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Long-Term Follow-Up After Fractional Flow Reserve–Guided Treatment Strategy in Patients With an Isolated Proximal Left Anterior Descending Coronary Artery Stenosis

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Objectives This study sought to evaluate the long-term clinical outcome of patients with an angiographically intermediate left anterior descending coronary artery (LAD) stenosis in whom the revascularization strategy was based on fractional flow reserve (FFR).

Background When revascularization is based mainly on angiographic guidance, a number of hemodynamically nonsignificant stenoses will be revascularized.

Methods In 730 patients with a 30% to 70% isolated stenosis in the proximal LAD and no significant valvular disease, FFR measurements were obtained to guide treatment strategy. When FFR was ≥0.80, the patients (n = 564) were treated medically (medical group); when FFR was <0.80, the patients (n = 166) underwent a revascularization procedure (revascularization group; 13% coronary artery bypass graft surgery and 87% percutaneous coronary intervention). A 100% long-term clinical follow-up (median follow-up: 40 months) was obtained. The 5-year survival of the medical group was compared with that of a reference population. For each patient, 4 controls were selected from an age- and sex-matched control population.

Results The 5-year survival estimate was 92.9% in the medical group versus 89.6% in the controls (p = 0.74). The mean diameter stenosis was significantly smaller in the medical than in the revascularization group (39 ± 14% vs. 54 ± 13%, p < 0.0001), but there was a large overlap between both groups. The 5-year event-free survival estimates (death, myocardial infarction, and target vessel revascularization) were 89.7% and 68.5%, respectively (p < 0.0001).

Conclusions Medical treatment of patients with a hemodynamically nonsignificant stenosis (FFR ≥0.80) in the proximal LAD is associated with an excellent long-term clinical outcome with survival at 5 years similar to an age- and sex-matched control population. (J Am Coll Cardiol Intv 2011;4: 1175–82) © 2011 by the American College of Cardiology Foundation

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The presence of a significant narrowing in the proximal left anterior descending coronary artery (LAD) is a generally accepted indication for treatment by either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) (1–3). Several small trials have compared these modalities of revascularization in patients with isolated stenoses in the proximal LAD (4–6). The very definition of a significant stenosis is, however, rarely questioned. In most trials, the presence of a 50% diameter stenosis by visual estimate in the proximal LAD has been a sufficient criterion for the patient to be randomized. It is now widely recognized that the angiogram is a poor tool to gauge the functional significance of a coronary stenosis. When revascularization is based mainly on angiographic guidance, it is unavoidable that a number of hemodynamically nonsignificant stenoses will be revascularized, whereas a number of stenoses deemed nonsignificant will be deferred inappropriately (7–9). Fractional flow reserve (FFR) is a well-validated method to quantify the impact of a coronary stenosis on myocardial perfusion (10,11). It is based on coronary pressure measurements obtained during maximal hyperemia. FFR has a high spatial resolution (at the level of a few millimeters) and can be obtained in a few minutes in the catheterization laboratory, allowing an "on the spot" decision about the appropriateness of revascularization (8,12,13).

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CI = confidence interval
FFR = fractional flow reserve
HR = hazard ratio
LAD = left anterior descending coronary artery
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography

The aim of the present study was to assess the long-term clinical outcome of patients with an angiographically equivocal LAD stenosis and in whom the revascularization strategy was based on the FFR.

Methods

Patient population. From 1999 to 2008, 6,107 patients with stable angina underwent coronary angiography and an FFR measurement in at least 1 coronary artery at the Cardiovascular Center, Aalst, Belgium. Among them, 852 patients presented with a stenosis between 30% and 70% by visual estimate in the proximal segment of the LAD (14,15) and no other stenosis of more than 30% elsewhere in the coronary tree. Patients presenting with a concomitant noncardiac life-threatening disease (n = 35), those requiring valvular surgery (n = 42), and those in whom the referring cardiologist decided not to take the FFR value into account to guide the treatment (n = 45) were not included in the analysis. In the remaining 730 patients, when FFR was ≥0.80, patients were treated medically ("medical group," n = 564); When FFR was <0.80, patients were treated by revascularization ("revascularization group," n = 166) (Fig. 1). All demographics and baseline clinical follow-up data were retrieved from the local database.

