Editorial

Fractional flow reserve at the crossroad between revascularization and medical therapy

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The current understanding of the pathophysiology of coronary artery disease relies on the potential adverse effect of myocardial ischemia (1). Even though the ischemia hypothesis has been placed at the core of the evaluation of patients with stable coronary artery disease, no clear evidence supports the benefit of revascularization in terms of hard clinical endpoints namely myocardial infarction and death (2).

Fractional flow reserve (FFR) is the ratio of hyperemic flow in the presence of an epicardial stenosis to hyperemic flow in the absence of this epicardial stenosis and can be calculated from the ratio of distal to proximal coronary pressure (3). FFR was derived from invasive coronary flow measurements and validated against non-invasive tests for ischemia detection (4-6). A series of trials have demonstrated the safety and cost-effectiveness of deferring interventions in absence of ischemia based on FFR (7). In addition, FFR has been shown to improve patient selection for percutaneous revascularization as compared with conventional coronary angiography (8). The most clinically relevant question, whether FFR-guided revascularization improves clinical outcomes compared to optimal medical therapy was the main hypothesis of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 2 trial (9).

FAME 2 was an international, prospective trial that randomized 888 patients with at least one epicardial coronary stenosis with an FFR ≤0.80 either to percutaneous coronary intervention (PCI) with current-generation drug-eluting stents or to optimal medical therapy (9). In contrast with previous trials, FAME 2 systematically assessed for epicardial vessel related myocardial ischemia where the benefit of PCI was more likely to be observed (2). The 1-year follow-up of FAME 2, showed a significant reduction in the composite primary endpoint of all-cause death, myocardial infarction and unplanned urgent revascularization with FFR-guided PCI, the benefit was driven by a reduction in urgent revascularization (9). The Data and Safety Monitoring Board (DSMB) prematurely halt recruitment based on a significant difference in the primary endpoint between the treatment strategies; this reduced the statistical power of the trial and left the clinical question of the potential benefit of FFR-guided PCI on hard clinical outcomes unanswered (9).

At 3-year follow-up, the benefit of FFR-guided PCI in terms of the primary outcome was maintained (10). Moreover, a significant benefit in the relief from angina compared with medical therapy was observed despite a 45% cross-over rate of patients initially allocated to the medical therapy arm alone to PCI. The incidence of revascularization and the higher requirement of antianginal medication in patients randomized to the medical therapy arm increased the cost of this strategy, and by three years no difference was found in cost between an FFR-guided PCI and medical therapy strategy (10).

In 2018, the 5-year follow-up of FAME 2 showed a sustained benefit of FFR-guided PCI in the rate of the primary end point with a hazard ratio of 0.46 (95% CI,

0.34 to 0.63; P<0.001). There was no significant difference between the PCI group and the medical-therapy group in the rate of death (5.1% and 5.2%, respectively; hazard ratio, 0.98; 95% CI, 0.55 to 1.75); however, the rate of myocardial infarction was reduced by 34% with PCI (8.1% and 12.0%; hazard ratio, 0.66; 95% CI, 0.43 to 1.00) and this difference was driven by a reduction in spontaneous myocardial infarction. Relief from angina was more pronounced with PCI than with optimal medical therapy up to three years; this difference was not statistically significant at five years but at that time, as many as 51% of patients initially assigned to receive medical therapy only had crossed over and received PCI (11).

FAME 2 is the first trial to show benefit of PCI in a hard endpoint such as myocardial infarction with the implication of a prognostic benefit of PCI in patients with documented ischemia defined by FFR. Some limitations should be acknowledged. The analyses of the individual components of the primary endpoint are statistically underpowered to detect a difference in clinical outcomes; 2,490 patients are required to have a 90% chance of detecting a significant reduction in myocardial infarction with FFR-guided PCI compared to medical therapy.

Several studies have shown the stable nature of coronary artery disease (11-13). In FAME 2, the Kaplan-Meier curve for myocardial infarction between PCI and medical therapy started to diverge after the third year of follow-up (11). As an initial strategy, medical therapy could be a suitable alternative to myocardial revascularization in patients with stable coronary artery disease. However, at long term and accounting for the relief of angina and resolution of ischemia the overall data favours myocardial revascularization and supports the concept of myocardial ischemia as one of the factors leading to adverse clinical events.

Since FAME 2, developments in the field of PCI and medical therapy have continued to show reduction in clinical events in patients with coronary artery disease. The SYNTAX II study, demonstrated the impact of a state-of-the-art PCI strategy on clinical outcomes. Patient selection based on predicted 4-year mortality, physiology guided PCI with resting indexes and use of thin strut drug-eluting stents with biodegradable polymer optimized by intravascular ultrasound improved clinical outcomes in patients with three vessel coronary artery disease (12). Moreover, the advent of new LDL reduction therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) or antiinflammatory therapy as adjunctive medical therapy in high risk patients have also shown to reduce of rates adverse events (13). A contemporary randomized trial utilizing these new therapies is required to further define the optimal treatment strategies in patients with stable coronary artery disease.

The findings of FAME 2 may lay perspective into the recent controversy surrounding the change of the primary endpoint of International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) study to include not just cardiovascular death and myocardial infarction—the study's initial primary endpoint—but also resuscitated cardiac arrest, hospitalization for unstable angina, and hospitalization for heart failure at 3-year follow-up (14,15). An early benefit of myocardial revascularization in hard clinical outcomes should not be expected. Late follow-up will be required to assess the differences in hard endpoints between PCI and medical therapy in patients with documented myocardial ischemia.

The results of FAME 2 put FFR central stage in the clinical decision-making process about treatment in patients with stable coronary artery disease. These results should reinforce the importance of combined anatomical evaluation and 'physiological thinking' in these patients. In the next decade, several options to invasive pressure wire assessment will facilitate widespread adoption of functional guided revascularization in routine clinical practice. Angiography-derived FFR methods have been shown to be accurate with respect to pressure-derived FFR without the need of vessel wiring or adenosine, resulting in a cost-effective approach for the management of patients referred to conventional angiography (16). Furthermore, non-invasive FFR derived from computed tomography (FFR_{CT}) has shown to be accurate, to improve resource utilization and based on the finding of FAME 2 has the potential to improve clinical outcomes by refining patient selection for revascularization and treatment planning in the non-invasive setting (17,18). Novel coronary physiology approaches are under development to enhance patient selection and treatment planning in patients with epicardial coronary artery disease undergoing PCI.

The era of personalised medicine has arrived. The current knowledge, largely based on traditional non-invasive testing, supports the concept that stenoses able to induce reversible ischemia should be revascularized. Yet, metrics for functional assessment are likely to change drastically in the near future. Individualized approaches encompassing patient's characteristics, biomarker and metabolic profiles, atherosclerotic plaque characterization, functional assessment

of coronary lesions and extent of disease for predicting outcomes may guide treatment decisions for a prognostic benefit in patients with stable coronary artery disease.

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Footnote

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