

# Long-Term Clinical Outcome After Fractional Flow Reserve–Guided Treatment in Patients With Angiographically Equivocal Left Main Coronary Artery Stenosis

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**Background**—Significant left main coronary artery stenosis is an accepted indication for surgical revascularization. The potential of angiography to evaluate the hemodynamic severity of a stenosis is limited. The aims of the present study were to assess the long-term clinical outcome of patients with an angiographically equivocal left main coronary artery stenosis in whom the revascularization strategy was based on fractional flow reserve (FFR) and to determine the relationship between quantitative coronary angiography and FFR.

**Methods and Results**—In 213 patients with an angiographically equivocal left main coronary artery stenosis, FFR measurements and quantitative coronary angiography were performed. When FFR was  $\geq 0.80$ , patients were treated medically or another stenosis was treated by coronary angioplasty (nonsurgical group;  $n=138$ ). When FFR was  $< 0.80$ , coronary artery bypass grafting was performed (surgical group;  $n=75$ ). The 5-year survival estimates were 89.8% in the nonsurgical group and 85.4% in the surgical group ( $P=0.48$ ). The 5-year event-free survival estimates were 74.2% and 82.8% in the nonsurgical and surgical groups, respectively ( $P=0.50$ ). Percent diameter stenosis at quantitative coronary angiography correlated significantly with FFR ( $r=-0.38$ ,  $P<0.001$ ), but a very large scatter was observed. In 23% of patients with a diameter stenosis  $< 50\%$ , the left main coronary artery stenosis was hemodynamically significant by FFR.

**Conclusions**—In patients with equivocal stenosis of the left main coronary artery, angiography alone does not allow appropriate individual decision making about the need for revascularization and often underestimates the functional significance of the stenosis. The favorable outcome of an FFR-guided strategy suggests that FFR should be assessed in such patients before a decision is made “blindly” about the need for revascularization. (*Circulation*. 2009;120:1505-1512.)

**Key Words:** bypass ■ fractional flow reserve, myocardial ■ ischemia ■ stenosis ■ stents

The incidental finding of an angiographically intermediate left main coronary artery (LMCA) stenosis has increased with the more liberal use of coronary angiography in acute coronary syndromes. Although recently questioned,<sup>1</sup> the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the use of coronary artery bypass grafting (CABG)<sup>2,3</sup> propose as a Class IA recommendation that CABG should be performed in patients with a significant LMCA stenosis. In earlier studies involving symptomatic patients with an LMCA stenosis, CABG has indeed been shown to improve survival significantly compared with medical treatment,<sup>4–8</sup> yet bypassing noncritically diseased coronary arteries leads to a high rate of disease progression in the grafted native artery<sup>9</sup> and is associated with a high rate of

graft atresia.<sup>10</sup> In addition, in the vast majority of these patients, the decision to operate is based mainly on angiography, yet angiography has limited accuracy in assessing actual stenosis severity, and there is great interobserver variability in lesions of the left main stem.<sup>11,12</sup> Pressure-derived fractional flow reserve (FFR) can be measured at the time of coronary angiography and identifies coronary lesions responsible for ischemia. FFR-guided revascularization strategies are associated with favorable clinical outcomes in patients with single-vessel or multivessel disease.<sup>13–15</sup> Because the long-term natural history of nonsignificant stenoses is very favorable, it was hypothesized that only patients with a significant left main stenosis, ie, capable of inducing myocardial ischemia, as detected by FFR would benefit from

Received September 4, 2008; accepted July 31, 2009.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.109.850073

a revascularization procedure. Accordingly, the main goal of the present study was to evaluate the long-term clinical outcome of an FFR-guided revascularization strategy in patients with angiographically equivocal LMCA stenosis.

