Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA trial): a randomised double-blind trial

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Summary (298/300 words)

Background

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

Methods

ORBITA is a multi-centre randomised blinded trial of PCI versus placebo procedure for angina relief, enrolling patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received six weeks of medication optimisation. Patients then had pre-randomisation assessment: (a) cardiopulmonary exercise testing, (b) symptom questionnaires, and (c) dobutamine stress echocardiography. They then underwent the blinded invasive procedure with 1:1 randomisation to PCI or placebo. After six weeks' follow-up, steps (a) to (c) were repeated at the final assessment. The primary endpoint was difference in exercise time increment between arms.

Findings

ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase, 200 patients were randomised between January 2014 to August 2017, 105 to PCI and 95 to placebo. Lesions had mean area stenosis 84·4% (SD 10·2), fractional flow reserve (FFR) 0·69 (SD 0·16) and instantaneous wave-free ratio (iFR) 0·76 (SD 0·22). There was no significant difference in the primary endpoint of exercise time increment between arms (PCI minus placebo 16·6 seconds, 95% CI -8·9 to 42·0, p=0·200). There was no mortality. Significant adverse events included 4 wire complications in the placebo group requiring PCI and 5 major bleeding events (2 PCI, 3 placebo).

Interpretation

In patients with medically treated angina and anatomically and haemodynamically severe coronary stenosis, PCI did not increase exercise time by more than placebo. Efficacy of invasive procedures can be assessed with placebo control, as is standard for pharmacotherapy.

Trial Registration

ClinicalTrials.gov identifier: NCT02062593

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Research in context

Evidence before this study

Over 300,000 percutaneous coronary interventions (PCIs) are carried out annually worldwide for relief of angina but no placebo-controlled trial has been performed. Single anti-anginal agents typically increase exercise time by over 45 seconds compared with placebo. ORBITA was designed conservatively, to detect an effect size of 30 seconds.

Added value of this study

ORBITA evaluated the efficacy of PCI beyond placebo to improve exercise capacity in patients with severe coronary disease on guideline-directed optimum medical therapy. The coronary stenoses were severe (average area reduction 84·4%) and had large haemodynamic effects (average FFR 0·69 and iFR 0·76). Despite PCI markedly improving haemodynamic and imaging indices, there was no significant difference between PCI and placebo in exercise time increment.

Implications of all the available evidence

The common clinical perception is that patients with stable angina have substantial symptom relief from PCI. ORBITA, the first blinded, randomised, placebo-controlled trial of PCI, shows that even with severe coronary stenosis, exercise capacity and symptoms are not improved to the extent expected. Physicians advising patients on interventional treatment choices for symptom relief should favour placebo-controlled data. ORBITA shows this is feasible and informative.

Introduction

Percutaneous coronary intervention (PCI) was originally introduced to treat stable angina.[1] Over 300,000 PCI procedures are carried out annually worldwide for stable angina. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed no difference in myocardial infarction and mortality rates between PCI and control.[2] Meta-analyses have shown similar results.[3]

Angina relief remains the primary reason to conduct PCI in stable coronary artery disease (CAD).[4] Guidelines recommend anti-anginal medication as first line, with PCI reserved for those patients who remain symptomatic.[5]

Many patients remain symptomatic despite medical therapy.[6] Unblinded randomised trials have shown significant angina relief and quality of life improvement from PCI.[7] However, symptomatic responses are subjective and include both a true therapeutic effect and a placebo effect.[8] Moreover, in an open trial, if patients randomised to no PCI have an expectation that PCI is advantageous, this may colour their reporting (and their physician's interpretation) of symptoms, artifactually increasing the rate of unplanned revascularization in the control arm. [4,9]

Placebo effects are known to be larger for invasive than non-invasive treatments.[10] Interventional cardiologists and patients with stable angina have a pre-conception that PCI offers symptomatic relief.[11] Additionally, cardiologists present a decisive approach to diagnosis and treatment which can lead to a greater placebo effect.[12] In the absence of blinding, the effect size of PCI on symptomatic endpoints may be overestimated because of the addition of the placebo effect to the true physiological effect of intervention.[13] In all previous trials, both investigators and patients were aware of the treatment allocation.[2,9] Therefore, before ORBITA, PCI had never been tested against placebo in a blinded randomised controlled trial.

Cardiologists have hitherto been resistant to conducting a placebo-controlled trial of angina relief from PCI for two main reasons. The first is the widespread perception that PCI unquestionably improves angina;[14] a perception based on unblinded clinical

experience. The second reason is that it might be unethical to expose patients to an invasive placebo procedure. However a systematic review of placebo-controlled surgical trials shows no evidence of harm to placebo groups.[15]

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 to 2%.[16]

Placebo-controlled randomised controlled trials show that single anti-anginal therapies provide 48 to 55 second improvements in exercise time.[17,18] ORBITA was designed to assess the effect of PCI against placebo on exercise time in patients with stable ischaemic symptoms. It was conservatively designed to be able to detect an effect size of 30 seconds.

