Is Exercise Treadmill Time or Reduction in Myocardial Ischemia the Appropriate Primary Endpoint to Assess Success of Percutaneous Coronary Intervention in Stable Angina (ORBITA)?

Vasken Dilsizian[1] and Madeline Erario[2]

[1]University of Maryland School of Medicine, Baltimore, Maryland; and [2]Department of Medicine, Inova Fairfax Hospital, Falls Church, Virginia

In patients with severe single-vessel coronary artery stenosis and stable angina, the Percutaneous Coronary Intervention (PCI) in Stable Angina (ORBITA) clinical trial showed improvement in myocardial ischemia more with PCI than with the placebo procedure as assessed by dobutamine stress echocardiography (*1*). However, reduction in stress-induced myocardial ischemia was designated to be a secondary endpoint in the ORBITA trial. Instead, it was exercise treadmill time that was selected as the primary endpoint for the clinical trial. Although relief of angina, in terms of stability, severity, and frequency, did not differ between PCI and placebo procedure groups, it would have been extremely important to determine whether the angina relief was greater in the subset of patients who had improvement in the myocardial ischemia index by echocardiography (indicating successful reperfusion with PCI) than in those who did not demonstrate reduction in dobutamine-induced myocardial ischemia.

The ORBITA clinical trial randomized 200 patients with greater than 70% single-vessel coronary artery disease to PCI versus placebo at 5 study sites in the United Kingdom. All patients received 6 wk of medication optimization, which included telephone consultations with a cardiologist 1–3 times per week followed by automated 1:1 randomization of patients to masked PCI or a placebo procedure. All patients underwent pre- and 6 wk postprocedure cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. The results showed no difference in the primary endpoint of exercise time increment between the PCI with drug-eluting stents and placebo procedure groups. Similarly, there was no difference in numerous secondary endpoints, such as angina severity, change in exercise time to 1-mm ST segment depression, peak oxygen uptake, and Duke Treadmill score beyond the effect of the placebo. However, the dobutamine stress echocardiography peak stress wall motion score (myocardial ischemia index) improved more with PCI than with placebo (*1*).

In the discussion section, the authors challenge the importance of myocardial ischemia, by stating that "clinicians have hoped there might be a simple entity named ischemia, which manifests as positive tests and clinical symptoms, and that treatment by PCI would eliminate all these manifestations concordantly" (*1*). Contrary to the authors' contention, myocardial ischemia was the only index that showed improvement in the PCI group beyond the effect of the placebo in the ORBITA trial. The results of the dobutamine stress echocardiography data highlight the significance of myocardial ischemia, manifesting as transient stress-induced wall motion abnormality (positive test) and improvement by PCI beyond the placebo effect among patients with single-vessel coronary artery disease. Consequently, it would be reasonable to predict a larger physiologic, symptomatic, and prognostic benefit from PCI among patients with multivessel coronary artery disease (not studied in the ORBITA trial) with more extensive areas of myocardial ischemia. Given that reduction in myocardial blood flow precedes regional wall motion abnormalities, it is anticipated that stress-induced reversible myocardial perfusion defects assessed with SPECT (in terms of relative radiotracer uptake) or with PET (with the added quantification of absolute myocardial blood flow in mL/min/g of tissue) would also show improvement by PCI treatment more than placebo in a similar double-blind, randomized controlled clinical trial (*2–6*).

DOES THE UNIQUE CLINICAL TRIAL DESIGN OF ORBITA MIRROR "REAL-LIFE" CLINICAL PRACTICE?

The authors concluded that "placebo-controlled efficacy data could be just as important for assessing invasive procedures, where the stakes are higher, as for assessing pharmacotherapy where it is already standard practice" (*1*). Because each patient in the ORBITA trial was faced with 2 markedly different therapeutic options (PCI vs. placebo procedure), eliciting patient consent to be randomized was undoubtedly challenging. In addition, recruiting sufficient investigators or primary care physicians to accept randomization for their patients is no easy matter, placing them in a state of clinical equipoise, particularly because PCI is considered (guideline-supported) standard clinical practice (*7*). Accordingly, the medical optimization phase of the ORBITA trial was designed to be more intensive than routine clinical practice to ensure patient recruitment and participation. It consisted of telephone consultations with a cardiologist 1–3 times per week, during which medications were introduced and up-titrated with at least 2 (an average of 3) antianginal therapies per patient, and all patients were pretreated with dual antiplatelet therapy. Although such aggressive medical optimization and follow-up with cardiologists may be important to ensure patient accrual and minimize patient attrition in clinical trials, unfortunately, such unique

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For correspondence or reprints contact: Vasken Dilsizian, Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland Medical Center, 22 S. Greene St., Room N2W78, Baltimore, MD 21201-1595.
E-mail: vdilsizian@umm.edu
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clinical trial design attributes may not necessarily deliver generalizable findings that mirror real life clinical practice.

THE ROLE OF PERSONALIZED MEDICINE

The conventional use of the term *personalized medicine* relates to biomarker-positive or genotype-specific patient treatments, commonly used in oncology. However, personalized medicine also applies to selecting specific treatment strategies based on the individual patient's preference and risk profile in cardiology. For example, a single-time-point invasive procedure must be weighed against long-term medical therapy.

The findings of the ORBITA trial were interpreted to demonstrate that in patients with medically treated angina and severe single-vessel coronary artery stenosis, PCI does not increase exercise time by more than the effect of a placebo procedure. However, it would not be unreasonable to suspect that there were individual patients in the ORBITA trial who not only benefited from reduction or elimination of myocardial ischemia and angina with PCI, but also exercised longer on the treadmill after PCI. Hence, results of multicenter clinical trials, even when conducted well, may not necessarily apply equally to all eligible patients.

Peak stress wall motion score (myocardial ischemia index) on dobutamine stress echocardiography was higher in patients who had undergone the placebo procedure (medical therapy) than in those who had PCI. What are the long-term consequences of regional wall motion abnormalities from chronic, repetitive ischemia in patients treated with medical therapy? Delayed recovery of regional wall motion after a transient period of ischemia is known as stunned myocardium. The ischemic episodes that ultimately lead to myocardial stunning can be single or multiple, brief or prolonged, but never severe enough to result in myocardial necrosis. Chronic repetitive stunning (often clinically unapparent) may ultimately lead to ultrastructural changes and hibernation (*8*). Interventions aimed at decreasing the frequency, severity, or duration of ischemic episodes with PCI by favorably altering the supply–demand relationship of the myocardium would result in improved contractile function. Would it not be preferable, therefore, to prevent ischemia in the first place? Thus, there may be an advantage of a single-time-point invasive procedure over the long-term side effects and cost of multipharmaceutical therapy.

CONCLUSION

Reduction in stress-induced myocardial ischemia was a secondary endpoint in the ORBITA trial, and the trial produced neutral findings for the overall predefined primary endpoint of exercise treadmill time. Admittedly, a secondary finding in the ORBITA trial should be viewed with cautious optimism and hypothesis generating for designing the next clinical trial. However, one must ask the question whether exercise treadmill time was the appropriate primary endpoint for the ORBITA trial in the first place? Given that angina represents the symptomatic sequelae of myocardial perfusion supply–demand mismatch, perhaps an imaging study that has a higher sensitivity for detecting myocardial ischemia would have been the more proper primary endpoint for the trial, rather than exercise treadmill time.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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