CLINICAL RESEARCH   **Interventional Cardiology**

Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention in Patients With Multivessel Coronary Artery Disease

2-Year Follow-Up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study

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Objectives   The purpose of this study was to investigate the 2-year outcome of percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR) in patients with multivessel coronary artery disease (CAD).

Background   In patients with multivessel CAD undergoing PCI, coronary angiography is the standard method for guiding stent placement. The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study showed that routine FFR in addition to angiography improves outcomes of PCI at 1 year. It is unknown if these favorable results are maintained at 2 years of follow-up.

Methods   At 20 U.S. and European medical centers, 1,005 patients with multivessel CAD were randomly assigned to PCI with drug-eluting stents guided by angiography alone or guided by FFR measurements. Before randomization, lesions requiring PCI were identified based on their angiographic appearance. Patients randomized to angiography-guided PCI underwent stenting of all indicated lesions, whereas those randomized to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was ≤0.80.

Results   The number of indicated lesions was 2.7 ± 0.9 in the angiography-guided group and 2.8 ± 1.0 in the FFR-guided group (p = 0.34). The number of stents used was 2.7 ± 1.2 and 1.9 ± 1.3, respectively (p < 0.001). The 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group (p = 0.02). Rates of PCI or coronary artery bypass surgery were 12.7% and 10.6%, respectively (p = 0.30). Combined rates of death, nonfatal myocardial infarction, and revascularization were 22.4% and 17.9%, respectively (p = 0.08). For lesions deferred on the basis of FFR >0.80, the rate of myocardial infarction was 0.2 % and the rate of revascularization was 3.2 % after 2 years.

Conclusions   Routine measurement of FFR in patients with multivessel CAD undergoing PCI with drug-eluting stents significantly reduces mortality and myocardial infarction at 2 years when compared with standard angiography-guided PCI. (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation [FAME]; NCT00267774)   (J Am Coll Cardiol 2010;56:177–84) © 2010 by the American College of Cardiology Foundation

With the introduction of drug-eluting stents (DES), the percentage of patients with multivessel coronary artery disease (CAD) in whom percutaneous coronary intervention (PCI) is performed, has increased (1). Because DES are expensive and are associated with potential late complications, their appropriate use is critical (2). However, in patients with multivessel CAD, identifying which lesions cause ischemia and warrant stenting can be difficult. Although coronary angiography often underestimates or overestimates a lesion's functional severity, it is still the standard technique for guiding PCI in patients with multivessel coronary artery disease (3).

Fractional flow reserve (FFR) is an index of the physiologic significance of a coronary stenosis and is defined as maximal blood flow in a stenotic artery as a ratio to normal maximal flow (4). It can be easily measured during coronary angiography by the ratio of distal coronary pressure measured with a coronary pressure guidewire to aortic pressure measured simultaneously with the guiding catheter during maximum hyperemia. An FFR value of 0.80 discriminates coronary stenoses responsible for ischemia with an accuracy >90% (4,5). Retrospective studies suggest that in patients with multivessel CAD, FFR-guided PCI is associated with a favorable outcome with respect to event-free survival (6).

For patients with multivessel coronary artery disease, identifying an approach to PCI that would result in a more judicious use of stents, while still achieving complete relief of myocardial ischemia, could improve clinical outcome and decrease health care costs. The objective of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study was to compare treatment based on measurement of FFR in addition to angiography to the current practice of treatment solely guided by angiography in patients with multivessel CAD amenable for PCI. The FAME study showed that after a follow-up of 1 year, the rate of major adverse cardiac events (MACE) was reduced significantly by approximately 30%, and similar high percentages of patients were free from angina (7). The purpose of this paper was to investigate whether the favorable outcome of FFR-guided PCI in the FAME study is maintained at 2 years.

