ORBITA – much ado about nothing?

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Title Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

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Summary

ORBITA was a placebo-controlled, multicentre, randomised trial of percutaneous coronary intervention (PCI) conducted in the UK. It enrolled patients with stable angina or equivalent symptoms and at least one angiographically severe lesion ≥ 70% in at least one vessel and vulnerable to PCI. Notable exclusions were patients admitted with an acute coronary syndrome, previous coronary artery bypass surgery and presence of disease in the left main stem. After enrolment there were two distinct phases to the trial that differentiated it from previous PCI trials. For the first 6 weeks all patients underwent an intensive medical optimisation phase during which antianginal therapy was titrated. All patients had (telephone) access to a study doctor who was responsible for optimising therapy based on patient history. The second phase, after this 6 week period, was a pre-randomisation assessment followed by the randomised (wire across lesion only vs. PCI) blinded procedure with both groups being treated with identical duration of dual antiplatelet therapy. During the intervention procedure, patients had auditory isolation with headphones playing music throughout. The outcome measures were angina (measured using Seattle Angina Questionnaire), quality of life (quantified using the 5 level EuroQol 5 dimensions), functional capacity using cardiopulmonary exercise testing and myocardial ischaemic burden with dobutamine stress echocardiography. Importantly, the clinical team including all staff present at the randomised blinded procedure were blinded to the results of the symptom burden and quality of life assessments.

The interventional procedure for all enrolled patients involved an invasive procedure consisting of intubation of the coronary artery with a guiding catheter (from either the radial or femoral artery) and crossing the lesion with an intracoronary wire to make a physiological assessment of the culprit vessel. The numerical result of the physiology display was not visible to the operator who followed the randomisation code to which the patient was allocated. For patients randomised to PCI, standard PCI procedure was followed with the use of drug-eluting stents optimised with post-dilatation. After stent deployment, the physiology measurement was repeated with the operator also being blinded to this figure.

After a follow up period of 6 weeks, patients had all pre-randomisation tests repeated. Once complete, patients and physicians were unblinded, with patients free to choose PCI after consultation with their physician.

The pre-specified primary endpoint of the study was the difference in exercise time between the groups. There were several secondary endpoints: change in peak oxygen uptake, change in exercise to 1 mm ST segment depression, angina severity based on Canadian Cardiovascular Society class, physical limitation, angina stability, angina severity (Seattle Angina Questionnaire), quality of life (EQ-5D-SL), Duke treadmill score and change in dobutamine stress echocardiography wall motion score.

Of 368 patients assessed for eligibility, 230 were enrolled and commenced on the medical therapy optimisation phase. Thirty patients subsequently withdrew leaving 200 patients (195 in CCS class II or III) for randomisation to either PCI or placebo.

With respect to the primary endpoint, there was no significant difference between groups in terms of increment in exercise time. Similar findings of significant difference were found for all secondary endpoints with the exception of the dobutamine stress echocardiography peak stress wall motion score. The latter showed a significant improvement following PCI.

For an interventional trial, it is important to note that there were no deaths in the trial. Four patients in the placebo

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group had complications from wire insertion and required emergency stent deployment to seal the coronary dissection.

Discussion

PCI is a widely accepted minimally invasive procedure for relief of symptoms associated with atherosclerotic cardiovascular disease (ASCVD). Its worldwide growth and acceptance over 40 years has ridden on the back of numerous trials favourably comparing intervention to optimal medical therapy.

Optimal medical therapy for ASCVD and angina control has seen marked advances[1] and guidelines for management of stable angina[2,3] recommend titration of several pharmacological agents with different and complementary mechanisms of action. The advent of newer classes of drugs holds the promise of making further advances in reducing the burden resulting from ASCVD.[4–6]

Until publication of ORBITA,[7] no trial had compared optimal medical therapy + PCI against optimal medical therapy + 'true' placebo, i.e. intubation of the culprit artery and crossing of lesion with a guidewire with the patient blinded. The investigators are to be commended in taking this difficult step, the results of which challenge both conventional wisdom and ingrained practice. The accompanying editorial[8] had a headline grabbing title declaring the study to be the 'Last nail in the coffin for PCI in stable angina?' However, as with any trial, the study raises important questions both in terms of the trial itself and its translation to clinical practice.

