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ORBITA and ISCHEMIA: what's the message?

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Abstract: Despite the absence of conclusive evidence from multiple randomized trials and meta-analyses that revascularization with percutaneous coronary intervention (PCI) reduces subsequent cardiac events (notably death or myocardial infarction [MI]), cardiologists have been nonetheless imbued with the long-held belief of PCI superiority in the management of stable ischemic heart disease (SIHD) and have continued to embrace a "PCI-first" approach despite international professional society guidelines that have advocated an optimal medical therapy (or "OMT-first") approach. In addition, PCI has been widely viewed by practicing cardiologists as being superior to OMT for angina relief and improving quality of life, which has been the principal justification for undertaking PCI in SIHD patients. However, the recent ORBITA trial showed no incremental benefit of PCI versus a sham PCI procedure on 6-week outcomes of treadmill walking time, angina frequency, or any indices of quality of life measures in SIHD patients with high-grade single-vessel epicardial coronary artery disease (CAD). These provocative findings raise the possibility that angina relief may not be a uniform finding in patients undergoing PCI; however, the ORBITA trial was small and lacked long-term follow-up. In contrast, the ongoing ISCHEMIA trial in patients with both multivessel CAD and moderate-to-severe ischemia at baseline is testing the superiority of revascularization plus OMT vs OMT alone (mean follow-up, 4.5 years) for a 5-component trial primary end point of cardiovascular death, MI, resuscitated cardiac death, or hospitalization for acute coronary syndrome or heart failure. Until the results of the ISCHEMIA trial are available in late 2019 or early 2020, the optimal management of SIHD will continue to be debated. ■ *Heart Metab*. 2019;78:4-8

Keywords: ISCHEMIA; ORBITA; percutaneous coronary intervention; stable ischemic heart disease

Introduction

Since the advent of coronary angiography more than 60 years ago, the diagnosis and treatment of coronary artery disease (CAD) has been predicated on the plausible assumption that "significant" flow-limiting atherosclerotic obstructions of the epicardial coronary arteries are the proximate cause of both angina and myocardial ischemia.[1] This paradigm has been proven in patients with an acute ST-segment elevation myocardial infarction (STEMI) with an occluded infarct-related coronary artery and in many high-risk patients with acute coronary syndromes (ACS) with a stenotic culprit coronary stenosis, where clinical benefit is derived from percutaneous coronary intervention (PCI). However, there is scant evidence that treating coronary obstructions in patients with chronic angina and stable ischemic heart disease (SIHD) reduces mortality and morbidity, despite the continued evolutions in stent design

Abbreviations

ACS: acute coronary syndromes; **BARI 2D:** Bypass Angioplasty Revascularization Investigation 2 Diabetes; **CAD:** coronary artery disease; **COURAGE:** Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation; **FAME:** Fractional Flow Reserve versus Angiography for Multivessel Evaluation; **FFR:** fractional flow reserve; **ISCHEMIA:** International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; **MI:** myocardial infarction; **OMT:** optimal medical therapy; **ORBITA:** Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; **PCI:** percutaneous coronary intervention; **SIHD:** stable ischemic heart disease; **STEMI:** ST-segment elevation myocardial infarction

and technology. Despite this, PCI remains a widely utilized (and often preferred) treatment for patients with chronic angina due to stable CAD.[1]

Thus, since the advent of PCI in 1977,[2] cardiologists have been imbued with the long-held belief of PCI superiority in stable CAD management and have continued to embrace a "PCI-first" approach, despite international professional society guidelines advocating for an optimal medical therapy (or "OMT-first") approach. This somewhat monolithic and anatomically driven practice paradigm, however, has not been challenged, despite the existence of compelling evidence that many angina patients (both men and women) do not have significant flow-limiting epicardial coronary obstructions as the singular cause of their symptoms and objective findings of ischemia.[3]

Since PCI for SIHD is procedurally nearly identical to that performed for STEMI or ACS, many physicians have accepted the premise that PCI would confer a more durable clinical benefit (ie, beyond symptom relief) in SIHD patients with flow-limiting coronary stenoses. This assumption has been challenged and largely undermined by two major randomized clinical trials—COURAGE and BARI 2D.[4,5] While neither study showed a reduction in death or death/myocardial infarction (MI) (follow-up periods, 5 to 7 years), both provided a compelling rationale for deferred revascularization and an up-front trial on OMT (ie, intensive pharmacotherapy, lifestyle intervention, and secondary prevention). Conversely, as an initial management strategy in patients with SIHD, PCI did not reduce death, MI, or other major cardiovascular events when added to OMT. These findings of strategic equivalence have now been observed to persist for up to 15 years.[6]

