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Angiographic Versus Functional Severity of Coronary Artery Stenoses in the FAME Study

Fractional Flow Reserve Versus Angiography in Multivessel Evaluation

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Objectives The purpose of this study was to investigate the relationship between angiographic and functional severity of coronary artery stenoses in the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study.

Background It can be difficult to determine on the coronary angiogram which lesions cause ischemia. Revascularization of coronary stenoses that induce ischemia improves a patient's functional status and outcome. For stenoses that do not induce ischemia, however, the benefit of revascularization is less clear.

Methods In the FAME study, routine measurement of the fractional flow reserve (FFR) was compared with angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease. The use of the FFR in addition to angiography significantly reduced the rate of all major adverse cardiac events at 1 year. Of the 1,414 lesions (509 patients) in the FFR-guided arm of the FAME study, 1,329 were successfully assessed by the FFR and are included in this analysis.

Results Before FFR measurement, these lesions were categorized into 50% to 70% (47% of all lesions), 71% to 90% (39% of all lesions), and 91% to 99% (15% of all lesions) diameter stenosis by visual assessment. In the category 50% to 70% stenosis, 35% were functionally significant (FFR $\leq$0.80) and 65% were not (FFR $>$0.80). In the category 71% to 90% stenosis, 80% were functionally significant and 20% were not. In the category of subtotal stenoses, 96% were functionally significant. Of all 509 patients with angiographically defined multivessel disease, only 235 (46%) had functional multivessel disease ($\geq$2 coronary arteries with an FFR $\leq$0.80).

Conclusions Angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% category but also in the 70% to 90% angiographic severity category. (J Am Coll Cardiol 2010;55:2816–21) © 2010 by the American College of Cardiology Foundation

The presence of inducible ischemia related to a coronary artery stenosis is important in deciding whether to revascularize such a stenosis. Reducing myocardial ischemia by revascularization improves a patient's functional status and outcome, whereas revascularization of nonischemic lesions is controversial (1–4). The recently published results of the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study support the evolving strategy of revascularization of ischemic lesions and medical treatment of nonischemic ones (5).

See page 2822

In patients with multivessel coronary artery disease (CAD), it is often difficult to determine which lesions are responsible for reversible ischemia. Noninvasive stress tests are often not able to accurately detect and localize ischemia (6). Therefore, the coronary angiogram is the standard for decision making about revascularization in such patients. In randomized trials

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evaluating coronary revascularization, as well as in daily practice in most catheterization laboratories, lesions with a diameter stenosis of ≥50% on the angiogram are generally considered for revascularization (7–9). Coronary angiography, however, may result in both underestimation and overestimation of a lesion's severity and is often inaccurate in predicting which lesions cause ischemia (10,11).

The fractional flow reserve (FFR) is an accurate and selective index of the physiological significance of a coronary stenosis that can be easily measured during coronary angiography. An FFR value of ≤0.80 identifies ischemia-causing coronary stenoses with an accuracy of >90% (12,13). In the randomized FAME study, FFR-guided percutaneous coronary intervention (PCI) with drug-eluting stents was compared with angiography-guided PCI in patients with multivessel CAD (5). The 1-year results of this study showed that FFR guidance of PCI significantly decreased the combined end point of death, myocardial infarction, and repeat revascularization. In this current analysis, we investigated the relationship between angiographic stenosis severity and functional stenosis severity as measured by the FFR. We also analyzed the number of functionally significant diseased coronary arteries (coronary arteries with an FFR ≤0.80) in all patients with angiographic 2- and 3-vessel disease in the FFR-guided arm of the FAME study.

Abbreviations and Acronyms

CAD = coronary artery disease

FFR = fractional flow reserve

PCI = percutaneous coronary intervention

Methods

Study population. In this subanalysis of the FAME study, the relationship between angiography and the FFR in all patients in the FFR-guided arm (n = 509) was analyzed. The FAME study protocol was described in detail previously (14). In brief, 1,005 patients with multivessel disease were randomly assigned to angiography-guided PCI (n = 496) or FFR-guided PCI (n = 509). Before randomization, the operator indicated all lesions with a diameter stenosis percentage of ≥50% requiring stenting. In cases of angiography-guided PCI, all indicated lesions were stented. In cases of FFR-guided PCI, patients first had FFR measured in each diseased coronary artery and only underwent stenting if the FFR was ≤0.80. The FAME study had liberal inclusion criteria to reflect daily practice of PCI in patients with multivessel CAD. More than 50% of all screened patients actually participated in the study, and the inclusion rate per participating center was 40 patients per year, which is high compared with other studies in this field. Exclusion criteria for the FAME study were angiographically significant left main CAD, previous coronary artery bypass surgery, cardiogenic shock, or extremely tortuous or calcified coronary arteries The FAME study protocol was approved for all participating centers by their respective internal review board or ethics committee.

