Review

Association of Coronary Stenosis and Plaque Morphology With Fractional Flow Reserve and Outcomes

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IMPORTANCE Obstructive coronary lesions with reduced luminal dimensions may result in abnormal regional myocardial blood flow as assessed by stress-induced myocardial perfusion imaging or a significant fall in distal perfusion pressure with hyperemia-induced vasodilatation (fractional flow reserve [FFR] ≤0.80). An abnormal FFR has been demonstrated to identify high-risk lesions benefitting from percutaneous coronary intervention while safely allowing revascularization to be deferred in low-risk lesions, resulting in a decrease in the number of revascularization procedures as well as substantially reduced death and myocardial infarction. While FFR identifies hemodynamically significant lesions likely to produce ischemia-related symptoms, it remains less clear as to why it might predict the risk of acute coronary syndromes, which are usually due to plaque rupture and coronary thrombosis.

OBSERVATIONS Although the atherosclerotic plaques with large necrotic cores (independent of the degree of luminal stenosis) are known to be associated with vulnerability to rupture and acute coronary syndromes, emerging evidence also suggests that they may induce greater rates of ischemia and reduced FFR compared with non–lipid-rich plaques also independent of the degree of luminal narrowing. It is proposed that the presence of large necrotic cores within the neointima may be associated with the inability of the vessel to dilate and may predispose to ischemia and abnormal FFR.

CONCLUSIONS AND RELEVANCE Having a normal FFR requires unimpaired vasoregulatory ability and significant luminal stenosis. Therefore, FFR should identify lesions that are unlikely to possess large necrotic core, rendering them safe for treatment with medical therapy alone. Further studies are warranted to determine whether revascularization decisions in patients with stable coronary artery disease could be improved by assessment of both plaque composition and ischemia.

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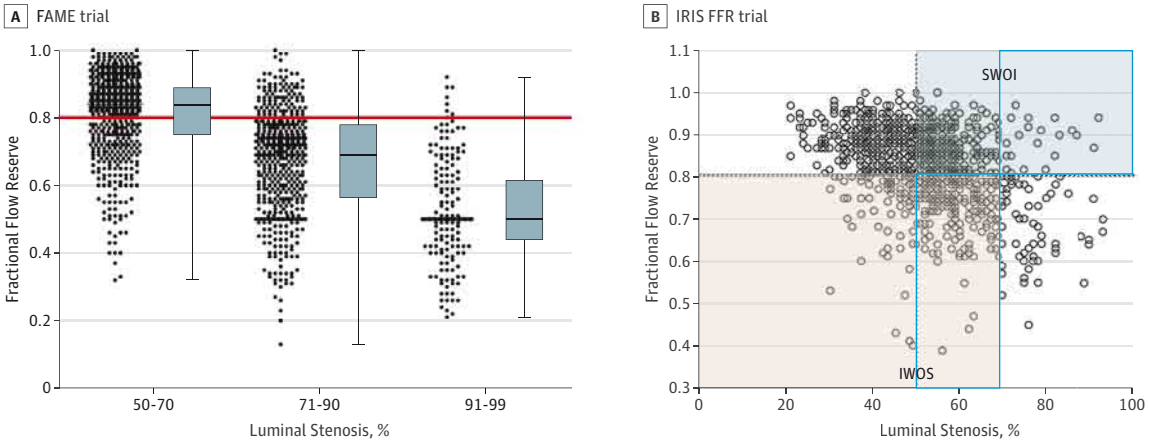
The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial[1,2] demonstrated that in patients with stable ischemic heart disease, an FFR-guided strategy to identify hemodynamically significant lesions requiring percutaneous coronary intervention (PCI) can safely defer revascularization in lower-risk lesions and reduce the number of procedures and rates of future urgent revascularization due to unstable angina or myocardial infarction (MI) compared with lesion selection by angiography alone. The FAME 2 trial[3,4] extended these findings and demonstrated that deferring PCI in lesions with an abnormal FFR results in high rates of progressive ischemic symptoms, unstable angina, and MI, which require revascularization within 1 to 2 years. These outcomes could be prevented by PCI.[1-4] Although FFR identifies hemodynamically significant lesions likely to produce ischemia-related symptoms, less clear is why FFR might predict the subsequent risk for ACS resulting from plaque rupture and coronary thrombosis, which is usually caused by lipid-rich plaques with distinct histological features.[5-13] These observations prompted us to explore whether plaque features of vulnerability and their physiologic properties are associated, causing a relevant pressure gradient across the lesion detectable by FFR.

