

Rediscovering the Orbit of Percutaneous Coronary Intervention After ORBITA

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The publication of the ORBITA trial (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) generated an immense amount of discussion, debate, and controversy.¹ The editorialists posed in their title whether the ORBITA trial is the “Last nail in the coffin for PCI [percutaneous coronary intervention] in stable angina?”² The ensuing press coverage has been extensive, although mostly 1-sided, and largely following the negative tone set by the editorial. The exchange on social media has been at times vitriolic, both pro and con. The number of tweets of the article (1716 as of February 25, 2018) now exceeds the number of patients enrolled by >7-fold. Thus, ORBITA has disrupted the orbit of PCI.

On a historical note, the first patient to undergo PCI was an ORBITA-like patient with successful treatment of an isolated proximal left anterior descending artery lesion, rendering the patient symptom-free for >20 years. It took 40 years to conduct ORBITA, a well-designed and -executed trial reporting that PCI for stable angina was not superior to a sham procedure in terms of exercise time, the trial's primary end point. The main strength of the trial was the sham design, a major step forward in coronary intervention, building on the use of sham designs in recent trials of renal denervation.³ The assessment of the primary end point at 6 weeks, precluding information on long-term outcomes, the inclusion of ~25% of patients with mild symptoms prerandomization, the large between-group difference in ostial and proximal lesions likely because of the small sample size, and the removal of patients after randomization, were all significant limitations of the trial (Table). An important unintended consequence of ORBITA has been a misunderstanding that the results might also apply to unstable angina or myocardial infarction.

Key scientific questions that have emerged are the following: To whom do the results potentially apply? What is the way forward? Today, it is estimated that patients fitting the criteria of ORBITA constitute ≈10% of patients undergoing PCI.⁴ An essential first step in these types of patients would be to assess the presence and magnitude of ischemia and whether invasive angiography should be performed. Among those patients who do not require angiography initially, an algorithm of stepped medical therapy should be instituted in keeping with current clinical practice guidelines. In those patients with continued lifestyle-limiting angina or intolerance to further escalation of medical therapy, coronary angiography should be pursued. Those patients with indeterminate lesions should undergo an invasive assessment (ie, fractional flow reserve or instantaneous wave-free ratio). Based on the totality of the findings, percutaneous revascularization (or surgical revascularization for complex multivessel disease) can be performed.

This algorithm seems appropriate for the present, but it does not address the seismic implications of ORBITA: that PCI might not actually offer incremental advantages in symptom relief among patients with stable angina. Then what of the future? Does ORBITA need to be replicated in a much larger sample size in an inter-

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Table. Strengths and Limitations of the ORBITA Trial

Strengths	Limitations
Appropriate hypothesis	Potential for selection bias because of patient removal after randomization
Appropriate primary end point	Baseline difference in exercise time between PCI and control exceeds treatment effect
Sham control	Low symptom burden (CCS classes 0–1) in ~25% of patients after escalation of antianginal therapy
Successful blinding procedures	Imbalance of ostial and proximal lesions in favor of control (57% vs 37%)
Appropriate PCI technique	Insufficient power to detect a clinically relevant difference between groups
Independent funding	Study question is limited to a minority of patients undergoing PCI in contemporary practice
Transparent reporting Protocol Coronary angiograms of all patients	Lack of extended follow-up results beyond 6 weeks

CCS indicates Canadian Cardiovascular Society; and PCI, percutaneous coronary intervention.

national study? We would answer yes, at least before the trial results should influence practices that are already compliant with the current guidelines. We predict that an adequately powered trial to evaluate whether PCI reduces angina compared with sham control in single-vessel disease would show significant improvements in angina burden, exercise time, and quality of life, in keeping with trends seen in ORBITA. However, one could question the need for such a trial, given large randomized trials of bare metal stents versus drug-eluting stents (active control trials) that have already shown significantly less angina burden in patients randomized to drug-eluting stents.

Should patients with more extensive multivessel coronary artery disease be included in a sham-controlled trial of PCI? It is difficult for us to envision that the benefits of PCI similar to those of coronary artery bypass grafting in terms of symptom relief and quality of life observed in patients with multivessel and left main disease are a placebo effect.⁵ Furthermore, because coronary artery bypass grafting reduces mortality versus PCI in complex multivessel disease in patients with diabetes mellitus, this also means that coronary artery bypass grafting for stable coronary disease reduces mortality versus medical therapy alone—unless one posits that PCI is actually raising mortality versus medical therapy, which is not supported by randomized data. Thus, it is likely that PCI of patients with sufficient ischemic or atherosclerotic disease burden would be able to demonstrate a reduction in mortality and myocardial infarction in a trial that enrolls a sufficient number of high-risk patients and follows them for a long

enough period of time. Nevertheless, funding and executing such a trial may be impractical.

Ongoing large trials, such as ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522), may provide critical data on the role of invasive management and specifically PCI in improving major clinical outcomes such as myocardial infarction and death compared with optimal medical management. If those hard end points are reduced—a high bar to clear—then the discussion of symptom relief and improvement in exercise capacity remains important but becomes less pressing. It is important to note that the primary end point of ISCHEMIA was recently changed because of an insufficient number of patients enrolled and, as a consequence, too few hard events. The redefined end point includes a broader array of clinically relevant events (cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure) that in some respects may substitute for an ORBITA-2, albeit without the sham control.

The role of PCI in acute coronary syndromes is firm based on large amounts of randomized data. In that setting, underutilization, especially in higher-risk patients and those with comorbidities, is the larger problem. In stable angina, the role of PCI will evolve as further data become available, and it remains a valuable adjunct rather than an alternative to medical therapy. Additional PCI trials will certainly be performed. As the incidence of stable coronary disease increases globally, there will be ample patients available to answer the pressing questions regarding the appropriate role of PCI and hopefully place PCI in its proper orbit.

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Disclosures

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