## Clinical Perspective on p 1512

### Methods

#### Patient Population

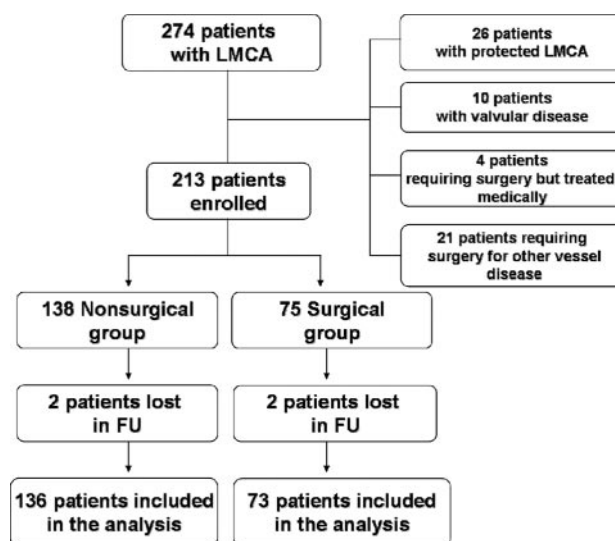
Between January 1999 and December 2007, 33 832 patients underwent coronary angiography. In 4534 of them, some degree of left main stenosis was found by visual estimation; in 1352 of them, the stenosis was considered  $<30\%$  by visual estimate by the operator, and no other measurement was performed; in 2908 of them, the stenosis was considered significant and/or the associated disease so severe that additional measurements were not deemed necessary to guide the clinical decision making. The main study population consisted of all consecutive patients ( $n=274$ ) in whom a left main stenosis was detected at angiography, in whom FFR was measured to determine the need for revascularization, and in whom at least a 6-month clinical follow-up was achieved. All demographic and baseline clinical data were retrieved from the database. Patients with protected left main stenosis (previous CABG with at least 1 patent graft to either the left anterior descending artery [LAD] or left circumflex artery [LCx];  $n=26$ ) and patients with other angiographic abnormalities or concomitant heart disease that required surgical correction were excluded from analysis (Figure 1). For reference, 2 other groups of patients were studied: 70 patients with a left main stenosis of  $<30\%$  diameter stenosis (DS) by visual estimate in whom no FFR measurements were performed (these patients were treated medically or underwent percutaneous coronary intervention [PCI] in another lesion) and 70 patients in whom the stenosis was considered  $>70\%$  by visual estimate (these patients underwent CABG).

#### Coronary Angiography

Diagnostic left heart catheterization and coronary arteriography were performed by a standard percutaneous femoral approach. After the diagnostic angiogram, a 6F guiding catheter was introduced into the LMCA. After administration of 200 to 300  $\mu\text{g}$  isosorbide dinitrate IC, the angiogram was repeated in the projection allowing the best possible visualization of the LMCA stenosis. The computer-based analysis system Siemens QuantCor.QCA (ACOM.PC 5.01, Siemens Medical Systems Inc, Malvern, Pa) based on the CAAS II system (Pie Medical Imaging, Maastricht, the Netherlands) was used for offline quantitative coronary angiography (QCA) analysis. All QCA measurements were performed by 2 independent observers who were blinded to patient clinical outcome and FFR data. The contrast-filled catheter was used for calibration. Minimal lumen diameter, percent DS by QCA analysis, reference diameter, and lesion length were measured preferably on end-diastolic images. The lesion segment was defined as ostial, middle (shaft), or distal. In our laboratory, coronary artery diameter measurements performed with the ACOM.PC 5.01 system have an interobserver variability of 0.11 mm and an intraobserver variability of 0.08 mm for mean lumen diameter on repeated analysis of the same frame.<sup>16</sup> In addition to this quantitative analysis, all angiograms were reviewed by 2 experienced cardiologists blinded to clinical outcome who were unaware of the FFR and the QCA values. Both physicians were asked whether the left main stenosis was significant or not significant or if they were unsure; they were also asked to provide an estimate of the percent DS.

#### Pressure Measurements

After administration of heparin 100 IU/kg IV, a pressure monitoring guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden) was calibrated and introduced into the guiding catheter. The wire was advanced up to the tip of the guiding catheter, and the pressure measured by the pressure wire was verified to be equal to the pressure measured by the guiding catheter. Next, the pressure wire was advanced further



**Figure 1.** Patient enrollment in the study. From 1999 to 2007, 274 patients with equivocal LMCA underwent pressure measurements in our center. Excluded were 26 patients with protected LMCA stenosis, 10 with concomitant valvular disease requiring surgery, and 25 with stenoses in arteries other than the LMCA that required surgery. Thus, 213 patients were included, 4 of whom (2 in each group) were lost during follow-up (FU). Finally, 136 patients in the nonsurgical and 73 in the surgical group were included in the analysis. For purposes of comparison, 2 other groups of patients also were studied (but are not shown): 70 patients with a left main stenosis of  $<30\%$  DS by visual estimate in whom no FFR measurements were performed (who were treated medically or underwent PCI in another lesion) and 70 patients in whom the stenosis was considered  $>70\%$  by visual estimate (who underwent CABG).

into the left coronary artery until the pressure sensor was located just distal to the LMCA segment. Maximum myocardial hyperemia was then induced by a continuous infusion of adenosine in the femoral vein at an infusion rate of  $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for  $>2$  minutes until steady-state hyperemia was achieved. When a stenosis was present in the LAD or LCx, the wire was placed either in the nondiseased artery or proximal to the first angiographically visible stenosis. The guiding catheter was always retrieved from the ostium (so as not to impede hyperemic blood flow) while leaving the pressure wire distal to the LMCA segment. During maximal hyperemia, LMCA FFR was calculated from the ratio of the simultaneously recorded mean aortic pressure to the mean coronary artery pressure as described previously.<sup>17</sup>

#### Patient Subgroups

The patients were prospectively divided into 2 groups based on the FFR measurements across the LMCA. In the nonsurgical group ( $n=138$ ), FFR of the LMCA was  $\geq 0.80$ , indicating that the stenosis was unlikely to be physiologically significant, so no bypass surgery was performed. If needed, PCI of a concomitant lesion elsewhere in the coronary tree was performed (52 lesions in 43 patients), and medical treatment was continued. In the surgical group ( $n=75$ ), FFR of the LMCA was  $<0.80$ , indicating functional significance; thus, CABG was performed. In addition to the analysis of the entire patient cohort, the angiographic, hemodynamic, and clinical outcome data of patients with an isolated LMCA stenosis ( $n=72$ ) were analyzed separately.

