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

*Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators**

Summary

Background **Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.**

Methods **ORBITA is a blinded, multicentre randomised trial of PCI versus a placebo procedure for angina relief that was done at five study sites in the UK. We enrolled patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received 6 weeks of medication optimisation. Patients then had pre-randomisation assessments with cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. Patients were randomised 1:1 to undergo PCI or a placebo procedure by use of an automated online randomisation tool. After 6 weeks of follow-up, the assessments done before randomisation were repeated at the final assessment. The primary endpoint was difference in exercise time increment between groups. All analyses were based on the intention-to-treat principle and the study population contained all participants who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02062593.**

Findings **ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase and between Jan 6, 2014, and Aug 11, 2017, 200 patients underwent randomisation, with 105 patients assigned PCI and 95 assigned the placebo procedure. Lesions had mean area stenosis of 84·4% (SD 10·2), fractional flow reserve of 0·69 (0·16), and instantaneous wave-free ratio of 0·76 (0·22). There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16·6 s, 95% CI –8·9 to 42·0, p=0·200). There were no deaths. Serious adverse events included four pressure-wire related complications in the placebo group, which required PCI, and five major bleeding events, including two in the PCI group and three in the placebo group.**

Interpretation **In patients with medically treated angina and severe coronary stenosis, PCI did not increase exercisetime by more than the effect of a placebo procedure. The efficacy of invasive procedures can be assessed with a placebo control, as is standard for pharmacotherapy.**

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Introduction

Percutaneous coronary intervention (PCI) was originally introduced to treat stable angina.[1] More than 500000 PCI procedures are done annually worldwide for stable angina. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed no difference in myocardial infarction and death rates between patients with stable coronary artery disease who underwent PCI and controls.[2] Meta-analyses have shown similar results.[3]

Angina relief remains the primary reason for PCI in stable coronary artery disease.[4] Guidelines recommend antianginal medication as first line therapy, with PCI reserved for the many patients who remain symptomatic.[5]

Data from unblinded randomised trials have shown significant exercise time improvement, angina relief, and quality of life improvement from PCI.[6–8] However, symptomatic responses are subjective and include both a true therapeutic effect and a placebo effect.[9] Moreover, in an open trial, if patients randomised to no PCI have an expectation that PCI is advantageous, this might affect their reporting (and their physician's interpretation) of symptoms, artifactually increasing the rate of unplanned revascularisation in the control group.[4,10]

Placebo effects are known to be larger for invasive than non-invasive treatments.[11] Interventional cardiologists and patients with stable angina often think that PCI offers symptomatic relief.[12] Additionally, cardiologists present a decisive approach to diagnosis and treatment, which can lead to an enhanced placebo effect.[13] In the absence of blinding, the effect size of PCI on symptomatic endpoints can be overestimated because of the addition of the placebo effect to the true physiological effect of intervention.[14] In all previous trials, both investigators and patients were aware of the treatment allocation.[2,8,10]

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*ORBITA investigators listed at the end of the Article.

Imperial College London, London, UK (R Al-Lamee MRCP, D Thompson MRCPI, S Sen MRCP, M Mielewczik PhD, R Petraco MRCP, C Cook MRCP, Y Ahmad MRCP, J Howard MRCP, Prof J Mayet FRCP, R Wensel MRCP, M Shun-Shin MRCP, Prof S A Thom FRCP, J E Davies MRCP, Prof D P Francis FRCP);
Imperial College Healthcare NHS Trust, London, UK (R Al-Lamee, D Thompson, S Sen, R Kaprielian FRCP, I S Malik FRCP, S S Nijjer MRCP, R Petraco, C Cook, Y Ahmad, J Howard, C Baker FRCP, R Assomull MRCP, Prof J Mayet, M Shun-Shin, Prof S Thom, J E Davies, and Prof D P Francis FRCP);
Cancer Research UK & UCL Cancer Trials Centre, University College London, London, UK (H-M Dehbi PhD);
Essex Cardiothoracic Centre, Basildon, UK (K Tang FRCP, J Davies MRCP, T Keeble MRCP);
Royal Devon and Exeter NHS Trust, Exeter, UK (A Sharp FRCP);
East Sussex Healthcare NHS Trust, Hastings, UK (R Gerber FRCP);
Royal Bournemouth and Christchurch NHS Trust, Bournemouth, UK (S Talwar MRCP);
and William Harvey Research Institute, Queen Mary University of London, London, UK (D Collier PhD)