Methods

Study design and participants

ORBITA was a multi-centre, randomised trial performed at five study sites in the UK: Imperial College Healthcare NHS Trust, Basildon and Thurrock University Hospitals NHS Trust, 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 enrolment. The Trial Steering Committee provided overall supervision of the trial with an independent chairperson leading the committee. Independent data monitoring was conducted. The independent Data Safety Monitoring Board adjudicated all study adverse events and had the authority to terminate the trial if necessary. The trial was registered with ClinicalTrials.gov identifier: NCT02062593. The protocol summary is published at http://www.thelancet.com/protocol-reviews/14PRT-06897.

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 ≥50% in a non-target vessel, acute coronary syndrome, previous coronary artery bypass graft surgery, left main stem coronary disease, contra-indications to drug-eluting stents, chronic total coronary occlusion, severe valvular disease, severe left ventricular systolic impairment, moderate-severe pulmonary hypertension, life expectancy <2 years, and inability to 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 six-week medical optimisation phase focussing on the initiation and up-titration of guideline directed anti-anginal therapy. Patients then had baseline pre-randomisation assessment, followed by the randomised blinded procedure.

The second phase was the six-week post-randomisation blinded period after which patients underwent the follow up assessment.

Enrolment

At enrolment patients completed the Seattle Angina Questionnaire[19] and EQ-5D-5L questionnaire.[20] Patients had baseline electrocardiograph (ECG), pulse, blood pressure measurements, and height and weight recorded measurements for calculation of body mass index.

Medical therapy optimisation phase

After enrolment, patients spent the initial six 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 Ltd, UK). Medications were introduced and up-titrated according to the trial protocol. The up-titration focussed on anti-anginal therapy, aiming for at least two anti-anginal therapies per patient (Table A3 in

Appendix 4). Medication side effects were recorded and patients had direct access at any time to the consultant cardiologist to make dose adjustments.

Pre-randomisation assessment

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

The clinical team, including all staff present at the randomised blinded procedure, were blinded to the results of (a) to (d).

Invasive assessment and randomised blinded procedure

All patients were pre-treated with dual antiplatelet therapy. In both arms the duration of dual anti-platelet therapy was the same and continued until the final (unblinding) visit. Coronary angiography was performed via radial or femoral arterial approach with auditory isolation using over-ear headphones playing music throughout the procedure.

Invasive assessment

In all patients, a research invasive physiological assessment of fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) was performed. After intracoronary nitrate administration, 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 (RAL) 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 140mcg/kg/min. Normalisation was documented before each measurement. After each measurement, the wire was checked for drift and, if

present, the wire was re-normalised and measurements repeated. After physiological assessment, incremental doses of sedatives (benzodiazepines and opiates) were administered until sedation was achieved.

Randomisation

After sedation was established, auditory isolation was continued, and the patient was randomised 1:1 to PCI or placebo procedure using a validated automated online randomisation tool (SRUB, Imperial College London). The randomisation sequence was computer generated at Imperial College London.

PCI

In the PCI arm, the clinical operator used drug-eluting stents to treat all lesions that were deemed 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 repeated. The clinical operator remained blinded to both pre-PCI and post-PCI values.

Placebo procedure

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

Blinding procedures and blinding index

No information regarding 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 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 can be found in Appendices 4 and 5.

Follow up investigations

After a follow-up period of six weeks, patients re-attended for a follow-up assessment, with the same tests as the pre-randomisation assessment.

Study participation was then complete, and patients and physicians were then unblinded to the treatment arm allocation. Patients who had the placebo procedure had the opportunity to choose to undergo PCI after consultation with their physician.

Cardiopulmonary exercise testing

All CPET investigations were performed using the QUARK CPET breath-by-breath metabolic measurement system (COSMED, Rome, Italy). A blinded physician (DT) and a blinded physiologist performed 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 (≥0.20mV associated with typical angina or in the first stage of exercise). The CPET endpoints were double reported by two physicians (DF and RW) blinded to treatment allocation and order. The Duke treadmill score was calculated using methods as previously described.[21]

Dobutamine stress echocardiography

Rest and stress cardiac regional wall motion was assessed using DSE. Investigations were performed by a blinded physician (DT) and blinded echo-sonographer. The 17-wall segment model was used for reporting. DSEs were double reported using an online DSE reporting tool by two imaging cardiology consultants (RA and DF) who were blinded to treatment allocation and order. Wall motion was scored at rest, during peak and at recovery using 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 using the 17-segment model, with scores averaged between the reporters.

