

# Correlations Between Fractional Flow Reserve and Intravascular Ultrasound in Patients With an Ambiguous Left Main Coronary Artery Stenosis

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**Background**—Intravascular ultrasound (IVUS) is being used to assess the significance of a left main coronary artery stenosis (LMCS). However, the cutoff values of IVUS parameters at which to predict a fractional flow reserve (FFR) of 0.75 are unknown.

**Methods and Results**—In 55 patients with an angiographically ambiguous LMCS, a pressure guidewire was used to calculate FFR, and IVUS parameters were calculated after automatic pullback. FFR averaged  $0.86 \pm 0.13$  (range, 0.55 to 1.0). IVUS minimum lumen diameter (MLD), minimum lumen area (MLA), cross-sectional narrowing (CSN), and area stenosis (AS) were  $3.8 \pm 0.61$  mm,  $7.65 \pm 2.9$  mm<sup>2</sup>,  $59 \pm 13\%$ , and  $47 \pm 19\%$ , respectively. Regression analysis demonstrated strong correlations between FFR and MLD ( $r=0.79$ ,  $P<0.0001$ ) as well as between FFR and MLA ( $r=0.74$ ,  $P<0.0001$ ). There were inverse, moderate correlations between FFR and CSN ( $r=0.69$ ,  $P<0.0001$ ), followed by those between FFR and AS ( $r=0.54$ ,  $P<0.0001$ ). Compared with FFR as the “gold standard,” an MLD of 2.8 mm had the highest sensitivity and specificity (93% and 98%, respectively) for determining the significance of an LMCS, followed by an MLA of 5.9 mm<sup>2</sup> (93% and 95%, respectively). Based on an FFR  $<0.75$  and an FFR  $\geq 0.75$ , the 38-month survival and event-free survival estimates (EFSEs) were both 100% and 100% versus 90%, respectively ( $P=NS$ ).

**Conclusions**—We conclude that (1) an IVUS MLD and MLA of 2.8 mm and 5.9 mm<sup>2</sup>, respectively, strongly predict the physiological significance of an LMCS and (2) among patients with an LMCS, an FFR of 0.75 is a strong predictor of survival and EFSE. (*Circulation*. 2004;110:2831-2836.)

**Key Words:** blood flow ■ imaging ■ ischemia ■ artery ■ coronary disease

Angiographic assessment of a left main coronary artery stenosis (LMCS) is often difficult and unreliable.<sup>1</sup> Furthermore, autopsy studies have demonstrated that in many situations in which the LMCS is mildly diseased, it is often reported as significantly stenosed by angiography.<sup>2</sup> A critical stenosis in this artery is best treated by surgical revascularization,<sup>3-6</sup> although percutaneous revascularization may emerge as a viable alternative in selected patient populations.<sup>7,8</sup> Long-term follow-up data indicate that bypass surgery for a significant LMCS is superior to medical therapy alone, offering a vastly better reduction in mortality.<sup>9-11</sup> On the other hand, too early an operation for a nonsignificant LMCS could lead to inappropriate use of available grafts and the premature closure of either the native vessel or the graft.

It has previously been shown<sup>12</sup> that a fractional flow reserve cutoff value of 0.75 is a promising parameter for choosing surgical revascularization versus medical therapy in these patients. One study described the value of intravascular ultrasound (IVUS) in LMCS<sup>13</sup> and recommended a number of IVUS parameters that would predict event rates. Although

these parameters were correlated with clinical outcomes, there have not been any further attempts with physiological measurements to support valid use of these cutoff values.

To date, despite the widespread use of IVUS to determine the significance of an LMCS in patients with an angiographically ambiguous LMCS, physiological correlations of IVUS parameters have not been studied. Therefore, the primary objective of the present study was to determine the cutoff values of a number of IVUS parameters that would predict the physiological significance of the LMCS. In addition, among patients with an ambiguous LMCS, we sought to determine the prognostic value of an FFR cut point of 0.75 that would determine whether to proceed with medical therapy or revascularization.

