ORBITA: What Goes Around, Comes Around... Or Does It?

Matthew Jackson and Azfar Zaman

Freeman Hospital, High Heaton, Newcastle-Upon-Tyne, UK

Abstract

Current guidelines recommend percutaneous coronary intervention (PCI) in patients with ongoing stable angina symptoms despite optimal medical therapy (OMT), although trials have shown no reduction in death or myocardial infarction. The recently published ORBITA trial compared OMT + PCI with OMT + 'placebo' PCI in patients with angina and single-vessel coronary artery disease (CAD), and found no significant difference in treadmill exercise time between the two groups after six weeks. The trial concluded that invasive procedures can be assessed with placebo control while numerous editorials interpreted the trial as showing that PCI has no role in the management of stable angina. However, the highly selected patient population, low ischaemic burden and level of symptoms and high proportion of non-flow-limiting stenoses on invasive physiological testing mean that, while ground-breaking in terms of its methodology, ORBITA does not add to the current evidence base supporting ischaemia-guided revascularisation if symptoms are not controlled on medical therapy alone.

Keywords

Stable angina, ORBITA, percutaneous coronary intervention, placebo controlled, fraction-flow reserve, coronary artery disease

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Correspondence: Prof Azfar Zaman, Freeman Hospital, High Heaton, Newcastle-Upon-Tyne, NE7 7DN. E: azfar.zaman@nuth.nhs.uk

Medical therapy has been the primary treatment for stable angina since nitroglycerin was first used in 1878. However, since the first successful percutaneous coronary intervention (PCI) procedure was performed in 1977, the role of PCI in patients with stable coronary artery disease (CAD) has been the subject of much study. Numerous trials have shown no reduction in death or myocardial infarction.^{1–5} However, these trials suggest that PCI is maybe more effective for managing angina symptoms than medical therapy alone.

The Angioplasty Compared To Medicine (ACME) study showed that 64 % of 96 patients in the PCI group were angina free compared with 46 % of 102 medically treated patients ($p=0.01$) at 6 months' follow-up, supported by a significant increase in exercise tolerance (2.1 minutes versus 0.5 minutes; $p<0.0001$).¹ The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial showed similar findings (21 % of patients were angina free following PCI versus 10 % who were angina free following medical therapy) at 30 days' follow-up using more contemporary versions of optimal medical therapy (OMT); however, this improvement was no longer present at 3 years.^{2,3}

Current guidelines recommend titration of several pharmacological agents with complementary mechanisms of action.^{6,7} However, analysis of the US National Cardiovascular Data Registry suggests that fewer than half of patients undergoing PCI for stable CAD receive OMT at the time of their PCI.⁸ Furthermore, the known placebo power of invasive procedures has not been established since the introduction of PCI. Studies in the 1950s and 1960s examined the effects of performing sham operations in patients planned for [internal mammary artery] ligation; one found that all sham patients exhibited improved exercise tolerance and used less glyceryl trinitrate compared with 75 % of patients who underwent IMA ligation;⁹ another showed

over half of patients in both groups had subjective improvement at 6 months.¹⁰

Trial Summary

The Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial is a multicentre, randomised, double-blinded trial enrolling patients with angina, preserved left ventricular systolic function and single-vessel CAD.¹¹ All 230 patients enrolled underwent a 6-week run-in period, during which time medical therapy was optimised with phone contact with a consultant cardiologist up to three times a week. Two hundred patients proceeded to be randomly allocated to PCI or ongoing medical therapy. All patients then underwent invasive physiological measurement of the study lesion. The patients were blinded to whether they underwent PCI or physiological measurement only and the physicians were blinded to the results of the physiological measurements. If patients were randomised to PCI, this was performed with drug-eluting stents with measurement repeated.