Correspondence to:
Dr Justin E Davies, Imperial College Healthcare NHS Trust, London W12 0HS, UK

ORBITA.trial@gmail.com

Research in context

Evidence before this study

More than 500 000 percutaneous coronary interventions (PCIs) are done annually worldwide for the relief of angina but no placebo-controlled trials have been done on the subject. Unblinded PCI is reported to increase exercise time by 96 s more than medical therapy. Single antianginal agents typically increase exercise time by more than 45 s compared with placebo so ORBITA was designed conservatively to detect an effect size of 30 s.

Added value of this study

ORBITA investigated the efficacy of PCI versus placebo to improve exercise capacity in patients with severe coronary disease who were receiving guideline-directed optimum medical therapy. The coronary stenoses were severe and had large haemodynamic effects. Despite PCI markedly improving haemodynamic and imaging indices, PCI did not improve exercise time compared with placebo.

Implications of all the available evidence

The common clinical perception is that patients with stable angina will receive substantial symptom relief from PCI. The results of ORBITA, the only blinded, randomised placebo-controlled trial of PCI, show that even with severe coronary stenosis, exercise capacity and symptoms are not improved significantly compared with a placebo intervention. Physicians advising patients on interventional treatment choices for symptom relief should favour placebo-controlled data. ORBITA shows this approach to be feasible and informative.

Cardiologists have so far been resistant to the idea of a placebo-controlled trial of angina relief from PCI for two main reasons. The first is the widespread perception that PCI unquestionably improves angina,[15] a perception that is based on unblinded clinical experience. The second reason is that it might be unethical to expose patients to an invasive placebo procedure. However, no evidence of harm to placebo groups was found in a systematic review of placebo-controlled surgical trials.[16]

When offering an invasive intervention for symptomatic relief, it is essential to know the true efficacy of the intervention, particularly when the patient could choose to continue conservative treatment instead. Moreover, although PCI has become progressively safer, there remains a complication rate of 1–2%.[17]

Evidence from placebo-controlled randomised controlled trials shows that single antianginal therapies provide improvements in exercise time of 48–55 s.[18,19] The Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial was designed to assess the effect of PCI versus placebo on exercise time in patients with stable ischaemic symptoms, Given the previous evidence, ORBITA was conservatively designed to be able to detect an effect size of 30 s.

Methods

Study design and participants

ORBITA was a multicentre, randomised trial done at five study sites in the UK: Imperial College Healthcare NHS Trust, Essex Cardiothoracic Centre, Royal Bournemouth and Christchurch Hospitals NHS Trust, East Sussex Healthcare NHS Trust, and Royal Devon and Exeter NHS Trust. The London Central Research Ethics Committee (reference 13/LO/1340) approved the study and written consent was obtained from all patients prior to their enrolment. The trial steering committee provided overall supervision of the trial with an independent chairperson leading the committee. Independent data monitoring was done. The independent data safety monitoring board adjudicated all study adverse events and had the authority to terminate the trial if necessary. The protocol summary is available online and the full protocol is included in the appendix.

Patients eligible for the trial were aged 18–85 years with angina or equivalent symptoms and at least one angiographically significant lesion (≥70%) in a single vessel that was clinically appropriate for PCI. Exclusion criteria were angiographic stenosis greater than or equal to 50% in a non-target vessel, acute coronary syndrome, previous coronary artery bypass graft surgery, left main stem coronary disease, contraindications to drug-eluting stents, chronic total coronary occlusion, severe valvular disease, severe left ventricular systolic impairment, moderate-to-severe pulmonary hypertension, life expectancy less than 2 years, and inability to give consent. Eligible patients were approached after diagnostic angiography. They were enrolled after giving written informed consent.

After enrolment, the study consisted of two consecutive phases (figure 1). The first was the 6-week medical optimisation phase, which focused on the initiation and up-titration of guideline directed antianginal therapy. Patients then had baseline pre-randomisation assessment, followed by the randomised blinded procedure. The second phase was the 6-week post-randomisation blinded period after which patients underwent the follow-up assessment.