Methods

Study design. The design of this study has been described previously (8). In eligible patients with multivessel CAD, the investigator indicated which lesions had stenosis of at least 50% and were thought to require PCI on the basis of angiographic appearance and clinical data. Patients were

then randomly assigned to either angiography-guided PCI or FFR-guided PCI. (Fig. 1). Patients assigned to angiographic guidance underwent stenting of all indicated lesions with DES. In patients assigned to FFR guidance, first FFR was measured in each diseased coronary artery and DES were placed in indicated lesions only if the FFR was 0.80 or less. The study protocol was approved by the internal review board of each participating center. An independent clinical event committee blinded to treatment assignment adjudicated all events. Data management and statistical analysis were performed by an independent data coordinating center. The study sponsors had no role in the methods, data acquisition, data analysis, reporting, or publication of this study.

Study population. Patients were included in the study if they had multivessel CAD, defined as coronary artery stenoses ≥50% diameter stenosis in at least 2 of the 3 major epicardial coronary arteries, which were thought to require PCI. Patients with ST-segment elevation myocardial infarction could be included if the infarction had occurred at least 5 days before PCI. Enrollment and PCI of patients
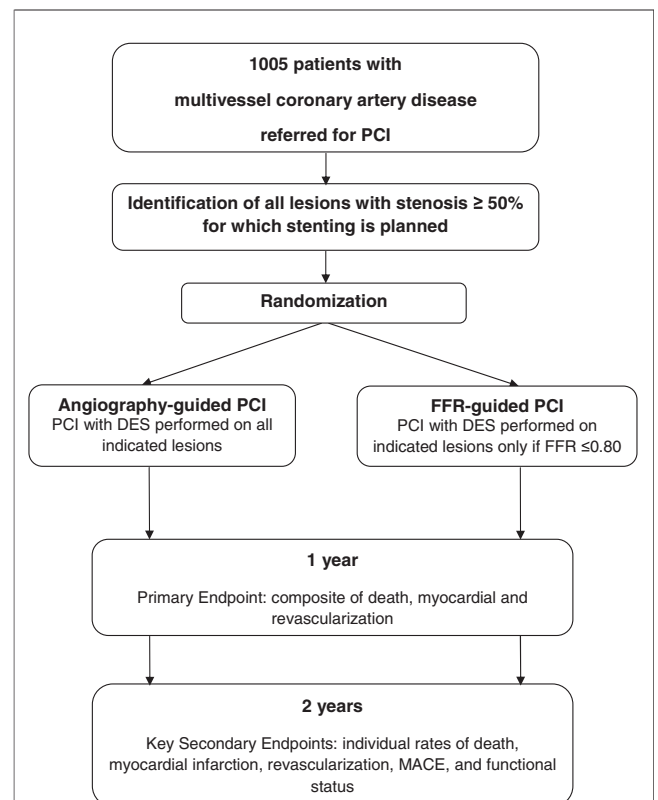
Figure 1   The FAME Study Flowchart

Flowchart of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. In all, 1,005 patients with multivessel coronary artery disease were randomly assigned to angiography-guided percutaneous coronary intervention (PCI) (n = 496) or fractional flow reserve (FFR)-guided PCI (n = 509). The key secondary end points at 2 years were individual rates of death, myocardial infarction, revascularization, major adverse cardiac events (MACE), and functional status. DES = drug-eluting stent(s).

with non–ST-segment elevation myocardial infarction could occur earlier than 5 days if the peak creatinine kinase was <1,000 IU. Patients who had undergone previous PCI could be included in the study. Patients with angiographically significant left main coronary artery disease, previous coronary artery bypass surgery, cardiogenic shock, extremely tortuous or calcified coronary arteries, a life expectancy of <2 years, pregnancy, or a contraindication to DES placement were excluded.

Treatment. The PCI was performed using standard techniques. The FFR was measured with a coronary pressure guidewire (Radi, St. Jude Medical, Uppsala, Sweden) at maximal hyperemia induced by intravenous adenosine, administered at 140 μg/kg/min through a central vein. Hyperemic pressure pull-back recordings were performed as described previously (8,9). All included patients were treated with aspirin and clopidogrel for at least 1 year. Quantitative coronary angiography was performed off line and is extensively described elsewhere (10,11).