Severity of Luminal Stenosis and FFR

Ischemia is best defined as an inadequate supply of oxygen relative to myocardial demand. The most widely used tests to assess ischemia are myocardial perfusion imaging (MPI) (noninvasive) and FFR (invasive). Myocardial perfusion imaging and FFR use the abnormal blood flow in the affected vessels as a surrogate marker for ischemia. In turn, this abnormal blood flow is related to relative or complete inability of the vessel to dilate on stress. Although the detection of ischemia is

Figure 1. Correlation Between the Degree of Luminal Stenosis by Coronary Angiography and Ischemia Detected by Fractional Flow Reserve (FFR)



A, In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial, among the 623 lesions with 50% to 70% stenosis, 218 (35.0%) had an FFR of 0.80 or less (FFR-verified ischemia without significant stenosis [IWOS]). Among 520 lesions with 71% to 90% stenosis, 104 (20.0%) demonstrated an FFR of greater than 0.80 (FFR-verified stenosis without ischemia [SWOI]). Boxes indicate first and third quartiles; horizontal lines in boxes, median; whiskers, minimum and maximum data distribution (modified from Tonino et al[18]). B, In a prospective study of 1000 patients (Study of the Natural History of FFR Guided Percutaneous Coronary Intervention[16] [IRIS FFR]), 343 of 605 coronary lesions (56.7%) with less than 50% angiographic stenosis had an FFR of greater than 0.80 (FFR-verified SWOI) (entire light blue area), whereas 75 of 461 lesions (16.3%) with less than 50% luminal stenosis had an FFR of 0.80 or less (FFR-verified IWOS) (light brown area). Using a cut point for a severe stenosis diameter of 70%, a large proportion of lesions with less than 70% angiographic diameter stenosis had an FFR of 0.80 or less (IWOS; entire red area). Among lesions with 50% to 70% angiographic diameter stenosis, approximately half were positive for FFR and half were negative for FFR (ie, no predictive value). Data points indicate degree of stenosis and corresponding FFR (modified from Park et al[15]).

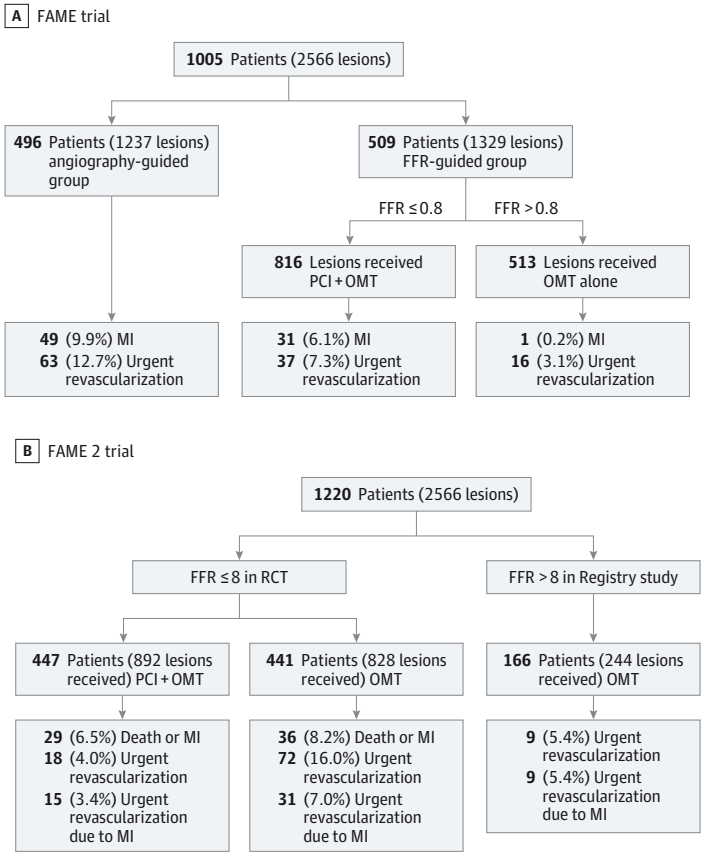
likely to be indicative of a severe epicardial coronary artery stenosis,[14] this association is not perfect.[2,15,16] Some severely stenotic lesions may not result in detectable ischemia (stenosis without ischemia [SWOI]), whereas other lesions with only a mild to moderate degree of angiographic stenosis may induce ischemia (ischemia without significant stenosis [IWOS]).[17] In the FAME study,[1,18] more than one-third of lesions with an angiographic 50% to 70% angiographic diameter stenosis demonstrated an FFR of 0.80 or less whereas one-fifth of lesions with a 71% to 90% angiographic diameter stenosis demonstrated an FFR greater than 0.80 (SWOI) (**Figure 1**A). In a separate prospective study of 1000 patients with 1129 coronary lesions,[15] more than one-half of lesions with greater than 50% angiographic diameter stenosis had an FFR greater than 0.80, whereas 1 in 7 lesions with less than 50% angiographic diameter stenosis had an FFR of 0.80 or less (IWOS) (Figure 1B). Among lesions with 50% to 70% luminal stenosis, approximately half had an FFR of 0.80 or less, whereas the other half had a normal FFR and no lesion-specific ischemia. These observations emphasize the importance of identifying factors beyond luminal stenosis that might contribute to inducible ischemia.

