Outcome Impact of Coronary Revascularization Strategy Reclassification With Fractional Flow Reserve at Time of Diagnostic Angiography

Insights From a Large French Multicenter Fractional Flow Reserve Registry

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Background—There is no large report of the impact of fractional flow reserve (FFR) on the reclassification of the coronary revascularization strategy on individual patients referred for diagnostic angiography.

Methods and Results—The Registre Français de la FFR (R3F) investigated 1075 consecutive patients undergoing diagnostic angiography including an FFR investigation at 20 French centers. Investigators were asked to define prospectively their revascularization strategy a priori based on angiography before performing the FFR. The final revascularization strategy, reclassification of the strategy by FFR, and 1-year clinical follow-up were prospectively recorded. The strategy a priori based on angiography was medical therapy in 55% and revascularization in 45% (percutaneous coronary intervention, 38%; coronary artery bypass surgery, 7%). Patients were treated according to FFR in 1028/1075 (95.7%). The applied strategy after FFR was medical therapy in 58% and revascularization in 42% (percutaneous coronary intervention, 32%; coronary artery bypass surgery, 10%). The final strategy applied differed from the strategy a priori in 43% of cases: in 33% of a priori medical patients, in 56% of patients undergoing a priori percutaneous coronary intervention, and in 51% of patients undergoing a priori coronary artery bypass surgery. In reclassified patients treated based on FFR and in disagreement with the angiography-based a priori decision (n=464), the 1-year outcome (major cardiac event, 11.2%) was as good as in patients in whom final applied strategy concurred with the angiography-based a priori decision (n=611; major cardiac event,11.9%; log-rank, *P*=0.78). At 1 year, >93% patients were asymptomatic without difference between reclassified and nonreclassified patients (Generalized Linear Mixed Model, *P*=0.75). Reclassification safety was preserved in high-risk patients.

Conclusion—This study shows that performing FFR during diagnostic angiography is associated with reclassification of the revascularization decision in about half of the patients. It further demonstrates that it is safe to pursue a revascularization strategy divergent from that suggested by angiography but guided by FFR. (***Circulation*. 2014;129:173-185.**)

Key Words: coronary angiography ■ coronary artery disease ■ fractional flow reserve ■ mortality ■ outcome assessment (health care)

Recent studies have demonstrated that additional diagnostic information is needed to choose the most appropriate therapy for patients who have coronary artery disease.[1] In particular, the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[2] have demonstrated that to perform a coronary revascularization by

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angioplasty based on the presence of a significant coronary artery disease (CAD) by angiography was not sufficient to provide meaningful clinical benefit to the patient.

Clinical Perspective on p 185

Accumulated evidence suggests that intracoronary physiology, in particular, fractional flow reserve (FFR), could be useful to help in selecting the appropriate therapy. Recent data suggest that FFR can be useful in guiding coronary revascularization in patients referred for a percutaneous coronary intervention (PCI) procedure (DEFER, Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME], Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 [FAME2]).[3–5] Currently, there is no report of the use of FFR in patients referred for diagnostic angiography, of its impact on the decision of coronary revascularization for the global population and for individual patients, and on the safety of this approach.

The R3F registry (Registre Français de la FFR) is the largest nationwide clinical FFR registry including patients with at least 1 ambiguous coronary lesion (n=1075). It was designed to evaluate the rate of reclassification of the patient coronary revascularization strategy by performing FFR at the time of diagnostic angiography, and its impact on 1-year clinical outcome, as well. A deciphered analysis of the role of FFR in the decision-making process leading to patient coronary revascularization was also preformed.

Methods

Patient Population

The R3F registry was designed to include 1000 consecutive patients with at least 1 angiographically ambiguous lesion (35%–65% by visual estimate) in a major epicardial coronary vessel evaluated by FFR at 20 French centers (October 2008 to June 2010). Baseline clinical and angiographic parameters were prospectively recorded in an e-CRF (Clinigrid). The performance and results of noninvasive tests to detect myocardial ischemia/CAD (stress ECG, stress single-photon emission computed tomography, stress echocardiography, stress magnetic resonance imaging, or computed tomography scan) before angiographic evaluation was also recorded. The research protocol was approved by relevant institutional review boards or ethics committees and by the Commission National Informatique et Liberté. All patients provided written informed consent to clinical follow-up and to storage and use of their clinical data.

Patient Definition and Recording of Baseline Characteristics

Hypertension was defined as a known blood pressure >140/90 mm Hg or use of antihypertensive drugs. Smoking was defined as acknowledged ceased/unceased smoking. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, use of hypoglycemic agents, or a history of physician-diagnosed diabetes mellitus. Family history of premature CAD was defined as CAD in a male first-degree relative <55 years of age or CAD in a female first-degree relative <65 years of age.

Clinical instability was defined as the occurrence of an acute coronary syndrome (ST-elevation myocardial infarction/non–ST-elevation myocardial infarction) within 15 days of the index procedure.

Angiography Procedure

Angiography was performed according to standard practice. Qualitative description of the angiography, including the number of diseased vessels was performed. Qualitative (American College of Cardiology/American Heart Association) and quantitative (reference diameter, minimal luminal diameter, percent stenosis, length) description of the FFR-investigated lesions were performed. A proximal lesion was defined as a lesion occurring in the first segment of each coronary vessel or in the left main coronary artery.

FFR Procedure

The FFR procedure was performed after the recording of angiographic parameters and was performed according to local standard practice. FFR could be done by the use of diagnostic or interventional catheters, and the number of investigated lesion(s) was not limited. Hyperemia was achieved by using adenosine administered through intracoronary bolus or intravenous infusion. The use of a high dose of adenosine (>100 μg as an intracoronary bolus) and of a decision cutoff of 0.8 were recommended.

Revascularization Strategy and Reclassification

As part of the e-CRF, investigators were asked to define prospectively their patient revascularization strategy a priori based on angiography alone before performing the FFR measurement and then, after the FFR measurement was performed, to define their final patient revascularization strategy decided once the FFR was performed. The use (or not=disregard) of the FFR information to achieve the final decision regarding coronary revascularization was also prospectively recorded.

This decision could be medical therapy, PCI, or coronary artery bypass surgery (CABG). Patients in whom a hybrid approach was chosen were classified as CABG. When a final decision of revascularization was reached for the patient, it could be performed immediately (PCI) or at a later stage (PCI or CABG).

Reclassification of the patient revascularization strategy was defined as a difference between the revascularization strategy a priori and the final revascularization strategy decided after performing the FFR measurement.

Clinical Follow-Up and End Points

Clinical follow-up was conducted and obtained in all patients at a median of 379 days (interquartile range, 368–413 days). Independent monitoring was performed. Angina status was obtained at 1, 6, and 12 months follow-up. Death, myocardial infarction, coronary revascularization, and stroke were adjudicated by an independent clinical event committee. All deaths were considered cardiovascular unless an unequivocal noncardiac cause could be established. Spontaneous and periprocedural myocardial infarction were recorded (see online-only Data Supplement for details). Revascularization was considered planned when it was decided at the time of the index procedure. It could be performed during the index procedure or at a later stage (within 60 days). Revascularization was considered unplanned when it was not performed as part of the index procedure or identified at the time of the index procedure. The planned/unplanned status of the revascularization was adjudicated.

The occurrence of a major cardiac event (MACE) was defined by the occurrence of death, myocardial infarction, or unplanned coronary revascularization.

