

Treating stable ischemic heart disease with percutaneous coronary intervention - The debate continues

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Nearly 20 ago, Dutch investigators conceptualized a technique of utilizing an intracoronary pressure-sensing guide-wire to evaluate the effect of an epicardial stenosis on myocardial blood flow (1,2), and thus assess the potential of a coronary stenosis to produce ischemia. Throughout the course of the next 15 years, these investigators undertook a number of cleverly designed and well-executed experiments in both animal models of coronary disease (3), and in various human registries (4-8), to validate the concept of fractional flow reserve (FFR). FFR was shown to result in a more selective approach of undertaking percutaneous coronary intervention (PCI), with deferral of PCI for non-ischemic lesions, irrespective of their angiographic severity, found to be safe over the longer term (7). Short of a definitive randomized controlled trial powered for hard clinical endpoints, and in a broader patient population, many interventional cardiologists, however, remained skeptical of the application of this technique in a real-world setting, and continued to rely on the traditional approach of visual assessment of angiographic stenosis severity, coupled with clinical information and results of stress-testing, to guide decision making in the cardiac catheterization laboratory. It wasn't until the completion of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial (9), where patients with multi-vessel coronary artery disease were randomized to an FFR-guided strategy or a traditional angiographic-guided approach, did the apparent clinical superiority of an FFR-based revascularization strategy become apparent. Patients randomized to the FFR-guided strategy underwent less stenting, experienced lower rates of death and myocardial infarction during 2-year follow-up, achieved at a lower economic cost (10). Accordingly, via the practical integration

of important physiological principles into the cardiac catheterization laboratory, FFR has revolutionized the approach to treating epicardial coronary stenoses, and is now considered by many to be the "gold-standard" invasive technique for the clinical assessment of myocardial ischemia.

Although PCI is known to improve clinical outcomes in patients with acute coronary syndromes (11), controversy still exists for the role of PCI for the management of stable ischemic heart disease (12-16). The benefit of an invasive strategy, however, seems to become apparent in those lesions with ischemic potential (17), even in the chronic stable setting (18). FAME did not involve a control arm to test the hypothesis of managing stable coronary artery disease with FFR-proven ischemic lesions, with optimal medical therapy alone. This formed the premise of the FAME 2 trial, with the aim of testing the hypothesis that in the era of current generation drug-eluting stents, in addition to contemporary antiplatelet, anti-atherosclerotic and anti-anginal therapies, that PCI plus the best available medical therapy versus best available medical therapy alone would be superior in reducing the rate of death, myocardial infarction or urgent revascularization among patients with stable, ischemic coronary artery disease, evaluated by FFR. Patients were selected by having at least one epicardial stenosis on coronary angiography deemed suitable for PCI (19). Patients who had no proven ischemic lesion by FFR were enrolled into a registry and managed with optimal medical therapy.

The study plan was to enroll 1,632 patients with a projected 2-year follow-up period. However, on the recommendation of the data and safety monitoring board, recruitment ceased after the enrollment of 1,220 patients, with a mean follow-up period of 7 months, due to the

highly significant difference in the rate of the primary end point between the PCI group and the medical-therapy group. The primary endpoint occurred in 56 patients in the medical-therapy group and 19 patients in the PCI group (12.7% *vs.* 4.3%, $P < 0.001$). The majority of these events stemmed from urgent, unplanned revascularization, with 49 occurring in the medical-therapy group and 7 in the PCI group, (11.1% *vs.* 1.6%, $P < 0.001$). Very few deaths (3 in medical-therapy group, 1 in PCI group, $P = 0.31$) or myocardial infarctions (14 in medical-therapy group, 15 in the PCI group, $P = 0.89$) occurred in this trial. In half of the cases of urgent revascularization, the need for repeat procedure was triggered by an elevation of cardiac biomarkers, ischemic ECG changes, or both. In patients entered into the registry, the primary endpoint occurred in 5 patients (3%), with no deaths and 3 myocardial infarctions (1.8%). The investigators concluded that stable patients with FFR-proven ischemic lesions, PCI with best available medical-therapy was superior to best medical-therapy alone, with best medical-therapy suited to those without proven FFR-proven coronary ischemia.