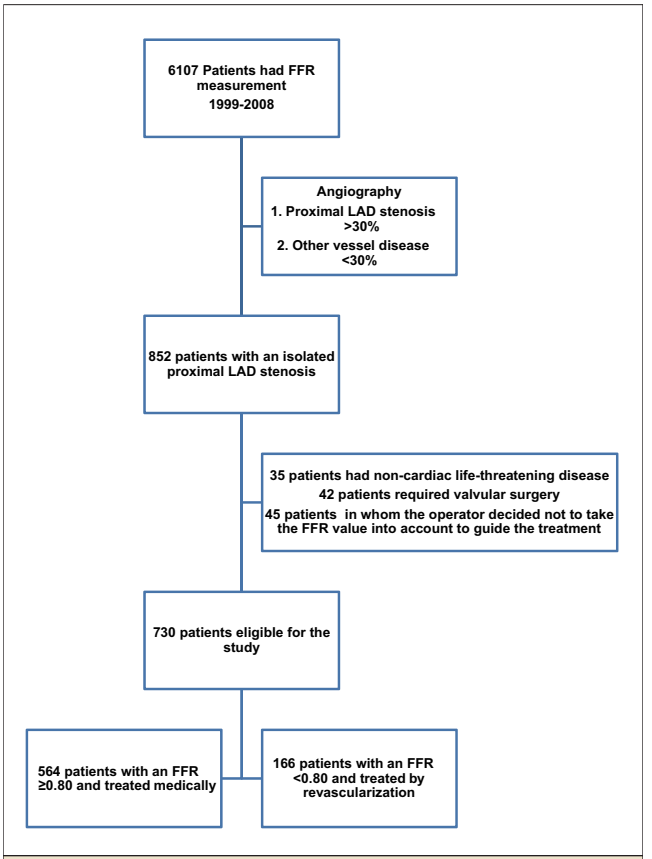

Figure 1. Flow Chart of the Study

FFR = fractional flow reserve; LAD = left anterior descending coronary artery.

Coronary angiography. Diagnostic left heart catheterization and coronary angiography were performed by a standard percutaneous femoral approach. After the diagnostic angiogram, a 6-F guiding catheter was introduced, and after administration of 200 μg of intracoronary isosorbide dinitrate, the angiogram was repeated in the projection allowing the best possible visualization of the proximal LAD stenosis.

In all patients, a visual estimate of the diameter stenosis of the proximal LAD stenosis was made by the operator. This value was used in the clinical report produced after the diagnostic angiogram. This value was also used for patient selection in the present study. In addition to this subjective analysis, quantitative analysis was obtained offline in a subset of 200 patients. Therefore, a computer-based analysis system, Siemens QuantCor QCA (ACOM.PC 5.01, Siemens Medical Systems Inc., Malvern, Pennsylvania) based

on the CAAS II system (Pie Medical Imaging, Maastricht, the Netherlands), was used. All quantitative coronary angiography (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 diameter stenosis by QCA analysis, reference diameter, and lesion length were measured preferably on end-diastolic images. 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 (16).

Pressure measurements. After administration of intravenous heparin 100 IU/kg, a pressure-monitoring guide wire (PressureWire, St. Jude Medical, Uppsala, Sweden) was calibrated and introduced into the guiding catheter. The wire was advanced up to the tip of the guiding catheter, and it was verified that the pressure measured by the pressure-monitoring guide wire was equal to the pressure measured by the guiding catheter. Next, the wire was advanced into the LAD until the pressure sensor was located in the mid to distal part of the LAD. Adenosine was administered to induce maximum hyperemia, either intravenously (140 μg/kg/min) or by intracoronary bolus (50 to 150 μg). Fractional flow reserve was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure-monitoring guide wire to mean aortic pressure measured by the guiding catheter. The measurement was performed twice, and FFR was taken as the average of both measurements.

