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Lessons from the trials

FAME 2 – The best initial strategy for patients with stable coronary artery disease: Do we have an answer at last?

Ahmed M ElGuindy[1,*], Robert O Bonow[2]

[1]Department of Cardiology, Aswan Heart Centre, Aswan, Egypt
[2]Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL USA
*Email: ahmed.elguindy@myf-egypt.org

BACKGROUND

Results of the Fractional flow reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial were recently presented at the European Society of Cardiology (ESC) meeting in Munich and published concurrently in the New England Journal of Medicine[1]. Interpretation of the results and clinical significance of the study continue to be topics of considerable controversy. FAME 2 is a randomized "all-comers" multicenter trial, designed to test the hypothesis that in patients with stable ischemic heart disease (IHD), stenting ischemia-producing stenoses – defined as fractional flow reserve (FFR) < 0.80 – plus optimal medical treatment (OMT), would reduce the composite end-point of death, nonfatal myocardial infarction (MI) and urgent revascularization, compared to OMT alone. Secondary endpoints included individual components of the primary endpoint, cardiac death, non-urgent revascularization and angina class. The trial was funded by St. Jude Medical, Inc.

DESCRIPTION

FAME 2 intended to randomize a total of 1,632 patients with stable IHD and one, or more, FFR-significant lesions suitable for percutaneous coronary intervention (PCI) to PCI plus OMT or to OMT alone with a projected follow-up period of 2 years. Patients without any FFR-significant lesions were not included in the trial but were enrolled in a registry and received OMT. Patient recruitment was stopped prematurely after randomizing 888 patients at the request of an independent data and safety monitoring board as a result of a highly significant difference in the incidence rates of the composite primary end-point between both groups.

All patients randomized to the PCI + OMT group received drug-eluting stents. The registry included 332 patients who had no documented FFR values less than 0.80 in any of the stenoses seen on coronary angiography.

After a mean follow up period of 7 months (214 ± 127 days), at least one of the components of the composite primary endpoint occurred in 19 patients (4.3%) in the PCI + OMT group versus 56 patients (12.7%) in the OMT group (hazard ratio with PCI = 0.32; 95% CI = 0.19–0.53; $p < 0.001$). Importantly, this difference was almost entirely driven by an increase in the need for urgent revascularization in the OMT group (49 patients) compared to the PCI + OMT group (7 patients) (hazard ratio with PCI = 0.13; 95% CI = 0.06–0.30; $p < 0.001$). There was no difference between both groups in terms of all-cause mortality or nonfatal MI; there were 3 deaths in the OMT group versus one death in the PCI + OMT group [hazard ratio with PCI = 0.33; 95% CI = 0.03–3.17; $p = 0.31$] and 14 MIs in the OMT group versus 15 MIs in the PCI + OMT group [hazard ratio with PCI = 1.05; 95% CI = 0.51–2.19; $p = 0.31$].

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At 6 months, patients undergoing PCI had significant symptomatic improvement – judged by the Canadian Cardiovascular Society class – compared to the OMT only group (relative risk with PCI + OMT = 0.46; 95% CI = 0.28–0.74; $p = 0.002$). However, this difference was no longer significant at 12 months (relative risk with PCI + OMT = 0.15; 95% CI = 0.02–1.19; $p = 0.07$). Given the premature termination of the study, less than 80 patients (in both randomized groups) were followed for 12 months or more. The incidence of the primary end-point in patients enrolled in the registry was quite low and did not differ from the PCI + OMT group but was significantly lower than the OMT only group. Again, this was solely driven by a higher need of urgent revascularization in the OMT group. The investigators concluded that in patients with stable IHD, FFR-guided PCI plus OMT decreases the need for urgent revascularization compared to OMT alone [1].

In trying to interpret the clinical significance of these results, several important points warrant consideration.