End points and 2-year follow-up. MACE were defined as a composite of death, myocardial infarction, or any repeat revascularization. The primary end point was the rate of MACE by 1 year. Secondary end points included death and myocardial infarction rates and MACE and its individual components at 2 years, procedure time, amount of contrast agent used, functional class at 1 and 2 years, and number of antianginal medications. Cost effectiveness was a secondary end point as well. Death was defined as all-cause mortality. Myocardial infarction was defined as a threefold or greater elevation of creatine kinase-myocardial band (CK-MB) level or new Q-waves in ≥2 contiguous leads of the electrocardiogram (ECG) (12). Total CK and CK-MB levels were measured in all patients between 12 and 24 h after PCI. After discharge, follow-up was performed at 1 month, 6 months, 1 year, and 2 years (13).

Statistical analysis. All enrolled patients were included in the analysis of primary and secondary end points according to the intention-to-treat principle. Categorical variables including the primary end point, and its components are described as proportions and were compared by chi-square test. Continuous variables are described as mean and standard deviation and were compared by unpaired t test or Mann-Whitney U test. A 2-sided p value of <0.05 was considered to indicate statistical significance. Kaplan-Meier curves are presented to describe the time-to-event distributions for the different end points. All statistical analyses were performed with SAS software version 9.1 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics and angiographic data. Between January 2006 and September 2007, 1,005 patients were included in 20 centers in the U.S. and Europe. Of these, 496 were randomly assigned to angiography-guided PCI and 509 to FFR-guided PCI. Baseline characteristics of the 2 groups

were similar, as were the number of indicated lesions and angiographic extent and severity of CAD (Table 1).

Procedural results. In all, 2,415 stents were placed, of which 2,339 (96.9%) were DES. Significantly more stents per patient were placed in the angiography-guided group compared with the FFR-guided group (2.7 ± 1.2 vs. 1.9 ± 1.3; p < 0.001) (Table 2). In the FFR-guided group, FFR was successfully measured in 94% of all lesions. In 874 (63%) lesions, FFR was 0.80 or less, and these lesions were stented as per protocol. In 513 (37%) lesions, FFR was >0.80, and these lesions were not stented. The procedure time was similar in the 2 groups (70 ± 44 min in the angiography-guided group and 71 ± 43 min in the FFR-guided group; p = 0.51). Significantly more contrast agent was used in the angiography-guided group than in the FFR-guided group (302 ± 127 ml vs. 272 ± 133 ml; p < 0.001). Length of hospital stay was 3.7 ± 3.5 days in the angiography-guided group versus 3.4 ± 3.3 days in the FFR-guided group (p = 0.05).

Adverse events and freedom from angina at 2 years. Complete 2-year follow-up was obtained in 93.6% of patients (36 were lost to follow-up in the angiography-guided group, and 29 were lost to follow-up in the FFR-guided group [p = 0.31]). All-cause mortality at 2 years was 3.8% (n = 19) in the angiography-guided group and 2.6% (n = 13) in the FFR-guided group (p = 0.25) (Table 3). Myocardial infarction occurred in 9.9% (n = 49) in the angiography-guided group and 6.1% (n = 31) in the FFR-guided group (p = 0.03). Of these patients, 13 (2.6%) fulfilled the Academic Research Consortium definition of definite or probable stent thrombosis in the angiography-guided group versus 8 patients (1.6%) in the FFR-guided group.

The 2-year rate of death or myocardial infarction, which was not a pre-specified secondary end point but is an important clinical variable, was 12.9% (n = 64) in the angiography-guided group and 8.4% (n = 43) in the FFR-guided group (p = 0.02). Revascularization rate was 12.7% (n = 63) in the angiography-guided group and 10.6% (n = 54) in the FFR-guided group (p = 0.30). After 2 years, MACE had occurred in 111 patients (22.4%) in the angiography-guided group and in 91 patients (17.9%) in the FFR group (p = 0.08). Event-free survival is shown by Kaplan-Meier curves (Fig. 2). At 2 years, 76% of the patients were free from angina in the angiography-guided group compared with 80% in the FFR-guided group (p = 0.14) (Fig. 3).