Clinical follow-up. Patients were sent a written questionnaire to report their clinical events. When needed, patients and/or their general practitioners were contacted by phone for additional information. If no satisfactory answer was obtained, information was obtained from the Belgian national population registry. Major adverse events were death from any cause, nonfatal myocardial infarction, or the need for revascularization of the LAD (either by CABG or by PCI). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

The 5-year survival in the medical group was compared with the survival of an age- and sex-matched reference population, namely the Rotterdam Study. The characteristics of this population are described in details elsewhere (17). In brief, the Rotterdam Study is a prospective cohort study ongoing since 1990 in the city of Rotterdam in the Netherlands. The objective of the Rotterdam Study is to study the incidence and risk factors of a variety of diseases, such as cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, and respiratory. As of 2008, 14,926 subjects, age 45 years or older, comprise the Rotterdam Study cohort. The Rotterdam Study cohort was chosen as a reference population, primarily because this cohort guarantees complete follow-up, including death. Second, health care and clinical practice are similar in the Netherlands and in Belgium, which is crucial to compare survival. For each patient from the Aalst medical group, we considered age and sex at study entry, and randomly selected 4 controls from the Rotterdam Study, matched by age and sex.

Statistical analysis. All analyses were performed with GraphPad Prism software, version 5 (GraphPad Software, La Jolla, California) and SPSS software, version 16.0 (SPSS/IBM, Armonk, New York). Summary descriptive statistics are reported as mean (SD) or counts (%), as appropriate. Continuous variables were compared between the 2 groups by independent samples *t* tests, and categorical variables were compared with Fisher exact or chi-square tests, as appropriate. The dependent variable in the analysis was time to first event during follow-up. Kaplan-Meier product limit curves for survival and major cardiac event-free survival were constructed and compared between the medical and the revascularization groups with the log-rank test. For the medical group of patients, Kaplan-Meier curves were also constructed and log-rank compared to provide a univariate assessment of the prognostic value of selected clinical and angiographic potential risk-factors. Variables with $p < 0.2$ at the univariate level were tested multivariately with a stepwise Cox proportional hazards regression model to determine which ones contain independent prognostic information. The thresholds for entry into and removal from the model were 5% and 10%, respectively. A conditional Cox regression analysis was conducted to calculate the hazard ratio of dying for the Aalst versus the Rotterdam population. All statistical tests were carried out at the 5% level of significance.

Results

Baseline clinical and angiographic characteristics. There were no differences in baseline clinical characteristics between the 2 groups except for sex and smoking habits (Table 1).

Angiographic and hemodynamic data. Figure 2 shows the correlation between the FFR values and the diameter stenosis as assessed by either visual estimate (Fig. 2A) or QCA (Fig. 2B). Mean FFR was 0.87 ± 0.05 in the medical group and 0.71 ± 0.08 in the revascularization group. The mean diameter stenosis assessed by visual estimate was significantly lower in the medical group (39.8 ± 10.4%) than in the revascularization group (54.0 ± 12.1%, $p < 0.0001$), but a large overlap of the values was present between the 2 groups. The mean diameter stenosis by QCA was also significantly lower in the medical group (38.5 ± 14.2%) than in the revascularization group (54.4 ± 12.6%, $p < 0.0001$), but the overlap between hemodynamically significant and nonsignificant stenoses was markedly less pronounced than for visual estimate. In the medical group,

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Table 1. Baseline Clinical Characteristics and Stenosis Characteristics of the Patients in the Medical Group and the Revascularization Group

	Medical Group (n = 564)	Revascularization Group (n = 166)	p Value
Age, yrs	68.7 ± 10.9	67.4 ± 10.1	0.207
Male	55%	76%	<0.0001
BMI, kg/m^2	26.8 ± 4.4	26.9 ± 4.1	0.747
Diabetes	16.8%	18.7%	0.641
Smoking habits	35.3%	45.8%	0.018
Hyperlipidemia	57.6%	58.4%	0.929
Hypertension	50.5%	48.8%	0.66
Family history of CAD	5.7%	8.4%	0.207
Aspirin	75.5%	87.8%	0.117
Statin	63.3%	61.2%	0.834
Beta-blockers	53.1%	57.1%	0.684
ACE-inhibitors/ARB	32.7%	38.8%	0.527
CCS class	1.8 ± 0.9	2.0 ± 1	0.164
NYHA functional class	1.5 ± 0.8	1.3 ± 0.9	0.235
LVEF	70.6% ± 13.6%	68.8% ± 15.1%	0.227
<30%	2.5%	1.9%	
30%–50%	8.5%	7.1%	
>50%	89.0%	91.0%	
LVEDP, mm Hg	15.4 ± 8.4	14.9 ± 6.2	0.504
Diameter stenosis	39.8% ± 10.4%	54.0% ± 12.1%	
Range	30%–70%	30%–90%	<0.0001
30%–50%	77.3%	23.6%	
50%–70%	22.6%	76.4%	
Pa, mm Hg	93.6 ± 17.8	90.7 ± 17.	70.07
Pd, mm Hg	82.2 ± 17.0	64.6 ± 14.5	<0.0001
FFR	0.87 ± 0.05	0.71 ± 0.08	

