Angina: the impact of baseline symptoms on the effect of PCI, relationships between ischaemia tests, design of a trial of PCI for stable angina, and development of a symptom app

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Statement of Originality

I hereby declare that the work presented in this thesis is my own.

Copyright Declaration

Dedication

I dedicate this thesis to my parents, Rita and Sam, for their unwavering support and motivation.

Acknowledgements

I am very grateful to the NIHR Academy for funding me and supporting my training.

I would like to thank my supervisors, Professor Darrel Francis and Dr Rasha Al-Lamee, for their tireless guidance and mentorship. I would also like to thank Dr James Howard for his patience and wisdom in advising me on data analysis as well as Dr Henry Seligman, Dr Chris Rajkumar, Dr Michael Foley, Dr Matthew Shun-Shin, Nina Bual, Juliet Holmes, Liz Owen, and Frances Wood for their endless hours of support. This work would also not have been possible without the dedication of all the ORBITA-2 investigators and staff at hospitals across the UK.

Finally I would like to thank the patients for giving so much of themselves and their time.

Truly, you have all been an inspiration.

Abstract

Current assessment and treatment of angina is based on substantial, but primarily observational, data for the mechanisms of coronary artery obstruction, ischaemia and chest pain, coupled with the sincere desire to reduce myocardial infarctions and deaths. The belief that percutaneous coronary intervention (PCI) provides event reduction and angina relief has been questioned following surprising results from randomised controlled trials.

This thesis addresses why unblinded trials find that PCI improves symptoms in stable angina but a blinded study, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA), did not find an exercise time benefit. I examine the link between symptoms, anatomy, and ischaemia which appears to be more complex than previously assumed.

Historical symptom descriptions, e.g. by epidemiologist Geoffrey Rose, gave rise to the concept of typical and atypical angina. This classification is intended to reflect the likelihood of the symptoms being due to coronary artery obstruction and, although not the original intention, to infer how likely revascularisation is to relieve the symptoms. In Chapter 3, I test whether the nature of symptoms predicts the placebo-controlled benefit of PCI.

Invasive coronary pressure indices such as Fractional Flow Reserve (FFR) were developed to determine the clinical significance of a coronary artery stenosis and are now considered gold standard for assessing coronary obstruction. FFR was originally mapped against multiple ischaemia tests treated dichotomously, in 45 patients. In Chapter 4, I examine the associations between the different ischaemic tests in ORBITA, treated dichotomously or continuously. I also assess the ability of anatomical severity, measured by quantitative coronary angiography (QCA), to predict the placebo-controlled benefit of PCI, using the ORBITA dataset.

It has been suggested that features of the ORBITA trial design contributed to the lack of treatment effect observed with PCI. ORBITA participants also felt that the trial design could be improved. They recommended using symptoms rather than exercise time as the primary endpoint. In Chapter 5 I describe my work on the design of the ongoing ORBITA-2 trial which addresses these design features. I incorporate daily documentation of symptoms on a smartphone application and a novel ordinal clinical outcome scale for angina as the primary endpoint, both developed in partnership with patients and experienced statisticians to provide a more accurate and patient-centred measure of health status in angina.

In Chapter 6 I present the development and validation of the symptom smartphone app using data from ORBITA-2 participants. This is the first study of a smartphone app for monitoring angina in a clinical trial. I assess the ability of ORBITA-2 participants in the Completion Assessment Group to complete the app, demonstrating feasibility, and the ability of ORBITA-2 participants in the Recall Assessment Group to recall numbers of episodes, showing the advantage of a daily documentation approach using the app.

This exploration of symptoms, anatomy and ischaemia using the ORBITA dataset, and experience with patients during the design and conduct of ORBITA-2, provides insight into ways management and research of angina could be improved.