At enrolment, patients completed the Seattle Angina Questionnaire[20] and 5 level version of the EuroQol 5 dimensions (EQ-5D-5L) questionnaire.[21] Patients had baseline electrocardiograph (ECG), pulse, and blood pressure measurements recorded, as well as height and weight to calculate body-mass index.

After enrolment, patients spent the first 6 weeks in the medical therapy optimisation phase of the protocol in which they had telephone consultations with a consultant cardiologist one to three times per week, supported by home measurements of pulse and blood pressure using equipment provided by the investigators (Omron M6 monitor, Omron, Kyoto, Japan). Medications were introduced and up-titrated in accordance with the trial

protocol. The up-titration focused on antianginal therapy, aiming for at least two antianginal therapies per patient (appendix). Medication side-effects were recorded and patients had direct access at any time to the consultant cardiologist to make dose adjustments.

Patients attended Imperial College London for pre-randomisation research assessment of symptom burden by Canadian Cardiovascular Society Class and the Seattle Angina Questionnaire, functional capacity with cardiopulmonary exercise testing (CPET), myocardial ischaemic burden with dobutamine stress echocardiography, and quality of life assessment with the EQ-5D-5L questionnaire. 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.

All patients were pretreated with dual antiplatelet therapy. In both groups, the duration of dual antiplatelet therapy was the same and continued until the final (unblinding) visit. Coronary angiography was done via a radial or femoral arterial approach with auditory isolation achieved by placing over-the-ear headphones playing music on the patient throughout the procedure.

Randomisation and masking

In all patients, a research invasive physiological assessment of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) was done. After the administration of intracoronary nitrate, a pressure wire was placed in the distal vessel at least three vessel diameters beyond the most distal stentable stenosis. The physiology display was only visible to a separate research interventional cardiologist (RA-L) who informed the clinical operator of signal quality but not the physiology values. The clinical operator was blinded to the physiology values and therefore did not use them to guide treatment. Intravenous adenosine was administered for FFR via a femoral venous line or antecubital fossa vein at 140 µg/kg per min. Normalisation was documented before each measurement. After each measurement, the wire was checked for drift and, if present, the wire was renormalised and measurements were repeated. After physiological assessment, incremental doses of sedatives (benzodiazepines and opiates) were administered until sedation was achieved.

After sedation was established, auditory isolation was continued, and the patient was randomised 1:1 to undergo PCI or the placebo procedure by use of a validated automated online randomisation tool (SRUB, Imperial College London, London, UK). The randomisation sequence was computer generated at Imperial College London and no stratification or blocking was used.

No information about the nature of the procedure (whether PCI or placebo) was transferred from the catheter laboratory staff to the recovery staff. The recovery staff were well rehearsed in their role of maintenance of blinding. Patients and subsequent medical caregivers were also blinded to treatment allocation. The study physicians present during the procedure had no further contact with the patient during the study. Details of blinding and testing of its efficacy are available in the appendix.

Procedures

For patients allocated PCI, the clinical operator used drugeluting stents to treat all lesions that were deemed to be angiographically significant, with a mandate to achieve angiographic complete revascularisation. Stent optimisation with post-dilatation was recommended. Intravascular ultrasound or optical coherence tomography were used as necessary. After PCI, iFR and FFR were measured again. The clinical operator remained blinded to both pre-PCI and post-PCI values.

In the placebo group, patients were kept sedated for at least 15 min on the catheter laboratory table and the coronary catheters were withdrawn with no intervention having been done.

After a follow-up period of 6 weeks, patients re-attended Imperial College London for a follow-up assessment, at which the same tests were done as at the pre-randomisation assessment.

