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EDITORIAL COMMENT

Benefits of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention*

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The ultimate goals of coronary revascularization in patients with coronary artery diseases are 2-fold: to alleviate anginal symptoms and to improve their prognosis. The landmark ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial showed that coronary revascularization can help relieve symptoms in patients but does little to improve the prognosis in patients with stable ischemic heart disease (SIHD).[1] The latest guidelines for coronary revascularization directly reflect these results, stating that revascularization is recommended to improve symptoms in patients with refractory angina despite medical therapy, but including the caveat the usefulness of percutaneous coronary intervention (PCI) to improve survival is uncertain.[2] After the ISCHEMIA trial, the role of PCI for patients with SIHD has been called into question, particularly in terms of the prognostic value.

In this issue of *JACC: Asia*, Hong et al[3] have shown clinical and economic benefits of fractional flow reserve (FFR)-guided PCI over angiography-guided PCI from the Korean nationwide insurance service database. In this study, clinical data and the medical costs were analyzed for 134,613 patients with either stable or unstable angina who underwent PCI between 2011 and 2017 in Korea. Among them, 129,497 patients had the angiography-guided PCI and 5,116 patients had the FFR-guided PCI. During the follow-up period, a primary outcome, defined as a composite of all-cause death and spontaneous myocardial infarction (MI), was observed less frequently in patients who underwent the FFR-guided PCI than those who underwent the angiography-guided PCI (7.0% vs 9.5%, adjusted HR [HR]: 0.773, 95% CI: 0.685-0.872; $P < 0.001$). This difference was driven by lower risks in the FFR-guided PCI of all-cause mortality (5.8% vs 7.7%, adjusted HR: 0.798, 95% CI: 0.698-0.913; $P = 0.001$) and by a lower incidence of spontaneous MI (1.6% vs 2.2%; adjusted HR: 0.751; 95% CI: 0.587-0.959; $P = 0.022$). In addition to these clinical benefits, cost-effectiveness has been demonstrated. The expense was greater for those with the FFR-guided PCI at the index admission than those with the angiography-guided PCI (median $6,265.10 vs $5,385.60; $P < 0.001$), but the FFR-guided PCI cost patients less after the index procedure than the angiography-guided PCI ($2,696.50 vs $3,142.10; $P < 0.001$), which resulted in the lower cumulative medical costs in the FFR-guided PCI than in the angiography-guided PCI.

In the field of evidence-based medicine, randomized controlled trials (RCTs) are deemed as the most reliable source of information, and can greatly impact on clinical practice. However, RCTs have inherent shortcomings such as a lack of external validity, insufficient study periods or population sizes, high costs, and time constraints, and therefore are not always reflective of real-world settings.[4] High-quality observational studies play an important role in complementing RCTs and can provide clinically relevant information. In this regard, this Korean observational study provides valuable information that was not captured in the pivotal FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) RCT, which compared the FFR-guided PCI and the angiography-guided PCI. One observation that emerges from this Korean study is the survival benefit of the

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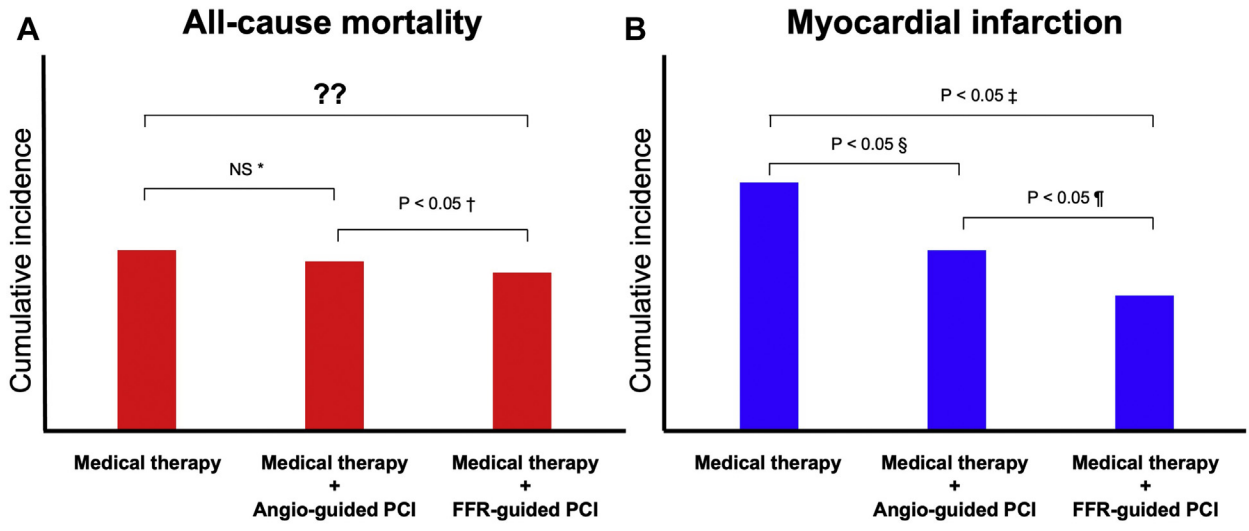
FIGURE 1 Benefits of FFR-Guided PCI