Quantitative coronary angiography

Intracoronary nitrate was administered to achieve vasodilatation prior to performing any fluoroscopic run. Fluoroscopic images from two angles at least 30 degrees apart were acquired prior to physiological assessment. Quantitative coronary angiography

(QCA) measurements were made offline using the McKesson Cardiology™ 14·0 QCA software system. QCA was double reported by two interventional cardiologists, blinded to treatment allocation, with scores averaged between the reporters.

Outcomes

The pre-specified primary endpoint of this study was change in exercise time on treadmill. Secondary endpoints included: change in peak oxygen uptake (peak VO2); change in exercise time to 1mm ST segment depression; angina severity as assessed by CCS class; physical limitation, angina stability, and angina frequency as assessed by the Seattle Angina Questionnaire; quality of life as assessed by the EQ-5D-5L questionnaire; Duke Treadmill score and change in DSE wall motion score index.

Statistical analysis

The primary endpoint of ORBITA was the difference between PCI and placebo arms in the change in treadmill exercise time. Recent single anti-anginal agents have been found to increase treadmill exercise time beyond placebo by over 45 seconds.[17,18] We designed ORBITA conservatively, to detect an effect size of invasive PCI smaller than a single anti-anginal agent: 30 seconds. We calculated that from the point of randomisation, a sample size of 100 patients per arm had >80% power to detect a between-arm difference in increment in exercise duration of 30 seconds, at the 5% significance level, using the 2-sample t-test of the difference between arms. This calculation assumed a between-patient standard deviation of change in exercise time of 75 seconds. There has been no previous trial of placebo-controlled trial of PCI. We therefore initially allowed for a one third dropout rate in the six-week period of medical optimisation between enrolment and randomisation and therefore planned to enrol 300 patients. In fact the dropout rate was much lower, and therefore only 230 patients had to be enrolled to randomise 200 participants.

The continuous endpoints were analysed using the 2-sample t-test of the difference between arms, and reported as the difference in mean change between study arms with 95% confidence intervals (CI) and p-values. Analyses calculated the difference as PCI minus placebo. Changes within study arms between pre-randomisation and

follow-up were described using a paired approach as the mean and 95% confidence interval of the change. The comparison between arms for time to 1mm 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 1mm ST depression at pre-randomisation but not at follow-up. Deterioration was defined as shortening of the time to 1mm ST depression, or having ST depression at follow-up but not at pre-randomisation.

Angina severity was compared between study arms using the chi-square test of independence at enrolment, pre-randomisation and follow-up. The analysis of change in angina severity between time points was based on the proportions of patients whose CCS class deteriorated or stayed the same, improved by one class, or improved by two classes. These proportions were compared between arms using the chi-square test of independence.

The Seattle Angina Questionnaire scales were derived from the patients' answers according to the published guidelines.[19] For the EQ-5D-5L, the overall health state value was calculated based on the five individual EQ-5D-5L questions using the value set for England.[20]

Blinding indices in the two study arms, for both the patients and the blinded medical team, were calculated using the method by Bang et al.[22] The recommended threshold of 20% to interpret the success or failure of blinding was applied.

All analyses were on the basis of intention-to-treat. The study population comprised all randomised participants. A p-value <5% was considered significant.

Role of funding source

This was an investigator-led trial sponsored by Imperial College London. The trial was funded by grants from: NIHR Imperial Biomedical Research Centre, Foundation for Circulatory Health, and Imperial College Healthcare Charity. Philips Volcano supplied the coronary pressure wires. NIHR Barts Biomedical Research Centre is the employer

of the independent chair of the trial steering committee (DC). The funders had no role in study design, data collection, data analysis, data interpretation, manuscript preparation or the decision to submit. 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 December 2013 and July 2017, 368 patients with angina and single vessel coronary disease were assessed for eligibility (Figure 2). Of these, 230 were enrolled and entered the medical therapy optimisation phase. Details of patients who were enrolled but later withdrew are given in Figure 2 and Appendix 6.

Two hundred patients (Table 1) were randomised to receive either PCI or placebo procedure between January 2014 and August 2017. There were no significant differences in the baseline demographics of the two groups. Almost all (97·5%) were in CCS class II or III at enrolment

Medical therapy in the two periods: enrolment to pre-randomisation and pre-randomisation and follow-up are shown in Table A4, A8 and A9 in Appendix 5. By randomisation 98%, 98% and 94% patients were taking aspirin, a second anti-platelet and a statin respectively in the PCI arm, and 98%, 99% and 96% in the placebo arm. By the time of randomisation 78% of patients were taking beta-blockers, and 91% were taking calcium channel antagonists in the whole group. The mean (SD) number of anti-anginal medications at enrolment, pre-randomisation, and follow-up was 0·90 (0·8), 2·8 (1·2), 2·9 (1·1) in the PCI arm and 1·0 (0·9), 3·1 (0·9), 2·9 (1·1) in the placebo arm (p=0·357, 0·097, 0·891 respectively).