Objectives

The primary objectives were (1) to describe the rate of reclassification of the patient's coronary revascularization strategy by an intention to use FFR in patients referred for coronary angiography; and (2) to evaluate the safety of reclassification of the patient coronary revascularization strategy by an intention-to-use FFR. Evaluation of the safety of reclassification of the revascularization strategy was done by comparing the occurrence of MACE in patients in whom the final revascularization strategy after performing the FFR was divergent from that suggested by angiography with the occurrence of MACE in patients in whom the final revascularization strategy was concordant to the one suggested by angiography.

Secondary objectives were (1) to evaluate the safety of reclassification on angina status during follow-up, (2) to evaluate the proportion and the outcome of patients in whom the results of the FFR measurement were disregarded by the investigators to achieve the final patient revascularization strategy; (3) to evaluate the safety of reclassification of the coronary revascularization strategy after performing FFR as an per use approach. This was evaluated by repeating the above analysis after the exclusion of patients in whom the FFR results were disregarded by the investigators; (4) analysis of the predictors of the a priori revascularization strategy for the patient; (5) analysis of the predictors of FFR used as a continuous variable; (6) analysis of the predictors of changes in revascularization strategy for the patient, including or not including FFR information.

Role of the Sponsors

The sponsors were responsible for data collection and data monitoring. Data analysis was performed under the instruction of the authors (E.V.B., P.D., and G.R.). The sponsor of the study had no role in data interpretation or writing of the report. The corresponding authors had full access to all the data and had final responsibility for the decision to submit for publication.

Statistical Analysis

Continuous variables are presented as mean±standard deviation, and continuous variables with skewed distribution are presented as median values (interquantile range). Discrete variables are presented as absolute numbers and percentages. For patient-related characteristics, differences among groups were evaluated using the *t* test, Wilcoxon rank sum test, or χ^2 test as appropriate. For lesion-related characteristics, to take into account the clustering within each patient, differences among groups were evaluated with the use of a mixed-effects model with fixed effect for lesion level and random effect, the intercept for patients. A Bonferroni correction was used for multiple testing.

The impact of the use of FFR on the change of revascularization choice (medical, PCI, CABG) was evaluated by the κ-statistics and the Bowker-McNemar test. Cumulative mortality rates were estimated with the Kaplan-Meier method and differences were tested with a log-rank test. The impact of reclassification by FFR on angina status during follow-up was evaluated by a Generalized Linear Mixed Model with fixed effect for time, reclassification status, and their interaction term and random effect for patients.

Univariable (multivariable) correlates of revascularization strategy or change of revascularization strategy were estimated by using an ordinal univariable (multivariable) logistic regression analysis. For that purpose, the dependent variable revascularization strategy was ordered: CABG>PCI>medical therapy. Similarly, the dependent variable change of revascularization strategy was categorized in 5 ordered grades: upgrade of strategy by 2 levels (eg, patients reclassified from medical treatment to CABG)>upgrade of strategy by 1 level (eg, patients reclassified from medical treatment to PCI or from PCI to CABG)>no change in strategy (patients not reclassified)>downgrade of strategy by 1 level (eg, patients reclassified from PCI to medical treatment or from CABG to PCI)>downgrade strategy by 2 levels (eg, patients reclassified from CABG to medical treatment). A multivariable linear regression analysis was performed to study the relationship between FFR and multiple categorical and continuous determinants. For multivariable analyses, all parameters with a $P<0.10$ by univariable analysis were entered in the models. To allow comparison between the models, when a parameter was entered in 1 model it was also entered in the others. For multivariable analyses including both patient- and lesion-related parameters, only 1 randomly chosen lesion per patient was included in the model. In addition, systematic adjustment for sex, participating centers (19 binary variables) was conducted.

All hypotheses were 2-tailed with a 0.05 type I error rate. Analyses were conducted using SPSS 17.0 (Chicago, IL) and the SAS system (SAS v9.2; SAS-Institute, Cary, NC).

Results

Clinical Characteristics of the Study Population

Seventy-five percent of the patients were men. Mean age was 65±11 years, 37% had diabetes mellitus (including 122 requiring insulin therapy), 46% had a previous MACE including 25% having had a previous myocardial infarction and 40% having a previous history of coronary revascularization (Table 1).

Eighty-one percent were in stable condition, whereas 19% had a recent acute coronary syndrome while LVEF was preserved (≥50%) in ≈80% of patients (Table 1). A noninvasive ischemic test had been performed in 61% of patients. Patients had nonsignificant (<50% stenosis) angiographic CAD (14%), significant (>50%) angiographic 1-vessel (39%), 2-vessel (28%), or 3-vessel disease (19%; Table 2).

Procedural and Angiographic Characteristics

In each patient, a mean of 1.32±0.66 (median, 1; range, 1–4) lesions were investigated by FFR (Table2). Most of the procedures were done through the radial approach (68%), with the use equally of 5F or 6F and diagnostic or intervention catheters (Table I in the online-only Data Supplement). Adenosine was almost exclusively administered intracoronary (intracoronary bolus, 99.2%) with the use of a high-dose (>100 µg) bolus (Table I in the online-only Data Supplement).

In most of the cases, the investigated lesion was located on the left anterior descending artery (LAD; 58%). The investigated lesion was proximally located in 35% of cases and was a typically ambiguous lesion as illustrated by a mean percent stenosis of 52%, a mean length of 13 mm, and a mean FFR of 0.82.

Strategy of Revascularization and Reclassification by FFR

The strategy a priori based on angiography alone was medical therapy in 55% and revascularization in 45% (PCI, 38%; CABG, 7%; Figure 1). The final strategy applied according to FFR measurements was medical therapy in 58% and revascularization in 42% (PCI, 32%; CABG, 10%; Bowker-McNemar test, $P=0.02$; Figure 1). However in individual patients, the final strategy based on the results of the FFR was different and reclassified from the strategy a priori in 43% of the cases (κ, 0.22; 95% confidence interval, 0.17–0.27; n=464; Table 1 and Figure 2A). Such reclassification was observed in 33% of a priori medical patients, in 56% of a priori PCI patients, and in 51% of a priori CABG patients (Figure 2B). Similar figures were observed when the 54 patients in whom the FFR results were actually disregarded by the investigators were excluded from the analysis (Table 1 and Figure I in the online-only Data Supplement).

Results of Noninvasive Tests and Revascularization Strategy

No test was performed in 38.6% of patients, 4.4% of patients had a negative test, 8.9% patients had a dubious test, and 48.1% had a positive test (Table 1). Among patients in whom a noninvasive test was performed (61.4%), the result of the test had a significant impact on the revascularization strategy

Table 1. Baseline Clinical Patient Characteristics According to Reclassification of the Patient Revascularization Strategy

