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A double-blind randomised placebo-controlled trial of percutaneous coronary intervention for the relief of stable angina without antianginal medications: design and rationale of the ORBITA-2 trial

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KEYWORDS

- drug-eluting stent
- fractional flow reserve
- non-invasive imaging
- stable angina

Abstract

Percutaneous coronary intervention (PCI) is frequently performed for stable angina. However, the first blinded trial, ORBITA, did not show a placebo-controlled increment in exercise time in patients with single-vessel disease, at 6 weeks, on maximal antianginal therapy. ORBITA-2 will assess the placebo-controlled efficacy of PCI on angina frequency in patients with single- or multivessel disease, at 12 weeks, on no antianginal therapy. ORBITA-2 is a double-blind placebo-controlled trial randomising participants with (i) angina at presentation, (ii) documented angina during the 2-week pre-randomisation symptom assessment phase, (iii) objective evidence of ischaemia, (iv) single- or multivessel disease, and (v) clinical eligibility for PCI. At enrolment, antianginals will be stopped, and angina questionnaires completed. Participants will record their symptoms on a smartphone application daily throughout the trial and will undergo exercise treadmill testing and stress echocardiography at pre-randomisation. They will then undergo coronary angiography with unblinded invasive physiology assessment. Eligible participants will then be sedated to a deep level of conscious sedation and randomised 1:1 between PCI and placebo. After the 12-week blinded follow-up period, they will return for questionnaires, exercise testing and stress echocardiography assessment. If angina becomes intolerable, antianginals will be introduced using a prespecified medication protocol. The primary outcome is an angina symptom score using an ordinal clinical outcome scale for angina. Secondary outcomes include exercise treadmill time, angina frequency, angina severity and quality of life. Trial registration: ClinicalTrials.gov: NCT03742050

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Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CTCA	computed tomography coronary angiography
DSMB	Data Safety Monitoring Board
FFR	fractional flow reserve
GI	gastrointestinal
MRC	Medical Research Council
MRI	magnetic resonance imaging
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
SAQ	Seattle Angina Questionnaire
iFR	instantaneous wave-free ratio

Introduction

More than 500,000 percutaneous coronary intervention (PCI) procedures are performed annually worldwide for stable coronary artery disease (CAD)[1]. The results of over 14,000 patients randomised to an invasive versus a conservative strategy, followed up for 4.5 years, showed no evidence of net reduction in mortality[2-5]. These procedures are principally performed to relieve angina.

Unblinded randomised controlled trials (RCT) have consistently shown angina relief from PCI[4,6-8]. The first blinded RCT, ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina), showed a surprisingly small placebo-controlled effect of PCI[9].

However, ORBITA may not have provided the definitive picture for several reasons. First, it only enrolled patients with single-vessel disease, to allow the effect size to be later regressed[10] against the severity of the lesion. Second, ORBITA participants received maximally tolerated antianginal medication to test the guideline-directed incremental effect of PCI on a background of antianginal therapy. This may have attenuated the potential benefit of PCI. Third, patients were enrolled based on clinically indicated PCI, with 94-96%[10,11] of patients having evidence of ischaemia before randomisation. Fourth, while patients needed to have symptoms prior to enrolment, there was no additional requirement to have angina episodes immediately before randomisation. 88% were in Canadian Cardiovascular Society (CCS) Class I to III at randomisation. This proportion was 89% in the FAME 2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) and 88% in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trials[3,12]. Fifth, it prespecified change in treadmill exercise time, rather than symptoms, as the primary endpoint, similar to the unblinded ACME (Angioplasty Compared to Medicine) trial of balloon angioplasty[6] and to mirror US Food and Drug Administration and the European Medicines Agency requirements for trials of antianginal therapy. Sixth, it selected a 6-week follow-up period, being long enough for resolution of ischaemia and short enough to be ethical and practical for the first placebo-controlled trial of PCI. Finally, ORBITA prespecified paired t-test methodology, as used by the positive unblinded ACME trial. This was not the most powerful statistical method for detecting treatment effect.

ORBITA-2 will provide the next test of the placebo-controlled efficacy of PCI in reducing angina, differing from ORBITA by parameters shown in **Table 1**.

Methods

STUDY DESIGN

ORBITA-2 is a multicentre double-blind randomised placebo-controlled trial to assess the efficacy of PCI for relief of stable angina in single- and multivessel coronary artery disease. The London Central Research Ethics Committee (reference 18/LO/1203) approved the study. The study design is shown in **Figure 1**.

A list of ORBITA-2 investigators is included in **Supplementary Appendix 1**.