Some cases of IWOS may be explained by the inability of angiography to discriminate the true lesion severity with accuracy owing to diffuse disease or other artifacts.[19] Microvascular disease can result in inducible ischemia as detected by an abnormal MPI finding or abnormal coronary flow reserve in the absence of a severe epicardial coronary artery stenosis, which explains some cases of IWOS. Unlike coronary flow reserve, however, FFR is derived from the epicardial pressure gradient on vasodilator-induced maximal coronary flow and excludes microcirculatory resistance. Therefore, FFR is largely independent of changes in the basal flow and status of the microcirculation or systemic hemodynamics,[20] and microvascular disease cannot explain FFR-positive IWOS. On the other hand, some cases of MPI-verified SWOI may be explained by short lesion length, redundancy of the arterial supply through collateral vessel formation, and a limited myocardial territory supplied by the diseased artery. As regards FFR, features such as lesion length, entrance angle, exit angle, size of the reference vessel, and absolute flow relative to the territory supplied are important in determining focal hemodynamic responses to hyperemia and might explain the discrepancy between the epicardial luminal narrowing and FFR-based physiologic significance of the lesion in many cases.[21,22] Regardless of the causes, angiography is recognized as a suboptimal method to assess the ischemic potential of an epicardial coronary stenosis.

Plaque Morphology and FFR

Although the factors discussed above explain IWOS and SWOI in some cases, they do not explain the discrepancy in many others. Recent reports have linked the presence of lipid-rich plaques to the presence of FFR-verified ischemia demonstrated to be independent of the degree of luminal narrowing.[23,24] In a concomitant study of radiofrequency intravascular ultrasonography (IVUS) and FFR[25] performed in coronary arteries with 50% to 70% angiographic diameter stenosis, only the lipid-rich plaque type correlated with a reduced FFR; the FFR was concomitantly lower in increasingly larger necrotic cores. These results were confirmed in a larger study of 407 coronary lesions in 252 patients who underwent coronary computed tomographic angiography (CTA), computed tomography–based FFR assessment, and invasive angiography and FFR assessment.[23] The presence of a large plaque volume, large low-attenuation plaque volume, and higher positive remodeling index were found to be strongly predictive of reduced FFR regardless of

Figure 2. Utility of Fractional Flow Reserve (FFR) in Differentiating High-Risk vs Low-Risk Plaques and Identifying Those Lesions in Need of Revascularization



The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) and FAME 2 trials have demonstrated that percutaneous coronary intervention (PCI) may be safely deferred in lesions with an FFR of greater than 0.80, and conversely those lesions with an FFR of 0.80 or less have an improved prognosis with PCI. In the FAME trial, among 513 with deferred angiography and severe lesions (FFR >0.80) in the FFR group, only 1 myocardial infarction (MI; 0.2%) occurred and only 16 (3.1%) urgent revascularizations among 513 lesions were needed during the 2-year follow-up, compared with 49 MIs (9.9%) and 63 urgent revascularizations (12.7%) in the angiography-guided group of patients. In the FAME 2 trial, in which lesions with an FFR of 0.80 or less were randomized to PCI with optimum medical therapy (OMT) vs OMT alone, the rates of postprocedural MI, total urgent revascularizations, and urgent revascularizations owing to MI were significantly higher in the OMT group compared with the PCI + OMT group and compared with the outcomes in a parallel registry OMT group of patients in whom the FFR was greater than 0.80 in all lesions. However, the rates of death and MI were not significantly different between the 2 groups[4]; an 8.2% chance of death or MI in 2 years was found in the FFR-positive lesions treated with OMT alone, not significantly different from the 6.5% rate in the OMT group (developed from the FAME and FAME 2 studies[1-4]).

