Making Sense of ORBITA and ISCHEMIA

Discussing the contributions of the ORBITA and ISCHEMIA trials to the ongoing debate surrounding revascularization in stable coronary artery disease.

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There are two aims for the management of stable coronary artery disease (CAD): improvement of angina symptoms and reduction in cardiovascular events. The role of revascularization in achieving these aims has been the subject of some scrutiny and controversy in recent years. This debate has recently been awakened by the publication and presentation of two randomized controlled trials: ORBITA and ISCHEMIA. This article discusses the impact of these trials on our understanding of revascularization, particularly percutaneous coronary intervention (PCI), in the management of stable CAD.

PCI FOR ANGINA IN STABLE CAD

Coronary angioplasty was developed as a treatment for angina in stable CAD, initially with simple balloon angioplasty.[1] The technique evolved with the development of bare-metal and, subsequently, drug-eluting stents. Now, modern coronary intervention is often guided and optimized with intracoronary imaging and invasive physiology.[2,3] During this development period, antianginal therapy has also advanced. Multiple individual antianginal medications have placebo-controlled trial data to support their use.[4-7] Current national and international guidelines advocate an initial medical strategy in the treatment of angina, with referral for revascularization recommended for patients who are on at least two antianginal drugs.[8]

For trials of pharmacotherapy, placebo control has long been considered the gold standard in testing the true therapeutic effect of a drug. In cardiology, placebo control in randomized trials of interventions for angina is not new. Prior to the development of coronary artery bypass graft (CABG) surgery, internal mammary artery ligation was an established surgical treatment option for angina. However, the first placebo-controlled trials of this technique showed no impact on angina or exercise capacity compared with placebo.[9,10] Decades later, lessons were learned from placebo-controlled trials of laser myocardial revascularization and renal denervation, showing that the true physical efficacy of a treatment on a subjective endpoint such as symptoms or blood pressure can only be known when the contribution of the placebo effect is known.[11-14] More recently, a coronary sinus reducer system (Reducer, Neovasc, Inc.) was compared with a placebo for the treatment of refractory angina. In the 104-patient study, there was a significant improvement in blinded angina symptoms with the Reducer but no significant improvement in exercise time.[15]

Before ORBITA, PCI for angina had not been tested against placebo in the 4 decades since its introduction. Unblinded randomized trials found consistent improvements in angina symptoms and quality of life. The ACME study from the early 1990s was the first randomized trial to assess balloon angioplasty in patients with single-vessel CAD, and the study found unblinded improvement in symptoms and exercise time after PCI.[16] The subsequent larger RITA-2 trial, which included patients with two- and three-vessel CAD, found unblinded symptom improvement with PCI and an initial improvement in exercise time, which attenuated by 1-year follow-up.[17] The role of revascularization in two- and three-vessel CAD was assessed further in MASS II from 2004, showing unblinded symptom benefit and exercise benefit with PCI and CABG.[18] The FAME 2 trial also demonstrated improvement in the secondary endpoint of unblinded angina relief.[19] In COURAGE, the secondary endpoint of unblinded angina relief initially improved in the treatment arm, but the effect was not maintained at 5-year follow-up.[20] These unblinded findings of angina improvement after PCI were encouraging, but the well-recognized, significant contribution of placebo seen in blinded trials of other interventions highlighted the need for a placebo-controlled PCI trial.

The Impact of the ORBITA Trial

ORBITA was the first placebo-controlled trial of PCI in stable CAD and was designed to detect the placebo-subtracted true physical efficacy of PCI on angina symptoms in patients on optimal medical therapy.[21] The trial recruited patients with angina and a significant (≥ 70%) stenosis in a single epicardial coronary artery. Participants entered into a 6-week period of intensive medical therapy optimization, aiming to have patients maintained on at least two antianginal drugs by the time of randomization (as is recommended before referral for PCI in national guidelines[8]). In the catheterization laboratory, all participants received auditory isolation with over-the-ear headphones, a coronary angiogram was obtained, and instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) were measured. Patients were then sedated to a deep level of conscious sedation. They were randomized to PCI or placebo and entered a 6-week blinded follow-up period. The primary endpoint was the difference in exercise time increment between the two groups. ORBITA found a smaller-than-expected effect of PCI on treadmill exercise time, which did not reach statistical significance (16.6 seconds; $P = .200$).[21] The limited effects on exercise capacity and symptoms were seen despite excellent anatomic and hemodynamic resolution of stenosis and near elimination of ischemia on follow-up stress echocardiography in the PCI group.