ELIGIBILITY CRITERIA

ORBITA-2 will enrol participants who are deemed eligible for PCI by their clinical teams and meet all 3 of the following criteria **(Table 2)**:

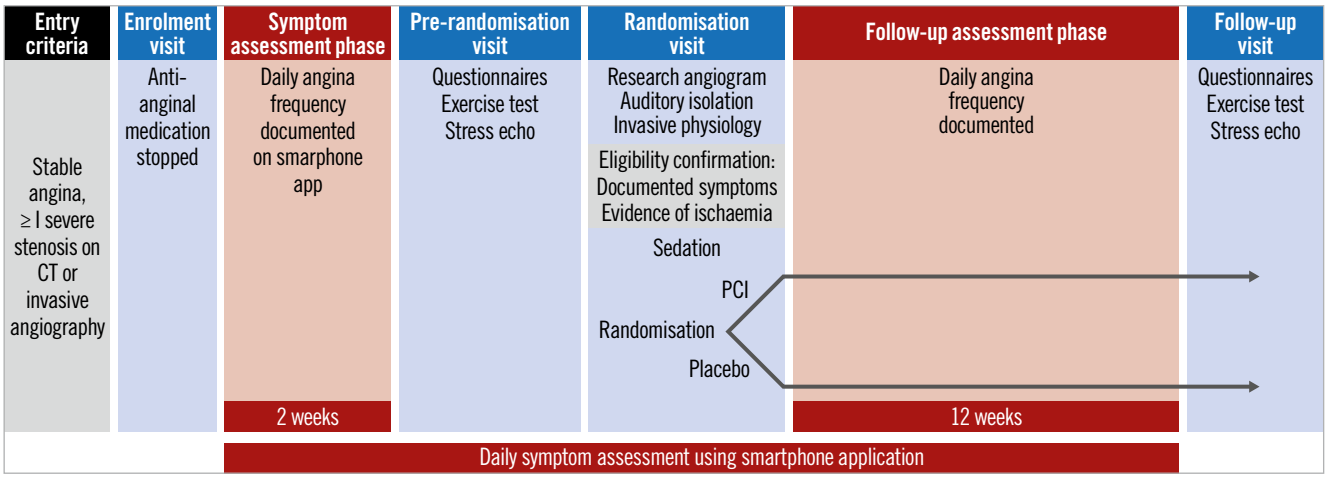

Figure 1. *ORBITA-2 study design. CT: computed tomography; PCI: percutaneous coronary intervention*

Table 1. Comparison of features between ORBITA and ORBITA-2.

Feature	ORBITA	ORBITA-2	Rationale
Coronary disease	Single-vessel	Single- and multivessel	More representative of patients referred for clinical PCI, only half of whom have single-vessel disease[22]
Enrolment	Only after invasive angiography	After either CT or invasive angiography	Representative of modern patient pathways
Requirement for symptoms	Originally referred for angina. Antianginals then given to optimise microvascular state without affecting coronary lesion. Not required to have ongoing symptoms in the days before randomisation.	Inclusion of a symptom assessment phase. Participants must have one or more documented angina episodes in 2-week symptom assessment phase	Maximise chance of detecting relief of angina by requiring documented angina in a prespecified narrow window of time after enrolment
Requirement for ischaemia evidence	As per clinical guidelines and FAME 2[12], only required for lesions of moderate anatomical severity.	Regardless of anatomical severity, required to have one or more tests suggestive of ischaemia, including FFR, iFR or any non-research, non-invasive tests	In ORBITA, 94% or 96%[10] had one or more positive pre-randomisation ischaemia tests. In ORBITA-2 this will be 100%
Primary outcome	Exercise treadmill time[9]	Angina symptom score using an ordinal clinical outcome scale	Relevant to all patients who present with angina; covers the entire 12-week follow-up period rather than a single time-point
Pre-randomisation phase	Established on ~3 antianginals	Stop antianginals. Only eligible for randomisation if one or more episodes of angina documented in 2 weeks	PCI being tested as monotherapy rather than as an add-on to antianginals
Duration of follow-up	6 weeks	12 weeks	Even more certain to be long enough to demonstrate effect

CT: computed tomography; FAME 2: Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; ORBITA: Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PCI: percutaneous coronary intervention

Table 2. Eligibility criteria. Participants require all 3 to enrol.