## Methods

### Study Population

From November 15, 2000 to February 21, 2003, 55 patients underwent assessment of an angiographically ambiguous LMCS at our center. The following were reasons for exclusion from the study:

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(1) recent myocardial infarction (<6 weeks); (2) unstable angina or the presence of hemodynamic instability; (3) significant 3-vessel disease and LMCS; (4) distal vessels that were totally occluded or that were supplying an akinetic territory by visual assessment of the LV angiogram; and (5) occurrence of ventricularization or hypotension during engagement of the LMCA artery (LMCA) ostium by diagnostic or guiding catheter. The institutional review board approved the study, and informed consents were obtained.

### Experimental Protocol

The LMCA was engaged with a 6F guiding catheter after administration of 100  $\mu$ g intracoronary nitroglycerin. A 0.014-in. pressure guidewire (WaveWire, Jomed) was set at zero, then the pressure transducer was normalized in the aorta while the guiding catheter was retracted from the ostium of the LMCA, and it was then positioned  $\approx$ 3 cm distal to the LMCA, preferably in the left anterior descending coronary artery (LAD). Fractional flow reserve (FFR) was calculated as Pd/Pa, where Pd (distal coronary pressure) and Pa (aortic pressure) were recorded simultaneously during maximal coronary hyperemia induced by intracoronary infusion of adenosine (42 to 56  $\mu$ g), as described previously.<sup>14,15</sup> In patients with an ostial LMCS, to avoid damping of the pressures, after adenosine injection the guiding catheter was retracted from the ostium of the LMCA. In patients with a distal LMCS, the pressure guidewire was advanced to both the LAD and the left circumflex coronary artery (LCx), and the FFR of these vessels was measured sequentially; then IVUS of a vessel with a lower FFR was performed. Patients in whom FFR was <0.75 underwent coronary artery bypass graft surgery (CABG). Among patients with a protected LMCS, the pressure transducer was positioned in either the LAD or LCx, where the graft to that artery was occluded or it was never bypassed, and FFR was then measured. If FFR was <0.75, stenting of the LMCA was performed. The cutoff value of 0.75 in deciding whether to proceed with bypass surgery or medical therapy was based on the results of a previous study.<sup>12</sup>

In patients in whom there were additional stenoses in the mid to distal LAD or LCx, the pressure transducer was positioned  $\approx$ 3 cm distal to the LMCS but proximal to the LAD or LCx stenosis, and FFR was measured. When the FFR of the LMCA was  $\geq$ 0.75, the pressure transducer was then advanced to the distal LAD and LCx, and FFR was remeasured. In patients in whom the FFR of the LAD or LCx was <0.75, after IVUS of the LMCA was performed, percutaneous coronary intervention (PCI) of either the LAD or LCx was performed. In patients in whom the FFRs of both the LAD and LCx were <0.75 or when there was a stenosis in the proximal LAD or LCx and the FFR was <0.75, CABG was performed.

### IVUS Imaging Protocol

After measurement of FFR, 100  $\mu$ g of intracoronary nitroglycerin was injected and IVUS was performed with a 3.2F, 30-MHz or a 2.9F, 40-MHz single-element mechanical transducer (Boston Scientific). Ultrasound images were recorded after initiation of automated pullback at 0.5 mm/s, starting at a point distal to the bifurcation of the LAD and LCx, and then the entire LMCA was imaged in retrograde fashion to the aorto-ostial junction. A SuperVHS videotape was used to record all studies for offline analysis.

### IVUS Analysis

All IVUS images were reviewed and analyzed for quantitative parameters by a skilled interpreter blinded to the FFR results and using computerized planimetry (Tape Measure, Indec Systems, Inc). Quantitative analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of IVUS.<sup>16</sup> The following IVUS parameters at the target lesion and reference segment were measured: (1) minimum and maximum lumen diameters (mm); (2) minimal lumen cross-sectional area (MLA, mm<sup>2</sup>); (3) plaque plus media cross-sectional area (CSA, mm<sup>2</sup>) equal to the external elastic membrane cross-sectional area (EEM CSA) minus the MLA; (4) cross-sectional narrowing (CSN), which was calculated as plaque plus media CSA divided by the EEM CSA; (5) the

reference segment, which was the normal-looking LMCA cross section located proximal or distal to the stenosis; in patients with a mid-LMCS, the average of measurements proximal and distal to the stenosis was selected; and (6) area stenosis (AS), calculated as the reference-lumen CSA-lesion MLA $\times$ 100/reference-lumen CSA. The stenosis site was the image slice with the smallest luminal CSA. In contrast, the largest plaque plus media CSA and EEM CSA were selected for analysis from the image slices with the same small-lumen CSA.

### Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) was performed by a skilled analyzer blinded to the results of IVUS and FFR and using validated, automated, edge-detection software (QCA-CMS 5.2 system, CMS-MEDIS), according to previously validated and published protocols.<sup>15</sup> After calibration with the outer diameter of the contrast-filled catheter as the standard, the minimum lumen diameter (MLD) in diastole was measured from angiographic projections with the tightest LMCS. The reference segment diameter was measured from an angiographically normal segment proximal to the LMCS; in patients with an ostial LMCS, a distal angiographically normal segment was analyzed.

### Follow-Up and Clinical Events

Follow-up information was collected by serial telephone interview every 6 months and office visit every year. Cardiac events included death, myocardial infarction, CABG, and PCI related to the LMCS or native coronary artery where FFR had previously been performed. Data on the severity and frequency of angina were obtained during office visit and telephone interview. The indication for cardiac catheterization was clinically driven and was performed only in patients who developed worsening angina or a myocardial infarction.

### Statistical Analysis

Continuous variables were analyzed by unpaired Student's *t* test, and categorical data were analyzed by the  $\chi^2$  test. To identify correlations between FFR and IVUS data, logistic regression analysis was performed with the use of Analyze-It software (Analyze-It Software, Ltd). Receiver operator characteristic analysis was performed with the use of Analyze-it software to determine the sensitivity and specificity of an FFR cut point of 0.75 to predict a variety of IVUS parameters. The rates of survival and freedom from major cardiac events were estimated by Kaplan-Meier time-to-event analyses. A probability value <0.05 was considered significant.

### Results

Fifty-five patients who met the criteria detailed under Methods and had technically adequate IVUS and FFR data constituted the study populations. The baseline clinical, angiographic, and IVUS characteristics of these patients are summarized in Table 1. MLD measured by IVUS was significantly greater than that measured by QCA ( $3.08\pm 0.6$  versus  $2.14\pm 0.86$ , respectively;  $P<0.001$ ).

Forty-one patients with an LMCS had an FFR  $\geq$ 0.75 (Table 2). Of these, 13 patients had an FFR <0.75 in either the LAD or LCx and underwent PCI; after PCI, FFR improved from  $0.67\pm 0.05$  to  $0.90\pm 0.04$  ( $P<0.01$ ). In addition, 4 patients had a diffuse stenosis in the mid to distal LAD and LCx and underwent CABG. In contrast, in 14 patients, the FFR of the LMCA was <0.75 (Table 2); of these 14 patients, 7 underwent CABG, and 7 patients had a protected LMCS and underwent PCI. In summary, 20 patients underwent PCI of the LMCS, LAD, or LCx; 11 patients underwent CABG; and 24 patients received medical therapy only.

Comparative data for QCA and IVUS in patients with an LMCS and an FFR  $\geq$ 0.75 versus an FFR <0.75 are listed in

**TABLE 1. Baseline Clinical, Angiographic, and IVUS Characteristics of Patients (n=55)**

Age, y	62±11
Diabetes mellitus, n	20
Hypertension, n	50
Smoking, n	39
Prior bypass surgery, n	13
Ejection fraction, %	50±6
Reference lumen diameter, mm (QCA)	4.21±1.0
MLD, mm (QCA)	2.14±0.86
Diameter stenosis, % (QCA)	49±15
Additional coronary artery disease	
1-Vessel disease, n	13
2-Vessel disease, n	4
MLD, mm (IVUS)	3.08±0.6
Minimum lumen CSA, mm <sup>2</sup> (IVUS)	7.65±3.0
CSN, % (IVUS)	59±13
AS, % (IVUS)	47±19
Plaque and media CSA, mm <sup>2</sup> (IVUS)	11±3.0
Ostial LM stenosis, n	20
Mid-LM stenosis, n	3
Distal LM stenosis, n	32

Abbreviations are as defined in text.