ORBITA highlighted the importance of a placebo control when assessing the efficacy of an intervention. The symptom and quality-of-life benefit seen previously in unblinded angioplasty studies was likely, in part, enhanced by the placebo effect. The true physical effect of the therapy may be less than previously thought.

Secondary analyses from ORBITA showed that one in five more patients were free from angina after PCI compared with placebo and that a lower FFR or iFR was associated with greater placebo-controlled improvement in ischemia (as assessed by stress echocardiography).[22] The most recently published ORBITA stress echocardiography analysis showed that the greater the prerandomization dobutamine stress echocardiography score, the greater the placebo-controlled impact on angina frequency.[23] The efficacy of PCI as a treatment for angina in the setting of multivessel CAD cannot be assessed by ORBITA, and further trials are needed.

Perhaps the most important conclusion from ORBITA is that placebo-controlled trials of interventions for subjective endpoints are informative, deliver new information, and should be as standard for testing interventional procedures as they are for pharmacotherapy.

PCI FOR CARDIOVASCULAR RISK REDUCTION IN STABLE CAD

After its conception as an intervention for symptom improvement, the question arose whether PCI could be a prognostic procedure, preventing myocardial infarction (MI) and death. This view may have been encouraged by the mortality benefit seen with PCI in the setting of acute coronary syndromes. A series of randomized trials were designed to assess this.[16-18] These smaller studies did not find a prognostic benefit with PCI. In response, the COURAGE trial was designed. The COURAGE trial enrolled patients with proximal epicardial coronary stenoses, angina, and noninvasive evidence of ischemia. The trial randomized 2,287 patients to PCI with optimal medical therapy or optimal medical therapy alone. Despite 18.5% of patients reaching the primary endpoint of death and nonfatal MI at the median 4.6 years of follow-up, no significant difference was found between the groups.[20]

The results of COURAGE shocked the interventional cardiology community. It was believed by some that the participants did not have a high enough burden of ischemia, thus affecting the outcomes. Therefore, the FAME 2 trial was designed to include patients after the diagnosis of ischemia by invasive physiology. In 888 patients with stable CAD and FFR ≤ 0.8 in at least one coronary artery, PCI was compared with no PCI. The primary endpoint in this unblinded study was death, MI, or urgent revascularization. The trial was stopped early due to a significantly higher number of urgent revascularization events in the conservative arm; however, this endpoint may have been influenced by bias in an unblinded trial. Furthermore, there was no difference in rates of the hard cardiovascular endpoints of mortality and MI between the two arms.[19,24]

Despite these data, we continue to believe there is a role for revascularization in reducing MI and cardiovascular mortality in certain clinical subsets. It seems biologically plausible that clinical outcomes are most likely to be modified in patients with the most severe disease and that ischemia assessment is a useful surrogate tool to characterize disease severity. Observational data suggest that the burden of ischemia is important and that outcomes may be improved by revascularization for the most ischemic patients.[25] However, these nonrandomized data sets have inherent limitations. For example, the conservative and revascularization patient groups may have been very different. Several external factors could also have influenced treatment strategy selection and, therefore, may have resulted in the different outcomes between the groups.