1. Angina or angina-equivalent symptoms
2. Anatomical evidence of a severe coronary stenosis in at least 1 vessel, either: – Invasive diagnostic coronary angiography indicating ≥70% stenosis – Computerised tomography coronary angiography (CTCA) indicating severe stenosis
3. Evidence of ischaemia, on any of the following tests: – Dobutamine stress echocardiography – Stress perfusion cardiac magnetic resonance imaging (MRI) – Nuclear medicine myocardial perfusion scan – Invasive pressure wire assessment suggestive of ischaemia, as judged by the interventional cardiologist, at the time of clinical or research coronary angiography

1. Angina or angina-equivalent symptoms
2. Anatomical evidence of a severe coronary stenosis in at least 1 vessel on invasive diagnostic angiography or computerised tomography coronary angiography (CTCA)
3. Evidence of ischaemia

For randomisation, the criteria are stricter and the following must also be met:

4. At least 1 episode of angina reported during the 2-week pre-randomisation period
5. Invasive diagnostic coronary angiogram indicating at least one ≥70% stenosis

The exclusion criteria are listed in **Supplementary Appendix 2**.

By design, some participants will be eligible for enrolment, but will not meet the criteria for randomisation at the time of the research angiogram. For example, a participant may have a severe stenosis on a positive CTCA but have non-flow-limiting disease on invasive physiology at the research angiogram, as judged by the interventionist, or more severe disease necessitating coronary artery bypass graft surgery. As another example, a participant may have an invasive coronary angiogram showing severe disease but have no symptoms during the 2-week symptom assessment phase using the daily smartphone application.

PRIMARY OUTCOME

The primary outcome is an angina symptom score measured daily. This is an ordinal clinical outcome scale designed for assessing health status in angina ranging from 0 to 79, as shown in **Supplementary Table 1**. The numbers represent a relative ranking without any assumption related to category spacing. It comprises the number of episodes of angina reported daily by the patient on a smartphone symptom application, units of antianginal medications, and high-level category overrides for unblinding due to intolerable angina, acute coronary syndrome and death. **Supplementary Table 2** shows the total daily dose of common antianginal medications considered to be one unit.

Participants will be asked once a week to record on the smartphone symptom application whether they had angina during the 2 activities that were described by the participant at enrolment as activities that provoke angina. This is intended to minimise

the risk that participants will not exert themselves sufficiently to induce angina and therefore mask their true angina health status.

We surveyed 38 consultant cardiologists and 8 patients for their views on the primary outcome. There was consensus in using an ordinal outcome scale, the ranking of relative worsening of health status in the sequence shown in **Supplementary Table 1**, and the counting of units of antianginal medications shown in **Supplementary Table 2**.

SECONDARY OUTCOMES

- Exercise treadmill time
- Angina severity as assessed by CCS Class
- Angina frequency measured by the symptom application
- Physical limitation, angina stability, quality of life, angina frequency and freedom from angina as assessed with the Seattle Angina Questionnaire (SAQ)
- Quality of life as assessed with the EuroQOL (EQ-5D-5L) questionnaire
- Quality of life as assessed with the MacNew questionnaire
- Breathlessness as assessed with the MRC (Medical Research Council) dyspnoea scale
- Dobutamine stress echocardiography score
- Need for antianginal medication introduction and uptitration
- Unblinding due to intolerable angina
- Admission for acute coronary syndrome (ACS)
- Death

ENROLMENT

At enrolment, written informed consent will be obtained. Eligibility will be checked. Symptoms will be assessed by CCS class and MRC dyspnoea score. Participants will complete questionnaires including the SAQ, the EQ-5D-5L, the MacNew heart disease health-related quality of life questionnaire and the Rose Angina Questionnaire. They will be taught how to use a smartphone symptom application for recording their symptoms. Patient involvement in the design of the symptom application is described in **Supplementary Appendix 3**. Participants who do not have a smartphone will be provided with a device and taught how to use it.

The application will notify the research team when participants have failed to report their symptoms. If 3 or more days are missed, participants will be prompted by research staff to enter their symptoms.

PRE-RANDOMISATION EVALUATION

Before randomisation, participants will document symptoms for 2 weeks off antianginals. If they are asymptomatic during this period, they will exit the trial.

Participants will then attend the pre-randomisation visit, when they will have an exercise treadmill test **(Supplementary Appendix 4)**, stress echocardiography **(Supplementary Appendix 5)**, and symptom and quality of life assessment.

MEDICATIONS

All medication changes will be made by the research team with informed consent from the participant. Decisions will be discussed with primary care practitioners as necessary.

1. Participants not already taking the following medications will be started on:

Dual antiplatelet therapy:

Standard loading doses will be used. Thereafter, aspirin 75 mg once daily with either clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily or prasugrel 5-10 mg once daily, dose adjusted for age and weight, will be administered.

Gastrointestinal (GI) protection:

If at high risk of adverse GI effects (based on previous GI ulceration, age or concomitant medications that increase risk), participants will be started on a proton pump inhibitor, lansoprazole 30mg once daily, in accordance with NICE guidance on gastro-oesophageal reflux disease and dyspepsia in adults (CG184).