#### Follow-Up and Clinical Events

All patients were followed up closely for an average of 3 years (range, 6 to 99 months) with clinical visits. Patients who were not seen at the outpatient clinic were sent a written questionnaire to report their clinical events, quality of life, and medications. When needed, patients or their general practitioners were contacted by phone for additional information. Major adverse events were death resulting

from any cause, myocardial infarction, coronary bypass surgery or repeat surgery, coronary angioplasty. Angiographic follow-up was performed only in case of recurrent complaints or coronary events.

**Statistical Analysis**

All analyses were performed with Graphpad Prism software, version 5, and SPSS software version 16 (SPSS Inc, Chicago, Ill). Summary descriptive statistics are reported as mean (SD) or counts (%) as appropriate. Continuous variables were compared between the medical and surgical groups by independent-samples *t* tests; categorical variables were compared by use of Fisher exact or  $\chi^2$  tests as appropriate. The dependent variable in the analysis was time to initial events during follow-up. Kaplan–Meier product-limit curves for survival and major cardiac event-free survival were constructed and compared between the 2 groups through the use of the log-rank test. For the nonsurgical group of patients, Kaplan–Meier curves were also constructed and compared by use of the log-rank test to provide a univariate assessment of the prognostic value of selected clinical and angiographic potential risk factors. Variables found to be significant at the univariate level were tested multivariately with a stepwise Cox proportional-hazards regression model to determine which contained independent prognostic information. The thresholds for entry into and removal from the model were 5% and 10%, respectively. All statistical tests were carried out at the 5% level of significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Baseline Clinical Characteristics**

Some of the baseline characteristics differ significantly between the 2 groups of patients in whom FFR was measured (Table 1). Age was lower in the surgical group, whereas the incidence of previous myocardial infarction and the number of stenoses in other coronary segments were lower in the nonsurgical group. There was no difference in the number of patients without anginal symptoms in whom the catheterization was performed because of dyspnea (28% in the surgical group versus 24% in the nonsurgical group). In 72 patients with pure left main disease, baseline characteristics were similar between the nonsurgical and surgical groups.

**Angiography Versus FFR**

The DS was significantly larger in the surgical group (44±13%) than in the nonsurgical group (35±12%; *P*<0.001; Table 2). A statistically significant relationship was found between FFR and both percent DS by QCA analysis (*r*=−0.38, *P*<0.001; Figure 2) and minimal lumen diameter (*r*=0.42, *P*<0.001). However, a large scatter of the data was observed. The sensitivity, specificity, and diagnostic accuracy of percent DS by QCA analysis >50% to predict an FFR <0.80 were 33%, 91%, and 71%, respectively. Among the 213 patients, 62 were misclassified on the basis of QCA: 13 patients had a DS >50% while the FFR was >0.80, and 49 patients had a DS <50% while the FFR was <0.80 ( $\kappa$  coefficient of concordance=0.27). When only the patients with an isolated LMCA stenosis are considered, the sensitivity, specificity, and diagnostic accuracy of percent DS by QCA analysis >50% to predict an FFR <0.80 were 26%, 92%, and 75%, respectively. Among the 72 patients with isolated LMCA stenosis, 18 were misclassified on the basis of QCA: 4 patients had a DS >50% while the FFR was >0.80,

**Table 1. Baseline Clinical Characteristics of the 2 Main Study Groups**

	Nonsurgical Group, FFR ≥0.80 (n=138)	Surgical Group, FFR <0.80 (n=75)	<i>P</i>
Age, y	68.1±10.6	64.2±9	0.007
Male, %	99 (71)	55 (73)	0.75
CCS class, %			0.37
1	21	19	
2	57	56	
3	14	21	
4	8	4	
NYHA class, %			0.01
1	64	40	
2	36	33	
3	0	27	
4	0	0	
Follow-up, mo	35±26	35±23	0.69
BMI, kg/m <sup>2</sup>	26.8±3.9	26.9±3.8	0.78
EF, %	67±16	64±19	0.14
Diabetes mellitus, n (%)	28 (20)	19 (25)	0.39
Hyperlipidemia, n (%)	86 (62)	51 (68)	0.37
Hypertension, n (%)	69 (50)	44 (59)	0.2
Smoking, n (%)	59 (43)	39 (52)	0.2
Family history, n (%)	12 (9)	2 (3)	0.15
Previous MI, n (%)	18 (13)	21 (28)	0.009
Previous PCI, n (%)	47 (34)	25 (33)	1
Previous CABG, n (%)	7 (5)	4 (5)	1

CCS indicates Canadian Cardiovascular Society; NYHA, New York Heart Association; BMI, body mass index; EF, ejection fraction; and MI, myocardial infarction.

and 14 patients had a DS <50% while the FFR was <0.80 ( $\kappa$  coefficient of concordance=0.22). Two examples of discordance between FFR values and angiographic appearance of LMCA lesions are shown in Figure 3.