A more recent trial, the FAME-2 trial,[7] undertaken in 888 patients randomized to fractional flow reserve (FFR)–guided (FFR ≤0.80) PCI plus OMT or to OMT alone, showed that the primary composite end point of death, MI, or urgent revascularization occurred in 4.3% in the PCI group and 12.7% in the OMT group (P<0.001), which was driven by a lower rate of urgent revascularization in patients assigned to PCI with OMT (1.6% vs 11.1%; P<0.001) during a relatively short (7-month) follow-up.[8] Further analysis of the FAME-2 trial results showed that the principal benefit associated with the FFR-guided PCI approach was only a reduction in the rate of hospitalization for unplanned revascularization, while there was no significant between-group difference in the rate of death, MI, or the composite of death or MI. Even extending the follow-up of FAME-2 to 2 and 5 years did not change the lack of benefit of FFR-guided PCI on the "hard" clinical outcomes of death and/or MI.[9,10] In fact, there were numerically more cardiac deaths at 5 years in the PCI group (n=11) vs the OMT group (n=7) (hazard ratio, 1.54; 95% CI, 0.60-3.98).[9] In addition, two recent meta-analyses of more than 5500 SIHD patients who were randomized to PCI versus OMT showed no reduction in cardiovascular events for the end points of death, MI, hospitalization for ACS, and freedom from angina.[11,12]

Despite the inability to demonstrate a salutary effect of PCI on even angina relief, most cardiologists still believe in the superiority of PCI for angina relief vs OMT, that is until the ORBITA trial, published in 2017, called this into question.[13] The results of ORBITA were unexpected because no incremental benefit was observed for treadmill walking time, or any objective measure of angina relief and quality of life among those who underwent PCI vs those who received a blinded sham procedure, although, by design, ORBITA only had a 6-week follow-up.[13] Nevertheless, for a small 200-patient cardiovascular outcomes trial, the impact of ORBITA has been both remarkable and profound. As the first sham-controlled trial of PCI in SIHD patients, all of whom had significant flow-limiting coronary stenoses (mean diameter stenosis, 84%), including an abnormal FFR (mean, 0.69), ORBITA was unable demonstrate an additive effect

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of FFR-guided PCI on treadmill exercise duration, the frequency and severity of angina, or several quality of life indices.[13] Considering that stenting a coronary artery with a mean 84% stenosis should have imparted an immediate clinical and physiologic benefit between treatment groups, even at 6 weeks, these provocative findings defied both expectations and conventional wisdom. One possible insight from ORBITA is that an interventional procedure that is expected to result in symptomatic improvement may, in part, be related to both the patient's and physician's belief that the procedure is therapeutically effective, which calls into serious question whether PCI has a truly definable therapeutic effect or whether the presumed benefit may, in part, be due to the patient's inherent belief of benefit, which Rajkumar et al[14] termed the "power of telling," or the potential benefit of "faith healing."

ORBITA was a rigorously designed and executed randomized trial that was undertaken using objective exercise and physiologic outcome measures before and after stabilization on OMT and well-validated quality of life metrics before and after randomization.[13] However, there are well-recognized limitations, including[15]:

- Small sample size
- Underpowered
- Unethical for subjecting subjects with significant flow-limiting CAD to a sham procedure (or deferred PCI for clinical need)
- Normal FFR in 28% to 32% of randomized patients (ie, no "physiologically significant," flow-limiting stenosis at the time PCI was undertaken after OMT intensification)
- All patients had single-vessel CAD
- Short 6-week duration of follow-up that some critics believed was too brief to assess potential PCI benefit
- Intensity of OMT for 6 weeks prior to the planned PCI vs sham PCI randomization was too labor-intensive and "not real-world," which was similar to the criticism that COURAGE encountered.[4,13]

One common question persisting post–ORBITA has been whether these trial results will change clinical practice. The answer to this question is "likely no" because the narrative will be that rates of PCI for stable CAD are declining, while more recent data from a large American College of Cardiology national PCI registry show that, based on "appropriateness use criteria," the percentage of patients undergoing "inappropriate PCI" (or "rarely appropriate PCI") is likewise declining.[16] However, what is not entirely clear at present is whether there has been an increase in "coding creep" to up-classify (or reclassify) CAD patients with "stable angina" to "unstable angina."[17] Since only a few states in the US mandate public reporting of PCI use and appropriateness data, which is both voluntary and not verified for accuracy or quality control, it is unclear how such data can be reliably ascertained and interpreted in the setting of an "honor system" without objective oversight.