The primary endpoint was improvement in treadmill exercise time between randomisation and follow up at six-weeks; no significant difference was noted (28.4 seconds after PCI versus 11.8 seconds in the placebo group, $p=0.20$). Analysis of secondary endpoints – change in peak oxygen uptake, change in exercise time to 1 mm ST-segment depression, angina severity as assessed by Canadian Cardiovascular Society (CCS) class, physical limitation, angina stability and angina frequency assessed with the Seattle Angina questionnaire, quality of life scores and Duke Treadmill score – supported these findings with only a small but statistical significant change in dobutamine stress echocardiography wall motion score index favouring PCI. These results have subsequently been presented as the “final nail in the coffin of PCI”, garnering significant interest in the mainstream media.¹²

Discussion

The ORBITA trial is the first true comparison between OMT with PCI and OMT with blinded placebo PCI with patients undergoing a sham PCI. The authors suggest PCI is no better than OMT in stable angina. However, closer analysis of the trial design and data casts doubt on the study conclusion.

First, the patient population studied is highly selective, excluding those with multi-vessel disease and impaired left ventricular function. The trial recruited at five large PCI centres for almost 4 years; only a small minority of patients planned to undergo PCI were suitable for enrolment. Second, although almost 98 % of patients had CCS II or III angina on enrolment, 23 % in the PCI arm and 25 % in the placebo arm had CCS 0-I angina by the end of the run-in period. Patients were taking three antianginal medications and had a Seattle Angina Questionnaire physical limitation score of around 70, indicating low to moderate limitation. Given this low level of symptoms, it would have been difficult to show an incremental benefit with PCI.

The short follow-up period means that the effects of PCI over a longer timespan are unclear; of note, the FAME 2 trial published at the same time, which compared PCI with OMT, showed a reduction of over 50 % in major adverse cardiac events (MACE) following PCI during the three-year follow-up period, although in a different patient population (one with multivessel disease).¹³ Although ORBITA was not designed to test MACE, we note that studies documenting time to event in the stable angina group suggest such events in patients who are medically managed peak after 12 months, and longer follow-up periods may be required to detect recurrence of angina after the initial 'honeymoon' period following the PCI or placebo procedure.

Finally, the use of fraction-flow reserve (FFR) is strongly encouraged in current guidelines to guide revascularisation in stable CAD. Fifteen-year outcome data clearly demonstrate postponing PCI in vessels with a FFR >0.75 to be safe and associated with a low rate of clinical endpoints.¹⁴ FFR-guided PCI in multivessel disease has also shown greater benefit from revascularisation than OMT.¹³ The ORBITA study recorded FFR

with a mean pre-procedure FFR of 0.67 (normal>0.8), suggesting severe ischaemia that should benefit from PCI, contradicting the above findings, although 28–32 % of randomised subjects had either normal FFR or instantaneous wave-free ratio, signifying a "physiologically normal" or non-flow limiting stenosis. These patients would not be expected to benefit from PCI based on published data although recent analysis of the ORBITA data suggests no significant interaction between lower FFR or instantaneous wave-free ratio (iFR) readings and either angina frequency score or freedom from angina.¹⁵

Conclusion

The ORBITA trial is a well-conducted trial and includes the novel 'true' placebo arm, a first in interventional cardiology. However, it does not significantly add to the current evidence base which suggests ischaemic guided revascularisation is more effective than PCI guided by symptoms and angiographic appearance in stable CAD. Indeed, the COURAGE trial has already shown patients with asymptomatic stable angina and a low ischaemic burden do not benefit from PCI although, like all previous trials in this area, it is not placebo controlled.

It also inadvertently raises questions about the role of a placebo procedure, as invasive FFR measurement is not without risk; clinically significant complications occurred in 6.3 % of patients, similar to rates seen in other FFR-guided PCI trials.^{16,17}

Longer-term results from the ORBITA study will be awaited with interest to see whether the initial trial findings are maintained. The ISCHAEMIA trial will also add further evidence in the subgroup of asymptomatic patients with a high ischaemic burden on non-invasive imaging.

In summary, while ORBITA has blazed a trail in conducting a true placebo-controlled PCI trial, several limitations to patient selection and trial design limit its extrapolation to everyday clinical practice. Reviewing ORBITA in the context of other studies, it remains the case that FFR-guided PCI continues to be the gold standard treatment for stable CAD in patients whose symptoms are not adequately controlled on OMT. ■

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