Outcome of the deferred lesions in the FFR-guided group. In the 509 patients in the FFR-guided group, 1,329 stenoses were successfully measured by FFR, of which 816 were stented (FFR ≤0.80) and 513 were deferred (FFR >0.80). During the follow-up of 2 years, among these 509 patients, 9 (1.8%) myocardial infarctions occurred after the index hospitalization of which 8 (1.6%) were related to a new lesion or were stent related, whereas only 1 (0.2%) myocardial infarction occurred in an originally

Table 1	Baseline Characteristics		
Characteristic	Angiography Group (n = 496)	FFR Group (n = 509)	p Value*
Demography			
Age, yrs	64.2 ± 10.2	64.6 ± 10.3	0.47
Sex			0.30
Male	360 (73)	384 (75)	
Female	136 (27)	125 (25)	
Clinical			
Angina (CCS class)			0.13
I	115 (23)	132 (26)	
II	165 (33)	170 (33)	
III	118 (24)	132 (26)	
IV	98 (20)	75 (15)	
History			
Previous myocardial infarction	180 (36)	187 (37)	0.84
Previous PCI	129 (26)	146 (29)	0.34
Diabetes mellitus	125 (25)	123 (24)	0.65
Hypertension	327 (66)	312 (61)	0.10
Current smoker	156 (32)	138 (27)	0.12
Hypercholesterolemia	362 (74)	366 (72)	0.62
Positive family history	190 (39)	205 (41)	0.49
Unstable angina			
With dynamic ECG changes	91 (18)	73 (14)	0.09
Without dynamic ECG changes	87 (18)	77 (15)	0.29
Left ventricular ejection fraction, %	57 ± 12	57 ± 11	0.92
Medication			
Beta-blocker	377 (76)	395 (78)	0.55
Calcium antagonist	96 (19)	121 (24)	0.09
Nitrates	179 (36)	167 (33)	0.27
ACE inhibitor/ARB	255 (51)	267 (52)	0.74
Statin	397 (80)	417 (82)	0.45
Aspirin	454 (92)	465 (91)	0.92
Clopidogrel	292 (59)	310 (61)	0.51
Angiography			
Indicated lesions per patient†	2.7 ± 0.9	2.8 ± 1.0	0.34
50%–70% narrowing	550 (41)	624 (44)	
70%–90% narrowing	553 (41)	530 (37)	
90%–99% narrowing	207 (15)	202 (14)	
Total occlusion	40 (3)	58 (4)	
Lesions segments 1, 2, 3, 6, 7, 11	960 (71)	1,032 (73)	0.27
Patients with proximal LAD lesion	186 (38)	210 (41)	0.22
Patients with total occlusion	37 (7.5)	54 (10.6)	0.08

Values are mean ± SD or n (%). *All categorical variables were compared by chi-square test; all continuous variables were compared by Mann-Whitney *U* test, except age, which was normally distributed and compared by *t* test. †Before randomization, the investigator indicated all lesions to be included in the study and classified them according to severity, by visual estimation, based on the angiogram.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; FFR = fractional flow reserve; LAD = left anterior descending artery; PCI = percutaneous coronary intervention.

deferred lesion (Fig. 4). In 53 (10.4%) patients in the FFR-guided group, 1 or more repeat revascularizations were performed, of which 37 (7.2%) were related to a new or restenotic lesion and only 16 (3.2%) to an originally deferred lesion.

Discussion

The FAME study showed that in patients with multivessel CAD, favorable outcome after routine measurement of FFR during PCI as compared with the standard strategy of PCI guided by angiography alone is maintained at 2-year follow-up. The combined rate of death and myocardial infarction as well as rate of myocardial infarction alone were significantly lower among patients in the FFR-guided group. Although the composite end point of death, myocardial infarction, or the need for revascularization was no longer significantly lower in the FFR-guided group, the absolute difference in event rates was similar to what was demonstrated at 1 year. The high percentage of patients free from angina was maintained at 2 years, and the FFR-guided strategy resulted in a similar, if not improved, functional status. Moreover, the outcome in initially deferred lesions on the basis of FFR