Lipid-lowering medication:

Atorvastatin 80 mg once daily will be preferred. If participants are already taking lower dose atorvastatin, simvastatin or pravastatin, this will be changed to atorvastatin 80 mg once daily. If taking rosuvastatin, this will be continued.

2. Other concomitant risk factor modifying medication

Antihypertensives:

Antihypertensives with antianginal properties will be stopped. Participants will be given a blood pressure monitor and asked to perform home readings. Blood pressure control will be monitored by the research team, and if required, antihypertensives will be added. Agents without antianginal properties will be preferred.

3. Antianginal medication

Regular antianginal medications will be stopped on enrolment. All participants will be given glyceryl trinitrate spray to be used when necessary. The need for starting regular antianginals will be determined by participant preference and patient reported symptoms. An individualised protocol for potential introduction of antianginal medications will be prepared for each participant by the research team. This protocol will be based on the participant's medical history, heart rate, blood pressure and any medication intolerance. The preferred sequence will be as follows: Bisoprolol, nifedipine MR, isosorbide mononitrate MR, nicorandil, ranolazine.

Antianginals started prior to randomisation will be stopped at randomisation and re-introduced according to participant preference and symptoms as described above, by the blinded research team.

INVASIVE PROCEDURE

For the invasive procedure, participants will wear over-the-ear headphones with auditory isolation. Radial or femoral vascular access will be used at the operator's discretion. Coronary angiography including pressure wire assessment with fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) will be performed for each ≥50% coronary stenosis, with the pressure wire placed at least 3 vessel diameters beyond the most distal stenosis. Intravenous adenosine will be administered for FFR via an

antecubital fossa vein at 140 µg/kg per min. Normalisation will be documented before each measurement. After each measurement, the wire will be checked for drift and, if present, the wire will be renormalised and measurements repeated.

If an operator is unable to pass a pressure wire, no value will be documented, and the images of that case will be published for later verification of anatomic severity.

At this point the operator will select vessels for treatment and the selection will be recorded in the online case report form prior to randomisation. To be eligible for randomisation, there must be evidence of ischaemia on FFR, iFR and/or any non-invasive ischaemia testing performed as part of routine clinical practice prior to enrolment. The non-invasive tests can include cardiac stress perfusion MRI, stress echocardiography or nuclear medicine myocardial perfusion scan depending on local clinical practice. The operators will not have access to the results of the additional stress echocardiography and exercise tests performed as part of the research study. This is an arrangement which preserves the utility of these measures as baseline stratifiers against which effect size can later be regressed[10,13].

RANDOMISATION AND BLINDING

Randomisation procedures will be conducted at high-volume PCI centres (currently 14 NHS hospital sites across England and Wales). Participants will be sedated, using incremental doses of intravenous benzodiazepines and intravenous opioids, to a deep level of conscious sedation such that they are unresponsive to verbal or tactile stimulus, but that airway, ventilation and cardiovascular function are maintained. They will then be randomised 1:1 to PCI or placebo procedure using computer-generated randomisation with block randomisation and block size between 8 and 16 (Randi – opensource clinical trials software). Randomisation will be performed in the catheter laboratory. The allocation will be communicated verbally to the catheter laboratory team. Participants randomised to placebo will be kept sedated in the catheter laboratory for a minimum of 15 minutes post-randomisation.

The participant, and caregivers outside the catheter lab, including ward staff and research staff involved in follow-up assessment and data analysis, will be blinded to treatment allocation. Our protocol will assess for accidental leakage of information to staff and to participants **(Supplementary Appendix 6)**. The blinding index[14] will be performed at the time of discharge from the randomised blinded procedure and at follow-up.

FOLLOW-UP EVALUATION

Stress echocardiography, exercise testing and symptom and quality of life assessment will be repeated 12 weeks after randomisation by blinded research staff.

UNBLINDING AND TRIAL END

After the follow-up tests, the participants will be unblinded. Routine medical care will be continued. For avoidance of doubt, research participation will end at the time of unblinding (but ACS and death status will be checked at 12 weeks if early unblinding was performed). This has two implications: first, there will be no merit in "long-term follow-up" beyond this point because unblinded symptom reporting is uninformative and can be misleading; and second, no decision the participant and clinician make at this stage will be considered "crossover" because the participant has exited the trial. Before being randomised the participant was clinically eligible for PCI, had discussed having PCI with their cardiologist, and had agreed to have the procedure. By participating in ORBITA-2, they will have offered researchers the potential to delay their PCI, only for the duration of the trial, and solely to help future participants with angina. It is therefore likely that most participants randomised to placebo will choose to have subsequent PCI.