All cardiopulmonary exercise tests were done with the QUARK CPET breath-by-breath metabolic measurement system (COSMED, Rome, Italy). A physician (DT) and a physiologist, both blinded to treatment assignment, did all tests. The test was continued until the development of limiting symptoms (angina, dyspnoea, or fatigue), heart rhythm or blood pressure abnormalities, or marked ST-segment deviation (≥0·20 mV associated with typical angina or in the first stage of exercise). The cardiopulmonary exercise test endpoints were double reported by two physicians (DPF and RW) blinded to treatment allocation and timepoint. The Duke treadmill score was calculated with methods that have been described previously.[22]

Rest and stress cardiac regional wall motion was assessed with dobutamine stress echocardiography. Investigations were done by a physician (DT) and echosonographer blinded to treatment group. The 17-wall segment model was used for reporting dobutamine stress echocardiography and was double reported with an online reporting tool by two imaging cardiology consultants (RA and DPF) who were blinded to treatment allocation and timepoint. Wall motion was scored at rest, during peak and at recovery by use of a quantitative score (normal scored as 1, hypokinetic scored as 2, akinetic scored as 3, dyskinetic scored as 4, and aneurysmal scored as 5). Rest and stress wall motion score indices were then calculated with the 17-segment model, with scores averaged between the reporters.

Intracoronary nitrate was administered to achieve vasodilatation before performing any fluoroscopic run. Fluoroscopic images from two angles at least 30° apart were acquired before the physiological assessment. Quantitative coronary angiography (QCA) measurements were made offline with the McKesson Cardiology 14.0 QCA software system. Quantitative coronary angiography was double reported by two interventional cardiologists, blinded to treatment allocation, with scores averaged between the reporters.

After the follow-up assessments, study participation was complete, and patients and physicians were then

unblinded to the treatment group allocation. Patients who had the placebo procedure had the opportunity to choose to undergo PCI after consultation with their physician.

Outcomes

The prespecified primary endpoint of this study was the difference in exercise time increment between the groups. Secondary endpoints were change in peak oxygen uptake (peak VO_2); change in exercise time to 1 mm ST segment depression; angina severity as assessed by Canadian Cardiovascular Society class; physical limitation, angina stability, and angina frequency as assessed with the Seattle Angina Questionnaire; quality of life as assessed with the EQ-5D-5L questionnaire; Duke Treadmill score, and change in dobutamine stress echocardiography wall motion score index.

Statistical analysis

The primary endpoint of ORBITA was the difference between PCI and placebo groups in the change in treadmill exercise time. Single antianginal agents have been found to increase treadmill exercise time by 48–55 s more than placebo.[18,19] We designed ORBITA conservatively, to detect an effect size from invasive PCI of 30 s, smaller than that of a single antianginal agent. We calculated that, from the point of randomisation, a sample size of 100 patients per group had more than 80% power to detect a between-group difference in the increment of exercise duration of 30 seconds, at the 5% significance level, using the two-sample t test of the difference between groups. This calculation assumed a between-patient standard deviation of change in exercise time of 75 s. There have been no previous placebo-controlled trials of PCI. We therefore initially allowed for a one-third dropout rate in the 6-week period of medical optimisation between enrolment and randomisation and therefore planned to enrol 300 patients. In fact, the dropout rate was much lower so only 230 patients had to be enrolled before 200 participants had been randomised.

We analysed the continuous endpoints with the two-sample *t* test of the difference between groups, and reported them as the difference in mean change between study groups with 95% CIs and p values. Analyses calculated the difference as PCI minus placebo. We described changes within study groups between pre-randomisation and follow-up using a paired approach as the mean and 95% CI of the change. The comparison between groups for time to 1 mm ST depression was made by a test of proportions between those showing an improvement versus those showing deterioration. Improvement was defined as a lengthening of time to ST depression, or having 1 mm ST depression before randomisation but not at follow-up. Deterioration was defined as shortening of the time to 1 mm ST depression, or having ST depression at follow-up but not before randomisation.

We compared angina severity between study groups with the χ^2 test of independence at enrolment, before randomisation, and follow-up. The analysis of change in angina severity between timepoints was based on the proportions of patients whose Canadian Cardiovascular Society class deteriorated or stayed the same, improved by one class, or improved by two classes. We compared these proportions between groups using the χ^2 test of independence.