The first COURAGE nuclear substudy is often described as showing higher survival rates with PCI in

patients with the highest baseline ischemic burden.[26] However, this post hoc study only included patients who had prerandomization myocardial perfusion and follow-up scans. Although patients with ischemia in the PCI arm had lower unadjusted risk of MI or death, the difference for both endpoints became nonsignificant when it was adjusted for baseline risk. In a subsequent nuclear substudy of COURAGE (which included 1,381 patients with moderate to severe ischemia, defined as ≥ 3 ischemic segments, who underwent prerandomization stress myocardial perfusion imaging),[27] the presence of prerandomization moderate to severe ischemia was similar between the PCI and conservative arms (P = .36). Furthermore, there was no difference in death or MI rates at follow-up between the two arms.

Meta-analyses assessing the prognostic effect of PCI in the setting of myocardial ischemia have shown opposing results, depending on the trials selected for inclusion.[28-30] Although guidelines continued to suggest that revascularization should be offered at an earlier stage to patients with the highest ischemia burden, the question of whether ischemia truly matters and how revascularization affects outcomes remained unanswered.[31]

The Impact of the ISCHEMIA Trial

The ISCHEMIA trial was designed to assess the impact of revascularization on death and MI in patients with stable CAD and moderate to severe ischemia. Exclusion criteria included left main stem stenosis, ventricular ejection fraction < 35%, estimated glomerular filtration rate < 30 mL/min, recent acute coronary syndrome, and "unacceptable angina at baseline." Patients underwent initial blinded CT coronary angiography to exclude those with left main stem disease or unobstructed coronary arteries. Patients were then randomized either to an initial invasive strategy (and potential subsequent revascularization with PCI or CABG) or to an initial conservative strategy (in which an invasive approach was reserved only for failure of medical therapy). The primary endpoint was a composite of cardiovascular death, MI, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest. A secondary endpoint in this unblinded study was improvement in quality of life.[32]

The ISCHEMIA trial, recently presented at the 2019 American Heart Association scientific sessions, did not find a significant reduction in the primary endpoint with an initial invasive strategy (hazard ratio, 0.93; P = .34) or in any prespecified secondary hard endpoints. There was no heterogeneity of treatment effect seen with one-, two-, or three-vessel coronary disease or with mild, moderate, or severe ischemia on prerandomization testing. In this unblinded trial, there was a significant improvement in angina symptoms and quality of life in the invasive arm compared with the conservative arm.[32]

These findings from the largest randomized trial in stable CAD should inform our practice. ISCHEMIA recruited a large proportion of patients with at least moderate myocardial ischemia and established a high level of modern, disease-modifying medical therapy.[33,34] Because no difference was found in the primary endpoint, we should be confident in pursuing an initial medical strategy for patients with stable CAD, even in the presence of significant myocardial ischemia. However, it is important to recognize those patients who were excluded from the trial—notably, those with significant left main stem stenosis, severe left ventricular impairment, severe renal impairment, recent acute coronary syndrome, and severe angina. We should be cautious in extrapolating the findings of ISCHEMIA to these groups.

FUTURE PERSPECTIVES

CAD remains a major cause of morbidity and mortality worldwide.[35] Medical therapy has a clear role in the management of stable CAD, but the role of revascularization is less clear. Although ORBITA and ISCHEMIA have advanced the discussion of PCI in stable CAD, the debate continues. ORBITA underlined the importance of blinding and a placebo control when assessing subjective endpoints. Similar methodology will now be used to assess PCI in the setting of multivessel coronary disease and more extensive myocardial ischemia in the ORBITA-2 trial.[36] ISCHEMIA has demonstrated results similar to its predecessor, COURAGE: in stable CAD, even in the presence of moderate to severe ischemia, PCI does not reduce the risk of MI or death.

CONCLUSION

ORBITA and ISCHEMIA should give us confidence to pursue a strategy of truly optimal medical therapy in stable CAD, for both cardiovascular risk reduction and for angina symptom relief. The role PCI plays alongside optimal medical therapy must be carefully considered. Specifically, in the majority of stable CAD subsets, the results of these trials should be used for shared decision-making with patients in discussing their treatment options. Lastly, PCI in the specific stable CAD groups not assessed in ORBITA and ISCHEMIA should be studied in randomized trials—with placebo control considered the gold standard method for assessing clinical endpoints of a subjective nature. ■

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