FAME-Trials Family: Physiology, Decision-Making, and Clinical Outcomes

Written by Toni Rizzo

Fractional Flow Reserve and FAME-Trials

Mohamed Sadaka, MD, Alexandria University, Alexandria, Egypt, discussed the use of fractional flow reserve (FFR) with angiography for detecting significant coronary artery stenosis. FFR is the only functional index that has been validated against a true gold standard. All studies performed in a wide range of clinical and angiographic conditions found an FFR threshold of 0.75 to 0.80 to detect significant stenosis, with a sensitivity of 90% and specificity of 100% [Pijls NHJ et al. *N Engl J Med* 1996].

Fractional Flow Reserve in Single-Vessel Disease

The Deferral of Percutaneous Coronary Intervention [DEFER] study assessed the safety of deferring percutaneous coronary intervention (PCI) for stenoses in patients without proof of ischemia scheduled for 1-vessel PCI (n=325) [Pijls NHJ et al. *J Am Coll Cardiol* 2007]. Patients who had an FFR ≥0.75 were randomized to medical therapy (Defer group) versus PCI (Perform group). PCI was performed in patients with FFR <0.75 (Reference group). After 5 years, the rates of death or myocardial infarction (MI) were 3.3% in the Defer group, 7.9% in the Perform group, and 15.7% in the Reference group. The event-free survival rates were 80%, 73%, 63% for the 3 groups, respectively. These results showed that the annual death rate is low (~1% per year) and PCI does not improve prognosis in patients with coronary artery disease (CAD) without ischemia.

Hamilos et al. [*Circulation* 2009] performed FFR and quantitative coronary angiography in 274 patients with equivocal left main coronary artery stenosis. Patients with FFR ≥0.80 were treated medically and those with FFR <0.80 were treated with coronary artery bypass graft. The results showed no significant difference in 5-year survival rates between the 2 groups. In a study of FFR-guided decision-making in patients with proximal left anterior descending artery stenosis, patients with FFR ≥0.80 versus FFR <0.80 had significantly lower rates of major adverse cardiac events (MACE; p=0.0019) and mortality (p=0.0479) [Muller O et al. AHA 2009].

Fractional Flow Reserve in Multivessel Disease

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial showed that reducing ischemia prevents death and MI in patients with multivessel disease (MVD) [Shaw LJ et al. *Circulation* 2008]. Patients with a ≥5% reduction in ischemia from baseline (n=82) had a lower unadjusted risk of death or MI compared with those with no significant reduction in ischemia (n=232; p=0.037; risk-adjusted p=0.26). The difference was even greater in the subgroup of patients with moderate to severe baseline ischemia (p=0.001; risk-adjusted p=0.08). The mean percentage of ischemic myocardium in patients treated with optimal medical therapy (OMT; n=155) changed from 8.6% before therapy to 8.1% at 6 to 18 months (mean change, –0.5%; 95% CI, –1.6 to 0.6; p=0.63). In patients treated with PCI plus OMT, the pretreatment ischemia percentage of 8.2% was reduced to 5.5% at 6 to 18 months (mean change, –2.7%; 95% CI, –1.7 to –3.8; p<0.001; PCI+OMT vs OMT; p<0.0001).

A meta-analysis of the Asymptomatic Cardiac Ischemia Pilot [ACIP], COURAGE SI, and Swiss Interventional Study on Silent Ischemia Type II [SWISSI-II] trials showed that mortality was significantly lower with PCI plus OMT (3.5%) versus OMT (9.4%) in patients with silent myocardial ischemia (n=619; risk ratio, 0.34; 95% CI, 0.20 to 0.60; p=0.0002) [Boden WE. ACC 2009].

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The objective of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation [FAME] study was to compare revascularization using angiography plus FFR with angiography only in patients with MVD. The primary endpoint was mortality, MI, or repeat revascularization at 1 year [Tonino PA et al. *N Engl J Med* 2009]. In the FFR-guided group, PCI was performed in patients with FFR ≤0.80. PCI was performed on indicated lesions in the angiography-guided group.