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; FFR = fractional flow reserve; FU = follow-up; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; *Pa* = mean aortic pressure; *Pd* = mean pressure distal to the stenosis.

127 patients (23%) had a diameter stenosis ≥50%. The sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of ≥50% diameter stenosis by visual estimate to predict an FFR value <0.80 were 77%, 73%, 45%, 92%, and 74%, respectively. The sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of ≥50% diameter stenosis by QCA analysis were 68%, 80%, 55%, 87%, and 77%, respectively.

Clinical follow-up. The 5-year survival estimates were similar for patients in the medical group and for age- and sex-matched controls (92.9% vs. 89.6%, respectively, p = 0.74). The hazard ratio (HR) of dying for the Rotterdam population versus the Aalst population was not statistically significant (HR Aalst: 1.03, 95% confidence interval [CI]: 0.68 to 1.57, p = 0.87) (Fig. 3).

In the revascularization group, 13% had CABG and 87% had PCI (25% using drug-eluting stents). Complete follow-up was obtained in 100% of patients for survival and 97% for event-free survival. The median follow-up for the survival endpoint was 39 ± 18 months in the medical group and 37 ± 19 months in the revascularization group (p = 0.342). The mean follow-up for survival free from major adverse cardiac events (MACE) was 38 ± 18 months in the medical group and 36 ± 19 months in the revascularization group (p = 0.25).

In the medical group, 30 (5.3%) patients died during follow-up. There were 2 (0.4%) myocardial infarctions, and 11 (2.0%) patients needed revascularization. In the revascularization group, 16 (9.6%) died during follow-up, there were 2 (1.2%) myocardial infarctions, and 26 (15.9%) patients needed revascularization. The Kaplan-Meier percent survival estimates at 5 years were 92.9% in the medical group and 87.4% in the revascularization group (p = 0.03) (Fig. 4A). The Kaplan-Meier percent survival free of death or myocardial infarction estimate at 5 years was 92.0% in the medical group versus 84.9% in the revascularization group (Fig. 4B). The Kaplan-Meier percent survival free of death, myocardial infarction, or target vessel revascularization estimate at 5 years was 89.7% in the medical group versus 68.5% in the revascularization group (p = 0.0019) (Fig. 4C). By multivariate analysis, age emerged as the only independent predictive factor for MACE (HR: 1.039, 95% CI: 1.005 to 1.073; log-rank p = 0.023) in the medical group. For the revascularization group, diabetes was the only significant independent predictive factor for MACE (HR: 2.88, 95% CI: 1.01 to 8.21; log-rank p = 0.048), age was at the limit of significance (HR: 1.05, 95% CI: 0.99 to 1.11; log-rank p = 0.065).

Among the 564 patients in the medical group, 127 (23%) had a diameter stenosis ≥50% by visual estimate. Their Kaplan-Meier percent survival estimate free of events at 5 years was similar to that in patients with a proximal LAD diameter stenosis <50% (92.1% vs. 88.8%, respectively, p = 0.42) (Fig. 5).

Discussion

This study indicates that patients with an angiographically dubious, but hemodynamically nonsignificant, isolated stenosis in the proximal LAD (as assessed in the catheterization laboratory by FFR measurements) have a favorable long-term outcome without mechanical revascularization. Indeed, patients with an FFR ≥0.8 in an isolated proximal LAD stenosis have a 92.0% survival estimate at 5 years.