Definitions of angiographic multivessel CAD and functional multivessel disease. Angiographic multivessel CAD was defined as stenoses ≥50% in at least 2 of the 3 major epicardial coronary arteries (angiographic 2- or 3-vessel disease), which the operator deemed to require stenting. Before randomization, the operator categorized the lesions according to visual angiographic stenosis severity into 50% to 70%, 71% to 90%, and 91% to 100% diameter stenosis. In those randomized to FFR guidance, if the FFR of a particular stenosis was >0.80, this stenosis was considered as functionally nonsignificant and no stent was placed. The angiographic disease in that respective artery was then classified as functionally not significant. The definition of functional 0-, 1-, 2-, or 3-vessel disease was made on the basis of the number of main arteries with an FFR ≤0.80. So, a patient with angiographic 3-vessel disease could be classified as having functional 0-, 1-, 2-, or 3-vessel disease, after FFR measurements.

FFR measurements. The FFR is defined as the ratio between distal coronary pressure and aortic pressure, both measured simultaneously at maximal hyperemia. Distal coronary pressure was measured with a coronary pressure guidewire (Certus Pressure Wire, St. Jude Medical, St. Paul, Minnesota). Maximal hyperemia was induced by intravenous adenosine, administered at 140 μg/kg/min via a central vein. Hyperemic pullback recordings were performed in all diseased arteries to discriminate focal from diffuse disease.

Statistical analysis. Categorical variables are expressed as proportions. Continuous variables are expressed as mean and SD. Angiographic lesion severity per category and the respective FFR value of each specific lesion were plotted in a box-and-whisker plot to show the degree of dispersion and skewness in the data and to identify potential outliers. The box-and-whisker plot was created with GraphPad Prism version 2.01 software (GraphPad Software Inc., La Jolla, California).

Results

Angiographic versus functional stenosis severity. In the FFR-guided arm of the FAME study, 509 patients with angiographic multivessel CAD were included. The baseline characteristics are listed in Table 1. In these 509 patients, 1,414 lesions were indicated before randomization (2.8 ± 1.0 lesions per patient). The FFR was measured successfully in 1,329 (94%) of the 1,414 lesions. Of the 85 lesions for which the FFR was not measured, in 58, it was because they were chronically occluded and in 27, it was due to technical reasons. These lesions were not included in this analysis. Of all 1,329 analyzed lesions, 620 (47%) were categorized in the 50% to 70% category, 513 (39%) in the 71% to 90% category, and 196 (15%) in the 91% to 99% category (Table 2, Fig. 1). Of all 1,329 lesions, 816 (61%) were below the ischemic threshold (FFR ≤0.80). Of the stenoses in the 50% to 70%

Table 1 Baseline Characteristics

Characteristic	FFR Group (n = 509)
Demographics	
Age, yrs	64.6 ± 10.3
Male sex	384 (75)
Clinical	
History	
Previous myocardial infarction	187 (37)
Previous PCI	146 (29)
Diabetes	123 (24)
Unstable angina	147 (29)
Left ventricular ejection fraction, %	57 ± 11
Angiography	
Indicated lesions per patient*	2.8 ± 1.0
Total indicated lesions	1,414
Lesions measured by FFR†	1,329
Chronic total occlusions‡	58

Values are mean ± SD or n (%). *Before randomization, the investigator indicated all lesions to be included in the study and classified them according to severity, by visual assessment, based on the angiogram. †All lesions successfully measured by the fractional flow reserve (FFR), thus excluding all chronic total occlusions (n = 58) and all lesions not assessed by the FFR due to technical reasons (n = 27). ‡Chronic total occlusions were assigned a default FFR value of 0.50 in the FAME study.
PCI = percutaneous coronary intervention.

category by visual assessment, in 402 (65%), the FFR was >0.80 and in 218 (35%), the FFR was ≤0.80. Of the stenoses in the 71% to 90% category, in 104 (20%), the FFR was >0.80 and in 409 (80%), the FFR was ≤0.80. In the 91% to 99% category, 7 (4%) stenoses had an FFR >0.80 and 189 (96%) had an FFR ≤0.80. In Figure 2, examples of the discrepancy between angiographic and functional stenosis severity are shown.