From 5 UK centres, the ORBITA investigators enrolled 230 patients with angina or equivalent symptoms, ischaemia, with at least one severe (defined as > 70% stenosis) in a single epicardial coronary vessel. Upon enrolment, all patients underwent 6 weeks of optimisation of medical therapy with initiation and up titration of antianginal therapy. Patient-physician interaction was frequent (up to 3 times a week) to keep prescriptions optimised and to monitor heart rate and blood pressure – a degree of contact that is unlikely to reflect real world practice. The authors state that, 'patients had direct access at any time to the consultant cardiologist to make dose adjustments.' Given this level of patient-physician interaction, patient adherence to medication would be expected to be better than that achieved in the real-world. So the trial comprised true optimal medical treatment in both arms. This level of interaction together with the run-in period of optimised antianginal medications meant that a substantial proportion of patients were angina-free going into the randomisation. At enrolment, of 200 patients included in the study, 195 (98%) had class II or III angina. At the time of randomisation, after 6 weeks of optimisation, 23% of the PCI arm and 25% of the placebo arm had CCS Class 0 or CCS Class 1 angina.

After randomisation, patients were assigned to PCI with a drug-eluting stent or a placebo procedure. The latter shared the same operative details up to passage of the coronary guidewire across the stenosis. Thereafter, only those patients randomised to PCI underwent balloon inflation of the coronary stenosis followed by drug-eluting stent insertion. Importantly, all patients underwent auditory isolation during the procedure to ensure blinding.

At follow-up, 6 weeks after randomisation, patients in both groups were receiving a mean of 2.9 medications. The primary outcome was change in exercise time on a treadmill. It is worth noting that all patients had very good exercise capacity at the time of their interventions, which would have made it difficult to show an incremental benefit with PCI at 6 weeks.

Secondary endpoints were change in peak oxygen uptake, change in exercise time to 1 mm ST-segment depression, angina severity, physical limitation, angina stability and angina frequency, Duke treadmill score, and change in dobutamine stress echocardiographic wall motion score index.

The results showed no difference between groups except for a statistically significant, but clinically insignificant, improvement in dobutamine stress echocardiographic wall motion score index in patients who underwent PCI. The ORBITA study has thus been reported 'unequivocally' as a negative study of PCI for stable angina. But what does the ORBITA study add to what is already known?

Ischaemia versus symptom guided revascularisation

Current guidelines recommend that there should be evidence of ischaemia, to be necessary for most stable patients before PCI is performed.[2,3]

Longitudinal studies of ischaemia (nuclear stress) guided revascularisation show greater benefit from revascularisation in those with global ischaemia and good prognosis than in those with minimal ischaemia.[9] However, the link between angiographic lesion severity and outcomes is less reliable and this 'anatomic-functional' mismatch can lead to inappropriate revascularisation treatments. Attempts at improving the predictive value of angiographic findings through use of tools to assess angiographic complexity[10] (e.g. SYNTAX score) have demonstrated some prognostic value but fractional flow reserve measurements overcome the anatomic-functional mismatch. Use of a fractional flow reserve (FFR) wire for assessment of ischaemia has been validated against future ischaemic outcomes.[11] Fifteen year outcome data clearly demonstrated postponing PCI in vessels with an FFR > 0.75 to be safe and associated with a low rate of clinical endpoints.[12] In a multivessel setting, the FAME-2 study showed that patients with an abnormal FFR (i.e. lesion specific ischaemia) benefit more from revascularisation than from optimal medical therapy.[13]

The ORBITA study recorded FFR with the mean FFR pre-procedure of 0.67 (normal > 0.8) suggesting severe ischaemia. However, on closer inspection of the data, 28–32% of randomised subjects had either normal FFR or instantaneous wave-free ratio signifying a 'physiologically

normal', or non-flow-limiting stenosis). Based on published data these patients would not be expected to benefit from PCI.[12,13] By randomising patients with normal FFR values, one would predict dilution of any potential benefit from PCI when compared to optimal medical therapy.