This 92.0% survival estimate is comparable to that observed in age- and sex-matched control individuals. We observed 30 deaths (all-cause mortality) in the medical group during the mean follow-up of 39 months, which corresponds to an annual death rate of 1.63%. This value is similar to the 1.5% annual death rate recently reported in individuals without known coronary artery disease but with multiple risk factors (≥3) (17).

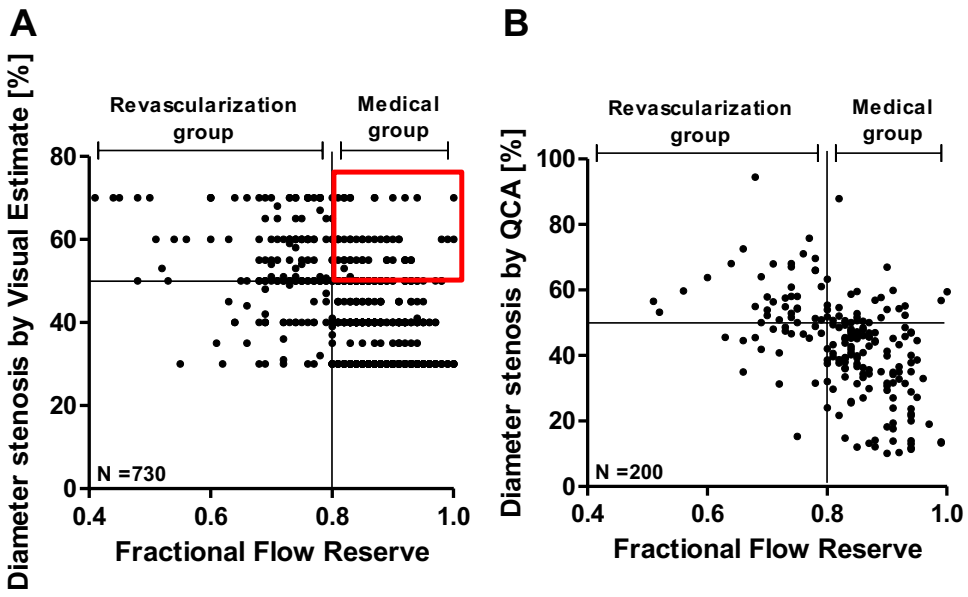
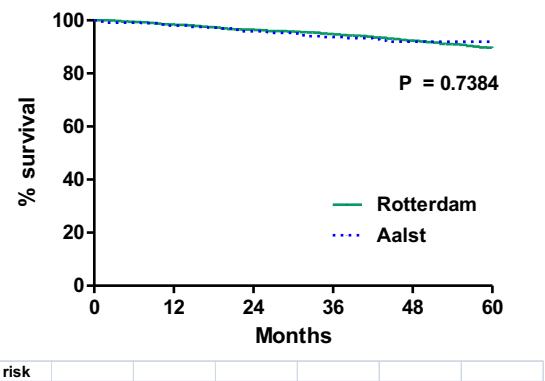


Figure 2. Comparison Between Anatomic and Functional Assessment of Proximal CAD

Fractional flow reserve (FFR) and diameter stenosis were assessed by visual estimate (Pearson correlation $r = -0.49$, $p < 0.0001$) **(A)** or by quantitative coronary angiography (QCA) (Spearman correlation $r = 0.51$, $p < 0.0001$) **(B)**. In the medical group, 127 patients (23%) had a diameter stenosis ≥50% **(red square)**.

In the present study, the survival free of MACE (all-cause mortality, myocardial infarction, and target vessel revascularization) of patients in the medical group was 89.7%. This value is higher than in similar patients but with a hemodynamically significant stenosis (FFR <0.80) and in whom revascularization was performed.

The present study extends the data of the randomized controlled DEFER trial in which patients with a hemodynamically nonsignificant stenosis were randomized to receive PCI or to be treated medically. The trial showed no superiority of PCI over conservative treatment in patients with 1-vessel disease and a hemodynamically nonsignificant stenosis (9). The present data extend the results of the DEFER trial because the number of patients with a nonsignificant stenosis is almost 6 times larger than in DEFER and because more than 10 times the number of patients with a proximal LAD were included. Hamilos et al. (16) showed that when angiographically equivocal left main coronary artery stenoses are hemodynamically nonsignificant, the clinical outcome is favorable without CABG. The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial also indicated that in patients with multivessel disease, PCI with drug-eluting stents that were restricted only to stenoses able to induce myocardial ischemia was associated with an approximately 30% reduction in death, myocardial infarction, and/or the need for a new revascularization after 1 and 2 years (8,13).



