. Cohen MV, Gorlin R. Main left coronary artery disease: clinical experience from 1964–1974. Circulation 1975;52:275–85.
11. Grondin CM, Dyrda I, Pasternac A, Campeau L, Bourassa MG, Lesperance J. Discrepancies between cineangiographic and postmortem findings in patients with coronary artery disease and recent myocardial revascularization. Circulation 1974;49:703–8.
12. Roberts WC. The coronary arteries in ischemic heart disease: facts and fantasies. Triangle Engl Ed 1977;16:77–90.
13. Arnett EN, Isner JM, Redwood DR, et al. Coronary artery narrowing in coronary artery disease: comparison of cineangiographic and necropsy findings. Ann Intern Med 1979;91:350–6.
14. Fisher LD, Judkins MP, Lesperance J, et al. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). Cathet Cardiovasc Diagn 1982;8:565–75.
15. Waller BF. Anatomy, histology, and pathology of the major epicardial coronary arteries relevant to echocardiographic imaging techniques. J Am Soc Echocardiogr 1989;2:232–52.
16. Isner JM, Donaldsen RF. Coronary angiographic and morphologic correlation. In: Waller BF, ed. Cardiac Morphology. Philadelphia: Saunders, 1984:571–92.
17. St Goar FG, Pinto FJ, Alderman EL, et al. Detection of coronary atherosclerosis in young adult hearts using intravascular ultrasound. Circulation 1992;86:756–63.
18. 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.
19. Alfonso F, Macaya C, Goicolea J, et al. Intravascular ultrasound imaging of angiographically normal coronary segments in patients with coronary artery disease. Am Heart J 1994;127:536–44.
20. Porter T, Sears T, Xie F, et al. Intravascular ultrasound study of angiographically mildly diseased coronary arteries. J Am Coll Cardiol 1993;22:1858–65.
21. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819–24.
22. Ehrlich S, Honye J, Mahon D, Bernstein R, Tobis J. Unrecognized stenosis by angiography documented by intravascular ultrasound imaging. Cathet Cardiovasc Diagn 1991;23:198–201.
23. Mintz GS, Painter JA, Pichard AD, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol 1995;25:1479–85.
24. 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.
25. Yamagishi M, Hongo Y, Goto Y, et al. Intravascular ultrasound evidence of angiographically undetected left main coronary artery disease and associated trauma during interventional procedures. Heart Vessels 1996;11:262–8.
26. Pirolo JS, Fredi JL, Shuman TA and Cardiovascular Surgery Associates. Intracoronary ultrasound-guided CABG in patients with angiographically noncritical lesions. Ann Thorac Surg 1997;64:375–9.
27. Hermiller JB, Buller CE, Tenaglia AN, et al. Unrecognized left main coronary artery disease in patients undergoing interventional procedures. Am J Cardiol 1993;71:173–6.
28. Gerber TC, Erbel R, Gorge G, Ge J, Rupprecht HJ, Meyer J. Extent of atherosclerosis and remodeling of the left main coronary artery determined by intravascular ultrasound. Am J Cardiol 1994;73:666–71.
29. Davies SW, Winterton SJ, Rothman MT. Intravascular ultrasound to assess left main stem coronary artery lesion. Br Heart L 1992;68: 524–6.
30. Ge J, Liu F, Gorge G, Haude M, Baumgart D, Erbel R. Angiographically "silent" plaque in the left main coronary artery detected by intravascular ultrasound. Coron Artery Dis 1995;6:805–10.
31. Potkin BN, Bartorelli AL, Gessert JM, et al. Coronary artery imaging with intravascular high-frequency ultrasound. Circulation 1990;81: 1575–85.
32. Nissen SE, Grines CL, Gurley JC, et al. Application of a new-phased-array ultrasound imaging catheter in the assessment of vascular dimensions: in vivo comparison to cineangiography. Circulation 1990; 81:660–6.
33. Tobis JM, Mallery JA, Gessert J, et al. Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. Circulation 1989;80:873–82.
34. 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.
35. Hodgson JM, Graham SP, Savakus AD, et al. Clinical percutaneous imaging of coronary anatomy using an over-the-wire ultrasound catheter system. Int J Cardiac Imaging 1989;4:186–93.
36. Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis: "a battered gold standard." J Am Coll Cardiol 1988;11:882–5.
37. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Koletti GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
38. Isner JM, Kishel J, Kent KM, Ronan JA, 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.
39. Detre KM, Wright E, Murphy ML, Takaro T. Observer agreement in evaluating coronary angiograms. Circulation 1975;52:979–86.
40. DeRouen TA, Murray JA, Owen W. Variability in the analysis of coronary arteriograms. Circulation 1977;55:324–8.
41. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation 1976;53: 627–32.
42. Sanmarco ME, Brooks SH, Blankenhorn DH. Reproducibility of a consensus panel in the interpretation of coronary angiograms. Am Heart J 1978;96:430–7.
43. Cameron A, Kemp HG, Jr, Fisher LD, et al. Left main coronary artery stenosis: angiographic determination. Circulation 1983;68:484–9.
44. Shub C, Vlietstra RE, Smith HC, Fulton RE, Elveback LR. The unpredictable progression of symptomatic coronary artery disease. A serial clinical-angiographic analysis. Mayo Clin Proc 1981;56:155–9.
45. Takaro T, Hultgren HN, Lipton MJ, Detre KM, and Participants in the Study Group. The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease: II Subgroup with significant left main lesions. Circulation 1976;54 Suppl III:III107–17.
46. European Coronary Surgery Study Group. Prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1980;2:491–5.
47. Lawrie GM, Morris GC Jr, Howell JF, Hines M, Chapman DW. Improved survival beyond 5 years after coronary bypass surgery in

patients with left main coronary artery disease. Am J Cardiol 1979; 44:612–5.
48. Loop FD, Lytle BW, Cosgrove DM, et al. Atherosclerosis of the left main coronary artery: 5 years results of surgical management. Am J Cardiol 1979;44:195–201.
49. Caracciolo EA, Davis KB, Sopko G, et al. for the CASS Investigators. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. Circulation 1995;91:2325–34.
50. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 1984;311:1333–9.
51. European Coronary Surgery Study Group. Long-term results of a prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1982;2:1173–80.
52. Varnauskas E, for the European Coronary Surgery Study Group. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988;319:332–7.
53. Lim JS, Proudfit WL, Sones FM, Jr. Left main coronary arterial obstruction: long-term follow-up of 141 nonsurgical cases. Am J Cardiol 1975;36:131–5.
54. Shimazu T, Hori M, Mishima M, et al. Clinical assessment of elastic properties of large coronary arteries: pressure-diameter relationship and dynamic incremental elastic modulus. Int J Cardiol 1986;13:27–45.
55. DeMots H, Bonchek LI, Rosch J, Anderson RP, Starr A, Rahimtoola SH. Left main coronary artery disease: risks of angiography, importance of coexisting disease of other coronary arteries and effects of revascularization. Am J Cardiol 1975;36:136–41.
56. Grossman E, Masserli FH. Diabetic and hypertensive heart disease. Ann Intern Med 1996;125:304–10.
57. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. JAMA 1979;241:2035–8.
58. Carrozza JP, Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. Ann Intern Med 1993;118:344–9.
59. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transmural coronary angioplasty. Circulation 1995;91:979–89.
60. Schartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Rozek MM. Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. Diabetes Care 1992;15:1156–67.
61. Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA. Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. Circulation 1993;88:2510–6.
62. Reaven GM. The hole of insulin resistence and hyperinsulinemia in coronary artery disease. Metabolism 1992;41 Suppl 1:16–9.
63. Colwell JA. Antiplatelet drugs and prevention of macrovascular disease in diabetes mellitus. Metabolism 1992;41 Suppl 1:7–10.
64. Lopes-Virella MF, Virella G. Lipoproteins and immune responses in the vascular wall and their contribution to atherosclerosis in diabetes. Metabolism 1992;41 Suppl 1:11–5.
65. Davi G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. N Engl J Med 1990;322: 1769–74.
66. Schneider DJ, Nordt TK, Sobel BE. Attenuated fibrinolysis and accelerated atherogenesis in type II diabetic patients. Diabetes 1993; 42:1–7.
67. Oskarsson HJ, Hofmeyer TG. Platelets from patients with diabetes mellitus have impaired ability to mediate vasodilation. J Am Coll Cardiol 1996;27:1464–70.