Patients, n (%)	Total Population (N=1075)	Total Nonreclassified (n=611)	Total Reclassified (n=464)	*P* Value	FFR Disregarded (n=47)	FFR Used for Decision: Nonreclassified *P* Value	FFR Used for Decision: Reclassified (n=441)	*P* Value*	*P* Value†
Clinical characteristics									
Age, y	64.7±10.7	65.1±10.8	64.2±10.6	0.30	64.9±10.8	65.2±10.8	64.2±10.6	0.82	0.30
Sex, male	809 (75.3)	458 (75.0)	351 (75.6)	1.00	33 (70.2)	438 (74.6)	338 (76.6)	1.00	1.00
Family history of CAD	242 (23.5)	117 (20.1)	125 (28.0)	0.29	11 (24.4)	113 (20.2)	118 (27.8)	0.80	0.18
Smokers	577 (53.7)	323 (52.9)	254 (54.7)	1.00	22 (46.8)	314 (53.5)	241 (54.7)	1.00	1.00
Hypertension	704 (65.5)	402 (65.8)	302 (65.1)	1.00	31 (66.0)	388 (66.1)	285 (64.6)	1.00	1.00
Dyslipidemia	695 (64.6)	383 (62.7)	312 (67.2)	0.48	29 (61.7)	369 (62.9)	297 (67.4)	1.00	0.54
Diabetes mellitus	385 (35.8)	213 (34.8)	172 (37.1)	1.00	13 (27.7)	206 (35.1)	166 (37.6)	0.67	1.00
Previous MI	271 (25.2)	144 (23.6)	127 (27.4)	1.00	16 (34.0)	135 (23.0)	120 (27.2)	0.40	1.00
Previous PCI	419 (39.0)	232 (38.0)	187 (40.3)	1.00	23 (48.9)	220 (37.5)	176 (39.9)	0.38	1.00
Previous CABG	39 (3.6)	21 (3.4)	18 (3.9)	1.00	1 (2.1)	20 (5.6)	18 (6.2)	1.00	1.00
Medications									
β-Blockers	669 (62.2)	370 (60.6)	299 (64.4)	0.58	37 (78.7)	352 (60.0)	280 (63.5)	0.05	0.75
ACE inhibitors	535 (49.8)	278 (45.5)	257 (55.4)	0.004	18 (38.3)	270 (46.0)	247 (56.0)	0.32	0.005
Statins	827 (76.9)	457 (74.8)	370 (79.7)	0.17	41 (87.2)	436 (74.3)	350 (79.4)	0.25	0.17
Aspirin	850 (79.1)	481 (78.7)	369 (79.5)	1.00	37 (78.7)	462 (78.7)	351 (79.6)	1.00	1.00
ADP antagonists	697 (64.8)	382 (62.5)	315 (67.9)	0.20	34 (72.3)	365 (62.2)	298 (67.6)	0.81	0.22
Clinical status									
Stable	865 (80.5)	486 (79.5)	379 (81.6)	0.38	35 (74.4)	470 (80.1)	360 (81.6)	0.28	0.53
Angina	248 (23.1)	140 (22.9)	108 (23.2)		12 (25.5)	134 (22.8)	102 (23.1)		
Class I	31 (2.9)	17 (2.8)	14 (3.0)		1 (2.1)	16 (2.7)	14 (3.1)		
Class II	166 (15.4)	98 (16.0)	68 (14.6)		8 (17.0)	96 (16.3)	62 (14.1)		
Class III	44 (4.1)	21 (3.4)	23 (5.0)		3 (6.4)	18 (3.1)	23 (5.2)		
Class IV	7 (0.7)	4 (0.7)	3 (0.6)		0 (0)	4 (0.7)	3 (0.7)		
Atypical	114 (10.6)	83 (13.6)	31 (6.7)		5 (10.6)	81 (13.8)	28 (6.4)		
No pain	503 (46.8)	263 (43.0)	240 (51.7)		18 (38.3)	255 (43.5)	230 (52.1)		
Unstable:	210 (19.5)	125 (20.5)	85 (18.3)		12 (25.5)	117 (19.9)	81 (18.4)		
Recent STEMI	36 (3.3)	24 (3.9)	12 (2.6)		1 (2.1)	23 (3.9)	12 (2.7)		
Recent non-STEMI	174 (16.2)	101 (16.5)	73 (15.7)		11 (23.4)	94 (16.0)	69 (15.6)		
Performance of noninvasive ischemic test									
Total performed:	660 (61.4)	373(61.1)	287 (61.9)	0.65	28 (59.6)	356 (60.7)	276 (62.6)	0.70	0.68
Stress ECG	256 (23.8)	149(24.4)	107 (23.6)		12 (25.5)	144 (25.0)	10 (23.4)		
Stress SPECT	195 (18.1)	117(19.1)	78 (16.8)		7 (14.8)	115 (19.5)	74 (13.4)		
Stress echocardiography	136 (12.7)	71(11.6)	65 (14.0)		4 (8.5)	69 (11.6)	63 (14.3)		
Not performed	41 5(38.6)	238(39.0)	177 (38.2)		19 (40.4)	231 (39.4)	165 (37.4)		
Results of noninvasive ischemic test									
Positive	517 (48.1)	287 (47.0)	230 (49.6)	1.00	22 (46.8)	272 (46.3)	223 (50.6)	1.00	0.63
Dubious	96 (8.9)	62 (10.2)	34 (7.3)		5 (10.6)	60 (10.2)	31 (7.0)		
Negative	47 (4.4)	24 (3.9)	23 (5.0)		1 (2.1)	24 (4.1)	22 (5.0)		
Not performed	415 (38.6)	238 (39.0)	177 (38.2)		19 (40.4)	231 (39.4)	165 (37.4)		
LVEF <30%	33 (3.1)	15 (3.2)	18 (5.2)	0.88	2 (6.2)	18 (4.0)	13 (4.0)	1.00	0.93
LVEF 30%–49%	151 (14.1)	79 (16.9)	72 (20.7)		8 (25.0)	75 (16.5)	68 (20.8)		
LVEF ≥50%	891 (82.8)	372 (79.8)	257 (74.1)		22 (68.8)	361 (79.5)	246 (75.2)		
Participating center	NA	NA	NA	0.75	NA	NA	NA	0.80	0.87

Values are numbers (%) or mean±standard deviation. ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass surgery; CAD, coronary artery disease; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; and STEMI, ST-elevation myocardial infarction.

**P*, difference between FFR disregarded and FFR used for decision.

†*P*, difference between nonreclassified and reclassified among patients FFR used for decision.

Table 2. Baseline Angiographic Characteristics According to Patient Reclassification of the Revascularization Strategy