The Seattle Angina Questionnaire scales were derived from the patients' answers in accordance with the published guidelines.[20] For the EQ-5D-5L, the calculation of the overall health state value was based on the five individual EQ-5D-5L questions using the value set for England.[21]

We calculated blinding indices in the two study groups, for both the patients and the blinded medical team, using the method by Bang and colleagues.[23] We applied the recommended threshold of 20% to interpret the success or failure of blinding.

All analyses were done on the basis of the intention-totreat principle. The study population comprised all randomised participants. We deemed a p value less than 0·05 to be significant.

This trial is registered with ClinicalTrials.gov, number NCT02062593. The protocol for this study was peer-reviewed and accepted by The Lancet; a summary of the protocol was published on the journal's website.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first, corresponding, and last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 18, 2013, and July 26, 2017, 368 patients with angina and single vessel coronary disease were assessed for eligibility (figure 2). Of these patients, 230 were enrolled and entered the medical therapy optimisation phase. Details of patients who were enrolled but later withdrew are shown in figure 2 and the appendix.

200 patients (table 1) were randomised to either PCI or the placebo procedure between Jan 6, 2014, and Aug 11, 2017. There were no substantial differences in the baseline demographics of the two groups. Almost all (195 [98%]) patients were in Canadian Cardiovascular Society class II or III at enrolment.

Medical therapy in the two periods, enrolment to pre-randomisation, and pre-randomisation and followup are shown in the appendix. By the time of randomisation, in the PCI group, 103 (98%) of 105 patients were taking aspirin, 103 (98%) were taking a second antiplatelet, and 99 (94%) were taking a statin, compared to 93 (98%), 94 (99%), and 91 (96%) of 95 patients, respectively, in the placebo group. At the same timepoint, in the whole study population, 156 (78%) of 200 patients were taking β blockers and 182 (91%) were taking calcium channel antagonists. The mean number of antianginal medications in the PCI group was 0·90 (SD 0·8) at enrolment, 2·8 (1·2) at pre-randomisation, and 2·9 (1·1) at follow-up, compared to the placebo group in which the mean number of medications was 1·0 (0·9; p=0·357), 3·1 (0·9; p=0·097), and 2·9 (1·1;

p=0·891), respectively.

Both blood pressure and heart rate were reduced between the enrolment and pre-randomisation measurements, and subsequently rose at the follow-up measurement. There were no differences between the trial groups in these values or in the changes between timepoints (appendix).

Fasting lipids, which were measured at the prerandomisation timepoint, showed mean total cholesterol of 3·4 mmol/L (SD 1·0) in the PCI group and 3·3 mmol/L (0·9) in the placebo group and LDL of 1·8 mmol/L (0·7) in the PCI group and 1·8 mmol/L (0·8) in the placebo group (appendix).

Procedural characteristics are shown in table 2. Most lesions were in the left anterior descending artery (138 [69%] of 200 patients). The coronary stenoses were angiographically and haemodynamically severe. Images of the coronary lesions of the first 12 patients to undergo randomisation are shown in figure 3, and images from all 200 randomised patients are shown in the appendix. Across all patients, the mean area stenosis by quantitative coronary angiography was 84·4% (SD 10·2), mean FFR was 0·69 (0·16), and mean iFR was 0·76 (0·22). 57 (29%) patients had FFR greater than 0·80 and 64 (32%) had iFR greater than 0·89. Lesion location and lesion distribution by quantitative coronary angiography are shown in the appendix.

All PCI was done with drug-eluting stents. The median length of stent implanted was 24 mm (IQR 18–33). Post-dilatation with a new balloon was done in 103 (75%) of 138 stents. After PCI, the mean FFR improved to 0·90 (SD 0·06; p<0·0001) and iFR to 0·95 (0·04; p<0·0001).

Complete pre-randomisation and follow-up data for exercise time were available in 104 patients in the PCI group and 90 patients the placebo group (dataset for all randomised patients and reasons for missing data are shown in the appendix). For the primary endpoint, there was no significant difference between groups in terms of increment in exercise time (table 3). Secondary endpoint analysis showed no significant difference between the groups in the change in the time to 1 mm ST depression (p=0·164) or change in peak oxygen uptake (–12·9 mL/min, 95% CI –90·2 to 64·3, p=0·741). The results of cardiopulmonary testing are shown in table 3.