(A) Survival benefits and **(B)** reduction of myocardial infarction by FFR-guided PCI as compared with angiography-guided PCI or medical therapy alone. FFR = fractional flow reserve; PCI = percutaneous coronary intervention. *Maron et al.[1] †Hong et al, Parikh et al, and Volz et al.[3,7,8] ‡Xaplanteris et al and Zimmermann et al.[9,10] §Chaitman et al, Navarese et al, and Bangalore et al.[11-13] ¶Hong et al and Zimmermann et al.[3,10,14].

FFR-guided PCI. In the FAME study, mortality was numerically lower in the FFR-guided PCI than in the angiography-guided PCI, but the difference was not statistically significant either at 1-year or 5-year follow-up.[5,6] However, this Korean study demonstrated the significantly lower all-cause mortality in the FFR-guided PCI than the angiography-guided PCI. This is not the first study showing the survival benefit of the FFR-guided PCI, because there have been 2 preceding largescale observational studies from the United States and Sweden showing the survival benefit of the FFR-guided PCI.[7,8] The former included 17,989 patients, and the latter had 23,860 patients. With sample sizes that are orders of magnitude greater than the FAME study, these 3 large observational studies have consistently shown the survival benefit of the FFR-guided PCI over the angiography-guided method. This Korean study is valuable not only in corroborating the survival benefit of FFR-guided PCI, but also in showing the benefit of the FFR-guided PCI being generalizable to an Asian population. A second observation is the reduction of MI in the FFR-guided PCI. The FAME study did show a lower incidence of MI in the FFR-guided PCI, but again, the difference was not statistically significant. This study has demonstrated the significant reduction of MI in the FFR-guided PCI. In the FAME study, the difference in the incidence of MI between the 2 strategies was mostly seen soon after the index procedure. Meanwhile, this more recent Korean study showed a divergence in the Kaplan-Meier curves of MI between the 2 strategies around 2 years after the index procedure, which was probably because Hong et al[3] only assessed spontaneous MI, but not periprocedural MI. These findings suggest that the FFR-guided PCI contributes to the reduction of spontaneous MI as well as periprocedural MI as compared with the angiography-guided PCI.

With these 2 observations, it is now clear that FFR-guided PCI is superior to the angiography-guided PCI in terms of lowering the risk of all-cause mortality and MI. However, a question that is pressing in the era after the ISCHEMIA trial is whether PCI can reduce these hard clinical events in patients with SIHD when guided by FFR as compared with medical therapy alone. An RCT that tackles this subject is the FAME II (Fractional flow reserve vs. Angiography for Multivessel Evaluation II) study.[9] Although the FAME II study only showed a trend toward decreased MI events, a subsequent meta-analysis of RCTs including FAME II showed that the FFR-guided PCI significantly decreased the incidence of MI.[10] Although PCI itself reportedly reduces the risk of MI even without FFR guidance,[11-13] MI events can be more effectively suppressed when PCI is guided by FFR than by

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angiography alone (Figure 1).[3,5,14] On the other hand, there has been no study demonstrating the survival benefit of the FFR-guided PCI over medical therapy alone.[9,10] Now that the survival benefit of the FFR-guided PCI has been demonstrated as compared with the angiography-guided PCI,[3,7,8] there is a significant need to explore whether the survival benefit of the FFR-guided PCI holds true when compared with medical therapy alone (Figure 1).

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