Patients, n(%)	Total Population (N=1075)	Total Nonreclassified (n=611)	Total Reclassified (n=464)	*P* Value	FFR Disregarded (n=47)	FFR Used for Decision Nonreclassified (n=587)	FFR Used for Decision Reclassified (n=441)	*P* Value*	*P* Value†
Number of diseased vessels (>50%)									
0	149 (13.9)	114 (18.7)	35 (7.5)	<0.0001	3 (6.4)	114 (19.4)	32 (7.3)	0.78	<0.0001
1	414 (38.5)	226 (37.0)	188 (40.5)		18 (38.3)	217 (37.0)	179 (40.6)		
2	301 (28.0)	152 (24.9)	149 (32.1)		18 (38.3)	141 (24.0)	142 (32.3)		
3 or left main	211 (19.6)	119 (19.5)	92 (19.8)		8 (17.0)	115 (19.6)	88 (20.0)		
Number of interrogated lesions (total)	1422	843	579		54	810	558		
Index lesion territory:									
LAD	830 (58.4)	460 (54.6)	370 (63.9)	0.001	35 (64.8)	442 (54.6)	359 (64.3)	0.57	0.001
RCA	219 (15.4)	141 (16.7)	78 (13.5)		5 (9.3)	139 (17.2)	75 (13.4)		
RCX	283 (19.9)	179 (21.2)	104 (17.9)		11 (20.4)	167 (20.6)	99 (17.7)		
Left main	90 (6.3)	63 (7.5)	27 (4.7)		3 (5.5)	62 (7.6)	25 (4.5)		
Lesion characteristics (ACC/AHA)									
A	300 (21.1)	196 (23.3)	104 (18.0)	0.007	10 (18.5)	187 (23.1)	103 (18.5)	0.99	0.009
B1	641 (45.1)	392 (46.5)	249 (43.0)		20 (37.0)	382 (47.2)	239 (42.8)		
B2	342 (24.1)	179 (21.2)	163 (28.2)		16 (29.6)	172 (21.2)	154 (27.6)		
C	134 (9.4)	71 (8.4)	63 (10.9)		8 (14.8)	64 (7.9)	62 (11.1)		
Proximal lesion	502 (35.3)	307 (36.4)	195 (33.1)	0.76	24 (44.4)	293 (36.2)	185 (33.2)	0.47	0.65
Reference diameter, mm	2.9±0.6	2.9±0.6	2.8±0.6	0.11	2.8±0.6	2.9±0.6	2.8±0.6	0.39	0.11
MLD, mm	1.4±0.7	1.4±0.7	1.3±0.8	<0.0001	1.3±0.4	1.4±0.7	1.3±0.8	0.07	<0.0001
Percent stenosis, %	52.7±13.0	51.5±13.2	54.4±12.5	<0.0001	54.0±11.3	51.4±13.3	54.4±12.5	0.15	<0.0001
Length, mm	12.8±8.1	12.6±7.5	13.1±8.9	0.01	15.5±16.6	12.5±7.4	12.8±7.7	0.01	0.01
FFR value	0.82±0.10	0.84±0.10	0.81±0.10	<0.0001	0.79±0.14	0.84±0.09	0.80±0.10	0.10	<0.0001
FFR ≤0.8	525 (36.9)	258 (30.6)	267 (46.1)	<0.0001	23 (42.6)	242 (29.9)	260 (46.6)	0.82	<0.0001
FFR ≤0.75	311 (21.9)	152 (18.0)	159 (27.5)	0.0001	18 (33.3)	140 (17.3)	153 (27.4)	0.07	<0.0001

Values are numbers (%) or mean±standard deviation. ACC/AHA indicates American College of Cardiology/American Heart Association; FFR, fractional flow reserve; LAD, left anterior descending artery; MLD, minimal luminal diameter; RCA, right coronary artery; and RCX, "Ramus Circumflexus" or circumflex artery.

**P*, difference between FFR disregarded and FFR used for decision.

†*P*, difference between nonreclassified and reclassified among patients FFR used for decision.

a priori (*P*=0.01). Patients with a more positive test—from negative to dubious and from dubious to positive—were more likely to have a revascularization proposed as a priori strategy (Figure 3).

However, once the FFR was performed, the rate of reclassification was not significantly different among the various groups of results of noninvasive test. Reclassification was observed in 42.6% of patients without any noninvasive test performed, in 49% of patients with a negative test, in 35% of patients with a dubious test results, and in 44.5% of patients with a positive test (*P*=0.65).

Reclassification of the Strategy of Revascularization and Clinical Outcome

The overall actuarial MACE (death, myocardial infarction, unplanned revascularization) rate at 1 year was 11.6%. In the 464 patients reclassified after FFR, the 1-year outcome was as good as in patients in the 611 nonreclassified patients whom (MACE, 11.2% versus 11.9%, log-rank *P*=0.78; Figure 4). A similar pattern was observed for each component of the MACE: death (2.1% versus 3.1%, log-rank *P*=0.74), myocardial infarction (1.5% versus 2.0%, log-rank *P*=0.44), or unplanned revascularization (8.4% versus 9.0%, log-rank *P*=0.81). Results after exclusion of patients in whom FFR results were disregarded are presented in Figure II in the online-only Data Supplement.

Most of patients (>90%) were free of angina during the 1-year follow-up. In reclassified patients > 94% remained free of angina at 1 month, 6 months, and 1 year follow-up. This figure was very similar to the one seen in nonreclassified patients in whom > 91% were free of angina at similar time points (*P*=0.75; Figure 4B). A similar observation was done, when the analysis was restricted to patients symptomatic at baseline (Figure III in the online-only Data Supplement).

Reclassification of the Strategy of Revascularization and Clinical Outcome: Subgroup Analyses

Three subgroups of interest were identified: diabetic patients requiring insulin (n=122), patients with a decreased left ventricular ejection fraction (LVEF; <50%, n=184), and patients with 3-vessel CAD by angiography (n=211). In each of the 3 populations, a significantly higher risk of MACE, or a

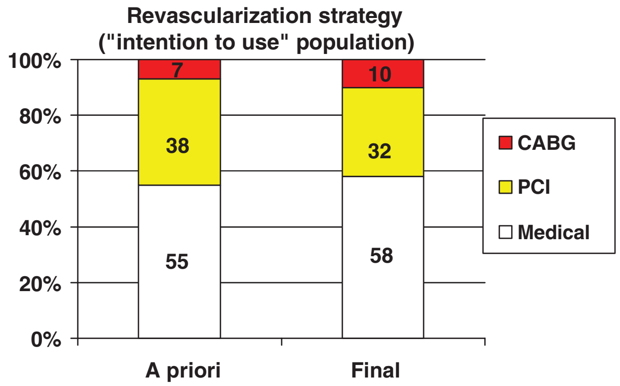

Figure 1. Revascularization strategy, medical, PCI, or CABG, as recorded after performing the angiography (a priori, **left**) and after performing the FFR (final, **right**) in the intentiontouse population. A modest change in the overall percentage of patients proposed for each type of revascularization can be observed (Bowker-McNemar test, *P*=0.02). CABG indicates coronary artery bypass surgery; FFR, fractional flow reserve; and PCI, percutaneous coronary intervention.

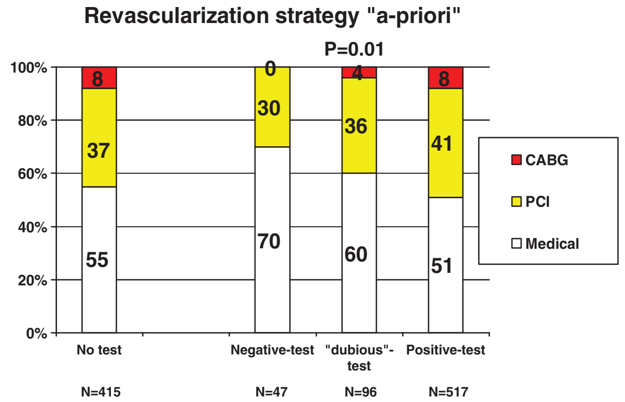

Figure 3. Revascularization strategy a priori according to the results of noninvasive tests. CABG indicates coronary artery bypass surgery; and PCI, percutaneous coronary intervention.

strong trend, was observed in comparison with patients without this condition: insulin-requiring diabetic patients versus others, 16.4% versus 11.1%, log-rank *P*=0.08; patients with decreased LVEF versus nondecreased LVEF, 14.7% versus 11.1%, log-rank *P*=0.16; and patients with 3-vessel CAD by angiography versus without 3vessel CAD, 16.6% versus 10.1%, log-rank *P*=0.01. In each of these 3 populations, however, reclassification remained safe. In insulin-requiring diabetic patients, reclassification was associated with a rate of events similar to nonreclassified patients (reclassified 16.6% versus nonreclassified 16.1%, log-rank *P*=0.94). In patients with a LVEF<50%, reclassification was associated with a nonsignificant trend toward a lower rate of events than in nonreclassified patients (reclassified 11.5% versus nonreclassified 17.5%, log-rank *P*=0.24). In patients with 3-vessel CAD, reclassification was also safe with a rate of events at 1 year of 14.1% in comparison with 18.5% in nonreclassified patients (log-rank *P*=0.51).