Both blood pressure and heart rate fell between enrolment and pre-randomisation measurement, and subsequently rose at the follow-up measurement. There were no differences between the trial arms in the values or their changes between time-points (Table A5 in Appendix 5).

Fasting lipids, which were measured at the pre-randomisation time-point, showed mean total cholesterol level of 3·4mmol/L (SD 1·0) in the PCI arm and 3·3mmol/L (SD 0·9) in the placebo arm and low-density lipoprotein of 1·8mmol/L (SD 0·7) in the PCI arm and 1·8mmol/L (SD 0·8) in the placebo arm (Table A6 in Appendix 5).

Procedural characteristics are shown in Table 2. The majority of lesions were in the left anterior descending artery (69·0%). The coronary stenoses were angiographically and haemodynamically severe. Images of the coronary lesions of the first 12 patients randomised are shown in Figure 3, and of all 200 randomised patients are shown in Appendix 7. Across all patients, the mean area stenosis by QCA was 84·4% (SD 10·2), the mean FFR was 0·69 (SD 0·16) and the mean iFR was 0·76 (SD 0·22). Fifty-seven patients (28.5%) had FFR>0.80 and 64 (32%) had iFR>0.89. Lesion location and lesion distribution by QCA are shown in Tables A10 and A11 in Appendix 5.

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

Complete pre-randomisation and follow-up data for exercise time was available in 104 patients in the PCI arm and 90 patients the placebo arm (dataset for all randomised patients is shown in Table A12 in Appendix 5 and reasons for missing data are shown in Appendix 6).

Peri-procedural and other serious adverse events are described in Appendix 6. There was no mortality. There were three peri-procedural major bleeding events (2 PCI, 1 placebo). In four patients in the placebo arm, PCI was required for a pressure-wire related complication. During the follow-up phase 1 patient (placebo arm) developed an acute coronary syndrome and 2 patients (placebo arm) had major bleeding on dual anti-platelet therapy.

In the primary endpoint, there was no significant difference between arms in the increment in exercise time (PCI minus placebo, 16·6 seconds, 95% CI -8·9 to 42·0,

p=0·200). The exercise time increments in the individual arms were 28·4 seconds (95% CI 11·6 to 45·1) in the PCI arm and 11·8 seconds (95% CI -7·8 to 31·3) in the placebo arm.

Secondary endpoint analysis showed no significant difference between the arms in the change in the time to 1mm ST depression (p=0·164) or change in peak oxygen uptake (-12·9ml/min, 95% CI -90·2 to 64·3, p=0·741). The results of cardiopulmonary testing are shown in Table 3.

CCS angina grade was assessed at all three time-points in all patients (Table 4 and Table A7 and Figure A1 in Appendix 5). There was no significant difference between the arms in the proportion of patients that improved by one CCS class or by two or more CCS classes (p=0·92).

Symptoms were assessed by the Seattle Angina and EQ-5D-5L questionnaires (Table 3). During the randomised blinded period there was no significant difference between arms 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) and the Seattle angina frequency (3·5, 95% CI -2·6 to 9·6, p=0·260). There was also no significant difference between the arms 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 not significantly different between arms (1·12, 95% CI -0·23 to 2·47, p=0·104).

The DSE peak stress wall motion score index (Table 3) improved more with PCI than placebo (-0·07, 95% CI -0·11 to -0·04, p<0·0001).

The primary assessment of blinding was prior to discharge from the randomisation procedure (Appendix 5). In the patients the blinding index was perfect (all responded “don’t know”) in the placebo arm and near perfect in the PCI arm (2/105 guessed, both correctly, blinding index 0·02, 95% CI -0·003 to 0·04).

After the patients completed the six week follow-up period, 80/105 PCI patients felt able to guess their treatment allocation, 50 correctly and 30 incorrectly (blinding index 0·19, 95% CI 0·05 to 0·33). In the placebo arm 69/91 felt able to guess, 34 correctly and 35 incorrectly (blinding index -0·01, 95% CI -0·16 to 0·14).

In the medical teams there was no evidence of unblinding at either time-point (Appendix 5).

Discussion

In ORBITA, the first blinded, placebo-controlled trial of PCI for stable angina, PCI did not improve exercise time beyond 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 incontrovertible 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 CCS class and the metrics of the Seattle angina and EQ-5D-5L questionnaires.

This may 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. Forgetting this, 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.[23] Often a therapy is thought to be so beneficial that a placebo-controlled trial is considered unnecessary and perhaps unethical, sometimes even attracting droll analogies to testing the need for a parachute.