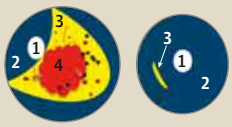
the degree of stenosis on multivariable analysis. Low-attenuation plaques (considered a CTA surrogate for necrotic core) with a positive remodeling index (termed 2-feature–positive plaque [2FPP]) have been reported to be associated with major adverse coronary events.[5,26] In another recent study of 484 coronary vessels,[24] comparison of coronary CTA-defined plaque characteristics and luminal stenosis and FFR assessed from CTA with invasive angiography and invasive FFR revealed that large low-attenuation plaques (volume >30 mm^3 on CTA) constituted the strongest lesion characteristic predictive of invasive FFR. Large low-attenuation plaques yielded diagnostic improvement for detecting lesion-specific ischemia by invasive FFR beyond degree of stenosis and other lesion characteristics, including lesion length.[24] In studies performing CTA and MPI concurrently,[23,27] the presence of 2FPP was associated with greater than 5% total myocardial ischemia burden, and conversely the presence of significant ischemia had a high positive predictive value for detecting 2FPP. The extent of luminal stenosis was not different between plaques that caused significant ischemia and those that did not; both demonstrated mean luminal stenosis of 75%.[27] Therefore, large lipid-rich, positively remodeled plaque (ie, 2FPP), and not only the stenosis severity, demonstrates a strong likelihood of inflicting myocardial ischemia.

This association between large necrotic cores and low FFR (independent of luminal stenosis) cannot be readily explained by the currently recognized determinants of physiologic lesion severity. Fractional flow reserve is presumed to measure the net physiologic effects of a coronary stenosis by maximally dilating the distal arteriolar bed with the administration of adenosine. Although the reduced FFR in the absence of severe stenosis (IWOS) cannot be explained by adenosine-mediated arteriolar dilatation, nitroglycerin (invariably given before adenosine administration) may not induce dilatation at the site of a plaque containing a large necrotic core with

Figure 3. Coronary Stenosis Severity, Fractional Flow Reserve (FFR), and Underlying Pathologic Features

Angiographic Diameter Stenosis Severity, %	FFR	No. of Lesions (% in Subgroup) [% in Entire Cohort]	Possible Histologic Feature
Normal	>0.80	0	
50-70	>0.80	402 (65) [33]	 2FNP with moderate luminal stenosis
	≤0.80	218 (35) [18]	 2FPP with moderate luminal stenosis
71-90	>0.80	104 (20) [8]	 2FNP with moderate to severe luminal stenosis
	≤0.80	409 (80) [33]	 2FPP with moderate to severe luminal stenosis
			 2FNP with severe luminal stenosis

Histological features:
1. Coronary artery lumen
2. Fibrous part of the plaque (entire navy blue area)
3. Necrotic core (entire yellow area) that includes neovascularization (small red lines), red blood cell leakage (red dots), macrophages (black stars), and intraplaque hemorrhage (4)