Patients in whom CABG was planned based on the analysis of clinical data, noninvasive tests, and angiography as the a priori option of revascularization were also safely reclassified by FFR (MACE in reclassified versus nonreclassified 10.0% versus 7.8%, log-rank *P*=0.71).

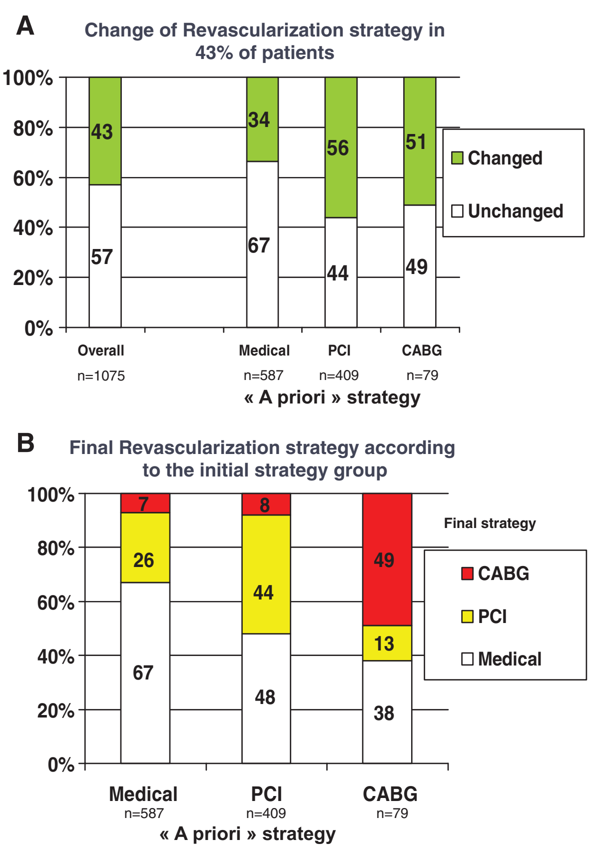

Figure 2. A, Reclassification of the revascularization strategy according to the revascularization strategy a priori. Despite minor overall changes, a change in strategy has been observed in 43% of all patients (κ, 0.22; 95% confidence interval, 0.17–0.27). **B,**Details of the final revascularization strategy applied in each group of revascularization strategy a priori. CABG indicates coronary artery bypass surgery; and PCI, percutaneous coronary intervention.

Predictors of Patient Coronary Revascularization Strategy and FFR

Predictors of the initial (a priori) strategy of revascularization as based on clinical and angiographic data by multivariable analysis are presented in Table 3. Six independent predictors of a more aggressive strategy (CABG>PCI>medical) were identified: lesion severity, number of diseased vessels by angiography, lesion complexity (American College of Cardiology/American Heart Association), diabetes mellitus, a younger age, and nonsmoking patients.

Seven independent predictors of a lower FFR value were identified and are presented in Table 4. Four of these predictors are similar to the predictors of the initial (a priori) revascularization strategy: lesion severity, number of diseased vessels by angiography, lesion complexity (American College of Cardiology/American Heart Association), and a younger age, whereas 3 are different: LAD location, lesion length, and a lower LVEF.

Correlates of changes of patient coronary revascularization by univariable analysis are presented in Tables 1 and 2 and

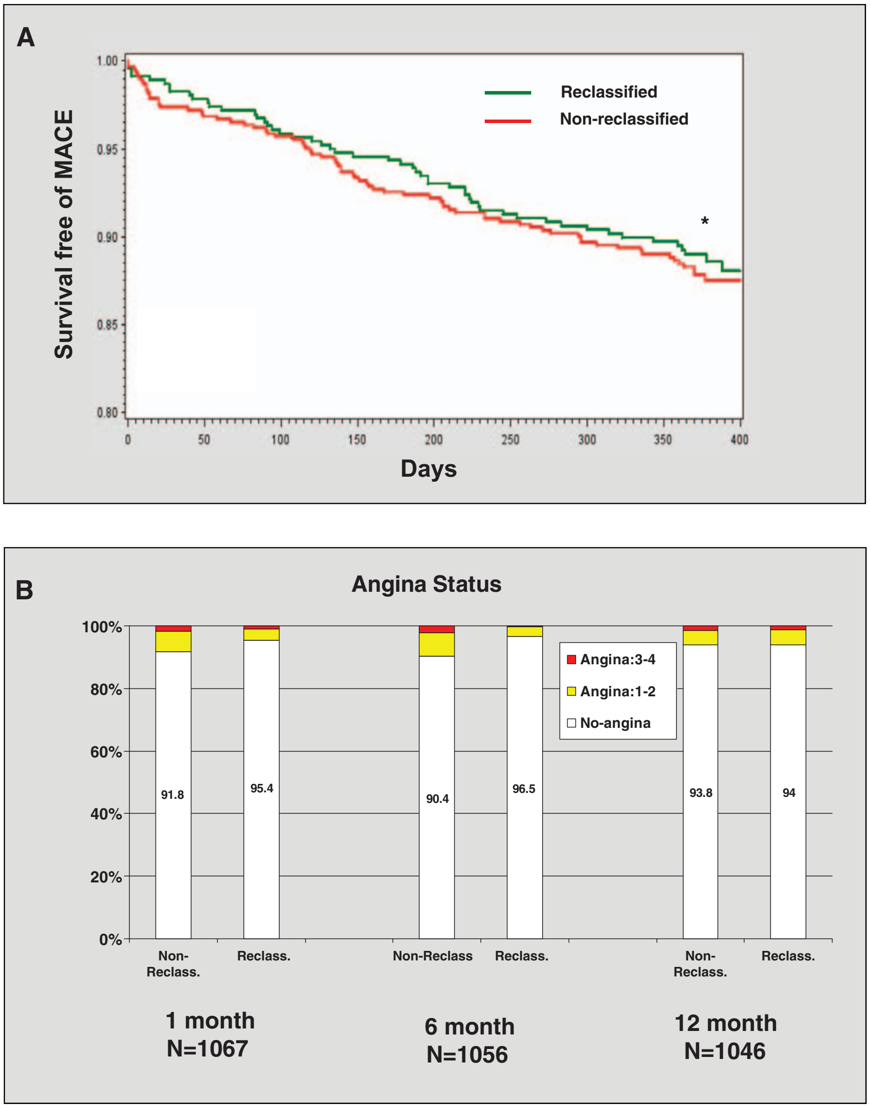

Figure 4. Safety of reclassification of the patient coronary revascularization. **A,** One-year MACE rate in reclassified (green) vs nonreclassified (red) patients in the intention-to use-population (*log-rank *P*=0.78). **B,** Angina status during follow-up in reclassified and nonreclassified patients (GLMM, *P*=0.75). GLMM indicates generalized linear mixed model; and MACE, major cardiac event.

Table I in the online-only Data Supplement. By multivariable analysis (Table 5), when FFR results were not included in the model, 5 independent predictors of a more aggressive revascularization strategy could be identified: LAD location, lesion length, proximal lesion, lesion severity, and a lower LVEF. Because 4 of them—LAD location, lesion length, lesion severity, and a lower LVEF—were strong predictors of a lower FFR value, when FFR results were added to the model, only 2 predictors were identified: a lower FFR value and a proximal lesion.