Forty years after the first PCI, ORBITA shows that placebo-controlled randomised trials remains necessary.

ORBITA has implications for our clinical understanding. 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 prevents us from exploring 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 is too optimistic.

Nevertheless ORBITA does not mean that patients should never undergo PCI for stable angina. Not all patients would be satisfied with taking multiple anti-anginal agents forever. They may prefer an invasive procedure with a small upfront risk for the potential to have fewer medications.

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

The trial was designed to achieve good quality background anti-anginal therapy as is recommended.[24,25] To minimise the period of deferral of PCI, which may 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 anti-anginal agents during the initial six weeks before randomisation. Achieving this required one to three consultations per week with a consultant cardiologist. The longest half-life of the drugs introduced was 40 hours for amlodipine. Because this

was second line it was never added in the final two weeks and therefore no patient had pharmacokinetically insufficient time. The changes in heart rate and blood pressure confirm physiological effects. Thirty-nine out of 230 enrolled patients had become free of angina (CCS 0) at the pre-randomisation time-point with anti-anginal therapy. This may have been due to the anti-anginal therapy or self-restriction of physical activity. Seventeen patients exited the trial at this time but 22 went forward for randomisation. The other 178 randomised patients (89%) had angina despite anti-anginal therapy. Of the randomised patients, the majority were taking at least two anti-anginal drugs.[24,25]

The ORBITA patients had ischaemia as evidenced by anginal symptoms, severe coronary disease, with haemodynamic severity similar to unblinded trials of PCI. In ORBITA the mean FFR was 0·69, comparable to 0·71 in FAME and 0·68 in FAME-2.[26,27] The 2017 guidelines state that PCI is appropriate for this cohort of patients with single vessel coronary disease and angina on at least two anti-anginals, with no requirement for any further tests.[28] Angiographic images of all 200 patients are shown in Appendix 7 for comparison with other trials.

ORBITA patients underwent a blinded procedure and were randomised to PCI or placebo. A placebo-controlled trial of PCI involves two major risks for participants, which need to be included in the informed consent process. First, dual anti-platelet therapy can cause major bleeding. Indeed, two placebo patients had major bleeding from erosive gastritis. Both patients subsequently underwent clinical stenting on proton pump inhibitor and dual anti-platelet therapy without further bleeding. Second, passing a pressure wire through tight lesions can disrupt the intima. Four patients in the placebo arm experienced this and therefore underwent unplanned stenting. Despite these events, there were no long-term clinical sequelae for any of the participants. Furthermore PCI has low short and long-term risks.

ORBITA was designed to detect a clinically relevant effect size. Contemporary placebo-controlled trials of single agent anti-anginal therapies have reported effect sizes of 48 to 55 seconds.[17,18] ORBITA was designed to be able to detect an effect size of 30

seconds (55% to 63% of a single anti-anginal 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 second effect. ORBITA is comparable in size to the 191 patient MARISA trial of single agent anti-anginal therapy.[18]

ORBITA only considered PCI for stable angina and has no implications for patients undergoing PCI for acute coronary syndrome including ST-elevation myocardial infarction for which morbidity and mortality advantages have been proven.

Study limitations

Although the participants had anatomically and physiologically severe lesions, we did not enrol patients with multi-vessel disease. Patients with more extensive territories of coronary disease might have a larger physiological benefit from PCI and 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 the majority of historical and current clinical practice of PCI for stable angina. Whether a future blinded trial with different entry criteria (e.g. 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 anti-anginal therapies and is the recommended for this by both the U.S. Food and Drug Administration authority and the European Medicines Agency.

The follow-up time was only six weeks, so that patients and physicians would not be deterred by the prospect of remaining indefinitely without the option of PCI. However

the anatomic and haemodynamic effects of stenting on the coronaries are immediate, and symptomatic and exercise test improvements from unblinded PCI is well documented at 30 days,[6] 37 days[29] and 6 weeks.[30] As a result of the limited duration of ORBITA, it cannot address long-term myocardial infarction and mortality endpoints. Other trials such ISCHEMIA (NCT01985360) will do this.

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

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

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

Conclusions

ORBITA made a blinded comparison of PCI and 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 arms. This first placebo-controlled trial of PCI for stable angina suggests that the common clinical observation of symptomatic improvement from PCI may well contain a large hidden placebo component. Placebo-controlled efficacy data may be just as important for assessing invasive procedures, where the stakes are higher, as for assessing pharmacotherapy where it is already standard practice.

Contributors

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Declaration of interests

Justin Davies and Jamil Mayet hold patents pertaining to the iFR technology.

Justin Davies and Andrew Sharp are consultants for Philips Volcano.