In this diagram, the various groups of lesions in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial are categorized according to their degree of luminal stenosis and FFR value. The possible underlying histological plaque features in each subgroup are postulated using the concepts developed in the text. Specifically, the likelihood of the presence of positively remodeled large-volume 2-feature–positive plaque (2FPP, with a positive remodeling index and a necrotic core) is represented in different groups of lesions according to the following observations: (1) The presence of large-volume 2FPP strongly predicts FFR-verified ischemia. (2) FFR-verified ischemia is a sensitive tool for detecting large-volume 2FPP. (3) Large-volume 2FPP is unlikely to be present in the FFR-negative subgroup; therefore, most plaques in the FFR-negative subgroup likely consist of nonatheromatous fibrotic lesions and less likely are associated with severe degree of luminal narrowing or long lesion length. (4) In the absence of significant luminal narrowing, FFR-verified ischemia is likely owing to the presence of large-volume (necrotic core) 2FFP. Lesion length and plaque volume are not depicted but may have a modulating effect on these considerations. (5) In the presence of a severe luminal stenosis (eg, angiographic diameter stenosis, >70%), an FFR of greater than 0.80 suggests a normal vessel's ability to dilate, which further argues against the presence of large-volume 2FPP (or long lesion length). Most plaques in this subgroup are therefore likely fibrous, not lipid-rich lesions, and have short lesion length. (6) In the presence of severe luminal narrowing, an FFR of 0.80 or less could be owing to the presence of lipid-rich 2FPP or a fibrous, long-length lesion. The criteria in this figure do not detect 1-feature–positive plaques, which may be represented in either category and may have an intermediate prognosis between 2FPP and plaque with no high-risk features. 2FNP indicates 2-feature–negative plaque; black and red dots, red blood cells leaked from incompetent vessels (developed from the FAME and FAME 2 studies[1-4]).

extraluminal expansion and positive remodeling. If a lipid-rich plaque is associated with local inability of the stenotic vascular segment to dilate to the same extent as the rest of the vessel (possibly owing to a maximally stretched vessel similar to the glagovian limit[28]), the result would be a relative pressure drop at the time of maximal hyperemia. This process could underlie some of the unexplained cases of IWOS. On the other hand, luminally stenotic plaques without large necrotic cores and without outwardly stretched vessels (eg, fibrotic or fibrocalcific plaques) may retain locally vasodilatory potential and at least partially explain SWOI.[29-31] If this explanation is valid, then the absence of ischemia may signal the presence of preserved vasodilatory capacity, which may also indicate that the plaque is unlikely to contain a large necrotic core.

Local oxidative stress and vascular inflammation have also been proposed to contribute to impaired vasodilator capacity.[30,31] The lipid-rich necrotic core, a hallmark of the vulnerable plaque, inflicts local oxidative stress[32] and thus could play a contributory role.[17] The relationship between plaque composition (fibrous, fibrofatty, fatty, or calcific as identified by IVUS radiofrequency spectral analysis) and the vasodilatory potential of the local epicardial coronary artery evaluated by acetylcholine challenge suggested that only the presence of a necrotic core was associated with impaired vasodilator responses.[29]

Figure 4. Differences in Fractional Flow Reserve (FFR)– and Angiography-Guided Therapies by Plaque Type

Based on the possible histological characteristics of each plaque type presented in Figure 5, the differences in FFR-guided treatment vs angiography-guided treatment are depicted. The chance of future events with each approach is estimated (range, + to ++++) based on plaque morphology-related prognostic data from prospective studies.[4,6] With FFR-guided therapy, nearly all high-risk lesions (including vulnerable plaques) are treated with percutaneous coronary intervention (PCI) plus optimum medical therapy (OMT), whereas lesions that are at low risk for future events are treated with OMT alone. In the angiography-guided therapy group, some lesions with angiographic diameter stenosis of 50% to 70% will be treated with PCI, whereas others will receive OMT alone, depending on the operator's assessment of the lesions' severity (which is known to have wide variability). Up to 35% of lesions in this subgroup in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial had an FFR of 0.80 or less. Therefore, the angiography-guided approach will leave some high-risk lesions with vulnerable features that do not undergo revascularization. This finding may in part explain the paradoxically increased rate of urgent revascularization during follow-up with angiography-guided therapy despite the greater use of initial PCI in addition to more frequent stent-related thrombosis and restenosis events. Moreover, angiography-guided therapy will lead to revascularization of many lesions that may safely be deferred to OMT alone, which increases the risk for periprocedural complications. Graphics for the possible histological features are described in Figure 3.