DATA MANAGEMENT

Data will be entered onto an electronic case report form (OpenClinica). Data from the smartphone application will be stored on a central server. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

DATA MONITORING

All adverse events will be reviewed by the independent Data Safety Monitoring Board (DSMB). The DSMB will also review clinically driven withdrawals and protocolised introduction and uptitration of antianginal medications.

SAMPLE SIZE CALCULATION

The trial is designed to detect a difference between arms in the change in angina symptom score units of one-third of a standard deviation of change in angina symptom units. Using a 2-sample t-test with a 2-sided alpha of 0.05 and 80% power, we calculated that we will need to randomise 284 participants across the active and control arms. Based on the experience of ORBITA we need to allow for a dropout rate of 7% and a crossover rate of 10% from the control arm and 2% in the active arm. This requires 396 enrolled participants. We plan to enrol 400. Crossover refers to a participant being randomised to 1 arm, but then having the treatment specified in the other arm before their participation in the trial ends and they are unblinded at 12-week follow-up. Since all efficacy analysis will be performed on the intention-to-treat basis, such crossover will attenuate the observed effect size.

RECRUITMENT STATUS

Recruitment for ORBITA-2 commenced in November 2018 and was paused in March 2020 due to the COVID-19 pandemic. A protocol amendment was made in May 2020 and recruitment resumed **(Supplementary Appendix 7)**. To date, 217 participants have been enrolled and 130 have been randomised.

STATISTICAL ANALYSIS PLAN

Data will be summarised as quartiles for continuous variables and proportions for categorical ones. Data will be analysed on

an intention-to-treat basis. The Bayesian posterior probability of efficacy is the primary evidence summary. The primary outcome of ORBITA-2 is the placebo-controlled efficacy of PCI on the angina symptom score using an ordinal clinical outcome scale for angina. We will use a Bayesian approach with a proportional odds model for the analysis of the primary outcome of angina symptom score adjusted for pre-randomisation angina symptom score. A first-order Markov model will be used to model within-patient correlation in serial measurements. The proportional odds model is efficient in testing the hypothesis while accommodating the statistical distribution and possible floor and ceiling effects. The R rmsb package blrm function will be used for computations[15]. The statistical model extracts maximum information from the outcome data's severity and timing of events to maximise power. The rationale for planned stratified analyses is described in **Supplementary Appendix 8**.

ORBITA was criticised for its statistical methods. A Bayesian approach addresses some of the limitations of p-values. Bayesian posterior probabilities prevent the conclusion of equivalent effects of two treatments on an outcome when the data do not support that interpretation[16].

DISSEMINATION PLAN

As in ORBITA, the primary result in ORBITA-2 will be analysed according to the prespecified analysis plan. Secondary analyses will also be subsequently conducted, testing for dependence of any treatment effect on pre-randomisation indices of ischaemia.

Discussion

ORBITA-2 should provide long-awaited evidence for managing stable angina by assessing the placebo-controlled effect of PCI on angina with no background antianginal therapy. This is important because PCI has associated healthcare costs and small, but non-negligible, risks of short- and long-term complications.

There are 3 principal challenges facing trials of angina treatment. The major challenge is that unblinded angina data are of little or no value. ORBITA and ORBITA-2 resolve this by blinding participants, research, and clinical teams to treatment allocation.

The second challenge is to capture the amount of angina reliably. The historical approach has been a questionnaire which is filled in by the participant at the end of a period, such as a month. This approach has been validated, in the sense that it has shown a correlation coefficient of –0.64 with the gold standard of daily documentation of symptoms[17]. However, it is limited by recall bias and, more importantly, patients may modify their activity levels resulting in reduced symptom frequency. In ORBITA-2 we take the opportunity of the ubiquitous availability of smartphones to capture this, through gold standard daily documentation. A similar approach was taken in the TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) trial, albeit with a non-smartphone electronic device[18]. Our daily reporting gives further opportunity to validate the monthly questionnaires and the potential to detect effects with greater temporal precision. Each day the symptom application asks the participant the number of episodes experienced and the intensity of the most severe episode on a visual analogue scale. Additionally, every week the symptom application asks whether the 2 angina-provoking activities that the participant prespecified at enrolment are still causing angina.

The third challenge facing trials of angina treatment was exemplified by Saxon et al, who found that, amongst patients who reported no angina, the clinician documented CCS Class II, III or IV in 20 to 46% of cases[19]. This may be because staff are influenced by collateral information, such as the anatomical or physiological severity of the lesion and whether it has been treated when grading the CCS. In the DEFER (Deferral of PTCA Versus Performance of PTCA) trial, simply learning that the lesion had an FFR above threshold was enough to reduce the proportion of patients with chest pain from 88% to 54%[20,21]. In FAME 2, the effect of gaining this knowledge was even greater, reducing the proportion of patients with CCS Class II-IV from 67% to 16%[12,21]. ORBITA dealt with this reporting bias by blinding both the participant and the staff member assessing the symptoms at follow-up. ORBITA-2 will do the same.