**Visual Estimate of the Angiogram Versus FFR and QCA**

All 213 films were estimated by the 2 reviewers. The relation between the FFR value and each reviewer’s assessment of the percent DS is shown in Figure 4.

In 158 patients (74%), there was agreement between the 2 reviewers; in 55 (26%), however, different estimations were made ( $\kappa$  coefficient of concordance=0.45). For the 158 patients in whom the classification was concordant, the sensitivity, specificity and diagnostic accuracy of the visual estimate of DS >50% to predict an FFR <0.80 were 46%, 79%, and 69%, respectively ( $\kappa$ =0.25). Among these 158 patients, 48 were misclassified on the basis of visual estimate of the angiogram: 23 patients had an estimated DS >50% while the FFR was >0.80, and 25 patients had an estimated DS <50% while the FFR was <0.80 ( $\kappa$  coefficient of concordance=0.25).

**Clinical Follow-Up**

Follow-up was obtained in 209 patients (136 in the nonsurgical group, 73 in the surgical group). Four patients were lost

**Table 2. Angiographic Characteristics and Pressure Data**

	Nonsurgical Group, FFR $\geq 0.80$ (n=138)	Surgical Group, FFR $< 0.80$ (n=75)	P
No. of diseased vessels, n (%)			
0*	52 (38)	19 (25)	0.07
1*	45 (32)	26 (35)	0.76
2*	30 (22)	18 (24)	0.73
3*	11 (8)	12 (16)	0.1
LAD, n (%)	55 (40)	38 (51)	0.15
LCx, n (%)	43 (31)	29 (39)	0.29
RCA, n (%)	42 (30)	33 (44)	0.052
Ostial type, n (%)	49 (35)	31 (41)	0.46
Mid type, n (%)	19 (14)	6 (8)	0.27
Distal type, n (%)	72 (52)	38 (51)	0.89
Stenosis, %	34.7 $\pm$ 12	44.2 $\pm$ 12.6	$< 0.0001$
MLD, mm	2.6 $\pm$ 0.66	2.01 $\pm$ 0.49	$< 0.0001$
Ref D, mm	4.04 $\pm$ 1.03	3.8 $\pm$ 0.8	0.17
FFR	0.88 $\pm$ 0.05	0.73 $\pm$ 0.06	$< 0.0001$
P <sub>a</sub> , mm Hg	94 $\pm$ 17	94 $\pm$ 17	0.97
P <sub>d</sub> , mm Hg	83 $\pm$ 15	69 $\pm$ 13	$< 0.0001$

RCA indicates right coronary artery; MLD, minimal lumen diameter; Ref D, reference diameter; P<sub>a</sub>, mean aortic pressure; and P<sub>d</sub>, mean pressure distal to the lesion.

\*In addition to the left main stenosis.

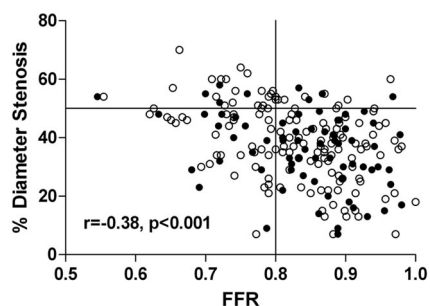
during follow-up (2 in each group). Mean follow-up was 35 $\pm$ 25 months.

In the nonsurgical group (FFR  $> 0.80$ ; n=136), 9 patients (6.5%) died during follow-up. There was 1 nonfatal myocardial infarction. CABG was performed in 9 patients, 1 of them 3 months after pressure measurements because of an unsuccessful PCI attempt in the LAD. In 4 patients, CABG was indicated because of progression of the stenosis in the left main artery. In 4 patients, CABG was indicated by the progression of stenoses in other arteries. PCI was performed during follow-up in 8 patients either in a vessel that had been treated initially (n=2) or in another vessel (n=6).

In the surgical group (n=73), 7 patients (9.6%) died during follow-up. There was no incidence of myocardial infarction. No patients underwent repeat cardiac surgery. PCI was performed in 4 patients, all in a native vessel.