Table 2	Procedural Results			
	Angiography Group (n = 496)	FFR Group (n = 509)	p Value*	
Procedure time, min†	70 ± 44	71 ± 43	0.51	
Contrast agent used, ml	302 ± 1	272 ± 133	<0.001	
Drug-eluting stents				
Drug-eluting stents used per patient	2.7 ± 1.2	1.9 ± 1.3	<0.001	
Total stent length, mm	51.9 ± 24.6	37.9 ± 27.8	<0.001	
Average stent diameter per patient, mm	2.96 ± 0.33	2.92 ± 0.36	0.13	
Lesions successfully stented‡	1,237 (92)	819 (94)	0.07	
Total drug-eluting stents used	1,359	980	<0.001	
FFR results				
Lesions successfully measured by FFR§	N/A	1,329 (94)		
FFR, all lesions	N/A	0.71 ± 0.18		
FFR ≤0.80, ischemic lesions	N/A	0.60 ± 0.14		
FFR >0.80, nonischemic lesions	N/A	0.88 ± 0.05		
Lesions with FFR ≤0.80	N/A	874 (63)		
Lesions with FFR >0.80	N/A	513 (37)		
Procedural and 1-yr costs				
Materials, U.S.$‖	6,007 ± 2,819	5,332 ± 3,261	<0.001	
Hospital stay at baseline admission, days	3.7 ± 3.5	3.4 ± 3.3	0.05	
Incremental health care costs at 1 year, U.S.$¶	14,357	12,291	<0.001	

Values are mean ± SD, n (%), or n. *All categorical variables were compared by chi-square test; all continuous variables and the variable "drug-eluting stents used per patient" were compared by Mann-Whitney *U* test. †Procedure time was defined as time from introduction of first catheter until removal of last guiding catheter. ‡Percentage of the lesions indicated at baseline (angiography group), percentage of the lesions with FFR ≤0.80 (FFR group). §Percentage of the number of all indicated lesions; of those 85 lesions without FFR measurement, 58 (4.1%) were the totally occluded arteries to which a default FFR value of 0.50 was assigned, whereas in 27 (1.9%) lesions, FFR could not be measured because of technical reasons. ‖The materials used during the index procedure (PCI) were recorded and their costs were calculated according to the actual local price and translated into U.S. dollars. ¶Incremental health care costs is the sum of the costs of materials used during the index procedure, the costs of hospitalization days for the index procedure, the costs for hospitalization days for major adverse cardiac events in the first year, and the costs for coronary artery bypass graft surgery or repeat PCI in the first year, if applicable.

N/A = not available; other abbreviations as in Table 1.

>0.80 was excellent, underscoring the safety of the FFR-guided approach.

In our study, the incidence of all types of adverse events was consistently reduced by roughly 30%. The absolute risk for MACE was reduced by 4.5%, which means that using FFR for 22 patients can prevent 1 adverse event. Routine measurement of FFR probably improved outcomes by allowing more judicious use of stents and equal relief of ischemia. Performing PCI of all angiographic stenoses, regardless of their ischemic potential, diminishes the benefit of relieving ischemia by exposing the patient to additional stent-related risk, whereas PCI of ischemic stenoses only (FFR ≤0.80) is beneficial because the risk of stent thrombosis or restenosis is outweighed by the significant reduction in the risk of ischemic events without stent placement. Thus, by systematically measuring FFR, the benefit of PCI

Table 3	End Points at 2 Years			
	Angiography Group (n = 496)	FFR Group (n = 509)	p Value*	RR With FFR Guidance (95% CI)
Events at 2 yrs				
Total number of events	142	106		
Number of events per patient	0.29 ± 0.60	0.21 ± 0.48	0.17	
Death	19 (3.8)	13 (2.6)	0.25	0.67 (0.33–1.34)
Myocardial infarction	49 (9.9)	31 (6.1)	0.03	0.62 (0.40–0.95)
CABG or repeat PCI	63 (12.7)	54 (10.6)	0.30	0.84 (0.59–1.18)
Death or myocardial infarction	64 (12.9)	43 (8.4)	0.02	0.65 (0.45–0.94)
Death, myocardial infarction, CABG, or repeat PCI	111 (22.4)	91 (17.9)	0.08	0.80 (0.62–1.02)
Functional status at 2 yrs				
Patients without event and free from angina†	284 (64.8)	315 (68.2)	0.29	
Patients free from angina†	332 (75.8)	369 (79.9)	0.14	
Number of antianginal medications‡	1.2 ± 0.8	1.2 ± 0.7	0.68	