Angina grade was assessed at all three timepoints in all patients (table 4 and appendix). There was no significant difference between the groups in the proportion of patients with improvements of one class or two or more classes from enrolment to prerandomisation (p=0·916), and from pre-randomisation to follow-up (p=0·633).

Symptoms were assessed with the Seattle Angina Questionnaire and EQ-5D-5L questionnaire (table 3). During the randomised blinded period there were no significant differences between groups in the change from pre-randomisation to follow-up in Seattle physical limitation score (2·4, 95% CI –3·5 to 8·3, p=0·420), Seattle angina frequency (3·5, –2·6 to 9·6, p=0·260), and Seattle angina stability score (0·9, –8.4 to 10.2, p=0·851). There was also no significant difference between the groups in the change in EQ-5D-5L (0·00, 95% CI –0·04 to 0·04, p=0·994)

The change in Duke treadmill score (table 3) was also not significantly different between groups (1·12, 95% CI –0·23 to 2·47, p=0·104). However, the dobutamine stress echocardiography peak stress wall motion score index (table 3) improved more with PCI than with placebo (–0·07, 95% CI –0·11 to –0·04, p<0·0001). Periprocedural and other serious adverse events are described the appendix. No patients died. There were three periprocedural major bleeding events (two with PCI and one with placebo). In four patients in the placebo group, PCI was needed for a pressure-wire related complication. During the follow-up phase, in the placebo group, one patient developed an acute coronary syndrome and two patients had major bleeding on dual antiplatelet therapy.

The primary assessment of blinding was before discharge from the randomisation procedure (appendix). At this timepoint, the blinding index was perfect in the patients (all responded "don't know") in the placebo group and nearly perfect in the PCI group (two of 105 guessed, both correctly, blinding index 0·02, 95% CI –0·003 to 0·04). After the patients completed the 6-week follow-up period, 80 of 105 patients who had PCI felt able to guess their treatment allocation, of whom 50 guessed correctly and 30 incorrectly (blinding index 0·19, 0·05 to 0·33). In the placebo group 69 of 91 patients felt able to guess, of whom 34 guessed correctly and 35 incorrectly (blinding index –0·01, –0·16 to 0·14). In the medical teams, there was no evidence of unblinding at either timepoint (appendix).

Discussion

In ORBITA, the first blinded, placebo-controlled trial of PCI for stable angina, PCI did not improve exercise time beyond the effect of the placebo. This was despite the patients having ischaemic symptoms, severe coronary stenosis both anatomically (84·4% area reduction) and haemodynamically (on-treatment FFR 0·69 and iFR 0·76), and objective relief of anatomical stenosis, invasive pressure, and non-invasive perfusion indices (FFR p<0·0001, iFR p<0·0001, stress wall motion score index p<0·0001). There was also no improvement beyond placebo in the other exercise and patient-centred endpoints, including Canadian Cardiovascular Society class and the metrics of the Seattle Angina Questionnaire and EQ-5D-5L questionnaire.

This result might seem to contradict the real-world experience that patients report relief of angina after PCI. However, real-world data inevitably mix physical effects with placebo effects. Forgetting this point, or denying it, causes overestimation of the physical effect.

The necessity for placebo-controlled trials has been rediscovered several times in cardiology, typically to considerable surprise.[24] Often a therapy is thought to be so beneficial that a placebo-controlled trial is deemed unnecessary and perhaps unethical. However, 40 years after the first PCI, ORBITA's findings show that placebo-controlled randomised trials remain necessary.

ORBITA has implications for our clinical understanding of stable angina. The concept of a simple linear link between a tight stenosis and angina is attractive to patients, easily explained by physicians, and biologically plausible. Moreover, since relieving the anatomical and haemodynamic features of stenosis by unblinded PCI is followed by the patient reporting angina relief, it is understandable that this link becomes generally accepted.

However, forgetting the potential magnitude of placebo effects prevents exploration of the inevitably complex relationship between anatomy, physiology, and symptoms. Clinicians have hoped there might be a simple entity named ischaemia, which manifests as positive tests and clinical symptoms, and that treatment by PCI would eliminate all these manifestations concordantly. Perhaps this notion is too optimistic.

