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EDITORIAL COMMENT

Predicting Outcomes After Percutaneous Coronary Intervention Using Relative Change in Fractional Flow Reserve*

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Fractional flow reserve (FFR) is a well-validated surrogate for ischemia, which is continuously correlated with the natural history of coronary artery disease as shown in multiple studies, including a meta-analysis and substudy from the FAME II (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (1,2). When measured after percutaneous coronary intervention (PCI), FFR continues to convey prognostic information (3), because now a revascularized lesion with high FFR basically has similar long-term outcome to an unstented lesion without an ischemic FFR value (4), whereas patients with low FFR after PCI have a significantly worse outcome. Pijls et al. (5) first reported that the rate of target vessel revascularization after PCI with bare-metal stents was 4.9% when the post-PCI FFR was >0.95, 6.2% when 0.90 to 0.95, and 20.3% when <0.90 at 6 months. In a more recent study using drug-eluting stents, Piroth et al. (3) showed that the rate of target vessel revascularization at 2 years was 2.4% when the post-PCI FFR was >0.92 and 7.0% when <0.88, reflecting the better outcome with drug-eluting stents. Similarly, Li et al. (6) reported that the rate of target vessel revascularization at 1 year was 3.8% vs. 8.8% using a post-PCI FFR cutoff value of 0.88 and Agarwal et al. (7) reported that the rate of target vessel revascularization at 31 months was 8% versus 12% using a post-PCI FFR cutoff value of 0.85. However, in these previous studies, few data are included regarding the contribution of residual diffuse disease versus stent-related issues to the poor long-term outcome in patients with a low FFR after apparently successful PCI. One way to determine which factor is playing a greater role in the low FFR would be to perform a pullback of the pressure wire after PCI during hyperemia.

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In this issue of *JACC: Cardiovascular Interventions*, Lee et al. (8) not only report on the prognostic impact of post-PCI FFR, but also investigate the added value of determining the %FFR change from pre- to post-PCI. In this multicenter, prospective registry from Korean and Japanese institutions using robust methodology, including a blinded core laboratory and external events adjudication committee, a total of 621 patients underwent PCI using second-generation drug-eluting stents based on positive pre-PCI FFR (≤0.80). Post-PCI FFR was obtained and %FFR change was calculated as (post-PCI FFR minus pre-PCI FFR)/pre-PCI FFR. The authors found that the best cutoff values for post-PCI FFR was 0.84 and for %FFR change was 15%, both of which were equally predictive of target vessel failure at 2 years. Interestingly, the %FFR change provided additional prognostic value to the low post-PCI FFR group (target vessel failure [TVF]: hazard ratio: 4.334, 95% confidence interval: 1.205 to 15.594; $p = 0.025$), but not to the high post-PCI FFR group (hazard ratio: 1.381, 95% confidence interval: 0.279 to 6.845; $p = 0.692$).

These findings may be explained by the fact that a patient with primarily a focal stenosis and little

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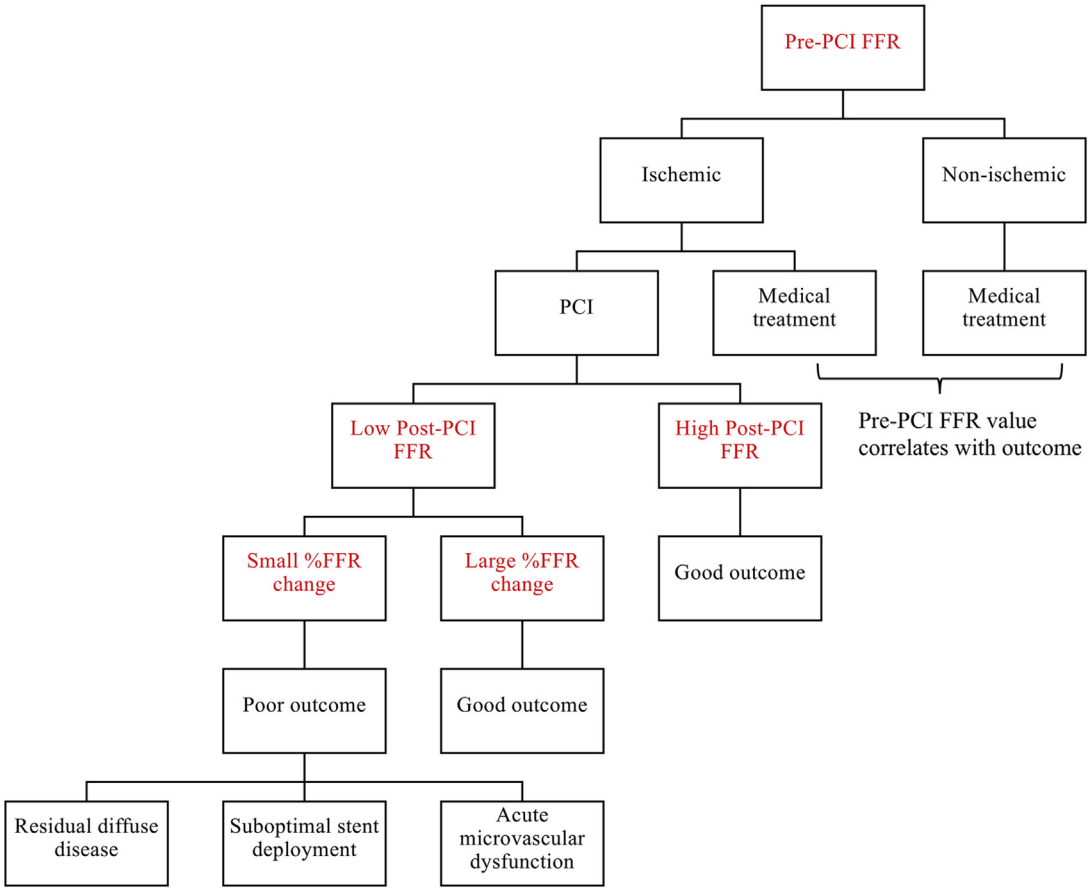
FIGURE 1 **Current Understanding of Pre-PCI FFR, Post-PCI FFR, and %FFR Change**