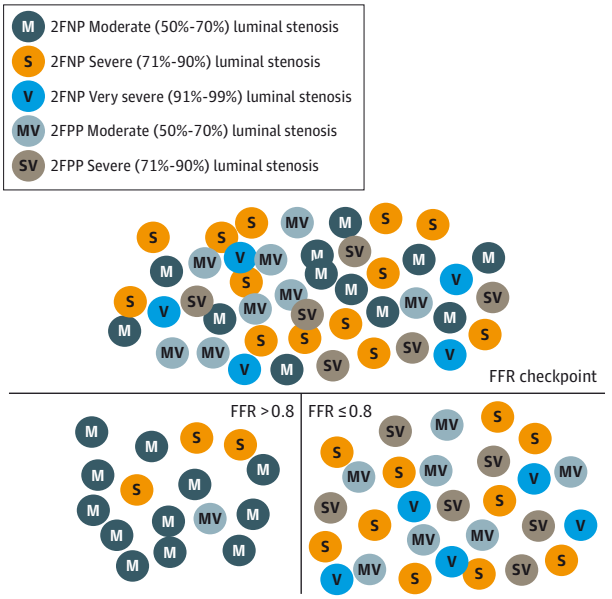
FFR and Subsequent Clinical Events

In the last decade, the identification of the hemodynamic significance of coronary artery lesions has become increasingly important. The FAME and FAME 2 studies demonstrated that revascularization guided by FFR is superior to angiography-guided therapy and optimum medical therapy (OMT).[1,4] In the FAME trial[1] (**Figure 2**A), the reduction in rates of major adverse cardiac events at 1 and 2 years with FFR-guided therapy compared with angiography-guided therapy was driven by a significant decrease in the incidence of MI and the need for urgent revascularization.[1,2] Analyses of the results of the FAME study[2] (Figure 2A) demonstrate that the superiority of the FFR-guided therapy most likely

emerges from safe deferral of FFR-negative lesions to OMT, decreasing unnecessary procedures and their consequent complications (Figure 2A). The FAME study also demonstrates that, compared with angiography-driven therapy, the FFR-guided strategy decreases the likelihood of MI by one-third (6.1% vs 9.9%) and urgent revascularization in a setting of MI by two-fifths (7.3% vs 12.7%). In the FAME 2 trial (Figure 2B), deferring PCI of stenotic lesions with an FFR of 0.80 or less resulted in higher rates of urgent revascularization (16.0% vs 4.0%) and postprocedure death or MI (8.2% vs 6.5%) compared with PCI for such lesions.[3,4] In that study,[3,4] the main difference in outcomes emerged from the need for urgent revascularization in the OMT group. As a result, it is currently believed that all FFR-positive lesions should be treated with revascularization. However, the rates of death and MI were not significantly different between the 2 groups in the FAME 2 study[4]; there was an 8.2% chance of death or MI in 2 years in the FFR-positive lesions treated with OMT alone, compared with 6.5% rate in the OMT group[4] (Figure 2B). Therefore, we can conclude from these observations that (1) lesions with negative FFR findings can be treated safely with OMT alone and (2) although lesions with positive FFR findings are at higher risk for future events, whether all FFR-positive lesions need revascularization remains unclear.

In FAME and FAME 2, an FFR-based strategy resulted in reduced rates of MI (and the composite outcome of death or MI), especially in the postprocedural period, and in reduced rates of new-onset ACS. This result raises an important issue. Although FFR identifies hemodynamically significant lesions likely to produce ischemia-related symptoms, how does FFR also predict the likelihood of ACS and MI that usually result from plaque rupture and coronary thrombosis?

Figure 5. Fractional Flow Reserve (FFR) as a Security Checkpoint for Detecting Plaques at High Risk for Future Events



Detection of ischemia is a sensitive (but not specific) measure for detecting large-volume 2-feature–positive plaque (2FPP, with a positive remodeling index and a necrotic core), independent of the angiographic degree of luminal stenosis. FFR-guided therapy thus may be considered a checkpoint that leaves very few large lipid-rich 2FPP—those with highest risk for future events—to medical therapy alone. On the other hand, FFR leads to revascularization of most lipid-rich 2FPP (moderate [MV] and severe [SV] vulnerable lesions) and plaque with a severe degree of luminal stenosis without features of vulnerability (severe [S] and very severe [V] nonvulnerable lesions). 2FNP indicates 2-feature–negative plaque; M, moderate nonvulnerable lesions.

Plaque Morphology: A Link Between FFR and Clinical Outcomes?