Number of significantly diseased coronary arteries from the angiographic and functional point of view. Of the 509 patients in the FFR-guided arm, 115 (23%) had angiographic 3-vessel disease, and 394 (77%) had angiographic 2-vessel disease (Fig. 3). Of all 115 patients with angiographic 3-vessel disease, 16 (14%) had functional 3-vessel disease, 49 (43%) had functional 2-vessel disease, 39 (34%) had functional single-vessel disease, and 11 (9%) had no functional disease at all.

Table 2 Lesion Characteristics per Category of Angiographic Stenosis Severity

	% Stenosis by Angiography*		
	50% to 70% (n = 620, 47%)	71% to 90% (n = 513, 39%)	91% to 99% (n = 96, 15%)
FFR >0.80	402 (65)	104 (20)	7 (4)
FFR ≤0.80	218 (35)	409 (80)	189 (96)
Mean FFR for all lesions	0.81 ± 0.12	0.67 ± 0.15	0.52 ± 0.15
Mean FFR >0.80	0.89 ± 0.05	0.87 ± 0.05	0.87 ± 0.04
Mean FFR ≤0.80	0.68 ± 0.10	0.62 ± 0.13	0.51 ± 0.13

Values are n (%) or mean ± SD. *Before randomization, the investigator indicated all lesions to be included in the study and classified them according to severity, by visual assessment, based on the angiogram. Only lesions successfully measured by fractional flow reserve (FFR) were included in this analysis.

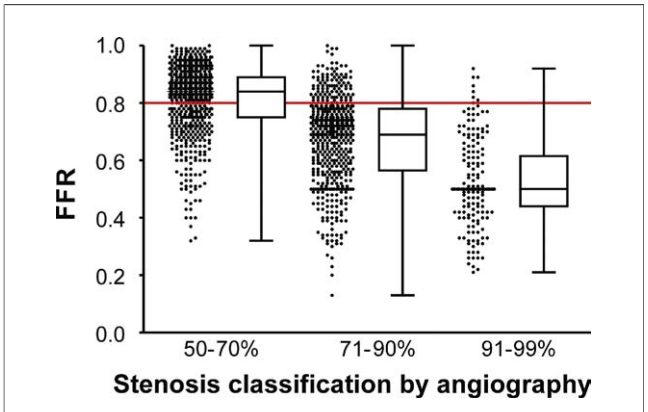

Figure 1 Angiographic Severity Versus Functional Severity of Coronary Artery Stenoses

Box-and-whisker plot showing the fractional flow reserve (FFR) values of all lesions in the categories of 50% to 70%, 71% to 90%, and 91% to 99% diameter stenosis. The **red horizontal line** corresponds to the FFR cut-off value for myocardial ischemia (FFR ≤0.80 corresponds with myocardial ischemia).

Of all 394 patients with angiographic 2-vessel disease, 170 (43%) had functional 2-vessel disease, 176 (45%) had functional single-vessel disease, and 48 (12%) had no functional disease at all.

Discussion

The most important finding in this study is that all stenoses with an angiographic severity of 50% to 70%, 65% were functionally nonsignificant and 35% were functionally significant by the FFR. Even in more severe stenoses between 71% and 90% angiographic stenosis severity, 20% of all lesions did not induce reversible myocardial ischemia as established by an FFR value above the ischemic threshold. Therefore, in patients with multivessel CAD, whether or not taking into account clinical data, one cannot rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50% and 90%. Only in the angiographic stenosis category >90%, visual lesion assessment corresponds well to a lesion's capability of inducing myocardial ischemia because 96% of such lesions are functionally significant by the FFR. Another important finding of this study is that assessment by the FFR of the number of functionally significant diseased coronary arteries in patients with angiographic multivessel disease often leads to a reduction in the number of diseased coronary arteries from a functional point of view. Of all patients with angiographic 3-vessel disease, 86% had only 2 or even less functionally significant diseased coronary arteries.