After the procedure, both patients and their care providers were blinded to treatment assignment, and a subsequent blinding index was recorded to assess validity of blinding. While the blinding index showed perfect results for care providers, for patients the results were less consistent. After completion of the 6-week follow-up period, 80 of 105 patients who had PCI felt able to guess their treatment allocation; 50 guessed correctly and 30 incorrectly. In the placebo group 69 of 91 patients felt able to guess; 34 guessed correctly and 35 incorrectly. Presumably, those guessing incorrectly believed they had received PCI and it is this group in whom it would be interesting to know effect as compared to the 34 who guessed correctly. Similarly, an analysis of results in the PCI arm between the 50 who guessed correctly against the 30 who guessed incorrectly may also shed light on the effect of placebo in this trial.

While testing the effect of placebo in an ethically approved research study is a well-established and accepted practice, utilising this effect in clinical practice is fraught with ethical issues. The American Medical Association created a policy concerning placebos stating that 'physicians may use placebos for diagnosis or treatment only if the patient is informed of and agrees to its use'.[14] Therefore, to use the placebo effect in clinical practice has led to accusations that doctors would be essentially lying to their patients when they prescribe something that they know isn't proven to work for the patient's particular condition.

The use of a 'true' placebo arm in testing novel devices (sham testing is the norm) is less frequent than in pharmacological intervention studies but in some studies the placebo effect has been so powerful as to negate the beneficial effect associated with the device being studied.[15] One reason for the dearth of real placebo trials in device studies is the incidence of procedure related complications and the ORBITA study illustrates the inherent risks. Of the 95 patients in the 'placebo' arm, 4 had wire related complications, necessitating bail out PCI, while 2 sustained post procedural major bleeding – a clinically significant complication rate requiring intervention of 6.3%. One patient in the placebo group had an acute coronary syndrome event during the 6 week follow up – a finding that is most likely coincidental but destabilisation of the atherosclerotic plaque following pressure wire assessment of the lesion cannot be excluded. These findings show the need for caution and diligence from both investigators and ethics committees when contemplating an appropriate placebo arm in a device intervention trial. Consenting patients to a placebo arm in clinical studies poses a challenge but this is magnified if placebo becomes a serious 'treatment' option in practice. It is easier (but not easy) to test the placebo effect in clinical trials than to test the effect of placebo in clinical practice.

ORBITA in context

The ORBITA study, beyond having a 'true' placebo arm (rather than sham) adds little to what was previously known about the benefit of percutaneous coronary intervention over medical therapy for stable angina, i.e. an ischaemia guided revascularisation strategy is more effective for PCI than a symptom guided one. As noted above, the DEFER study was the first to question the validity of angiographic assessment of stenosis severity and showed conclusively that patients with stable angina and a FFR measurement of > 0.75 had excellent long term outcomes with medical therapy. By including patients with FFR readings above this cut off, the ORBITA investigators biased the results in favour of the placebo arm. Equally, including patients above this cut-off in the PCI arm would dilute the benefit seen following revascularisation. Second, the duration of follow up (6 months) chosen for follow up was also unlikely to demonstrate superiority over PCI in this mixed group (based on FFR measurements) of patients. A recent meta-analysis confirms a continuous and independent relationship between the FFR's numerical value and subsequent outcomes.[16] Barbato et al. found a non-linear relationship between FFR and major adverse cardiovascular events.[17] This report also documented time to event in this stable angina group, showing major adverse cardiovascular events in the medically managed group to peak after 12 months.

The accompanying editorial[8] talked of the 'last nail in the coffin for PCI in stable angina' and rightly lauded the placebo treatment arm – a first for coronary intervention trials. However, given the serious complication rates in the placebo arm, ORBITA will give much food for thought to patients and ethics committees when contemplating a 'true' placebo arm in future interventional trials. Inadvertently, it may just have put the first nail in the coffin for 'true' placebo controlled PCI trials.

In summary, the ORBITA study will not change existing guidelines for the treatment of stable angina. It simply confirms the findings of an earlier study[18] in a similar population, that in patients with *asymptomatic* stable angina and low ischaemia burden, PCI has no benefit[19]. In this particular patient population, the PCI coffin had been buried some time ago.

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