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List of Abbreviations

ACE inhibitors = angiotensin-converting enzyme inhibitors

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CCS Class = Canadian Cardiovascular Society Class

CPET = cardiopulmonary exercise testing

CT = computed tomography

CTCA = computerised tomography coronary angiography

DSMB = data and safety monitoring board

ECG = electrocardiogram

ePROMS = electronic patient-reported outcome measures

FFR = fractional flow reserve

GI = gastrointestinal

GTN = glyceryl trinitrate

iFR = instantaneous wave-free ratio

MI = myocardial infarction

MRC = Medical Research Council

MRI = magnetic resonance imaging

ORBITA = Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina

PCI = percutaneous coronary intervention

PET = positron-emission tomography

POBA = plain balloon angioplasty

QCA = quantitative coronary angiography

SAQ = Seattle Angina Questionnaire

SPECT = single-photon emission computerised tomography

Chapter 1 Introduction

There is substantial randomised placebo-controlled evidence for pharmacotherapy achieving the major treatment goals in coronary artery disease, namely prevention of death or myocardial infarction (MI) and reduction of angina(1,2). For the former goal, the principal elements are statins and, for secondary prevention, antiplatelet drugs such as aspirin. Along with this come agents that reduce blood pressure such as ACE inhibitors. For the latter goal, agents that alleviate angina include beta-blockers, calcium-channel blockers and nitrates. While there are a wide variety of such agents, the common theme is that their effects have been demonstrated in placebo-controlled randomised trials.

The randomised evidence for coronary revascularisation for prognostic benefit is primarily for acute coronary syndromes, and not stable coronary artery disease(3). Physicians had assumed the same benefit would be seen in stable coronary artery disease but trials have not shown a reduction in events(4–8).

More emphasis is now being placed on the angina relief provided by percutaneous coronary intervention (PCI). However the only blinded trial of PCI for stable angina, Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA), suggests the benefit may be much smaller than previously believed(9).

Elective coronary revascularisation for prognosis

Observational data suggested that the quantity of ischaemia (Figure 1.1) or extent of coronary disease (Figure 1.2) was powerfully associated with mortality and that outcomes from patients who had undergone coronary artery bypass grafting (CABG) or PCI were better than seemingly similar patients who had not(10). However, observational studies comparing recipients and non-

recipients of a treatment are not a substitute for randomised controlled trials. One can adjust for confounders such as age but many different considerations go into the decision to revascularise or not. These are much harder to measure and therefore control for. In standard clinical databases, they may not even be documented because they arise from powerful but difficult-to-verbalise assessments such as the ‘end of the bed test’, which all physicians are familiar with.

The first randomised trial to report MI and mortality rates of PCI in stable CAD was in the plain balloon angioplasty (POBA) era. The Angioplasty Compared with Medicine (ACME) trial randomised 212 patients with angiographically severe single vessel CAD to POBA versus no POBA(8). It found no significant difference in MI or mortality at 6 months.

Subsequent trials, including RITA-2(4), MASS(5) and MASS II(11), were also not a test of modern PCI as most patients received POBA or bare metal stents(12). Still, there was no prognostic benefit. RITA-2 produced a surprising result in that there was a significantly higher rate of death and MI with PCI (6.3% vs 3.3%, p=0.02). Even though this was the primary endpoint, the conclusion of the abstract put the emphasis on angina relief(4).

The FAME-2 trial randomised 888 patients with stable coronary artery disease and FFR ≤ 0.8 to PCI and medical therapy or to medical therapy alone. The primary endpoint was composite of death, myocardial infarction, or urgent revascularisation. This study was prematurely terminated due to benefit in the treatment group. There was a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical therapy group (hazard ratio with PCI, 0.32; 95% confidence interval, 0.19 to 0.53; P<0.001). The difference was driven by high rates of urgent revascularisation in the medical therapy group. Myocardial infarctions and death were also much lower in the PCI group although not statistically significant with confidence intervals just crossing 1.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomised 2,287 patients with significant coronary disease and ischaemia to PCI or no PCI(7). Although PCI was effective at reducing ischaemia, it had no effect on death and MI.

A significant criticism of COURAGE was that physicians may have held back from randomising the patients who were most likely to benefit from PCI. In other words, once they saw a coronary angiogram with a very severe lesion, they might be too fearful to leave the patient without PCI. While this may have taken place, when stratified by the amount of ischaemia at baseline, there was no tendency for patients with more ischaemia to benefit more from PCI(13).