No at risk						
Aalst	466	410	341	262	173	109
Rotterdam	1868	1839	1803	1772	1725	1675

Figure 3. Kaplan-Meier Estimates for the Medical and Control Group

Patients in the medical group are compared with age- and sex-matched individuals from the Rotterdam Study (17).

Clinical practice guidelines currently recommend revascularization when stress testing reveals myocardial ischemia. Therefore, assessing the presence or absence of myocardial ischemia by stress electrocardiography or imaging remains central to determine the appropriateness of revascularization therapy in patients with stable coronary artery disease (1,18). This approach is justified by studies demonstrating that a patient's outcome depends on the presence and extent of ischemia (19,20). In addition, the outcome benefit from revascularization therapy is proportional to the presence and

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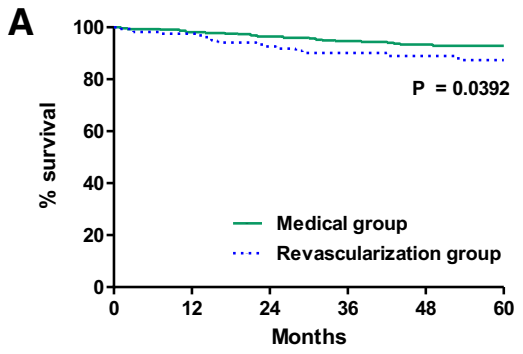
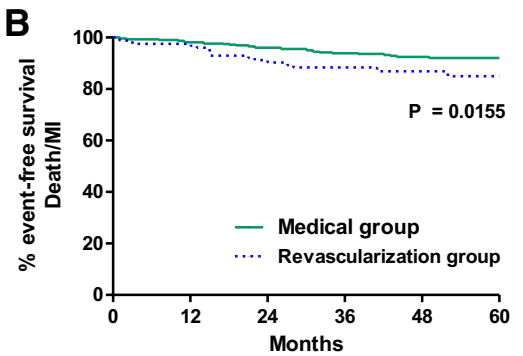
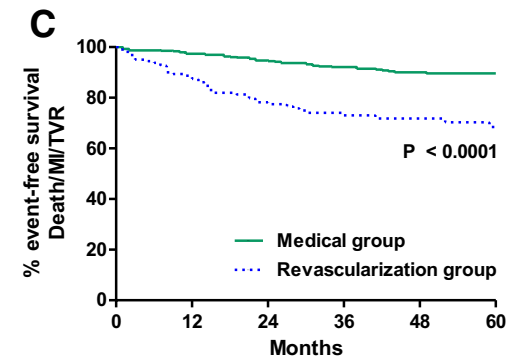


No at risk						
Medical group	564	503	423	332	220	140
Revasc. group	166	150	118	88	66	44



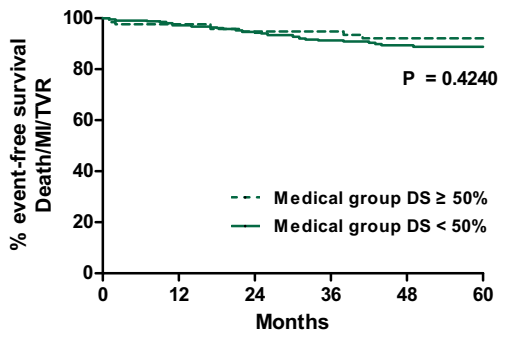
No at risk						
Medical group	544	480	398	309	207	129
Revasc. group	164	135	98	71	50	37



No at risk						
Medical group	544	480	398	309	207	129
Revasc. group	164	135	98	71	50	37

Figure 4. Kaplan-Meier Estimates for the Medical and the Revascularization Group

Shown are percent survival **(A)**, percent survival free from death or myocardial infarction **(B)**, and survival free of major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) **(C)**.