Table 2. By QCA analysis, MLD measured by QCA was significantly greater in patients with an FFR  $\geq 0.75$  than it was in those with an FFR  $< 0.75$ . In contrast, all IVUS parameters were significantly greater in patients with an FFR  $\geq 0.75$  than in those with an FFR  $< 0.75$  (Table 2). The difference between mean FFR values in the 2 groups was also highly significant ( $P < 0.001$ ).

Linear regression analysis demonstrated strong correlations between FFR and IVUS parameters, including MLD ( $r = 0.79$ ,  $P < 0.0001$ ; Figure 1A), as well as between FFR and MLA ( $r = 0.74$ ,  $P < 0.0001$ ; Figure 1B). There were inverse, moderate correlations between FFR and CSN ( $r = 0.69$ ,  $P < 0.0001$ ; Figure 1C), followed by FFR and AS ( $r = 0.54$ ,

**TABLE 2. Comparison of Angiographic and IVUS Parameters in Patients With an FFR  $< 0.75$  and an FFR  $\geq 0.75$** 

	FFR $\geq 0.75$ (n=41)	FFR $< 0.75$ (n=14)	P
QCA parameters			
Reference lumen diameter, mm	4.25±0.95	4.16±1.0	0.78
MLD, mm	2.32±0.86	1.70±0.83	0.015
Diameter stenosis, %	47±11	45±11	0.68
IVUS parameters			
MLD, mm	3.43±0.47	2.26±0.25	<0.001
Lumen CSA, mm <sup>2</sup>	9.29±2.76	4.0±9.6	<0.001
CSN, %	52±11	76±10	<0.001
AS, %	40±15	69±14	<0.001
Plaque and media CSA, mm <sup>2</sup>	10.14±3.14	13.84±2.84	<0.001
FFR	0.91±0.14	0.67±0.06	<0.001

Abbreviations are as defined in text.

$P < 0.0001$ ). In contrast, a weak correlation was found between FFR and MLD as measured by QCA (Figure 1D).

By IVUS, an MLD cut point of 2.8 mm had the highest sensitivity, specificity, and predictive accuracy of 93%, 98%, and 96%, respectively (Figure 2A), followed by an MLA of 5.9 mm<sup>2</sup>, with a sensitivity, specificity, and predictive accuracy of 93%, 95%, and 94%, respectively (Figure 2B), to predict the physiological significance of the LMCS as determined by FFR. A CSN cut point of 67% had a sensitivity and specificity of 90% and 88% (Figure 2C), respectively, followed by an AS of 50%, with a sensitivity and specificity of 86% and 80%, respectively, to predict the physiological significance of the LMCS (Figure 2D).