Limitations

Due to the COVID-19 pandemic, some patients were not able to have exercise testing and stress echocardiography. These assessments were interrupted for a short period of a few months in 2020, when the frequency of enrolment had also decreased, therefore it is unlikely there will be substantial missing data. However, the primary outcome data are remotely collected via the smartphone application, which has therefore been largely unaffected by the impact of the pandemic.

Conclusion

ORBITA-2 will build on the results of ORBITA by assessing the placebo-controlled effect of PCI on angina with no background antianginal therapy in both single- and multivessel disease. Novel features include the use of an ordinal clinical outcome scale for angina and daily symptom reporting using a smartphone application. It will also provide a further opportunity to look for predictors of the placebo-controlled effect of PCI.

Impact on daily practice

ORBITA-2 will provide placebo-controlled data on the efficacy of PCI on symptoms in patients off antianginal medications. An ordinal clinical outcome scale for angina was designed in partnership with patients to be a relevant, informative, and inclusive primary outcome. This outcome incorporates daily documentation of angina episodes on a novel smartphone application. This larger trial, with longer follow-up, will more definitively establish the efficacy of PCI.

Guest Editor

This paper was guest edited by Franz-Josef Neumann, MD; Department of Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany.

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Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. ORBITA-2 Investigators

Dr Fairoz Abdul, Dr Firas Al-Janabi, Dr Rasha Al-Lamee, Dr Christopher Baker, Dr Richard Bogle, Dr Alison Calver, Dr Gerald Clesham, Dr Graham Cole, Dr Derek Connolly, Prof Nick Curzen, Dr John Davies, Dr Jason Dungu, Dr Darrel Francis, Dr Rodney Foale, Dr Reto Gamma, Dr Nearchos Hadjiloizou, Dr Peter Haworth, Dr James Howard, Dr Alamgir Kabir, Dr Raffi Kaprielian, Dr Thomas Keeble, Dr Ramzi Khamis, Dr Masood Khan, Dr Tim Kinnaird, Dr Tushar Kotecha, Dr Timothy Lockie, Dr Iqbal Malik, Dr Jamil Mayet, Dr Sukhjinder Nijjer, Dr Peter O'Kane, Dr Vasileios Panoulas, Dr Ricardo Petraco, Dr Lal Mughal, Dr Punit Ramrakha, Dr Helen Routledge, Dr Neil Ruparelia, Dr Sayan Sen, Dr Amarjit Sethi, Dr Matthew Shun-Shin, Dr Manas Sinha, Dr Rohit Sirohi, Dr James Spratt, Dr Kare Tang, Dr Jasper Trevelyan, Dr James Wilkinson, Dr Rupert Williams

Supplementary Appendix 2. Exclusion criteria

1. Age younger than 18
2. Acute coronary event in last 6 months
3. Previous coronary artery bypass graft surgery
4. Significant left main stem coronary disease
5. Chronic total occlusion in the target vessel
6. Contraindication to percutaneous coronary intervention or drug-eluting stent implantation
7. Contraindication to antiplatelet therapy
8. Severe valvular disease

9. Severe left ventricular systolic impairment (ejection fraction ≤35%)
10. Severe respiratory disease (requiring long term oxygen or symptoms deemed by investigator to be more likely attributable to respiratory disease)
11. Life expectancy less than 2 years, pregnancy, inability to consent

Supplementary Appendix 3. Patient involvement in the design of the symptom application

The ORBITA-2 symptom smartphone application requires the participant to define their angina in their own words and then report the number of episodes of this symptom for each day. It also requires the participant to report for each week if they experienced angina with 2 activities that were set by the participant at enrolment as triggering their symptoms. The symptom application approach permits not only a quantitative assessment of the time course of angina evolution during the blinded period, but also a time-to-event analysis of occurrence of first angina episode.

Through the ORBITA experience and working with the ORBITA focus group (consisting of previous participants in ORBITA), we designed ORBITA-2 to focus on what patients say is most important to them; namely, having less symptoms. The smartphone application was co-designed with the ORBITA patient focus group that consists of previous participants in the ORBITA study, including co-author P. McVeigh. They recommended that the primary endpoint should be angina symptoms rather than exercise time, because it was a more patient-orientated endpoint. Ability to exercise, assessed by exercise test, is relevant but only 1 part of the picture.