The Kaplan–Meier percentage survival estimates at 5 years were 89.8% in the nonsurgical group and 85.4% in the surgical group ( $P=0.48$ ; Figure 5A). Event-free survival rates at 5 years were 74.2% and 82.8% in the nonsurgical and surgical groups, respectively ( $P=0.5$ ; Figure 5B). Events were equally distributed over time in both groups. Relief of or improvement in anginal symptoms was reported by 54% of patients in the nonsurgical group and by 59% of patients in the surgical group ( $P=NS$ ). The remaining patients either did not report any change in symptoms or indicated thoracic complaints different from their initial medical condition.

When only the patients with an isolated LMCA stenosis are considered, The Kaplan–Meier percentage survival estimates at 5 years were 100% in the nonsurgical group and 75% in the



**Figure 2.** Scatterplots showing the distribution of percent DS and the corresponding FFR values. The dots represent patients with isolated LMCA stenosis.

surgical group ( $P=0.32$ ). Event-free survival rates at 5 years in the nonsurgical and surgical groups were 70% and 66%, respectively ( $P=0.54$ ).

When the 2 groups of patients who were included for reference and in whom no FFR had been obtained are considered, the Kaplan–Meier percentage survival estimates at 5 years were 92.2% in those with a  $< 30\%$  angiographic narrowing (who were treated medically or by PCI of  $\geq 1$  other lesions) and 92.8% in those with a  $\geq 70\%$  stenosis (who had CABG;  $P=0.99$ ). Event-free survival rates at 5 years were 64.3% and 82.6%, respectively ( $P=0.035$ ).

### Factors Predictive of Clinical Events

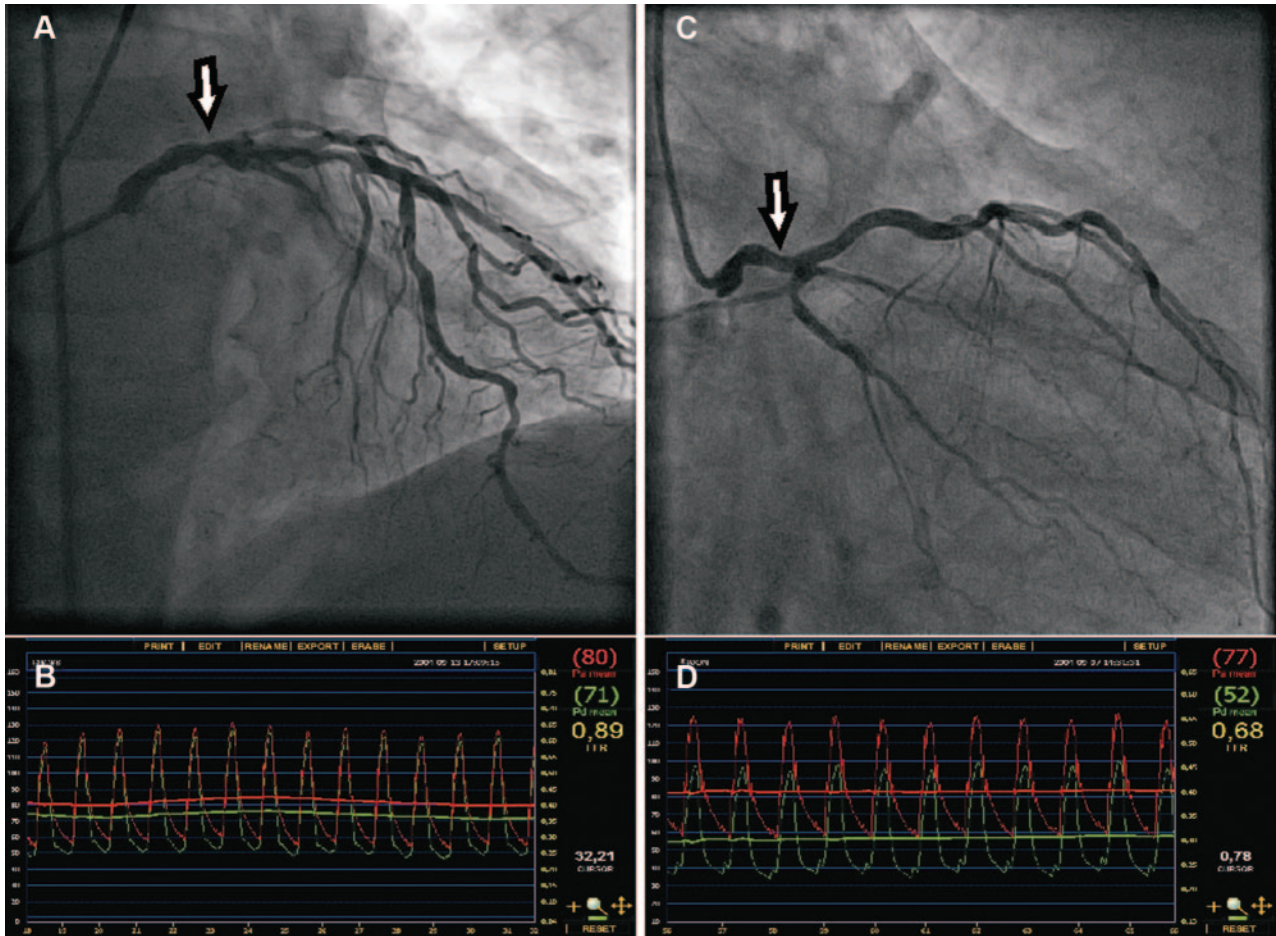
Variables that could potentially predict major adverse cardiac event-free survival in the nonsurgical group were analyzed by univariate Cox regression analysis (Table 3). Ejection fraction and the presence of a stenosis in the LAD, LCx, or right coronary artery were included in a multivariable model to predict the presence of major adverse cardiac events in the nonsurgical group. Stepwise Cox regression analysis showed that the right coronary artery was the sole significant independent predictor for progression to major adverse cardiac events ( $\chi^2=10.425$ ,  $P=0.001$ ).