The relations between the initial revascularization strategy, the final strategy, and FFR values are presented in Figure 5. In initially medical patients, a low FFR value was associated with a more aggressive revascularization strategy. The opposite is seen in patients initially considered for CABG. An example of the later case is presented in Figure 6.

Illustration of the importance of lesion length and lesion location (LAD and left main; an example of typical proximal lesion) as identified by FFR on the decision regarding revascularization is presented in Figure IV in the online-only Data Supplement. LAD location and longer lesions were consistently associated with a more aggressive revascularization strategy, regardless of what the initial revascularization strategy was proposed (Figure IVA and IVB in the online-only Data Supplement). The proportion of left main lesion investigated was very low in patients considered for PCI (<3%). It was higher in patients considered for medical therapy or CABG (>7%). In addition, in these 2 groups, there was a dichotomous choice (medical or CABG, but not PCI) on the final revascularization strategy (Figure IVC in the online-only Data Supplement).

Discussion

This study, based on the largest nationwide registry available, demonstrates that when FFR is performed in patients referred for coronary angiography with at least 1 ambiguous coronary lesion, the FFR information is used for the medical decision of revascularization in 95% of cases. It further demonstrates that changes in the proportion of patients undergoing medical therapy, PCI, or CABG associated with FFR is modest, whereas reclassification of the revascularization

Table 3. Correlates of Patient Coronary Revascularization Strategy a Priori as Based on Clinical and Angiography Parameters (CABG>PCI>Medical): A Multivariable Analysis

	Odds Ratio*	Lower CI	Upper CI	*P* Value
Lesion severity (1% decrease of % stenosis) by angiography*	1.03	1.02	1.04	<0.0001
Number of diseased vessels by angiography				<0.0001
1	2.41	1.52	3.84	
2	2.64	1.64	4.24	
3	3.75	2.31	6.08	
Lesion complexity ACC/AHA: B2/C vs A/B1 by angiography†	1.52	1.20	1.93	0.0005
Diabetes mellitus	1.42	1.13	1.78	0.003
Age (1-y increase)	0.98	0.97	0.99	0.005
Smoking	0.76	0.60	0.96	0.02
Noninvasive testing (reference group: not done)				0.06
Not positive	0.65	0.45	0.93	
Positive	0.89	0.702	1.13	
Clinical instability	1.27	0.96	1.68	0.07
Lesion length (1-mm increase) by angiography†	0.99	0.97	1.01	0.10
Proximal lesion (including left main) †	1.07	0.84	1.36	0.58
LVEF (reference group: <30%)				0.73
30%–50%	1.11	0.75	1.40	
>50%	1.21	0.79	1.55	
LAD location†	0.97	0.77	1.22	0.80
Male sex	1.03	0.70	1.31	0.87
Previous revascularization	1.08	0.55	1.99	0.95

Other parameters in the model: investigating centers and catheter approach. ACC/AHA indicates American College of Cardiology/American Heart Association; CABG, coronary artery bypass surgery; CI, confidence interval; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.

*Estimated odds ratio represents the odds of CABG vs PCI and also the odds of PCI vs medical therapy.

†For each patient, 1 randomly chosen lesion was entered in the model.

strategy at the individual patient level is as high as 43%. It finally demonstrates that it is safe, in terms of angina status and clinical events, to pursue a revascularization strategy divergent from that suggested by angiography alone, when guided by FFR. Additional subgroup analyses demonstrate that the safety is preserved in high-risk populations, and multivariable analyses demonstrate that FFR allows correcting for underestimation of the importance of important characteristics such as an LAD location of the lesion or a long lesion.

Present Study Relative to Previous FFR Studies

The present study, based on the largest multicenter nationwide clinical FFR registry, is the first to investigate the role of FFR in the decision-making process regarding coronary revascularization at a patient level. Although it is an important clinical issue, it has not been investigated before. A large number of patients have been included in the DEFER, FAME, and FAME2 trials,[3–5] but these studies included only patients in whom the diagnostic angiography had already been performed and who were preselected for PCI. The question regarding the role of FFR in patients in whom all options, from medical treatment to CABG, were considered were not touched on in these previous studies.

FFR and Reclassification of Coronary Revascularization Strategy at a Population Level

The DEFER study,[3] in whom only patients preselected for PCI were included, demonstrated that half of the patients could be safely deferred from PCI based on the FFR results. Since the publication of that study, there has been a general conception that extensive use of FFR would be associated with a major decrease in the use of coronary revascularization, PCI in particular.

One of the major findings of the present study is the demonstration that, when applied to an unselected population, the use of FFR is associated with a modest change on the overall use of coronary revascularization. In our patient population, the overall proportion of patients referred for coronary revascularization was relatively stable (from 45% to 42%), whereas the proportion of patients referred to PCI decreased marginally (from 38% to 32%).

Although this could be considered as a surprise, these results are not contradictory to the results of the DEFER study. Indeed, in the part of our study population similar to those included in the DEFER study, eg, the patients already considered for PCI based on angiography, we confirmed the results of the DEFER trial with a deferral rate of 48%. However, in a difference from the DEFER trial, the present study included

Table 4. Correlates of a Higher FFR Value: A Multivariable Analysis

	Estimates	Lower CI	Upper CI	*P* Value
LAD location*	–0.05	–0.06	–0.03	<0.0001
Lesion length (1-mm increase)*	–0.01	–0.01	–0.01	<0.0001
Lesion severity (1% decrease of % stenosis)*	–0.01	–0.01	–0.01	<0.0001
Number of diseased vessels (reference group=0)				<0.0001
1	–0.02	–0.03	–0.01	
2	–0.04	–0.06	–0.03	
3	–0.03	–0.05	–0.02	
Age (1-y increase)	0.01	0.01	0.01	<0.0001
Lesion complexity ACC/AHA: B2/C vs A/B1 by angiography*	–0.01	–0.02	–0.01	0.001
LVEF (reference group <30%)				0.008
30%–50%	0.03	0.02	0.05	
>50%	0.04	0.03	0.06	
Noninvasive testing (reference group: not done)				0.15
Not positive	0.01	–0.01	0.02	
Positive	–0.01	–0.02	0.01	
Clinical instability	–0.01	–0.02	0.01	0.37
Previous revascularization	–003	–0.01	0.01	0.61
Proximal lesion (including left main)*	0.01	–0.01	0.01	0.61
Male sex	–003	–0.01	0.01	0.63
Diabetes mellitus	–0.01	–0.01	0.01	0.78
Smoking	0.001	–0.01	0.01	0.83

Other parameters in the model: investigating centers and catheter approach. ACC/AHA indicates American College of Cardiology/American Heart Association; CI, confidence interval; FFR, fractional flow reserve; LAD, left anterior descending artery; and LVEF, left ventricular ejection fraction.

*For each patient, 1 randomly chosen lesion was entered in the model.

a broader population. Patients initially considered for other options, such as medical treatment or bypass surgery, were also redirected to PCI based on FFR results (26% and 13%, respectively), thus attenuating the effect observed in the DEFER-like part of our population.

Reclassification of Coronary Revascularization Strategy by FFR at Patient Level and Clinical Outcome

Another important finding of the present study is to demonstrate that, although the overall proportions of patients directed to the respective treatment modality was only slightly modified, at an individual patient level, 43% of patients underwent reclassification of their treatment modality. This was observed in all groups of patients and ranged from 33%, in patients initially considered for medical therapy, to 51% and 56% in patients considered for CABG and PCI, respectively.