No at risk						
Medical gr. DS < 50%	417	364	307	232	140	87
Medical gr. DS ≥ 50%	127	116	91	77	53	42

Figure 5. Kaplan-Meier Estimates in the Medical Group According to Percent Diameter Stenosis

Patients with a fractional flow reserve >0.80 are compared according to the percent diameter stenosis (DS) by visual estimate.

extent of demonstrable ischemia before intervention (21,22). Despite the apparent central role of ischemia, data derived from privately insured patients' insurance-claims databases or Medicare databases have shown that more than 50% of patients with stable coronary artery disease lack an objective definition of ischemia by noninvasive testing before PCI (23,24). This disconnect between recommendation and clinical practice is not necessarily probative of misutilization (25). Indeed, in daily practice, a variety of clinical factors limit the feasibility and the spatial accuracy—and therefore the clinical usefulness—of noninvasive stress testing. These factors, rarely acknowledged in trials and meta-analyses, include obesity, advanced age, orthopedic problems, the presence of a bundle branch block, decreased left ventricular function, diffuse disease, the coexistence of valvular disease, the presence of left ventricular hypertrophy, or a prior myocardial infarction. These factors certainly contribute to the fact that a sizable proportion of patients undergo coronary angiography before functional testing. The latter may come second and, in many patients, will never come at all. FFR makes it possible to obtain both anatomic and functional data during the same examination (catheterization session).

After the left main coronary artery, the proximal LAD is the segment with the largest distribution area. It is therefore generally accepted that the presence of a stenosis in the proximal LAD weighs more in the prognosis than any other coronary segment (15,26). The presence of a narrowing of more than 50% luminal reduction in the proximal segment of the left anterior coronary artery often triggers a revascularization procedure (18,27). Hannan et al. (28) showed that approximately one-third of multivessel disease patients indicated for CABG according to the guidelines, actually received PCI. Yet, the presence of a stenosis in the proximal LAD often tipped the balance toward CABG (28,29). The present data also confirm the very poor relationship between the angiographic appearance of a coronary stenosis and its hemodynamic significance (16,30,31). Almost one-half of the stenoses gauged by visual estimate to be between 50% and

70% were hemodynamically nonsignificant, whereas 10% of lesions between 30% and 50% were hemodynamically significant. On top of the intrinsic inaccuracies of the angiogram, the latter morphological approach of vessel dimension does not take into account the myocardial mass supplied by the vessel: a similar degree of stenosis at angiography will have a different functional significance depending on the extent of perfused myocardial mass. In contrast, pressure-derived FFR measurements integrate both vessel anatomy and myocardial mass, as well as the contribution of collateral circulation. Practically, this indicates that when revascularization is based mainly on angiographic guidance, it is unavoidable that a number of hemodynamically nonsignificant stenoses will be revascularized, whereas a number of stenoses deemed nonsignificant will be deferred inappropriately (7–9,32).

Study limitations. This observational study has the limitations inherent to nonrandomized trials. The comparison was made between 2 patient populations in whom the treatment strategy was different and determined upfront by the measurement of FFR. The study does not indicate that the decision to revascularize stenoses with an FFR lower than 0.80 was justified. However, during the recruitment period (1999 to 2008), we felt it inappropriate not to propose revascularization to patients presenting with complaints and a hemodynamically significant stenosis in the proximal LAD.

Another caveat is that only a very low number (5.8%) of patients with non–myocardial infarction acute coronary syndromes are included. The conclusions should, therefore, be restricted to patients with stable coronary artery disease. Outcomes regarding different routes of adenosine administration also are not provided.

Finally, a large number of patients with a stenosis of <50% were included in this registry, although in these stenoses, revascularization is generally not contemplated. Yet, the data show, on the contrary, that in a large artery such as the proximal LAD, the angiogram often underestimates the true severity of the stenosis.

Conclusions

In patients with an isolated stenosis in the proximal LAD that is angiographically equivocal but unable to induce myocardial ischemia as assessed by FFR, medical treatment is associated with a favorable clinical outcome after 3 to 5 years. This finding supports the strategy of deciding about revascularization based on both anatomic and functional information obtained simultaneously in the catheterization laboratory.

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Key Words: fractional flow reserve ■ proximal left anterior descending coronary artery ■ myocardial ischemia.