Values are n, mean ± SD, or n (%). *All categorical variables were compared by chi-square test; all continuous variables and the variable "number of events per patient" were compared by Mann-Whitney *U* test. †Patients with missing information on angina status were excluded from the analysis. ‡Antianginal medications included beta-blockers, calcium antagonists, nitrates.

CABG = coronary artery bypass graft surgery; CI = confidence interval; RRR = relative risk reduction; other abbreviations as in Table 1.
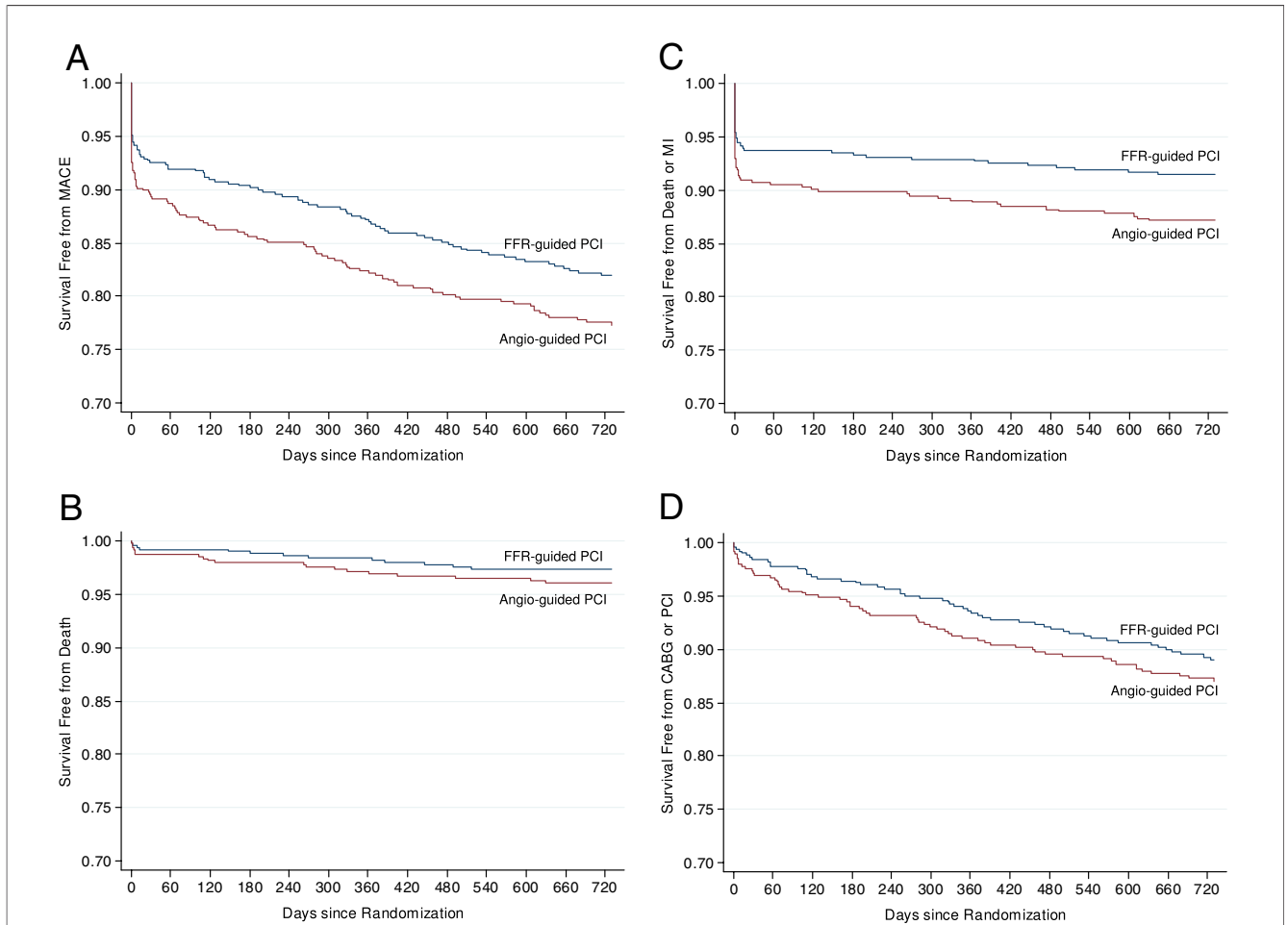
Figure 2   Kaplan-Meier Survival Curves