1. The need for "urgent revascularization" in FAME 2 was essentially determined on clinical grounds. Revascularization was deemed urgent when a patient was admitted to the hospital with persistent or increasing chest pain – with or without ST-segment/T-wave changes and/or elevated biomarkers – and the procedure was performed during the same hospital admission. These presentations were eventually judged to meet the definition of an acute coronary syndrome by an independent clinical events committee whose members were unaware of the treatment assignments. Less than half the patients who underwent urgent revascularization had elevated biomarkers or ECG changes suggestive of myocardial ischemia. However, subgroup analysis restricting the definition of "urgent revascularization" to patients with elevated biomarkers or ECG changes still found a significantly lower rate of urgent revascularizations in the PCI + OMT group compared to the OMT-only group (83% relative risk reduction, $p < 0.0001$).
2. Being a non-blinded trial, the possibility that the treating physician might have had a lower threshold to perform PCI in a patient with a documented physiologically significant lesion(s) cannot be ignored. Similarly, the fact that patients who were randomized to the OMT-only group and were sent home knowing that they had a significant "narrowing" in their vessels that was not "fixed" cannot be easily overlooked as a potential source of bias. Again, the aforementioned subgroup analysis eliminates the effect of this bias to some extent.
3. The rigorousness of medical treatment used in studies such as COURAGE and FAME 2 is arguably unachievable in routine clinical practice in most if not all settings [1,2]. All patients in FAME 2 were prescribed aspirin, beta-blocker (alone or in combination with a calcium channel blocker or a long-acting nitrate), angiotensin II-converting enzyme inhibitor (or angiotensin-receptor blocker) and a statin ± ezetimibe. All patients who smoked were counseled regarding smoking cessation. Diabetic patients were referred to a diabetes specialist to receive the best available anti-diabetic regimen. All patients were given a medication tracking form to record weekly use of drugs and doses. This intensity of therapy is optimal but often not provided in many clinical settings.
4. FAME 2 advocates the routine use of FFR for *all* angiographically significant stenoses, a strategy which is well beyond the current recommendations of both the American and European practice guidelines that restrict the use of FFR to assess the functional significance of 50–70% and 50–90% stenoses respectively [3,4], as summarized in this issue of the journal [5]. At this stage, it is difficult to judge whether this extensive use of FFR is achievable in day-to-day practice given the considerable time, complexity and cost implications. This strategy, however, did identify 332 patients (25% of the FAME 2 population) who might have otherwise undergone PCI if the decision was solely based on visual assessment of their coronary stenoses, thus sparing them the potential immediate and longer-term hazards of an unnecessary intervention. Importantly, these patients had a very low event rate with OMT alone. A cost effectiveness analysis of FAME 2 recently presented at the Transcatheter Cardiovascular Therapeutics meeting in Miami showed that FFR-guided PCI is a cost-effective alternative to OMT in patients with stable IHD who have functionally significant stenoses, estimated at $53,000 per quality-adjusted life year [6].
5. Although the benefit of PCI in patients with FFR-significant lesions was observed in most patient subgroups, patients who seemed to derive the most benefit were those with FFR values < 0.65 ($p = 0.01$ for the interaction). It is quite appealing to believe that these patients represent a higher-risk group who are most likely to benefit from an early invasive strategy; however, this should be regarded as a hypothesis-generating observation rather than a conclusion.

WHAT HAVE WE LEARNED?

FFR has an excellent negative predictive value. Patients with stable IHD and FFR-insignificant lesions have a very low rate of adverse events including the need for urgent revascularization. In contrast, among patients with stable IHD and FFR-significant lesions, a strategy of early PCI plus OMT reduces the need for future urgent revascularization and possibly acute coronary syndromes compared to OMT alone. Importantly, the vast majority of patients with stable angina and significant epicardial CAD do well with OMT alone. In FAME 2, only 6% of such patients needed urgent/unplanned revascularization. Estimating the area of myocardium at risk using nuclear perfusion imaging has previously been shown to be valuable in identifying the subgroup of patients who will most likely benefit prognostically from an invasive strategy [7]. It remains to be seen whether FFR can provide similar information in this patient population (FFR < 0.65?).

FAME 2 inadvertently raises some unanswered questions: Should all patients with SIHD be referred to coronary angiography and when? What is the clinical value of estimating the area of myocardium at risk and arguably the value of stress imaging altogether in risk stratifying patients with SIHD? What are the long-term hazards of prolonged dual anti-platelet therapy and late/very late stent thrombosis and would these late events have changed the overall results of the trial? Similarly, would a longer follow-up period have allowed for restenosis to emerge as a possible complication in patients undergoing PCI? Finally, given the premature termination of the study, the possibility of a falsely exaggerated treatment benefit and/or failure to recognize a true effect will never be reliably ruled out. It is hoped that the results of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number, NCT01471522) will provide more definitive results on the long-term superiority of revascularization plus OMT compared to OMT only in patients with stable IHD with respect to "harder" end-points, i.e. death and MI. Until then, FAME 2 provides – for the first time – *reasonable* evidence that the benefit of PCI in patients with stable IHD and physiologically significant stenoses may extend beyond symptom improvement.

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