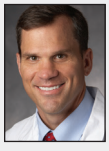
Insights Into the FAME 2 and ORBITA Trials

Drs. William Fearon and Ajay Kirtane discuss what the data mean for patients with stable coronary artery disease undergoing percutaneous coronary intervention, applicability in patients with severe disease, and what they would have changed in terms of study design.



WILLIAM FEARON, MD
Director of Interventional Cardiology
Stanford University Medical Center
Professor of Medicine (Cardiology)
Stanford University School of Medicine
Stanford, California
wfearon@stanford.edu
Disclosures: Research support from Abbott Vascular, Acist Medical, CathWorks, and Medtronic; consulting relationship with Boston Scientific Corporation and HeartFlow.

AJAY J. KIRTANE, MD, SM, FACC, FSCAI
Associate Professor of Medicine
Columbia University Medical Center
Chief Academic Officer, Center for Interventional Vascular Therapy
Director, NYP/Columbia Cardiac Catheterization Laboratories
New York, New York
(212) 305-7060; akirtane@columbia.edu
Disclosures: Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific Corporation, Abbott Vascular, Abiomed, Cardiovascular Systems, Inc., CathWorks, Siemens, Philips, ReCor Medical, and Spectranetics Corporation; personal funding for conference honoraria and travel/meal expenses only.

Findings from the FAME 2 and ORBITA trials were presented at the 29th annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium, which was held October 30 to November 2, 2017 in Denver, Colorado.

The FAME 2 trial was a prospective, randomized controlled trial conducted at 28 sites in Europe and North America that enrolled 1,220 patients with stable angina and angiographically documented coronary artery disease (CAD) suitable for percutaneous coronary intervention (PCI) (see *The FAME 2 Trial at a Glance* sidebar). The goal of the study was to assess clinical outcomes and cost-effectiveness of PCI guided by fractional flow reserve (FFR) compared with best medical therapy.[1]

The ORBITA trial was a prospective, multicenter, randomized, blinded, placebo-controlled study that randomized 200 patients with severe (≥ 70%) single-vessel stenosis from five sites in the United Kingdom to PCI or a placebo procedure (see *The ORBITA Trial at a Glance* sidebar). The objective was to assess symptom relief associated with PCI, as measured by difference in exercise time increment between groups.[2]

What do the FAME 2 and ORBITA trials tell us about treating CAD with PCI?

Dr. Fearon: The take-home message from both FAME 2 and ORBITA regarding PCI in patients with stable CAD is that the benefit of PCI is optimized in patients who have higher degrees of myocardial ischemia and who are experiencing the most symptoms. In ORBITA, 29% of patients in the PCI arm had FFR values above 0.80. We know these patients do just as well, if not better, with medical therapy as compared with PCI. In FAME 2, patients had to have at least one lesion with an

THE FAME 2 TRIAL AT A GLANCE

OBJECTIVE

- To assess clinical outcomes and cost-effectiveness of FFR-guided PCI and best medical therapy (MT) compared with best MT alone

DESIGN

- Prospective randomized controlled trial conducted at 28 sites in North America and Europe
- Enrolled 1,220 patients with stable angina and angiographically documented one-, two-, or three-vessel CAD suitable for PCI with drug-eluting stents
- FFR measured across all lesions deemed angiographically significant
- Patients with ≥ 1 stenosis in a major coronary artery with an FFR ≤ 0.80 were randomized
- Randomization: FFR-guided PCI with second-generation drug-eluting stents and best MT or best MT alone

PRIMARY OUTCOME MEASURE

- Rate of major adverse cardiac events (MACEs), defined as a composite of death resulting from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to unplanned revascularization
- Events were adjudicated by an independent clinical events committee blinded to treatment assignment
- Costs were calculated based on resource utilization and Medicare reimbursement rates
- Changes in quality-adjusted life-years (QALYs) were assessed using the EuroQoL five dimensions at baseline, 1 month, and 1, 2, and 3 years
- All analyses were by intent to treat

RESULTS

- Enrollment was stopped early per the recommendation of a data safety monitoring board due to a significant difference in the primary endpoint
- 888 patients were randomized
  - 447 to FFR-guided PCI + best MT
  - 441 to best MT alone
- At 3 years, MACE occurred in 10.1% in the PCI group vs 22% in the MT group ($P < .001$)
- Initial costs were higher in the PCI group vs the MT group ($P < .001$), but mean cumulative costs at 3 years were not significantly different ($P = .94$)
- The incremental cost-effectiveness ratio for PCI vs MT at 2 and 3 years was $17,300 and $1,600 per QALY, respectively

CONCLUSION

- PCI improves outcomes and is cost-effective compared with MT alone in patients with stable CAD

FFR ≤ 0.80 in order to be randomized to medical therapy or PCI. This restricted the population to those with true ischemia. In ORBITA, patients had symptoms for an average of 9 months before being included in the study. This long duration of symptoms prior to inclusion coupled with the excellent exercise tolerance (9 minutes on average) and the relatively small amount of ischemia on the stress echocardiogram all point to the fact that ORBITA patients were a minimally symptomatic and minimally ischemic group, which is less likely to benefit from PCI.