Rasha Al-Lamee, Sayan Sen, Ricardo Petraco, Christopher Cook and Sukhjinder Nijjer receive speaker's honoraria from Philips Volcano.

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References

1. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978; **1**(8058): 263.
2. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *The New England journal of medicine* 2007; **356**(15): 1503-16.
3. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous Coronary Intervention Outcomes in Patients With Stable Obstructive Coronary Artery Disease and Myocardial Ischemia: A Collaborative Meta-analysis of Contemporary Randomized Clinical Trials. *JAMA internal medicine* 2013.
4. Spertus JA, Maron DJ, Cohen DJ, et al. Frequency, predictors, and consequences of crossing over to revascularization within 12 months of randomization to optimal medical therapy in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. *Circulation Cardiovascular quality and outcomes* 2013; **6**(4): 409-18.
5. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2014.
6. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *The New England journal of medicine* 2008; **359**(7): 677-87.
7. Wijeysundera HC, Nallamothu BK, Krumholz HM, Tu JV, Ko DT. Meta-analysis: effects of percutaneous coronary intervention versus medical therapy on angina relief. *Ann Intern Med* 2010; **152**(6): 370-9.
8. Ernst E, Resch KL. Concept of true and perceived placebo effects. *Bmj* 1995; **311**(7004): 551-3.
9. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *The New England journal of medicine* 2014; **371**(13): 1208-17.
10. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? *J Clin Epidemiol* 2000; **53**(8): 786-92.
11. Rothberg MB, Sivalingam SK, Kleppel R, Schweiger M, Hu B, Sepucha KR. Informed Decision Making for Percutaneous Coronary Intervention for Stable Coronary Disease. *JAMA internal medicine* 2015; **175**(7): 1199-206.
12. Thomas KB. General practice consultations: is there any point in being positive? *Br Med J (Clin Res Ed)* 1987; **294**(6581): 1200-2.
13. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA : the journal of the American Medical Association* 1995; **273**(5): 408-12.

14. Goff SL, Mazor KM, Ting HH, Kleppel R, Rothberg MB. How cardiologists present the benefits of percutaneous coronary interventions to patients with stable angina: a qualitative analysis. *JAMA internal medicine* 2014; **174**(10): 1614-21.
15. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. *Bmj* 2014; **348**: g3253.
16. Means G, End C, Kaul P. Management of Percutaneous Coronary Intervention Complications. *Curr Treat Options Cardiovasc Med* 2017; **19**(4): 25.
17. Borer JS, Fox K, Jaillon P, Lerebours G, Ivabradine Investigators G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* 2003; **107**(6): 817-23.
18. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *Journal of the American College of Cardiology* 2004; **43**(8): 1375-82.
19. Garratt AM, Hutchinson A, Russell I, Network for Evidence-Based Practice in N, Yorkshire. The UK version of the Seattle Angina Questionnaire (SAQ-UK): reliability, validity and responsiveness. *J Clin Epidemiol* 2001; **54**(9): 907-15.
20. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ* 2017.
21. Mark DB, Hlatky MA, Harrell FE, Jr., Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987; **106**(6): 793-800.
22. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004; **25**(2): 143-56.
23. Shun-Shin MJ, Howard JP, Francis DP. Removing the hype from hypertension. *Bmj* 2014; **348**: g1937.
24. National Institute for Health and Care Excellence (NICE). Management of stable angina. *NICE Clinical Guidance CG126* 2016.
25. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology* 2012; **60**(24): e44-e164.
26. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *The New England journal of medicine* 2012; **367**(11): 991-1001.
27. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *The New England journal of medicine* 2009; **360**(3): 213-24.
28. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of

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29. Barmeyer A, Meinertz T. Anaerobic threshold and maximal oxygen uptake in patients with coronary artery disease and stable angina before and after percutaneous transluminal coronary angioplasty. *Cardiology* 2002; **98**(3): 127-31.
30. Williams SG, Stables RH, Wright DJ, Taylor S, Thompson D, Tan LB. Relationship of serum cardiac markers following successful percutaneous coronary intervention and subsequent exercise capacity in patients with chronic stable angina: a pilot study. *Cardiology* 2005; **103**(2): 63-7.