Nevertheless the findings of ORBITA do not mean that patients should never undergo PCI for stable angina. Not all patients would be satisfied with taking multiple antianginal agents forever. They might prefer an invasive procedure with a small procedural risk for the potential to need fewer medications.

The ORBITA protocol had specific features. The medical therapy optimisation phase was intentionally intensive, consisting of one to three telephone consultations per week with a consultant cardiologist supported by home blood pressure and heart rate measurements. This phase ensured a high level of antianginal therapy within just 6 weeks and facilitated the enrolment and retention of patients with severe coronary disease.

The trial was designed to achieve good quality background antianginal therapy, as is recommended.[25,26] To minimise the period of deferral of PCI, which could have been a barrier to participation, the medical optimisation phase was designed to be more intensive than routine clinical practice. Patients were up-titrated to an average of three antianginal agents during the initial 6 weeks before randomisation. Achieving this required several consultations per week with a consultant cardiologist. The longest half-life of the drugs introduced was 40 h for amlodipine. Because amlodipine was second-line therapy, it was never added in the final 2 weeks and therefore no patient had pharmacokinetically insufficient time for therapeutic effect. The changes in heart rate and blood pressure between baseline and randomisation confirm physiological effects. 39 of 230 enrolled patients had become free of angina at the pre-randomisation timepoint with antianginal therapy, perhaps due to the antianginal therapy or self-restriction of physical activity. 17 of these patients left the trial at this time but 22 went forward for randomisation. The other 178 (89%) patients randomised had angina despite antianginal therapy. Of the patients who underwent randomisation, most were taking at least two antianginal drugs.[25,26]

The ORBITA patients had ischaemia as evidenced by anginal symptoms and severe coronary disease, with haemodynamic severity similar to unblinded trials of PCI. In ORBITA the mean FFR was 0·69, similar to the means of 0·71 in FAME and 0·68 in FAME-2.[27,28]

The 2017 guidelines state that PCI is appropriate for this cohort of patients with single-vessel coronary disease and angina who are on at least two antianginals, with no requirement for any further tests.[29] Angiographic images of all 200 patients are shown in the appendix for comparison with other trials.

A placebo-controlled trial of PCI involves two major risks for participants, which need to be included in the informed consent process. First, dual antiplatelet therapy can cause major bleeding. Indeed, two patients in the placebo group had major bleeding from erosive gastritis. Both patients subsequently underwent clinical stenting on proton pump inhibitor and dual antiplatelet therapy without further bleeding. Second, passing a pressure wire through tight lesions can disrupt the intima. Four patients in the placebo group had this problem and therefore underwent unplanned stenting. Despite these events, there were no long-term clinical sequelae for any of the participants. While placebo-controlled trials have some risks, PCI also has some risk.

ORBITA was designed to detect a clinically relevant effect size. Contemporary placebo-controlled trials of single-agent antianginal therapies have reported improvements in exercise time of 48–55 s.[18,19] ORBITA was designed to be able to detect an effect size of 30 s (55–63% of the effect of a single antianginal agent), which is a relatively conservative goal for an invasive therapy that has a small but non-negligible risk. In practice the variability in exercise time increments was slightly larger than predicted and therefore the trial could in retrospect be considered to be powered for a 34 s effect. ORBITA is comparable in size to the MARISA trial of single-agent antianginal therapy, which had 191 patients.[19]

ORBITA only investigated PCI for stable angina and the results have no implications for patients undergoing PCI for acute coronary syndrome, including ST-elevation myocardial infarction for which morbidity and mortality advantages from PCI have been proven.[30]

Although the participants had anatomically and physiologically severe lesions, we did not enrol patients with multivessel disease. Patients with more extensive territories of coronary disease might receive a larger physiological benefit from PCI and have no obvious reason for a larger placebo effect.

In the four-decade history of PCI, decision making has been primarily based on symptoms and angiographic appearance, and patients and their clinicians have been reporting angina relief after PCI. ORBITA's design reflects much historical and current clinical practice of PCI for stable angina. Whether a future blinded trial with different entry criteria (eg, restricting entry according to invasive coronary pressure measurements) would have different results remains unknown.