They also highlighted that the questionnaires used in ORBITA placed a large burden of responsibility on participants to accurately recall episodes and inducibility of angina over a 28-day period without any assistance. This was the reason to introduce daily symptom reporting and develop the ORBITA-2

smartphone application. They felt that angina frequency may have been under-reported due to modifications that they had implemented in their daily activities to prevent induction of angina. Applying these changes, such as avoiding stairs or brisk walking, obliged them to report "no symptoms over the last 4 weeks" even though they were limited by angina. As one participant said, "You don't have to have angina, to be limited by angina". For this reason, they designed into the application, repeatable forms of activity which might induce angina. It was important to them that these activities could be individualised. Therefore, at set-up, the application asks each participant to identify two activities that cause angina; these are then reported each week. Finally, the participants reported that it was difficult to answer questions about chest pain, when their sensation was not pain, but another form of discomfort. For this reason, the application asks them to define their "angina" symptoms in their own words so that they can be reminded of those words when later reporting the frequency and intensity of episodes.

Supplementary Appendix 4. Exercise test

The modified Bruce protocol will be used. The exercise test will be continued until 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 endpoints will be double-reported by 2 assessors who are blinded to the allocation arm and time-point of the test (pre-randomisation or follow-up).

Supplementary Appendix 5. Stress echocardiography

For stress echocardiography, beta-blockers will be omitted beforehand. All participants will receive Sonovue contrast to improve endocardial border definition unless contraindicated. Participants will receive a dobutamine infusion starting with 10 μg/kg/min followed by 20 μg/kg/min, 30 μg/kg/min and 40 μg/kg/min in 3-minute stages. In participants who have an "inadequate" heart rate response to dobutamine, atropine may be administered in 300 mcg increments to a maximum dose of 1200 mcg.

Stress echocardiography analysis will be performed blinded to treatment allocation and phase (pre-randomisation or follow-up), using an online reporting tool. Each scan will receive 12 opinions through being examined twice by 6 imaging consultants who were blinded to treatment allocation, time-point of the scan, their colleagues' opinions, and (on the second viewing) their own first opinion. Stress echocardiography results will be presented in a manner that represents the number of hypokinetic segments. The left ventricle is divided into the standard 17 segments. Wall motion is scored as follows: normal=0, hypokinetic=1, akinetic=2, dyskinetic=3, or aneurysmal=4. These individual wall abnormality scores at peak stress will be summed. Both opinions from all 6 consultants will then be averaged. This stress echocardiography score can be broadly converted to a classical wall motion score index as follows: wall motion score index=1+(stress echo score)/17.

Supplementary Appendix 6. Test of blinding

The ward clinical staff will be asked to guess the treatment allocation at the time of discharge from the blinded procedure. Participant blinding will be assessed at the time of discharge from the randomised blinded procedure. For completeness, the same question will also be asked when they attend for follow-up. However, at that time participants will have the benefit of knowing their own symptomatic response and therefore this will no longer strictly be a valid measure of blinding. The blinded research staff will be asked to guess the treatment allocation from all information available to them at the follow-up visit prior to speaking to the participant. Participants and staff will be asked to guess one of the following: (1) PCI, (2) Placebo, (3) Don't know. Participants and medical staff will be asked to state the certainty of their answers from grade 1-5 with 5 being most sure.

Supplementary Appendix 7. Protocol amendment due to the COVID-19 pandemic

At sites where it was possible, recruitment resumed in May 2020 with the following protocol amendments as clinically necessary due to COVID-19:

- Omission of exercise testing and of stress echography when these tests will not be clinically available or when additional hospital visits will be deemed high risk
- Replacement of in-person enrolment with enrolment via phone

For the randomisation procedure, local COVID-19 policies for patients attending for elective procedures will be adhered to, including mask use and social distancing measures. The patient-centred and app-delivered primary endpoint is well-suited to being maintained regardless of COVID-19 precautions.

Supplementary Appendix 8. Stratified analyses

Clinicians use heuristics to speculate on whether PCI will improve angina in individual participants. Importantly, we convey these heuristics to medical students and other staff as part of their training and include them in guidelines. For example, we teach that the location, radiation and exertional relationship of symptoms, positive stress echocardiography, positive exercise test, low FFR or low iFR are favourable signs of symptom relief from PCI. However, no study had tested whether these heuristics were true, using placebo-control. We built into ORBITA the potential to assess this by recruiting a broad range of patients clinically eligible for PCI, and not restricting eligibility to any 1 of those parameters. If we had restricted eligibility, it would have been impossible to test whether the parameter predicted benefit.