So did FAME 2 produce a conclusive answer of how to manage patients with stable, angiographically documented coronary artery disease? How does this trial compare to the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) (13), considered by many to be the most contemporary randomized trial for managing stable ischemic heart disease? Several caveats regarding FAME 2 warrant consideration. There are very few instances where halting a randomized clinical trial early in its course actually helps one to understand the true potential of the treatment strategies evaluated. In stopping FAME 2 early, with a mean 7-month follow-up rather than the anticipated 24-month period as prespecified by the protocol, there was not enough time to ascertain the potential longer-term effects of stent implantation. As such, a major criticism of FAME 2 is that it while it perhaps succeeds in highlighting a short-term treatment benefit of an FFR-guided PCI strategy in reducing the need for urgent revascularization, it falls short in highlighting the long-term clinical benefit of this strategy over best available medical therapy. Furthermore, in both the FAME and FAME 2 trials, it remains unclear as to how investigators deemed a lesion suitable for PCI on the basis of angiographic and clinical data. In clinical practice, physicians typically have additional information, including stress testing and perfusion imaging, to guide PCI, particularly in the setting of multi-vessel disease. It is also unclear whether patients

returning for urgent revascularization, did so for treatment of lesions identified at baseline, or whether angiographic progression of bystander lesions occurred.

Immediate comparisons between FAME 2 and COURAGE have been inevitably made. While COURAGE was considered landmark by many, in confirming the safety of medical therapy in patients with stable ischemic heart disease, a number of caveats also need to be considered. Firstly, a remarkable 35,539 patients underwent assessment for suitability, with only 3,071 meeting the eligibility criteria. As such, questions remain as to whether the study population could be generalized to the real world setting. Furthermore, one-third of medically treated patients crossed-over to requiring PCI. Despite this, the PCI-group still failed to achieve lower rates of death and myocardial infarction. COURAGE was also undertaken in the bare-metal stent era, as well in the midst of a change in practice in favor of dual anti-platelet therapy following PCI occurring mid-way during the running of this trial. Thus, the nature of interventional practice in COURAGE, including the 21% rate of repeat revascularization, is simply not applicable to contemporary practice, and this is where the interventional treatment of patients in FAME 2 reflects current clinical practice.

While there is still a lot of focus on the efficacy of the differing treatment strategies in patients with stable ischemic coronary disease, we must not overlook the favorable prognosis of patients with angiographically documented, but non-ischemic lesions by FFR, who were entered into the FAME 2 registry, and managed medically. The angiographic findings of this group were not dissimilar to the randomized cohort, with 90% of patients having at least 1 epicardial stenosis of $>50\%$ diameter. The absence of ischemia, however, despite the angiographic findings, portended a 3% MACE rate. This finding should be viewed as an equally important finding from FAME 2, as it underscores the importance of ischemia as an adverse prognosticator, as well as the efficacy of contemporary medical therapies. A COURAGE sub-study identified those with ischemia reduction on serial myocardial perfusion imaging following PCI to have a lower rate of death or myocardial infarction at follow-up. Those with residual ischemia also had worse clinical outcomes (18). Hence, the presence or absence of ischemia should remain a fundamental component of investigating a patient with suggestive symptoms pertaining to coronary artery disease.

The National Institutes of Health is funding the ongoing International Study of Comparative Health

Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number NCT01471522), which represents a particularly anticipated trial in this arena. ISCHEMIA is designed to test the hypothesis that revascularization plus medical therapy is superior to medical therapy alone for patients with stable ischemic heart disease, presenting with at least moderate-severe ischemia on non-invasive testing. Although the debate will continue as to the longer term benefit of PCI for stable ischemic coronary disease, we can now be confident that the presence of myocardial ischemia in a patient should alert us of the 'vulnerable' nature of this patient, and that ischemia reduction or elimination via means of the most appropriate therapy remains an important treatment goal in such individuals.

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