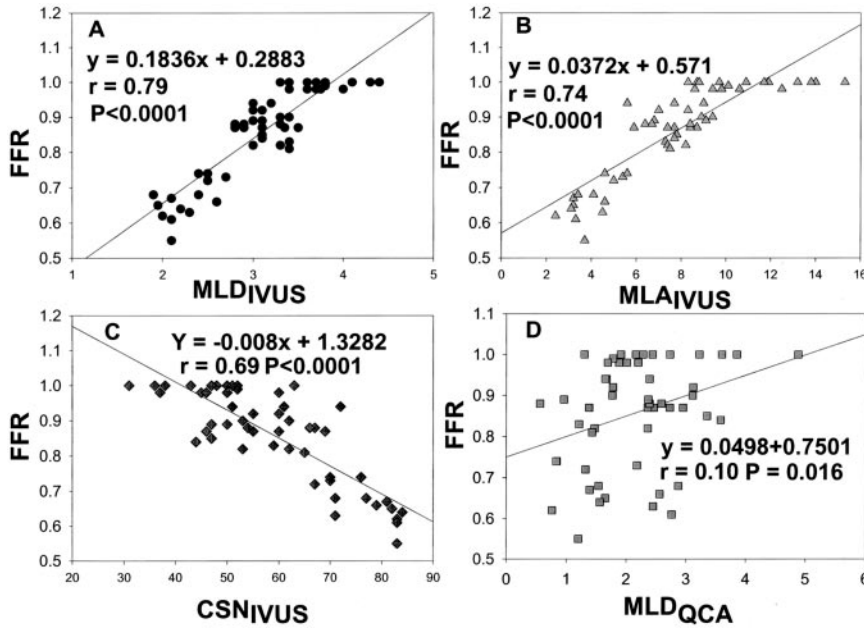
### Procedural Safety and Follow-Up

There were no complications related to the procedures, including those involved in performing FFR, IVUS, PCI, and CABG. Among patients in whom the FFR of the LMCA was  $> 0.75$ , 4 patients who had stenoses of the mid to distal LAD and LCx and underwent CABG were excluded from follow-up; consequently, data were collected for 37 patients. During the follow-up period, 3 noncardiac deaths occurred. Two patients were admitted with chest pain to another hospital; after cardiac catheterization, CABG was performed. In addition, 3 patients were admitted with worsening angina; cardiac catheterization, FFR, and IVUS of the LMCA were performed. In the first patient, disease progression was noted in the LCx, and PCI was performed. In the second patient, FFR and IVUS demonstrated that the LMCS was not significant; however, there were new stenoses in the vein grafts to the LCx as well as to the right coronary artery, and PCI was performed. In the third patient, coronary angiography demonstrated a 50% stenosis in the LMCA; however, both FFR and IVUS demonstrated that the LMCS was not significant and not different from that in the original study, and medical therapy was continued. At the end of follow-up, 10 patients were in Canadian Cardiovascular Society angina class 1 to 2, and 24 patients were free from angina.

Among patients in whom the FFR of the LMCS was  $< 0.75$  and underwent revascularization (14 patients), no event occurred during hospitalization and follow-up. At the end of follow-up, 3 patients were in Canadian Cardiovascular Society angina class 1 to 2, and 11 patients were free from angina. In patients with an LMCS and an FFR  $< 0.75$  versus an FFR  $\geq 0.75$ , the Kaplan-Meier estimated survival and event-free survival rates at 38 months of follow-up were both 100% and 100% versus 90%, respectively ( $P = \text{NS}$ ; Figure 3).

### Discussion

To the best of our knowledge, the present study is the first report to demonstrate that using IVUS-determined MLD and MLA cutoff values of 2.8 mm and 5.9 mm<sup>2</sup>, respectively, provide the best sensitivity and specificity to predict the physiological significance of an LMCS and are well correlated with an FFR cut point of 0.75. We also demonstrate that when decision-making about revascularization is based on physiological data, a significant number of patients (37 patients in our series, or 67%) can be spared from unnecessary CABG or PCI. The present study also demonstrates that