Tables

Table 1: Baseline characteristics

	PCI (n=105)	Placebo (n=95)	All (n=200)
Age (years)	65·9 (9·5)	66·1 (8·4)	66·0 (9·0)
Male	74 (70·5%)	72 (75·8%)	146 (73·0%)
BMI	28·0 (4·7)	29·5 (5·1)	28·7 (5·0)
Diabetes	15 (14·3%)	21 (22·1%)	36 (18·0%)
Hypertension	72 (68·6%)	66 (69·5%)	138 (69·0%)
Hyperlipidaemia	81 (77·1%)	62 (65·3%)	143 (71·5%)
Current smoker	11 (10·5%)	15 (15·8%)	26 (13·0%)
Previous MI	5 (4·8%)	7 (7·4%)	12 (6·0%)
Previous PCI	10 (9·5%)	15 (15·8%)	25 (12·5%)
LV systolic function			
Normal	98 (93·3%)	85 (89·5%)	183 (91·5%)
Mild impairment	3 (2·9%)	7 (7·4%)	10 (5·0%)
Moderate impairment	4 (3·8%)	3 (3·2%)	7 (3·5%)
CCS class			
I	2 (1·9%)	3 (3·2%)	5 (2·5%)
II	64 (61·0%)	54 (56·8%)	118 (59·0%)
III	39 (37·1%)	38 (40·0%)	77 (38·5%)
Angina duration (months)	9·5 (15·7)	8·4 (7·5)	9·0 (12·5)

Data are mean (SD) and n (%). BMI= body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. LV=left ventricle. CCS=Canadian Cardiovascular Society.

Table 2: Procedural characteristics

	PCI (n=105)	Placebo (n=95)	p value	All (n=200)
Procedural time (min)	90 (27)	61 (17)	**<0·0001**	76 (27)
Vessel name			0·509	
LAD	72 (68·6%)	66 (69·5%)		138 (69·0%)
RCA	17 (16·2%)	15 (15·8%)		32 (16·0%)
Cx	9 (8·6%)	10 (10·5%)		19 (9·5%)
OM1	4 (3·8%)	0 (0%)		4 (2·0%)
D1	2 (1·9%)	2 (2·1%)		4 (2·0%)
IM	1 (1·0%)	2 (2·1%)		3 (1·5%)
Serial lesions	17 (16·2%)	12 (12·6%)	0·475	29 (14·5%)
Area stenosis by QCA (%)	84·6 (10·2)	84·2 (10·3)	0·781	84·4 (10·2)
Median (IQR)	86·0 (77·5-92·7)	84·9 (77·1-93·0)		85·7 (77·4-93·0)
FFR	0·69 (0·16)	0·69 (0·16)	0·778	0·69 (0·16)
Median (IQR)	0·72 (0·57-0·82)	0·73 (0·59-0·80)		0·72 (0·57- 0·81)
iFR	0·76 (0·22)	0·76 (0·21)	0·751	0·76 (0·22)
Median (IQR)	0·85 (0·68-0·92)	0·85 (0·68-0·89)		0·85 (0·68-0·90)
Drug-eluting stent type				
Everolimus-eluting	83			
Zotarolimus-eluting	52			
Biolimus-eluting	3			
Stent length (mm)	24 (18-33)			
Median (IQR)				
Stent diameter (mm)	3·1 (0·5)			
Post-dilatation performed	103 (75%)			
FFR post-PCI	0·90 (0·06)			
Median (IQR)	0·90 (0·87 - 0·94)			
iFR post-PCI	0·95 (0·04)			
Median (IQR)	0·94 (0·92-0·97)			

Data are mean (SD) and n (%) unless otherwise stated. PCI=percutaneous coronary intervention. LAD=Left anterior descending. RCA=Right coronary artery. Cx=Circumflex. OM1=First obtuse marginal. D1= First Diagonal. IM=Intermediate. QCA=Quantitative coronary angiography. FFR=Fractional flow reserve. iFR=Instantaneous wave free ratio. Post-dilation was carried out in 103/138 stents (75%)