In ORBITA-2, we are again collecting information to permit baseline stratified analyses. We will examine the utility of features of symptoms such as the nature, location, radiation, exertional relationship, and whether there is concomitant breathlessness. Just as in ORBITA, the interventional operators will not have access to the pre-randomisation research exercise test and research stress echocardiography results. This will preserve the ability to test their predictive power for placebo-controlled benefit. Clinicians will have access to any prior clinically conducted tests for ischaemia because they are part of the patient's natural pathway to clinical PCI.

Testing whether baseline stratifiers predict outcomes requires the baseline stratifier to have a non-curtailed range. For example, to test whether positive baseline stress echocardiography score predicts placebo-controlled benefit from PCI, a trial cannot restrict itself to randomising only participants with a positive pre-randomisation stress echocardiography result.

ORBITA showed that baseline FFR and iFR had no predictive value for the placebo-controlled symptomatic response to PCI. To be able to reveal this, the trial included patients across a wide range of FFR and iFR, whose angina symptoms were nevertheless indicated for PCI, because of a tight lesion, or other markers of inducible ischaemia. Because of a non-equipoise state on the utility of FFR and iFR on predicting PCI response, operators were kept blinded to the value.

In ORBITA-2 we have made the compromise that the FFR and iFR values are revealed to the operator. This will likely curtail the distribution of FFR and iFR in the randomised participant group and will restrict the potential to identify whether FFR and iFR predict benefit (as implied by current guidelines) or have limited utility (as implied by ORBITA).

Supplementary Table 1. Ordinal clinical outcome scale for angina.

Grade	Number of angina episodes in a day	Units of antianginal medication	Unblinding due to intolerable angina	Acute coronary syndrome	Death
0	0	0	No	No	No
1	1	0	No	No	No
2	2	0	No	No	No
3	3	0	No	No	No
4	4	0	No	No	No
5	5	0	No	No	No
6	6 or more	0	No	No	No
7	0	1	No	No	No
8	1	1	No	No	No
9	2	1	No	No	No
10	3	1	No	No	No
11	4	1	No	No	No
12	5	1	No	No	No
13	6 or more	1	No	No	No
14	0	2	No	No	No
15	1	2	No	No	No
16	2	2	No	No	No
17	3	2	No	No	No
18	4	2	No	No	No
19	5	2	No	No	No
20	6 or more	2	No	No	No
21	0	3	No	No	No
22	1	3	No	No	No
23	2	3	No	No	No
24	3	3	No	No	No
25	4	3	No	No	No
26	5	3	No	No	No
27	6 or more	3	No	No	No

28	0	4	No	No	No
29	1	4	No	No	No
30	2	4	No	No	No
31	3	4	No	No	No
32	4	4	No	No	No
33	5	4	No	No	No
34	6 or more	4	No	No	No
35	0	5	No	No	No
36	1	5	No	No	No
37	2	5	No	No	No
38	3	5	No	No	No
39	4	5	No	No	No
40	5	5	No	No	No
41	6 or more	5	No	No	No
42	0	6	No	No	No
43	1	6	No	No	No
44	2	6	No	No	No
45	3	6	No	No	No
46	4	6	No	No	No
47	5	6	No	No	No
48	6 or more	6	No	No	No
49	0	7	No	No	No
50	1	7	No	No	No
51	2	7	No	No	No
52	3	7	No	No	No
53	4	7	No	No	No
54	5	7	No	No	No
55	6 or more	7	No	No	No
56	0	8	No	No	No
57	1	8	No	No	No
58	2	8	No	No	No
59	3	8	No	No	No

60	4	8	No	No	No
61	5	8	No	No	No
62	6 or more	8	No	No	No
63	0	9	No	No	No
64	1	9	No	No	No
65	2	9	No	No	No
66	3	9	No	No	No
67	4	9	No	No	No
68	5	9	No	No	No
69	6 or more	9	No	No	No
70	0	10	No	No	No
71	1	10	No	No	No
72	2	10	No	No	No
73	3	10	No	No	No
74	4	10	No	No	No
75	5	10	No	No	No
76	6 or more	10	No	No	No
77	N/A	N/A	Yes	No	No
78	N/A	N/A	N/A	Yes	No
79	N/A	N/A	N/A	N/A	Yes

Supplementary Table 2. Total daily dose of antianginal medication considered to be 1 unit.

Medication	Total daily dose in mg
Bisoprolol	5
Atenolol	25
Amlodipine	2.5
Nifedipine	20
Isosorbide mononitrate MR	30
Isosorbide mononitrate SR	25
Diltiazem	120
Nicorandil	20
Ranolazine	750
Ivabradine	5

In practice, an example participant would score 0 at enrolment. The participant gets 2 episodes of angina on day 4 therefore scoring 2. The participant starts amlodipine 5 mg once a daily and has no episodes of angina that day thus scoring 14. The next day they have 1 episode of angina thus scoring 15.