### Discussion

The present study shows that the long-term clinical outcome of patients with an LMCA stenosis in whom surgery was deferred on the basis of FFR values  $> 0.80$  is favorable and similar to that of patients in whom CABG was performed on the basis of FFR values  $< 0.80$  and that the correlation between angiographic assessment, by either QCA or visual estimate, and FFR is poor because angiography frequently underestimates the actual severity of LMCA stenosis.

### CABG in Patients With LMCA Stenosis

Overall, CABG improves survival significantly, and the presence of an LMCA stenosis is generally considered an indication for CABG.<sup>18,19</sup> A meta-analysis of 7 large randomized studies of CABG versus medical treatment in patients with multivessel disease with or without LMCA stenosis demonstrated that the risk reduction in mortality was  $\approx 3$  times larger in patients with an LMCA stenosis than in patients with 3-vessel disease.<sup>20</sup> Nevertheless, subgroup analysis of the Coronary Artery Surgery Study (CASS) registry showed that surgery did not prolong survival in patients with



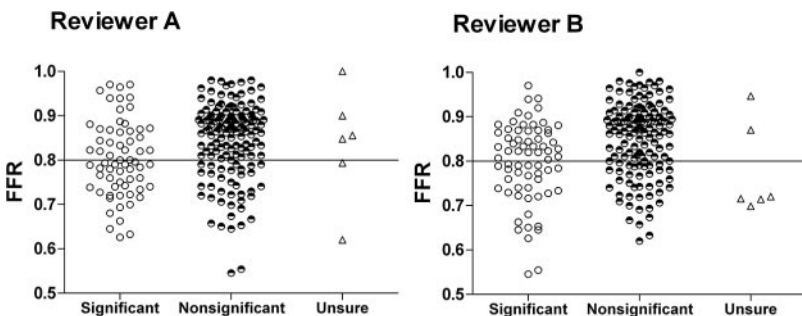
**Figure 3.** Examples of discordance between the angiographic appearance and the FFR values of left main lesions. A, An angiographically tight left main stenosis with an FFR value of 0.89 (B). C, An angiographically mild left main stenosis with an FFR value of 0.68 (D).

LMCA <60% DS especially when left ventricular function was normal and there was no stenosis in the right coronary artery.<sup>7</sup> Because angiography was used to evaluate stenosis severity, it is likely that some of these patients actually had hemodynamically nonsignificant stenoses and others, not included in these studies, might have had significant LMCA stenosis. In the present study, a separate analysis of 72 patients with “pure” LMCA stenosis demonstrated similar clinical results. In addition, the 5-year survival estimate for patients with a stenosis <30% in whom FFR had not been measured was similar to that for patients with stenoses between 30% and 70% in whom the need for revascularization was based on FFR measurements. Taken together, these