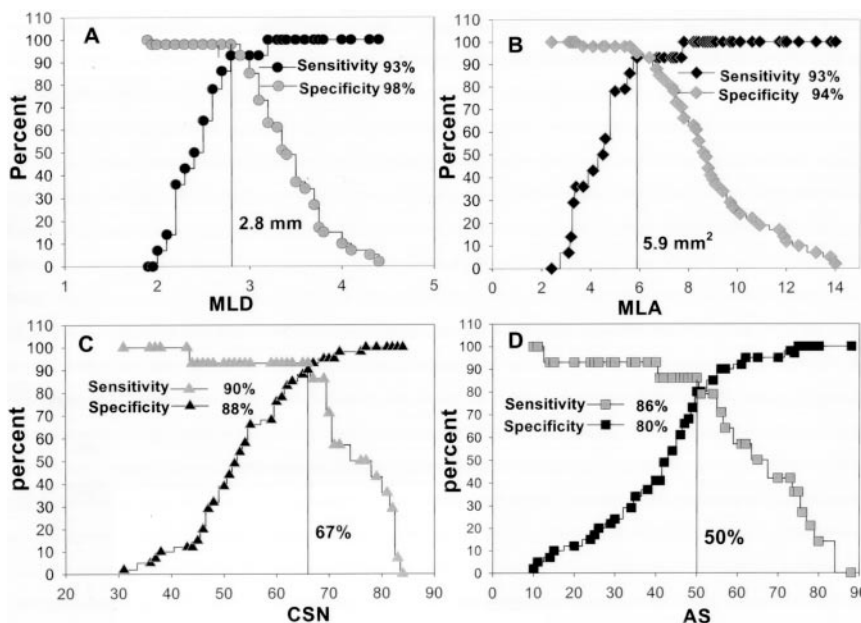


**Figure 1.** A, Correlation between IVUS MLD and FFR ( $r=0.79$ ,  $P<0.0001$ ). B, Correlation between IVUS MLA and FFR ( $r=0.74$ ,  $P<0.0001$ ). C, Correlation between IVUS CSN and FFR ( $r=0.69$ ,  $P<0.0001$ ). D, Correlation between QCA MLD and FFR ( $r=0.10$ ,  $P=0.78$ ). Abbreviations are as defined in text.

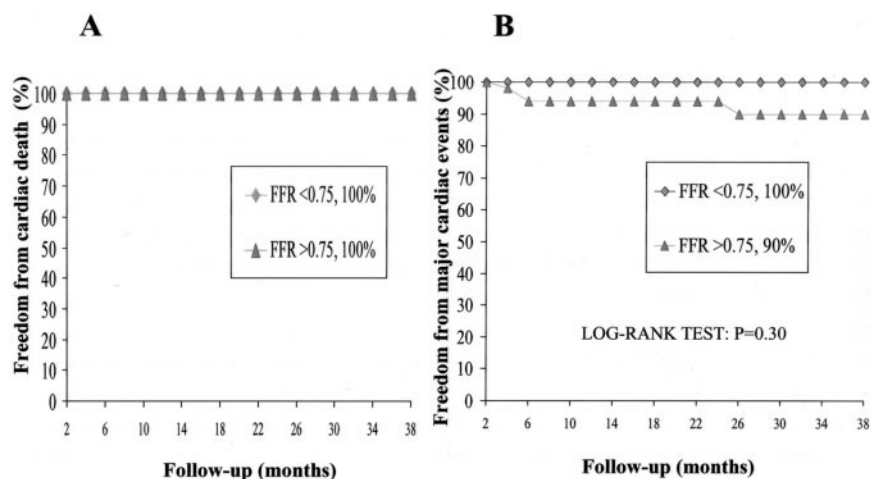
in patients with an ambiguous LMCS, a decision based on an FFR cut point of 0.75 to proceed with revascularization or medical therapy is associated with excellent 38-month survival and event-free survival rates. On the other hand, revascularization of a nonsignificant LMCS might actually increase the event rates owing to premature closure of bypass grafts or the process of restenosis. Likewise, the present study corroborates the study of Bech et al,<sup>12</sup> who found that in patients with an LMCS, an  $FFR \geq 0.75$ , and deferred revascularization, there was no occurrence of myocardial infarction or cardiac death during 3-year follow-up. In addition, Bech et al<sup>17</sup> have shown that in patients with moderate coronary stenosis, an  $FFR > 0.75$ , and deferred PCI, the cardiac mortality and myocardial infarction rate was only 1% per year, which is significantly lower than that reported after

deployment of paclitaxel-eluting stents.<sup>18</sup> It is interesting to note that even in the era of drug-eluting stents, stenting of a nonsignificant coronary stenosis has no prognostic advantage.