THE ORBITA TRIAL AT A GLANCE

OBJECTIVE

- To assess symptom relief associated with PCI in patients with medically treated angina and anatomically and hemodynamically severe single-vessel coronary stenosis

DESIGN

- Prospective, multicenter, randomized, blinded, placebo-controlled study
- Five study sites in the United Kingdom
- 230 patients with severe (≥ 70%) single-vessel stenosis were enrolled
- After enrollment, patients received 6 weeks of medication optimization and then underwent prerandomization assessments (ie, cardiopulmonary exercise testing, symptom questionnaires, dobutamine stress echocardiography)
- After the medication optimization phase, patients were randomized 1:1 to PCI or a placebo procedure
- PCI operators were blinded to all research test data and used only nonresearch clinical information
- Prerandomization assessments were repeated after 6 weeks of follow-up

PRIMARY OUTCOME MEASURE

- Change in exercise time on a treadmill after 6 weeks
- All analyses were by intent to treat

RESULTS

- 200 patients were randomized (PCI, n = 105; placebo, n = 95)
- Complete prerandomization and follow-up data were available for 104 patients in the PCI group and 90 patients in the placebo group
- No significant difference in exercise time increment between groups (P = .2)
- No deaths; serious adverse effects included four pressure wire-related complications in the placebo group requiring PCI and five major bleeding events (two in the PCI group, three in the placebo group)

CONCLUSION

- There was no significant difference in exercise time after 6 weeks in patients with stable angina between the PCI and placebo groups

Dr. Kirtane: These trials tell us that we need to be cognizant of exactly which patients we are offering therapy to and that we need to recognize not only their preferences, but also their specific clinical syndrome and anatomy. Once we have integrated all of those elements, we can effectively determine who the best patients are for a therapy such as PCI.

What is the true take-home message of the ORBITA trial?

Dr. Kirtane: The short-term benefit in terms of exercise duration and symptom relief of PCI is determined by how effectively patients are managed at baseline on medical therapy and by the severity of the patient's disease. That is, at least in terms of disease extent and potentially, pending further analyses, how great the flow abnormality attributed to the coronary lesion is when determining the effectiveness of a therapy such as PCI.

Dr. Fearon: There is less benefit of PCI compared with a sham procedure and medical therapy in low-risk, stable patients with minimal or atypical symptoms and little ischemia. The study also re-emphasizes the pow-

erful effect of placebo. It would be interesting to see how much greater symptom relief would be in patients undergoing coronary artery bypass graft (CABG) surgery as compared with a sham CABG procedure. We already know that patients receiving a placebo pill have significant improvement in angina when compared with an antianginal medication.

Can anything from ORBITA be applied to patients with more severe disease and/or symptoms?

Dr. Kirtane: The principles of the trial can apply to many patients, although I would be hesitant directly extrapolating the data. Let's say you have two-vessel disease in a patient who is minimally symptomatic. If the two involved vessels are the posterior descending artery and the obtuse marginal artery, then one could likely apply the results of ORBITA. But, ORBITA was an experiment in a sense, with a very time-limited course; it was only 6 weeks, only 200 patients, and the patients were on very maximal medical therapies.

So, for a large proportion of patients, these study limitations reflect neither the severity of disease that they have nor the way they're actually treated in clinical practice. The results of ORBITA should be informative in the sense that we don't want to overestimate how good PCI could be. ORBITA should keep us grounded, and I think that's an important message.

Dr. Fearon: We will have to wait for the investigators to perform an analysis that stratifies patients based on the FFR value. One would expect to see a greater benefit from PCI in patients with the lowest FFR values. It is unfortunate that the ORBITA investigators did not include patients with multivessel CAD.

Could/should ORBITA have been designed differently? If so, in what way?

Dr. Fearon: There are a number of design flaws in the ORBITA trial. The main flaws include (1) investigators should not have been blinded to the FFR values, and only patients with abnormal FFR values should have been included and randomized; (2) inclusion should not have been restricted to patients with single-vessel disease, as this is the minority of patients we treat; and (3) the primary endpoint should have been at least out to 1 year.

Dr. Kirtane: In retrospect, if you wanted to design the next study to definitively show that PCI could improve symptoms or quality of life or otherwise, then perhaps it would be designed to include patients with more severe symptoms. Such patients would have some physiologic flow abnormality at baseline and their medical therapy would be medical therapy that they actually would want to take in their daily life. In my experience, I do not see many patients who want to be on three antianginal agents for the long term, even for symptom relief.

What impact will the results of ORBITA and FAME 2 have on your practice?

Dr. Kirtane: For me, directly, it will not have a huge impact because I already modified my practice when the results of the COURAGE trial came out. I don't base my decisions for PCI solely on anatomy, and I do use physiology in a large proportion of cases where the clinical decision is difficult. I have discussed the study results with my patients, as well as other studies. So, in that respect, I'll mention the study to them, but I don't think it will change the decision-making.

I think the biggest point to make out there for all interventional, as well as noninterventional, physicians is that we have to be focused on treating the patient and understanding the data behind all the therapies we offer to patients, whether the therapies are medical therapy, PCI, or even surgery. If we're realistic about the way in which we can actually help patients, then we'll do the best job for those individual patients.

There are physicians who say, "This lesion should be treated because it just looks tight." I don't think that's the right way to practice. On the other hand, there are people who only administer medical therapy and don't even consider revascularization, and that's not right either. I think, ultimately, all of these trials allow us to focus on treating the patient in order to hopefully get us the best outcomes.

Dr. Fearon: Based on FAME 2, if I have a patient with stable symptoms and a coronary lesion in a major epicardial vessel with an abnormal FFR, I will perform PCI up front and not necessarily wait for the patient to fail medical therapy. FAME 2 demonstrated that PCI in patients with abnormal FFR improves outcomes, improves symptoms and quality of life, and results in similar costs at 3 years and therefore is a very cost-effective strategy. At this point, I do not think ORBITA will have a significant impact on my practice. ■

1. Fearon WF, Nishi T, De Bruyne B, et al. Clinical outcomes and cost-effectiveness of fractional flow reserve–guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation. 2018;137:480-487.

2. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet. 2018;391:31-40.