Because the final decision regarding coronary revascularization was divergent from the one suggested by angiography in 43% of patients, it was important to evaluate the safety of such an approach. This issue was slightly touched on in the DEFER, FAME, and FAME2 studies, demonstrating that it was safe to defer coronary revascularization based on FFR in patients preselected for PCI based on the initial angiography. However, the safety of choosing a different option than the one suggested by angiography in an unselected population including all treatment modalities had not been evaluated before. This is therefore another major finding of the present study—to extend these previous observations to a more general population and to demonstrate that it is safe, both in terms of angina status and of global and individual major clinical events, to pursue a revascularization strategy guided by FFR if from to the one suggested by angiography alone.

Subgroup analyses further suggest that the safety of FFR-based reclassification is also preserved in high-risk populations known to benefit from coronary revascularization such as insulin-requiring diabetic patients, patients with a decreased LV function, or patients with 3-vessel CAD by angiography. The same is true for patients initially planned for CABG.

Finally, and although selection biases cannot be excluded, it is interesting to note that, when the decision regarding coronary revascularization was based on FFR, the 1-year MACE rate was significantly lower than in the small population (n=47) in whom FFR findings were disregarded (10.1% versus 19.1, log-rank *P*=0.04).

Parameters Associated with Medical Decision of Coronary Revascularization

Beside the evaluation of the relationship between FFR and the severity of coronary stenoses by angiography,[6–8] no study has investigated extensively the relationship between FFR and baseline clinical and angiographic parameters. In addition, to date, no study has attempted to use this information to

Table 5. Correlates of Changes of Patient Coronary Revascularization Strategy From the a Priori Decision to the Final Decision (CABG>PCI>Medical): A Multivariable Analysis

	Odds Ratio*	Lower CI	Upper CI	*P* Value
Model Without Inclusion of FFR				
LAD location*	1.60	1.25	2.05	0.0002
Lesion length (1-mm increase) by angiography†	1.03	1.01	1.05	0.0008
Proximal lesion (including left main)†	1.33	1.04	1.72	0.03
Lesion severity (1% increase of % stenosis) by angiography†	1.01	1.00	1.02	0.04
LVEF (reference group: <30%)				0.04
30%–50%	0.61	0.32	1.19	
>50%	0.51	0.27	0.94	
Number of diseased vessels by angiography				0.11
1	0.90	0.59	1.38	
2	0.88	0.57	1.36	
3	1.27	0.82	1.98	
Diabetes mellitus	1.22	0.95	1.57	0.12
Noninvasive testing (reference group: not done)				0.17
Not positive	1.04	0.71	1.48	
Positive	1.34	0.91	1.79	
Smoking	1.17	0.88	1.57	0.30
Age (1-y increase)	0.99	0.98	1.01	0.49
Male sex	1.03	0.90	1.15	0.50
Previous revascularization	1.10	0.82	1.48	0.51
Clinical instability	1.03	0.70	1.50	0.89
Lesion complexity ACC/AHA: B2/C vs A/B1 by angiography†	1.01	0.67	1.42	0.97
Model with inclusion of FFR				
Lower FFR value (0.01 unit decrease)†	1.12	1.10	1.14	<0.0001
Proximal lesion (including left main)†	1.47	1.09	1.98	0.01
Diabetes mellitus	1.18	0.94	1.47	0.11
Number of diseased vessels by angiography				0.15
1	0.75	0.47	1.19	
2	0.57	0.34	0.93	
3	0.71	0.42	1.19	
LVEF (reference group: <30%)				0.19
30%–50%	0.62	0.29	1.32	
>50%	0.54	0.27	1.09	
LAD location†	1.22	0.894	1.65	0.21
Noninvasive testing (reference group: not done)				0.27
Not positive	0.88	0.66	1.08	
Positive	1.22	0.91	1.71	
Smoking	1.15	0.840	1.64	0.33
Lesion length (1-mm increase) by angiography†	1.01	0.99	1.03	0.34
Noninvasive test performed	1.15	0.85	1.56	0.35
Lesion severity (1% increase of % stenosis) by angiography†	1.00	0.98	1.01	0.71
Previous revascularization	1.10	0.89	1.65	0.54
Clinical instability	1.03	0.74	1.48	0.82
Age (1-y increase)	1.00	1.00	1.00	0.84
Male sex	1.02	0.89	1.18	0.89
Lesion complexity ACC/AHA: B2/C vs A/B1 by angiography†	1.01	0.68	1.41	0.91

Other parameters in the model: investigating centers and catheter approach. ACC/AHA indicates American College of Cardiology/American Heart Association; CI, confidence interval; FFR, fractional flow reserve; LAD, left anterior descending artery; and LVEF, left ventricular ejection fraction.

*Estimated odds ratio represents the odds of change of 1 level of revascularization strategy.

†For each patient one randomly chosen lesion was entered in the model.

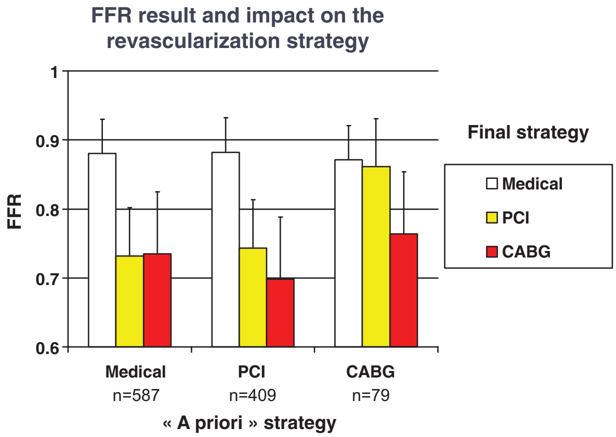

Figure 5. Minimal FFR value per patient for each combination of strategy a priori and of final strategy. CABG indicates coronary artery bypass surgery; FFR, fractional flow reserve; and PCI, percutaneous coronary intervention.

decipher the physician's decision-making process regarding coronary revascularization.

The present study confirms that there is a significant relationship between the degree of coronary stenosis by angiography and the FFR value. Most of the previous studies have insisted, however, on the wide and clinically nonrelevant relationship between these 2 parameters.[6–8] As demonstrated in the present study, this observation is likely because the degree of coronary stenosis is not the only independent parameter associated with FFR. Six other independent parameters have been identified, including the number of diseased vessels by angiography, LVEF, a younger age, and lesions characteristics such as LAD location, long lesion, and complex lesion.

The present study further demonstrates that, although some of these characteristics are already considered by clinicians when making their decision of coronary revascularization based on angiography, in particular, the number of diseased vessels and lesion characteristics such as the degree of stenosis and lesion complexity, others are not considered. This is the case for lesions located at the LAD and long lesions where the physiological significance is increased.

Our study demonstrates also the importance of investigating proximal lesions, the left main in particular, where the result of FFR is usually associated with a dichotomous decision and can lead to critical changes in the revascularization strategy: medical treatment to bypass surgery and vice versa.