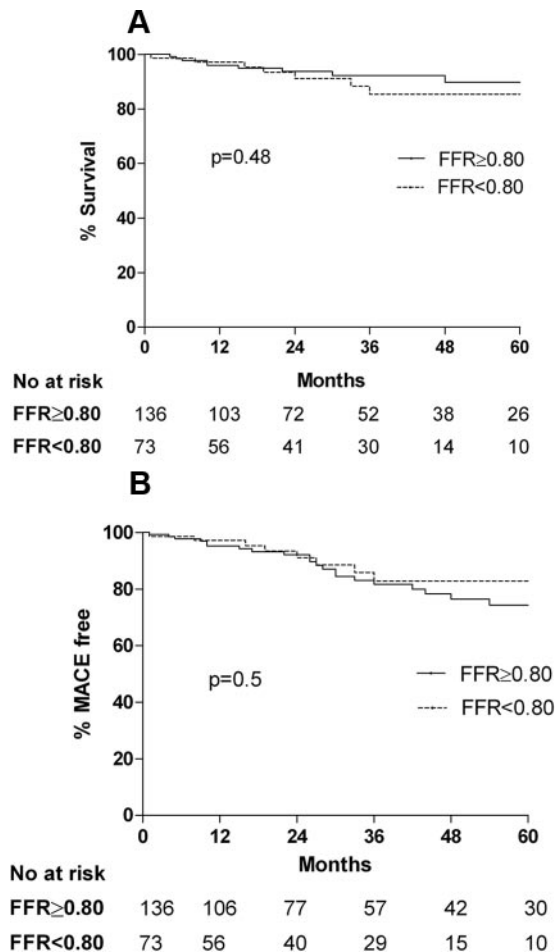
results suggest that FFR is useful in distinguishing patients who may benefit from CABG from those who may not. The event-free survival in patients with an LMCA stenosis <30% but in whom no FFR measurement was performed was lower than in patients with an equivocal stenosis and in whom FFR was >0.80. This finding suggests that late events occurring in the group with FFR >0.80 are not likely due to left main events because they occur to an even greater extent in the group with LMCA stenosis <30%.

**Angiography in Evaluating LMCA Stenoses**

In daily clinical practice and in most studies, a significant LMCA stenosis is defined by a DS ≥50%. In the EuroHeart



**Figure 4.** Relation between FFR values and the 2 reviewers' visual estimations (lesions were classified as significant, nonsignificant, and unsure).



**Figure 5.** Kaplan–Meier mortality curves showing percent survival (A) and major adverse cardiac events (MACE; B) in the 2 study groups. There is no difference between the nonsurgical and surgical groups.

survey, the presence of an LMCA stenosis was reported in 9% of all patients in whom a  $\geq 50\%$  narrowing was noticed at coronary angiography.<sup>21</sup> It is well known that angiography is a poor reflector of physiology,<sup>22,23</sup> but the LMCA is one of the most challenging lesions for the angiographer. The interobserver variability is very large.<sup>11</sup> In the present study, the interobserver concordance was only 52% (Figure 5). In addition, QCA did not perform better than visual assessment in detecting a hemodynamically significant stenosis. There may be several reasons for the discrepancy between angiographic and hemodynamic assessments of LMCA stenoses. First, the catheter may overlap with the origin of the LAD and the LCx; in addition, spillover of contrast medium and incomplete mixing of blood and contrast medium in the proximal part of the LMCA may render the evaluation of an ostial lesion difficult. Second, the LMCA is generally short, and when present, atherosclerosis is often distributed diffusely so that a normal segment is lacking. This leads to an underestimation of the “reference” segment and thus to an underestimation of LMCA stenoses by both visual estimation and QCA. Third, the myocardial mass that depends on the LMCA is large, so the amount of blood that flows through it is great. Substantial transstenotic flow, in turn, induces large

**Table 3. Univariate Cox Regression Analysis for Different Variables Potentially Related to Major Adverse Coronary Event–Free Survival in the Nonsurgical Group**

	Hazard Ratio	95% Confidence Interval	P
Hypertension	1.61	0.73–3.56	0.24
Diabetes mellitus	1.30	0.52–3.26	0.57
Previous MI	1.07	0.32–3.60	0.91
EF	0.97	0.95–0.99	0.04
No. of diseased vessels	1.53	1.04–2.25	0.03
LAD	1.66	0.75–3.66	0.21
LCx	1.35	0.60–3.03	0.46
RCA	2.46	1.10–5.47	0.027
Angina (CCS class)	1.04	0.62–1.72	0.89
DS	1	0.97–1.04	0.86
MLD	0.59	0.08–4.39	0.61
FFR	0.004	0.001–38.81	0.24

MI indicates myocardial infarction; EF, ejection fraction; CCS, Canadian Cardiovascular Society; and MLD, minimal lumen diameter.

pressure gradients, especially during hyperemia. This explains why the relationship between angiography and FFR is different in LMCA stenoses compared with most other segments of the coronary tree, in which the angiogram often tends to overestimate the actual lesion severity. Finally, revascularization strategies based solely on an angiogram are often inappropriate in patients with an LMCA stenosis. In the present study, 23% of patients had an LMCA stenosis  $\leq 50\%$  while the FFR was  $< 0.80$ . If the decision about revascularization had been made solely on the angiogram, these patients might have been denied CABG despite the presence of a hemodynamically significant stenosis. On the contrary, 6% of patients had an LMCA stenosis  $> 50\%$  while the FFR was  $\geq 0.80$ . These patients might have undergone CABG for a hemodynamically nonsignificant stenosis.