What the results of ORBITA do show us, however, is that cardiologists also need to be honest about the fact that our biases and pre-existing beliefs of PCI may often color the way we approach this discussion with patients about the presumed benefits of PCI. For example, when even a stable CAD patient is found to have a flow-limiting coronary stenosis during angiography, what is frequently conveyed to the patient in the catheterization lab (along with the frightening visual image of a coronary angiographic obstruction or narrowing) is the potential for an impending catastrophic event: that is, if we don't intervene and "fix this blockage" immediately, the risk of MI or death may occur. In this context, who could blame a patient for acquiescing to PCI? However, I suspect there is little discussion about the lack of PCI benefit on improved survival or reduced MI in the setting of the cardiac catheterization laboratory where the ease and convenience of undertaking ad hoc PCI is frequently compelling for the interventional cardiologist to attempt.[18] The results of ORBITA, along with those of COURAGE,[4,6] BARI 2D,[5] and even FAME-2[7-9] should teach us that we should provide our patients and their families with factual, transparent information about the risks and benefits of all CAD treatment approaches (eg, PCI, coronary bypass surgery, and OMT),[19] and specifically, that we may now need to start informing our patients that PCI may not necessarily improve their angina—or that perhaps only a minority of patients may experience significant, durable angina relief.

However, an even greater reason why the results of ORBITA are unlikely to change contemporary clinical practice is that it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and cardiovascular death. Neither COURAGE and BARI 2D explicitly

required that enrolled patients had to demonstrate moderate-to-severe ischemia on noninvasive testing, and, while all patients in COURAGE did have objective evidence of myocardial ischemia at baseline, most appeared to have mild-to-moderate ischemia. In addition, all the previous "strategy trials" comparing OMT with or without PCI were uniformly undertaken after the results of coronary angiography were known to the study investigators, which introduces the possibility that bias may have led to the decision not to randomize patients to OMT or PCI once the coronary anatomic results were apparent.

For these reasons, a large, multinational randomized trial, funded by the US National Institutes of Health, has been under way since 2012 to address these key (and yet unresolved) clinical questions. The ISCHEMIA trial (NCT01471522) has enrolled 5179 patients with multivessel CAD and objective evidence of at least moderate ischemia at baseline as assessed by stress echocardiography, treadmill exercise testing, myocardial perfusion imaging, or cardiac magnetic resonance imaging. Of note, all subjects with moderate-to-severe ischemia at baseline first undergo a blinded coronary computed tomography angiography assessment to exclude left main stem CAD and the absence of obstructive epicardial CAD, after which eligible patients are randomized to an invasive strategy of revascularization of choice (PCI with third-generation drug-eluting stents (DES) or coronary bypass surgery with OMT) or a conservative strategy of OMT alone, with coronary angiography and revascularization reserved only for OMT failure. The primary end point is a composite of cardiovascular death, nonfatal MI, resuscitated sudden cardiac death, or hospitalization for ACS or heart failure in a time-to-first-event analysis during an average 4.5-year follow-up. The ISCHEMIA trial is scheduled to conclude on June 30, 2019. Key secondary outcomes include quality of life and the composite end point of cardiovascular death or MI. It is anticipated that the results of the ISCHEMIA trial will inform clinical practice regarding the benefit of revascularization plus OMT versus OMT alone in a higher-risk population of SIHD patients than has been previously subjected to prospective study.

In summary, perhaps the time has come for a paradigm shift in how we view stable CAD. The results of trials to date have failed to show a conclusive benefit for PCI in SIHD patients concerning "hard" clinical outcomes. The results of ORBITA likewise tell us that even short-term angina relief may not be uniformly achieved in all patients despite successful stenting of high-grade coronary stenoses using DES guided by FFR. These findings suggest that we may need to expand our scientific thinking about the many causes and mechanisms of both angina and myocardial ischemia, particularly in stable CAD patients, and we need to uncouple the singular association between obstructive CAD and epicardial coronary revascularization, which is largely unsupported by rigorous trial data and evidence-based medicine. Angina and ischemia have many causes, and, until the results of the ISCHEMIA trial are published, both the evaluation and treatment of SIHD patients need to be tailored to the individual patient, with particular emphasis on the continued use and benefits of OMT.[19] ■

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