In contrast to IVUS, QCA parameters did not predict the physiological significance of the LMCS. Of note, MLD as measured by QCA was greater in patients who had an  $FFR \geq 0.75$  than in those who had an  $FFR < 0.75$ , but MLD did not discriminate which stenoses were physiologically significant and which were not; furthermore, as shown in Figure 1D, no correlation was found between MLD and FFR. Similar observations were also reported by others<sup>12,13</sup>; that MLD by QCA neither discriminated the functional significance of an LMCS nor predicted future event rates. Similarly, a number of studies<sup>3,19</sup> have reported that in the presence of an LMCS, QCA was the least reproducible in any coronary arterial



**Figure 2.** Sensitivity and specificity curves of ischemic cut point of FFR and IVUS parameters: A, Best agreement with FFR cut point of 0.75 was found when MLD by IVUS was 2.8 mm (sensitivity, 93%; specificity, 98%). B, Best agreement with FFR cut point of 0.75 was found when MLA by IVUS was 5.9 mm<sup>2</sup> (sensitivity, 93%; specificity, 94%). C, Best agreement with FFR was found when CSN by IVUS was 67% (sensitivity, 90%; specificity, 88%). D, Best agreement with FFR was found when AS by IVUS was 50% (sensitivity, 86%; specificity 80%). Abbreviations are as defined in text.



**Figure 3.** A, 38-month Kaplan-Meier freedom from cardiac death estimate in patients with LMCS and FFR <0.75 (n=14) who underwent revascularization vs those with FFR ≥0.75 (n=37) who were continued on medical therapy. B, 38-month Kaplan-Meier freedom from major cardiac events estimate in patients with FFR <0.75 vs those with FFR ≥0.75. Two events in the FFR ≥0.75 group were interventions due to progression of disease elsewhere in coronary tree. Abbreviations are as defined in text.

segment, and there was significant intraobserver as well as interobserver variability in the angiographic assessment of an LMCS. Likewise, when angiographic assessment of an LMCS was compared with that of IVUS, there was a very high percentage of patients with an angiographically normal LMCA who were found to have coronary disease by IVUS.<sup>20</sup> In addition, Abizaid et al<sup>13</sup> reported that in patients with an LMCS, IVUS MLD was correlated poorly with QCA MLD; these investigators also reported that in contrast to IVUS, QCA MLD and the percent diameter stenosis were not predictive of event rates.

IVUS is very useful in defining the 3-dimensional structural characteristics of an LMCS, and it has previously been shown that IVUS MLD is predictive of event rates.<sup>13</sup> In addition, in a prospective study of 56 patients, Wolfhard et al<sup>21</sup> used IVUS to assess an angiographically equivocal LMCS. Patients who had an AS >50% and an MLD <3 mm underwent CABG, but the physiological significance of the LMCS was not assessed. A correlation between IVUS parameters and FFR was examined in only 1 study,<sup>22</sup> but patients with an LMCS were excluded. The present study has validated the findings of Abizaid et al<sup>13</sup> that an IVUS MLD <3 mm was linked to an increase in event rates. In the present study, intracoronary adenosine was used to induce hyperemia; however, the state of the art for physiological measurements in the ostial LMCS, as reported by Bach et al,<sup>12</sup> is intravenous adenosine into a femoral vein, with slight retraction of the guiding catheter from the ostium during hyperemia.

**Clinical Implications and Conclusions**

Because IVUS parameters and FFR are significantly correlated and are predictive of cardiac event rates and because QCA is unreliable, the use of either IVUS or FFR to assess the significance of an LMCS is highly recommended. IVUS provides detailed anatomic information in patients in whom stenting of the LMCS is being considered. However, analysis of IVUS data requires a higher degree of expertise, and IVUS is more expensive to perform than FFR. Moreover, FFR measurement is easier to perform and to interpret than is IVUS and does not require additional instrumentation. In addition, FFR can be used easily to investigate other arteries

and to make pullback curves along the arteries with a high spatial resolution to detect the source of ischemia in more complex patients, even in those with diffuse disease, as was the case in 4 patients in our study.

The present study demonstrates strong correlations between IVUS parameters and FFR and also demonstrates that a decision-making strategy to assess the significance of an LMCS predicated on the use of either an FFR cut point of 0.75 or validated IVUS parameters with FFR including the MLD and MLA cutoff values of 2.8 mm and 5.9 mm<sup>2</sup>, respectively, is safe and superior to angiography. Furthermore, among patients with an LMCS, an FFR cut point of 0.75 to proceed with medical therapy or revascularization is a strong predictor of survival and event free survival rates.

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