### Invasive Assessment of LMCA Stenosis

Using intravascular ultrasound (IVUS), Abizaid et al<sup>24</sup> demonstrated that minimal cross-sectional area was the most important predictor of cardiac events at 1 year. Jasti et al<sup>25</sup> found a relatively good correlation between IVUS measurements and FFR in selected patients with LMCA stenosis. In 214 patients with angiographically indeterminate LMCA stenosis, Fassa et al<sup>26</sup> reported that an IVUS-guided treatment strategy makes it possible to defer revascularization safely in patients with a nonsignificant LMCA stenosis. Accordingly, these authors reported no benefit of revascularization in patients with a minimal lumen area  $\geq 7.5$  mm<sup>2</sup>, whereas deferral of revascularization for patients with a minimal lumen area  $< 7.5$  mm<sup>2</sup> was associated with a very poor prognosis, emphasizing the need for accurate assessment of LMCA stenosis severity. Yet, IVUS is limited by calcifications and the difficulty of maintaining the catheter coaxial during pullback, which may lead to an overestimation of the size of the artery lumen. FFR does not share these limitations. FFR requires only a guidewire,<sup>27</sup> is highly reproducible,<sup>28</sup> and identifies ischemic stenoses very accurately even in angio-

graphically “intermediate” stenoses.<sup>11</sup> In addition, FFR accounts for the myocardial mass that needs to be perfused by the stenosis under study.<sup>29</sup> This implies that, in contrast to the single cross-sectional area derived from IVUS or QCA, FFR takes into account the presence of an infarcted territory distal to the stenosis and the presence of competitive flow (from collaterals or open bypass grafts).

### Limitations

The first limitation of this study is its nonrandomized design. Second, patients were included only when the left main stenosis was considered angiographically ambiguous by the operator; ie, additional functional information was needed for appropriate clinical decision making about revascularization. The subjectivity of this inclusion criteria may have led to a selection bias because the results of the present study underscore that even angiographically mild left main stenosis may be hemodynamically significant. Nevertheless, the study patients represent patients in daily clinical practice in whom the operator felt that obtaining functional information is important for clinical decision making. Third, patients with a protected LMCA stenosis were excluded. In these patients, FFR provides a reliable index of the potential of the LMCA stenosis to induce myocardial ischemia. However, the natural history of these patients is likely to be very favorable, especially with a patent internal mammary artery grafted on the LAD.<sup>30</sup> In addition, most of these patients are not candidates for redo surgery and can be treated by PCI. Fourth, stenoses present in the LAD or LCx tend to increase the FFR measured across the LMCA stenosis. The influence of an LAD and/or LCx lesion on the FFR value of the left main depends on the severity of this distal stenosis but even more on the size of the vascular territory supplied by this vessel. In the present study, patients were excluded from analysis when they obviously required surgical revascularization for a lesion other than the left main. Finally, IVUS data were not obtained. We believe that IVUS can be helpful when PCI of the left main is contemplated. However, to decide whether revascularization should be performed, FFR is more appropriate because this index integrates all morphological and physiological aspects of a stenosis.

### Clinical Implications

Given the critical prognostic importance of appropriate decision making in LMCA stenoses and the frequent underestimation of LMCA stenosis at angiography, the present clinical outcome data after an FFR-guided revascularization strategy suggest that FFR measurements should be obtained in patients with equivocal LMCA stenosis instead of “blindly” making the decision about revascularization based solely on angiography. Distinguishing the patients in whom surgery can safely be deferred and, more important, those patients in whom CABG should not be denied might improve long-term survival in these patients.

### Acknowledgment

We would like to thank Josefa Cano for her help in obtaining the follow-up data.

### Source of Funding

This work was supported by the Meijer Lavino Foundation for Cardiovascular Research.

### Disclosures

None.

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### CLINICAL PERSPECTIVE

Significant left main coronary artery stenosis is an accepted indication for surgical revascularization. Angiography alone has limited accuracy in assessing actual stenosis severity, and there is great interobserver variability in lesions of the left main coronary artery. Consequently, ambiguous left main coronary artery disease sometimes results in considerable uncertainty as to which therapeutic strategy may be best for the patient. Fractional flow reserve (FFR) can be measured at the time of coronary angiography and identifies coronary lesions responsible for ischemia. Because FFR-guided revascularization strategies are associated with favorable clinical outcomes in patients with single-vessel or multivessel disease, the main goal of this retrospective study was to evaluate the long-term clinical outcome of an FFR-guided revascularization strategy in patients with angiographically equivocal left main coronary artery stenosis. Patients with FFR  $\geq 0.80$  were treated medically or percutaneously, and patients with FFR  $< 0.80$  were treated surgically. The 5-year survival and 5-year event-free survival estimates were similar in the 2 groups. Angiographic assessment of the lesions, either by quantitative coronary angiography or by visual estimation, failed to identify the stenosis significance in almost one third of the total patient population. Angiography alone does not allow appropriate individual decision making about the need for revascularization in patients with equivocal left main coronary artery lesions and often underestimates their functional significance. FFR should be assessed in such patients before a decision is made “blindly” about the need for revascularization.