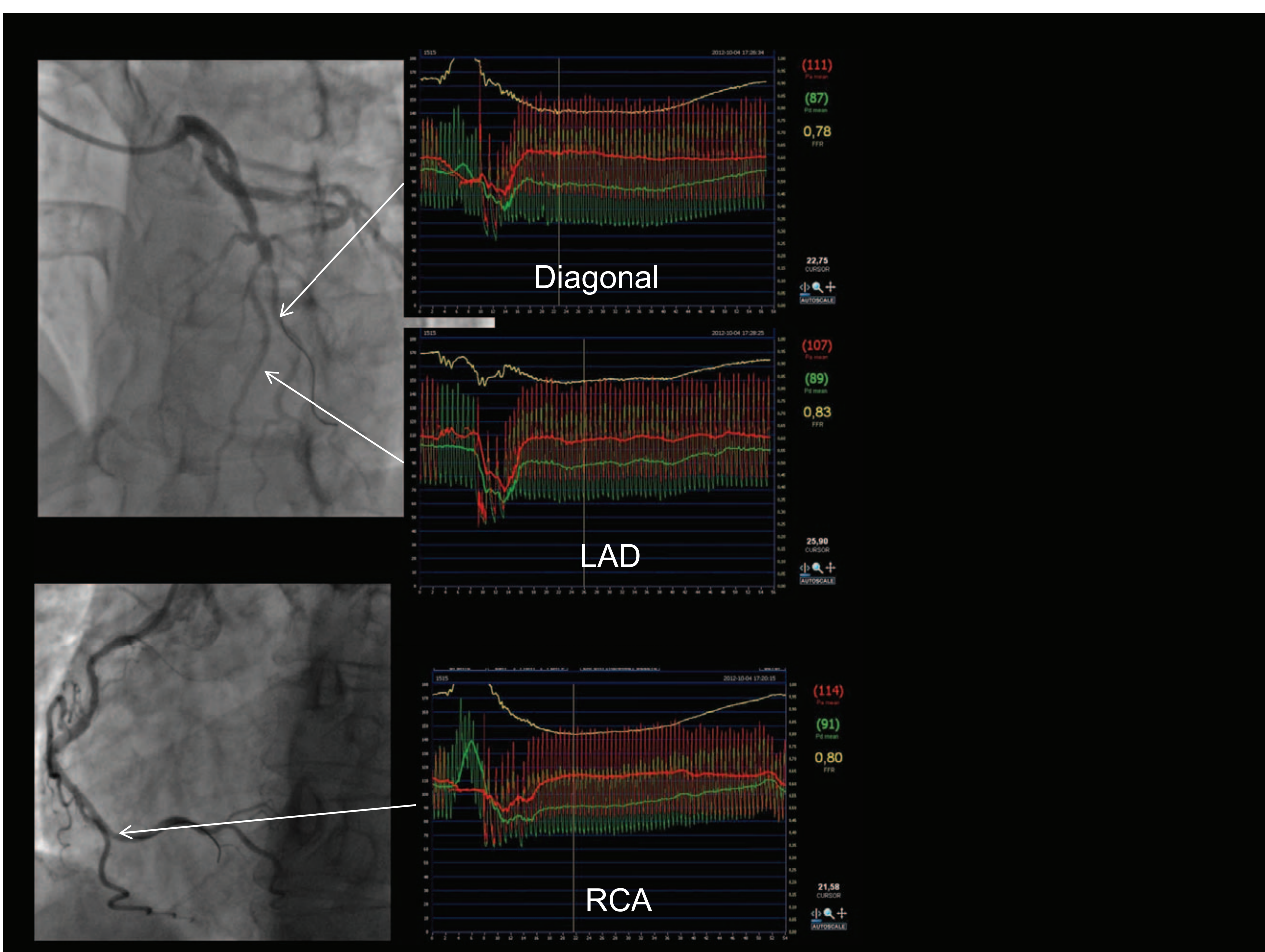

Figure 6. Example of patient with atypical chest pain, dubious noninvasive test, and 2-vessel CAD considered for surgery. FFR was measured in LAD (0.83), diagonal branch (0.78), and RCA (0.80). Because of the negative FFR in LAD and RCA and the small area at risk in the diagonal branch, the patient underwent medical treatment. CAD indicates coronary artery disease; FFR, fractional flow reserve; LAD, left anterior descending artery; and RCA, right coronary artery.

Study Limitations

The present study is a prospective observational study; as such, it is appropriate for evaluation of per-patient changes, but has some inherent limitations regarding the interpretation of outcome events. In particular, we cannot exclude a potential treatment bias that might have occurred in deciding whether to do another revascularization or not during follow-up. In addition, the role of unmeasured confounders cannot be excluded. Several measures were undertaken, however, to limit this risk. First, the decision of revascularization a priori was recorded just before performing the FFR, while extensive clinical, noninvasive, and angiographic information was available to the investigators. Second, the final decision of revascularization was recorded immediately after performing the FFR. Therefore, the only additional meaningful information between the 2 decisions was the availability of FFR results. Third, the multivariable analyses demonstrating that FFR was the most significant independent predictor of the reclassification process.

Although providing important information, results in subgroups will have to be confirmed by studies dedicated to these populations.

Coronary angiography and FFR were evaluated at each site without a central reading, and this could have induced some heterogeneity among participating centers. This issue was minimized by including participating centers well trained in both techniques. It was also taken into account in multivariable analyses where the adjustment for participating centers was performed. In addition, no significant differences among centers were detected regarding the analysis of these parameters and the rate of MACE of the population.

Clinical Implications

The present study provides important information on the clinical use of FFR in patients referred for coronary angiography. It demonstrates that, in this population, the use of FFR is associated with reclassification of the revascularization decision in about half of the patients. It further demonstrates that it is safe to pursue a revascularization strategy divergent from that suggested by angiography alone, but guided by FFR measurements. This is also one of the first studies to look at borderline lesions with FFR rather using FFR to determine borderline lesions.[4,5] The present data further support the concept of physiology-guided coronary revascularization and provide an important basis for future studies.

Attractive alternatives to FFR, such as FFR-CT[9,10] or instant wave-free ratio,[11,12] have recently been developed. Although initials reports have been promising, their use in tailoring the patient decision of coronary revascularization remain to be demonstrated.

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CLINICAL PERSPECTIVE

Although recent data suggest that fractional flow reserve (FFR) can be useful in guiding coronary revascularization in patients referred for a percutaneous coronary intervention procedure (DEFER, Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME], Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 [FAME2]), its benefit in patients referred for diagnostic angiography remains unclear. The present report investigated the role of FFR in the choice of treatment modalities in 1075 patients referred for diagnostic angiography in 20 French centers. It first demonstrates that the use of FFR marginally changes the proportion of patients referred to each treatment modality. The strategy a priori based on angiography was medical therapy in 55% and revascularization in 45% (percutaneous coronary intervention, 38%; coronary artery bypass surgery, 7%). The applied strategy after FFR was medical therapy in 58% and revascularization in 42% (percutaneous coronary intervention, 32%; coronary artery bypass surgery, 10%). It further demonstrates that the use of FFR is associated with reclassification of the initial treatment modality in 43% of cases: in 33% of a priori medical patients, in 56% of patients undergoing a priori percutaneous coronary intervention, and in 62% of patients undergoing a priori coronary artery bypass surgery. Finally it shows that reclassification by FFR (n=464) is associated with a major cardiac event rate (11.2%) and a proportion of patients free of angina (94%) at 1-year similar to patients in whom FFR results concurred with the angiography-based decision. To conclude, this study shows that performing FFR during diagnostic angiography is associated with reclassification of the treatment modality in about half of the patients. It demonstrates that it is safe to pursue a revascularization strategy divergent from that suggested by angiography alone when guided by FFR. It further supports the concept of physiology-guided coronary revascularization and provides an important basis for future studies.

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