Kaplan-Meier survival curves according to study group for survival free from **(A)** major adverse cardiac event (MACE), **(B)** death, **(C)** death or myocardial infarction (MI), and **(D)** revascularization. The **red curve** indicates the angiography-guided percutaneous coronary intervention (PCI) group; the **blue curve** indicates the fractional flow reserve (FFR)-guided PCI group. CABG = coronary artery bypass graft surgery.

can be maximized by accurately discriminating the lesions for which revascularization will provide the most benefit.
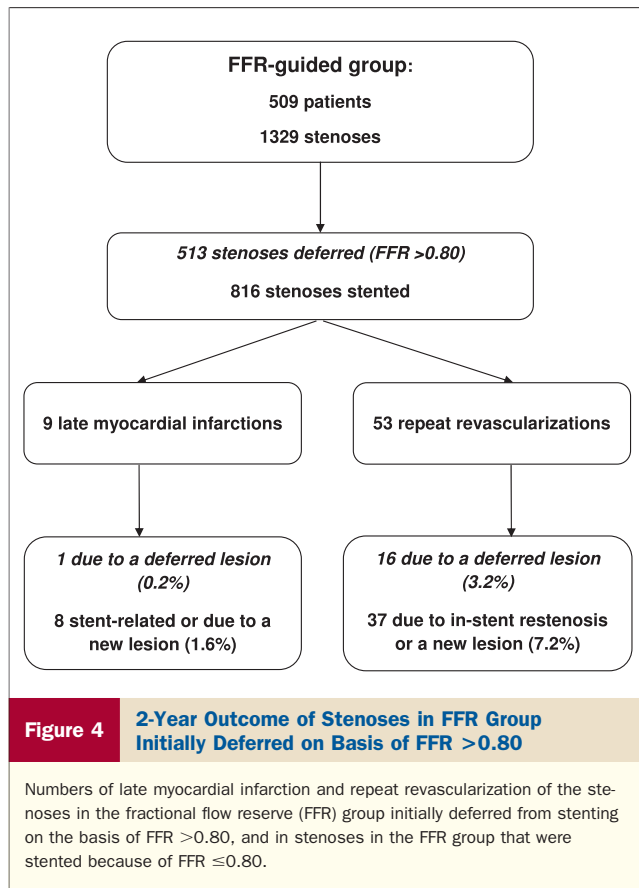
Strengths and limitations of the FAME study. The FAME study has several specific strengths that should be mentioned. First, because of the liberal inclusion and few exclusion criteria, the study truly reflects everyday practice in performing PCI for multivessel disease. This position is further corroborated by the fact that 53% of all screened patients were actually included in the study (7) and that 43 patients were included per center per year, both numbers exceptionally high for this kind of study (14,15).