Myocardial ischemia causes symptoms and affects outcome (1–4). Therefore, the decision to revascularize a coronary artery stenosis should be guided by the presence of myocardial ischemia. Noninvasive stress testing, especially in the setting of multivessel CAD, is often inaccurate in

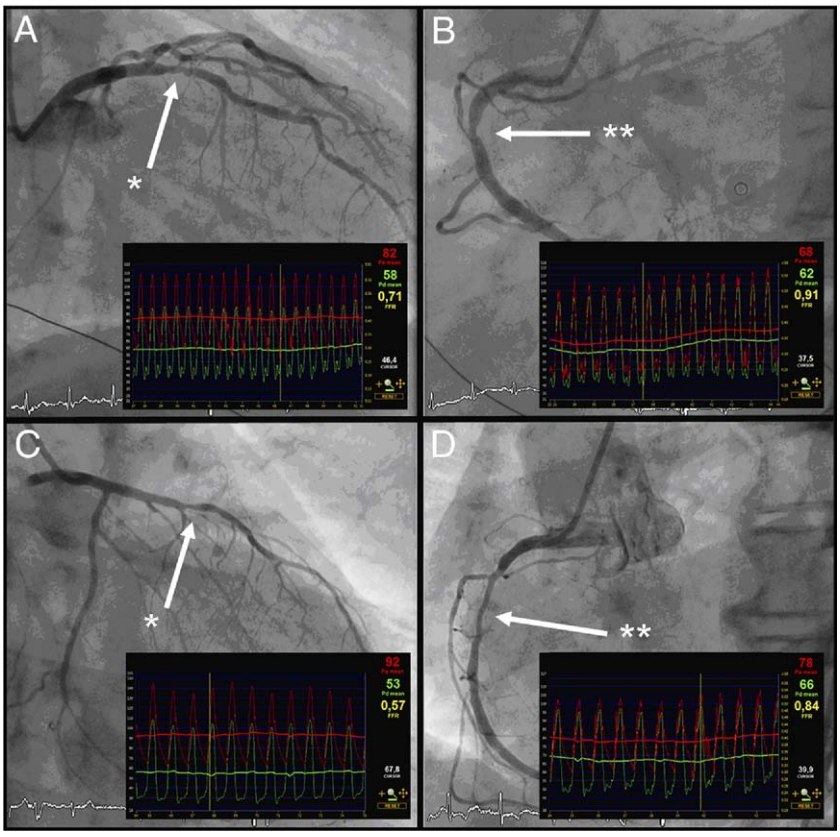

Figure 2 **2 Patients With 2 Equally Severe Stenoses by Angiography But Completely Different Functional Importance as Assessed by the FFR**

A stenosis in the left anterior descending artery **(A, arrow with asterisk)** and a stenosis in the right coronary artery **(B, arrow with double asterisks)** of a patient in the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study. Both lesions were categorized as 50% to 70% stenosis severity by the operator by visual assessment. After randomization to the FFR-guided arm of the FAME study, the FFR was measured in both arteries. The FFR was below the ischemic threshold of 0.80 in the left anterior descending artery (0.71; functionally significant). Subsequently, the left anterior descending artery was stented according to FAME study protocol. The FFR of the right coronary artery was 0.91, indicating a functionally nonsignificant stenosis, and was therefore not stented. **(C, D)** Another patient in the FAME study in which the operator categorized both lesions as 70% to 90%. The left anterior descending artery stenosis **(C, arrow with asterisk)** was functionally significant (FFR = 0.57) and treated by stent placement. The FFR of the right coronary artery stenosis (0.84) **(D, arrow with double asterisks)** was above the ischemic threshold of 0.80. The right coronary artery was not stented. Abbreviation as in Figure 1.

selecting which of several lesions are responsible for reversible myocardial ischemia (6). Furthermore, noninvasive stress testing is performed in less than one-half of the patients undergoing elective PCI (15). As a consequence, selection of stenoses to be stented is mostly just guided by the standard coronary angiogram. Additional functional information by the FFR can, however, be obtained online, is more specific, and has a better spatial resolution (13,16–18) From this and other studies, it is obvious that angiographic stenosis severity corresponds poorly with the presence of myocardial ischemia and is inferior to FFR measurements (19–21). This is also the most probable explanation for the favorable results of the FAME study (5), which showed a significant decrease of 30% to 35% for all types of events in the FFR-guided group at 1 year after PCI with drug-eluting stents in multivessel disease patients.

It should be realized that in all previous randomized studies that compared the different treatment modalities of CAD (i.e., optimal medical therapy alone, optimal medical therapy with PCI, or optimal medical therapy with coronary artery bypass surgery), the selection of lesions to be treated by PCI with stenting was based on angiographic assessment alone—in the best case, combined with clinical data—without certainty that only those lesions responsible for inducible ischemia were stented. In the recently published SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) study, PCI with drug-eluting stents was inferior to coronary artery bypass surgery in patients with angiographic 3-vessel disease (9). In that study, the decision to revascularize a stenosis was based on clinical data and the coronary angiogram alone. In both arms of the SYNTAX study, the treatment goal was complete revascularization from an angiographic point of view. In contrast, in the FFR-guided arm of the FAME study, the goal was complete functional revascularization, and, according to the results of the FAME study, such a strategy was superior to the strategy of complete anatomic revascularization.