At 1 year, the primary endpoint occurred in 13.2% of the FFR group versus 18.3% of the angiography group (p=0.02). The number of drug-eluting stents (DES) per patient was 1.9±1.3 in the FFR group versus 2.7±1.2 in the angiography group (p<0.001). Less contrast agent was used in the FFR group (272±133 mL) versus the angiography group (302±127 mL; p<0.001). The rate of MACE was lower in the FFR versus angiography group by 2.9% at 30 days, 3.8% at 90 days, 4.9% at 180 days, and 5.3% at 360 days.

At 2 years, among 509 FFR-guided patients with 513 deferred lesions, there were 31 MIs, of which 22 were periprocedural; 9 were late MIs, 8 due to a new lesion or stent-related, and 1 (0.2%) due to an originally deferred lesion [Pijls NHJ et al. *J Am Coll Cardiol* 2010]. In this group, there also were 53 repeat revascularizations (37 in a new lesion and/or a restenotic lesion); 16 of these were in originally deferred lesions (6 without FFR or despite FFR >0.80), 10 of which showed clear progression.

This study showed that, in patients with MVD, revascularization based on angiography plus FFR compared with angiography alone reduces MACE and death/MI rate by about 30%, despite using fewer stents and less contrast medium. FAME challenges the definition of MVD and the concept of completeness of revascularization.

The FAME 2 study evaluated FFR-guided PCI plus OMT versus OMT alone in patients with stable CAD in randomized and registry cohorts [De Bruyne B et al. *N Engl J Med* 2012]. Stable patients scheduled for 1, 2, or 3 vessel DES stenting had FFR in all target lesions. In the randomized cohort, patients with at least 1 stenosis with FFR ≤0.80 were randomized to PCI plus OMT or OMT. In the registry cohort, patients with all FFR >0.80 were treated with OMT. The independent data and safety monitoring board recommended halting patient recruitment due to a significantly increased risk of MACE among patients randomized to OMT alone compared with patients randomized to OMT plus FFR-guided PCI.

The primary endpoint, a composite of death, MI, or urgent revascularization, occurred in 4.3% in the PCI plus OMT group and 12.7% in the OMT group (HR with PCI, 0.32; 95% CI, 0.19 to 0.53; p<0.001). This difference was driven by a reduction in revascularization (1.7% vs 12.1%; HR, 7.63; 95% CI, 3.24 to 18.0; p<0.0001). The harder endpoints of death or MI were not reduced with PCI plus OMT (3.4% vs 3.9%; HR, 0.61; 95% CI, 0.28 to 1.35; p=0.22). There was no significant difference in revascularization rates between the randomized PCI plus OMT group and the registry OMT group (p=0.54).

Based on the DEFER and FAME studies, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularization [Wijns W et al. *Eur Heart J* 2010] recommend FFR-guided PCI for detection of ischemia-related lesions when objective evidence of vessel-related ischemia is not available. According to the 2011 American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions Guideline for percutaneous coronary intervention [Levine GN et al. *Circulation* 2011], FFR is reasonable to assess angiographic intermediate coronary lesions (50% to 70% diameter stenosis) and can be useful in guiding revascularization decisions in patients with stable ischemic heart disease.

Stent for Life: Egypt

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Almost 2 years ago, Egypt was chosen to be 1 of 10 countries to participate in the international Stent for Life (SFL) Initiative. The mission of the SFL Initiative in Egypt, presented by Mohamed Sobhy, MD, Alexandria University, Alexandria, Egypt, is to improve delivery and patient access to the life-saving indications of percutaneous coronary intervention (PCI), thereby reducing the mortality and morbidity of patients suffering from acute coronary syndromes.

Before the initiative, there was no consistent pathway for a patient experiencing an acute myocardial infarction (AMI) to access medical care. The patient might call a cardiologist, private hospital, private insurance physician, or emergency medical system (EMS). Only ambulances from specialized cardiac hospitals had a physician on board, and most of them were not properly trained. Electrocardiograms were only available in new ambulances. With no clear unified protocol, patients were taken to the nearest hospital. Additionally, cardiac catheterization labs were not prepared to treat AMI patients and not all were open 24/7. Before the initiative, only 8% of AMI patients in Egypt were treated with primary PCI (p-PCI) and more than 60% did not receive any reperfusion therapy. With the SFL initiative, Egypt aims to increase p-PCI to about 22%.