Second, the majority of the stenoses was located in the proximal or mid-segments of the 3 major coronary arteries, and in almost 40% of the patients, a proximal left anterior descending artery stenosis was 1 of the target lesions. Furthermore, patients who had undergone PCI in the past were not excluded, as is mostly the case in other studies comparing outcome after different treatment modalities in multivessel CAD (14–17).
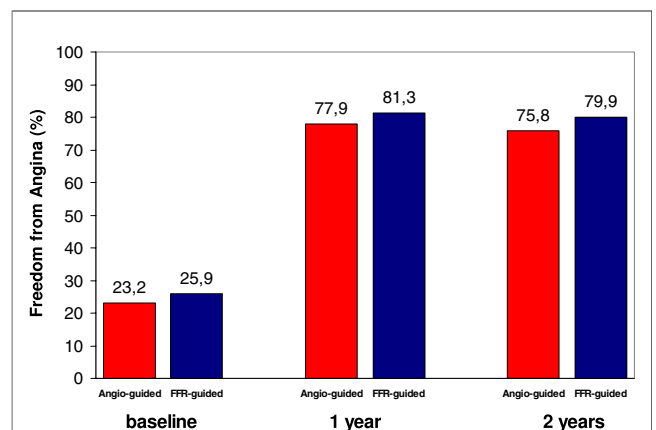
Figure 3   Patient Follow-Up

Percentage of patients treated by angiography-guided strategy **(red bars)** and fractional flow reserve (FFR)-guided strategy **(blue bars)** who were completely free from angina at baseline, and at 1- and 2-year follow-up.

| **Figure 4** | **2-Year Outcome of Stenoses in FFR Group Initially Deferred on Basis of FFR >0.80** |

Numbers of late myocardial infarction and repeat revascularization of the stenoses in the fractional flow reserve (FFR) group initially deferred from stenting on the basis of FFR >0.80, and in stenoses in the FFR group that were stented because of FFR ≤0.80.

Third, the reduction of event rate by 30% was consistently present for all types of events. Fourthly, the high percentage of patients free from angina after 2 years underlines that PCI—especially when applied appropriately—is a very effective way to eliminate ischemia and improve quality of life. Lastly, the very low late infarction and late revascularization rate of initially deferred lesions underscores the safety of an FFR-guided approach to PCI for multivessel disease.

Our results also suggest that outcomes of PCI as compared with those achieved by medical treatment, such as in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (12,14) or by coronary artery bypass graft surgery, such as in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (15), might be improved if the PCI is performed with FFR guidance, ensuring a functionally complete revascularization with more appropriate use of stents (10). A substudy of the COURAGE trial (18), which demonstrated lower rates of death or myocardial infarction in those patients with the greatest relief of ischemia, further supports the concept that PCI should be guided by physiologic considerations and not solely by anatomic ones.

It has been suggested that including stenoses of 50% to 70% in the FAME study might have biased the outcome because many interventionalists would not stent such lesions. However, just for these lesions (1,174 of a total of

2,764 stenoses), the correlation between anatomic and physiologic severity was worse. Not stenting such stenoses on the basis of the angiogram would have left untreated a hemodynamically significant stenosis in 35% of all lesions (11).

It can be questioned whether the difference in events is due to the first 48 h with catch-up of events thereafter. However, that was not the case. The number of small, periprocedural infarctions (CK-MB 3 to 5 times the upper limit of normal) was low: 3.2% and 2.4%, respectively; and absolute differences in MACE were 2.2% at hospital discharge, 5.1% at 1 year, and 4.5% at 2 years, whereas the difference in rate of myocardial infarction even further increased at the advantage of the FFR-guided group during the second year of follow-up.

Another potential limitation could be that FFR measurement requires some extra manipulations, preferably a central venous line if intravenous adenosine is used, and some basic knowledge about interpretation. But given a well-designed infrastructure in the catheterization laboratory and an experienced interventionalist, it is a simple and quick procedure to be performed without significant delay, as shown in this study.

Finally, the current data are restricted to a 2-year follow-up. Theoretically, unstented lesions in the FFR-guided group could progress and lead to future events beyond this time horizon. We intend to collect data up to a follow-up of 5 years for the present study.

Conclusions

In patients with multivessel CAD undergoing PCI with DES, routine measurement of FFR as compared with PCI guided by angiography alone results in a significant reduction of the rate of mortality and myocardial infarction at 2 years, and supports the evolving paradigm of revascularization of ischemic lesions and medical treatment of nonischemic ones.

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