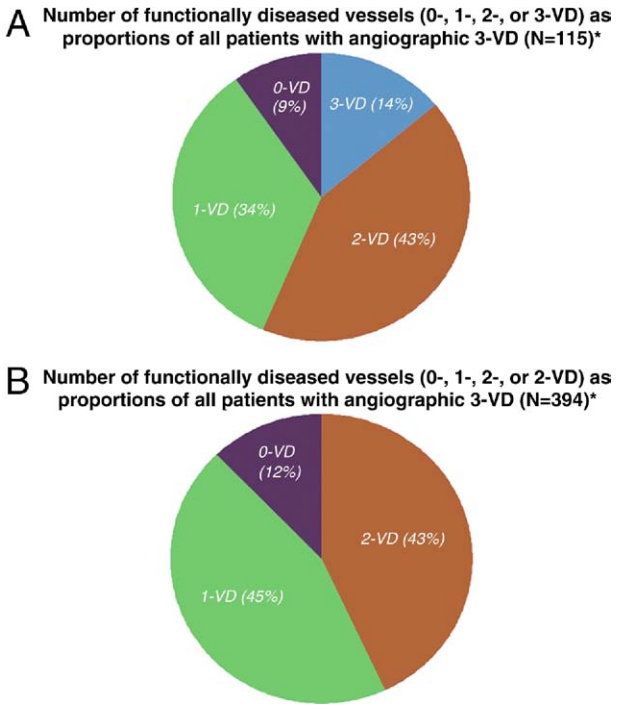

Figure 3 **Proportions of Functionally Diseased Coronary Arteries in Patients With Angiographic 3- or 2-Vessel Disease**

All 509 patients had 3-vessel **(A)** or 2-vessel **(B)** disease by the angiographic coronary artery disease definition. Angiographic coronary artery disease (CAD) is defined as the number of major epicardial coronary arteries (left anterior descending artery, right circumflex artery, right coronary artery) with at least 1 stenosis of ≥50%; the minimum is 2 and the maximum is 3. In all of these patients, the FFR was measured in all angiographically diseased coronary arteries. The respective numbers of diseased coronary arteries by the definition of functional CAD are displayed in the respective segments. Functional CAD is defined as the number of major epicardial coronary arteries with at least 1 stenosis with an FFR ≤0.80; the minimum is 0 and the maximum is 3. VD = vessel disease; other abbreviation as in Figure 1.

Although indirect comparison among studies should be made with caution, one might speculate that if the PCI arms in the SYNTAX trial, COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (7), and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (22) had been FFR guided, it would have improved the outcome of PCI compared with the other treatment modalities. Further randomized studies are mandatory to prove this hypothesis.

In addition to improving prognosis, a critically important goal of revascularization is improvement of angina. Although fewer stents were used, FFR-guided PCI in the FAME study resulted in freedom from angina after 1 year in 81% of the patients, which is high compared with other studies with comparable patients treated by angiographically-guided stenting or medical therapy alone (7,9). This means that selective stenting based on the FFR is very effective in eliminating angina.

Study limitations. The selection of lesions in the FAME study was based on the operator's visual interpretation of the angiogram together with clinical data. It is well-known that there is a high interobserver variability in assessing anatomic coronary stenosis severity, but we do not believe that this induced bias in the class of lesions in this study because the FFR was measured after the lesions had been classified. This reflects daily practice in the catheterization laboratory. Moreover, the operator knew that there was a 50% chance that the patient would be randomized to angiographic guidance alone and that stenting of all identified lesions would be required by the protocol. Thus, the operator was forced to only identify those lesions that he or she truly deemed worthy of PCI based on the angiogram and clinical data.

Conclusions

In patients with multivessel CAD, coronary angiography is an inappropriate tool to identify ischemia-producing stenoses as detected by the FFR. This discrepancy between angiographic and functional stenosis severity is not only present in the 50% to 70% stenosis range but also in the 71% to 90% stenosis range.

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Key Words: coronary angiography ■ drug-eluting stent ■ fractional flow reserve ■ multivessel coronary artery disease ■ percutaneous coronary intervention.