This trial set an objective and continuous variable as the primary endpoint: difference in exercise time increment between PCI and placebo. There are many other possible symptom-based variables, but exercise time has proved to be a discriminating test for

many antianginal therapies and is recommended for this purpose by both the US Food and Drug Administration and the European Medicines Agency.

The follow-up time was only 6 weeks, so that patients and physicians would not be deterred by the prospect of remaining indefinitely without the option of PCI. The anatomic and haemodynamic effects of stenting on the coronaries are immediate, and symptomatic and exercise test improvements from unblinded PCI are well documented at 30 days,[6] 37 days,[31] and 6 weeks.[32] As a result of the limited duration of ORBITA, it cannot address long-term myocardial infarction and mortality endpoints. Other trials such ISCHEMIA (NCT01471522) will do this.

In ORBITA, the extent of coronary disease (one vessel vs multivessel) was judged visually, as is common practice in diagnostic angiography. It is unlikely that the non-target vessels in the patients were entirely normal.

Epicardial arteries are the focus of most clinical attention because they are visible and amenable to procedural intervention. However, patients might differ in microvascular physiology. Ischaemia from non-target vessel or from microvascular disease could have contributed to angina that the PCI procedure would not have improved.

Any trial using exercise testing as an endpoint might experience a training effect. However, the combination of randomisation, placebo-control, and blinding should distribute this effect equally between groups.

ORBITA made a blinded comparison of PCI and a placebo procedure in patients with stable angina and anatomically and haemodynamically severe coronary stenosis. The primary endpoint of exercise time increment showed no difference between groups. This first placebo-controlled trial of PCI for stable angina suggests that the common clinical observation of symptomatic improvement from PCI might well contain a large placebo component. Placebo-controlled efficacy data could be just as important for assessing invasive procedures, where the stakes are higher, as for assessing pharmacotherapy where it is already standard practice.

Contributors

RA-L, DT, RW, JED, SAT, DPF (principal investigator), and DC (independent chairman) were members of the steering committee. RA-L, DPF, JED, and SAT were on the writing committee. H-MD, MM, MS-S, and JH were part of the data analysis committee. RA-L, DT, RW, JED, SAT, and DPF were responsible for the conception and design of the study. RA-L, SS, KT, JD, TK, RK, ISM, SSN, RP, CC, YA, CB, AS, RG, and ST were responsible for data acquisition in the cardiac catheter laboratory. DT, RA, JM, and DPF were responsible for data acquisition in the echocardiography laboratory, and DT, RW, and DPF were responsible for data acquisition in the exercise laboratory. H-MD was the study statistician. RA-L, DPF, JED, and SAT were responsible for the data interpretation and writing of the report.

ORBITA study investigators

Rasha Al-Lamee, David Thompson, Sayan Sen, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Matthew Shun-Shin, Jamil Mayet, Jaspal Kooner, Simon Thom, Justin Davies, Darrel Francis, and Ramzi Khamis (Imperial College London, London, UK and Imperial College Healthcare NHS Trust, London, UK); Kare Tang, John Davies, and Thomas Keeble (Essex Cardiothoracic Centre, Basildon, UK); Raffi Kaprielian, Iqbal Malik, Sukhjinder Nijjer, Amarjit Sethi, Christopher Baker, Punit Ramrakha, Ravi Assomull, Rodney Foale, Nearchos Hadjiloizou, Masood Khan, Michael Bellamy, Ghada Mikhail, and Piers Clifford (Imperial College Healthcare NHS Trust, London, UK); Andrew Sharp (Royal Devon and Exeter NHS Trust, Exeter, UK); Robert Gerber (East Sussex Healthcare NHS Trust, Hastings, UK); Suneel Talwar, Peter O'Kane, Terry Levy, and Rosie Swallow (Royal Bournemouth and Christchurch NHS Trust, Bournemouth, UK); and Roland Wensel (Imperial College London, London, UK).

Declaration of interests

JED and JM hold patents pertaining to the iFR technology. JED and AS are consultants for Philips Volcano. RA-L, SS, RP, CC, and SSN have received speaker's honoraria from Philips Volcano. JED and TK have received research grants from Philips Volcano. All other authors declare no competing interests.

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