Table 3: Endpoints

Total exercise time		
Exercise time (seconds)	**PCI (n=104)**	**Placebo (n=90)**
Pre-randomisation	528·0 (178·7)	490·0 (195·0)
Follow-up	556·3 (178·7)	501·8 (190·9)
Δ (Pre-randomisation to follow-up)	28·4 (95% CI 11·6 to 45·1)	11·8 (95% CI -7·8 to 31·3)
Difference in Δ between arms	16·6 (95% CI -8·9 to 42·0) (p=0·200)	
Time to 1mm ST depression		
Time to 1mm ST depression (seconds)	**PCI**	**Placebo**
Pre-randomisation	n=27 479·7 (141·4)	n=18 471·1 (128·7)
Follow-up	n=23 472·7 (129·1)	n=21 470·1 (176·0)
p value between arms	p=0·164	
Peak oxygen uptake		
Peak oxygen uptake (ml/min)	**PCI (n=99)**	**Placebo (n=89)**
Pre-randomisation	1715·0 (638·1)	1707·4 (567·0)
Follow-up	1713·0 (583·7)	1718·3 (550·4)
Δ (Pre-randomisation to follow-up)	-2·0 (95% CI -54·1 to 50·1)	10·9 (95% CI -47·2 to 69·0)
Difference in Δ between arms	-12·9 (95% CI -90·2 to 64·3) (p=0·741)	
Physical limitation		
SAQ-Physical limitation	**PCI (n=100)**	**Placebo (n=88)**
Pre-randomisation	71·3 (22·5)	69·1 (24·7)
Follow-up	78·6 (24·0)	74·1 (24·7)
Δ (Pre-randomisation to follow-up)	7·4 (19·7) (95% CI 3·5 to 11·3)	5.0 (21·2) (95% CI 0·5 to 9·5)
Difference in Δ between arms	2·4 (95% CI -3·5 to 8·3) p=0·420	
Angina frequency		
SAQ-Angina frequency	**PCI (n=103)**	**Placebo (n=90)**
Pre-randomisation	63·2 (20·4)	60·0 (25·1)
Follow-up	74·4 (21·4)	67·7 (22·1)
Δ (Pre-randomisation to follow-up)	11·2 (20·3) (95% CI 7·2 to 15·1)	7.7 (22·7) (95% CI 2·9 to 12·4)
Difference in Δ between arms	3·5 (95% CI -2·6 to 9·6) p=0·260	
Angina stability		
SAQ-Angina stability	**PCI (n=102)**	**Placebo (n=89)**
Pre-randomisation	64·7 (25·5)	68·5 (24·3)
Follow-up	60·5 (23·7)	63·5 (25·6)
Δ (Pre-randomisation to follow-up)	-4·2 (33·4) (95% CI -10·7 to 2·4)	-5·1 (31·6) (95% CI -11·7 to 1·6)

Difference in Δ between arms	0·9 (95% CI -8·4 to 10·2) p=0·851	
Quality of life		
EQ-5D-5L QOL	**PCI (n=103)**	**Placebo (n=89)**
Pre-randomisation	0·80 (0·21)	0·79 (0·22)
Follow-up	0·83 (0·21)	0·82 (0·20)
Δ (Pre-randomisation to follow-up)	0·03 (0·14) (95% CI 0·00 to 0·06)	0·03 (0·17) (95% CI 0·00 to 0·07)
Difference in Δ between arms	0·00 (95% CI -0·04 to 0·04) p=0·994	
Peak stress wall motion index score		
Peak stress wall motion index score	**PCI (n=91)**	**Placebo (n=70)**
Pre-randomisation	1·08 (0·12)	1·07 (0·11)
Follow-up	1·02 (0·05)	1·09 (0·14)
Δ (Pre-randomisation to follow-up)	-0·05 (0·12) (95% CI -0·08 to -0·03)	0·02 (0·10) (95% CI -0·01 to 0·04)
Difference in Δ between arms	-0·07 (95% CI -0·11 to -0·04) **(p<0·0001)**	
Duke treadmill score		
Duke treadmill score	**PCI (n=104)**	**Placebo (n=90)**
Pre-randomisation	4·24 (4·82)	4·18 (4·65)
Follow-up	5·46 (4·79)	4·28 (4·98)
Δ (Pre-randomisation to follow-up)	1·22 (4·36) (95% CI 0·37 to 2·07)	0·10 (5·20) (95% CI -0·99 to 1·19)
Difference in Δ between arms	1·12 (95% CI -0·23 to 2·47) (p=0·104)	

Data are mean (SD) unless otherwise specified. Time to 1mm ST depression was compared between the arms as the proportion of patients whose time to ST depression improved versus deteriorated, in the patients who had 1mm ST depression on at least one time-point. SAQ=Seattle angina questionnaire. PCI=percutaneous coronary intervention. QOL=quality of life**.** Peak stress wall motion index score and Duke treadmill score data are shown for the patients who had both pre-randomisation and follow-up tests.

Table 4: Changes in Canadian Cardiovascular Society Angina Grade

	From enrolment (Table 1) to pre-randomisation			From pre-randomisation to follow-up		
Change in CCS	**PCI (n=105)**	**Placebo (n=95)**	**p value**	**PCI (n=105)**	**Placebo (n=91)**	**p value**
No change or deterioration	63 (60%)	59 (62%)	0·916	51 (49%)	54 (57%)	0·475
1 class improvement	27 (26%)	22 (23%)		27 (26%)	22 (23%)	
≥2 class improvement	15 (14%)	14 (15%)		27 (26%)	19 (20%)	

PCI=percutaneous coronary intervention. CCS=Canadian Cardiovascular Society

Figure legends

Figure 1

ORBITA study overview diagram

Figure 2

Consort diagram

CCS = Canadian Cardiovascular Society angina severity grading

BP = Blood pressure

HR = Heart rate

CPET = Cardiopulmonary exercise testing

DSE = Dobutamine stress echocardiography

Figure 3

Coronary angiograms of the first 12 consecutively randomised patients

The target vessel is marked with an asterisk.