Examining the outcomes of different types of stenoses in the FAME trials allows formulation of a hypothesis regarding their possible underlying composition (**Figure 3**). As mentioned before, plaques with large necrotic cores should be predictive of ischemia and ACS. Conversely, despite luminal narrowing, the absence of ischemia (reflecting preserved vasodilatory capacity or SWOI) indicates plaques without large necrotic cores. This finding suggests that ischemia may be a sensitive but not specific surrogate for the presence of a positively remodeled plaque with a large necrotic core and that the lack of ischemia indicates absence of such lipid-rich plaques with a normal vasodilator response.[27] Therefore, in the FAME trial, an FFR value of greater than 0.80 in 104 lesions with angiographic stenosis severity of 71% to 90% might suggest the absence of large necrotic core–carrying 2FPP in that subgroup. Conversely, the 218 plaques with intermediate luminal stenosis (50%-70% by angiography) with an FFR of 0.80 or less probably indicates large-volume 2FPP or longer lesions in which the severity could not be determined accurately by angiography (Figure 3).

Because an abnormal FFR indicates a very severe stenosis or a plaque with a large lipid burden or both, treating all FFR-positive stenoses with PCI will lead to the revascularization of most plaques with features of vulnerability independent of the degree of luminal narrowing. On the other hand, treating all stenoses with a normal FFR with OMT alone appears to be safe, because such stenoses would have little, if any, large lipid-rich 2FPP (**Figure 4**). The study by Motoyama et al[26] demonstrated that 2FPP was associated with the highest (22.5% for 27 months) event rate; events were more likely to occur in those with larger volumes, bigger necrotic cores, and a greater positive remodeling index. This more severe 2FPP, which might be associated with impaired local vasodilator capacity, would likely cause ischemia or FFR positivity. In the study by Motoyama et al,[26] plaque without a positive remodeling index or low-attenuation plaque had a very low (<0.5% during 27 months) event rate. The long-term follow-up of these patients in a subsequent study[33] indicated that the 10-year event rates in positively remodeled stenosis with lipid-rich 2FPP is 9-fold higher than in the luminally stenotic lesions without 2FPP.[33] Similarly, among patients treated with OMT in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study,[13] ACS events during 3 years occurred in only 5 of 1650 plaques (0.3%) that by radiofrequency IVUS had a plaque burden of less than 70%, a lumen area of greater than 4.0 mm^2, and no thin-cap fibroatheroma.

We therefore propose that the benefit of FFR-guided therapy is based on the association of local vasodilator reserve and features of plaque vulnerability, that is, the extent of vascular

remodeling, plaque volume, and size of the necrotic core. Fractional flow reserve is thus able to identify lesions indirectly with a low risk for plaque rupture and coronary thrombosis that may be treated effectively with OMT alone, while also identifying probably most lesions at high risk for future ACS and those producing unacceptable degrees of angina owing to extreme luminal compromise.

Conclusions

Normal vasodilatory capacity is a prerequisite for lack of a significant pressure drop during hyperemia. Hence, a coronary stenosis with a normal FFR has a low likelihood of having plaques with high-risk features. This finding makes FFR a reliable tool to detect sizable vulnerable plaques independent of the severity of luminal narrowing. The deferral of FFR-negative lesions to OMT is therefore safe and avoids unnecessary revascularization and stent procedures, reduces periprocedural complications, and results in fewer late stent-related events (thrombosis and restenosis) compared with a more liberal angiography-guided approach. In essence, FFR may be considered a security checkpoint that prevents most plaques with vulnerable features from going undetected (**Figure 5**).

The combination of ischemia testing (eg, MPI and invasive or noninvasive FFR) with plaque composition assessment (eg, CTA, radiofrequency IVUS, and optical coherence tomography) to guide revascularization decisions may further improve risk stratification and patient outcomes compared with either strategy alone. As tools to assess plaque composition become prospectively validated to predict subsequent major adverse cardiac events, which was demonstrated with radiofrequency IVUS in the PROSPECT study,[13] future trials should be performed to compare the utility of FFR alone vs plaque composition assessment alone vs a combined approach in guiding revascularization decisions for patients with stable coronary artery disease and those with stabilized ACS.

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Study concept and design: Ahmadi, Narula.
Acquisition, analysis, or interpretation of data: Ahmadi, Stone, Serruys, Wong, Nørgaard, O'Gara, Chandrashekhar, Narula.
Drafting of the manuscript: Ahmadi, Stone, Leipsic, Narula.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ahmadi, Shaw, Narula.
Administrative, technical, or material support: Ahmadi, Narula.
Study supervision: Leipsic, Narula.

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