According to a pre-PCI FFR value of a lesion, decision of revascularization or medical treatment will be made. If medically treated either in ischemic or nonischemic range, the pre-PCI FFR value will continuously correlate with an outcome, in other words, the natural history of coronary artery disease. When a lesion is revascularized, measurement of post-PCI FFR may be considered. If a post-PCI FFR value is high, a good outcome will be expected. On the other hand, if a post-PCI FFR value is low, calculation of %FFR change may be considered. If a %FFR change is large, a good outcome will be expected. If a %FFR change is small, a poor outcome is expected due to possible residual diffuse disease, suboptimal stent deployment, or the existence of microvascular dysfunction. FFR = fractional flow reserve; PCI = percutaneous coronary intervention.

diffuse disease who has a high post-PCI FFR will have a large or small %FFR change depending on the original severity of the epicardial stenosis. And they will generally have a good outcome regardless, as was seen in this study where the TVF rate was similar between the small and large %FFR change groups (2.8% vs. 2.6%; p = 0.691) when the post-PCI FFR was high. The lack of prognostic difference based on % FFR change in patients with high post-PCI FFR also suggests the importance of achieving functionally complete revascularization as shown in 2 recent studies (9,10).

On the other hand, in a patient with a focal stenosis but more predominant diffuse residual disease, the post-PCI FFR will be low even after successful PCI of the focal lesion. In this scenario, PCI will lead to a small %FFR change if the stented lesion was not very severe, as was seen in this study where this group of patients with low post-PCI FFR and small %FFR change had the highest pre-PCI FFR values on average. On the other hand, PCI will lead to a large % FFR change if the stented lesion was severely narrowed, despite the presence of diffuse residual disease. The TVF rate was higher in the group with small %FFR change compared with the group with the large %FFR change (14.3% vs. 4.1%; p = 0.014), suggesting the importance of diffuse residual atherosclerotic disease on long-term outcome.

Another explanation for the increased rate of TVF in the patients with low post-PCI FFR and small % FFR change, besides residual diffuse epicardial disease, is acute microvascular dysfunction related to embolization of plaque or thrombus at the time of PCI. Periprocedural myocardial infarction has been associated with adverse longer-term outcomes. The authors (8) do not report post-PCI troponin levels, which would shed light on this possibility.

A final explanation for the increased adverse event rate in this group, which may be the most likely reason, is that these patients had milder focal epicardial disease (higher pre-PCI FFR) and subsequent stenting had less effect on relieving ischemia (lower post-PCI FFR) because of residual diffuse disease. These patients may have therefore remained more symptomatic leading to repeat coronary angiography and PCI. The increase in TVF was driven entirely by target vessel revascularization and not by death or myocardial infarction, which were low in all groups. A recent substudy from stable patients in the FAME 1 and FAME 2 trials found that the delta FFR from pre-PCI to post-PCI correlated with improvement in quality of life after PCI, with the group with the lowest change in FFR having the least improvement in quality of life and angina (11).

What should an operator do if a low post-PCI FFR and small %FFR change is measured? First, one can perform a slow pullback of the pressure wire during maximal hyperemia to identify whether the low FFR is a result of diffuse disease (or an angiographically undetected focal lesion) proximal or distal to the stent or due to poor stent deployment. Intravascular imaging can also be performed to evaluate the stent deployment. Further expansion of the stent can be performed if necessary, or another stent can be deployed if there is an edge dissection. In the case of diffuse disease and a gradual FFR drop, seen more often in patients with diabetes mellitus, hypercholesterolemia, and older age, optimizing medical therapy is the best option (**Figure 1**).

Finally, a word of caution for interpreting the results from our East Asian colleagues and applying them to the U.S. health care setting. The event rates, especially hard endpoints, are generally low, partly because of the low-risk population and possibly because of the higher penetration of intravascular imaging (12). On the other hand, the rate of repeat revascularization may be artificially high, given that many post-PCI patients still undergo routine coronary angiographic follow-up (13).

Lee et al. (8) should be congratulated on conducting this rigorous international registry and highlighting the concept of change in FFR as an additional predictor of outcomes after PCI. Future studies are warranted to validate their new concept for stratifying post PCI patients.

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