The solution to a reluctance to randomise patients with a severe lesion is to randomise before the exact coronary anatomy is known. This was the approach taken in the subsequent ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches)(6). It randomised 5,179 patients with moderate or severe ischaemia on stress testing to an initial invasive or conservative strategy before invasive coronary angiography based on a blinded core laboratory adjudicated CT coronary angiogram.

ISCHEMIA showed no difference in the primary endpoint of death from cardiovascular causes, MI or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest.

ISCHEMIA excluded certain groups of patients because leaving them without revascularisation was considered too risky (patients with left main stem disease on CT scan or poor left ventricular function) or too burdensome (for patients with severe symptoms). Randomised controlled data are still needed to understand if revascularisation improves outcomes in these patients.

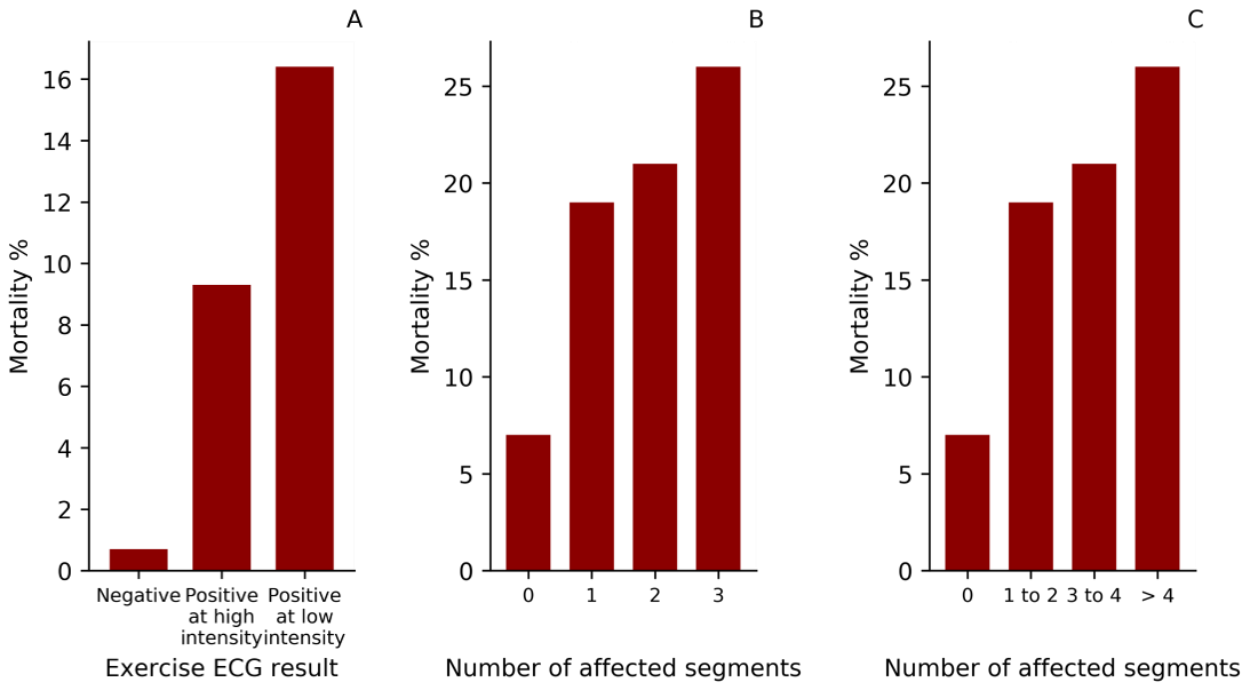

Figure 1.1 Relationship between three common non-invasive tests and mortality. (A) Exercise ECG and 5-year mortality, n=429(14). (B) Stress echo and 8-year mortality, n=3156(15). (C) Thallium SPECT and 2.5-year mortality, n=340(16). Adapted from Nowbar et al(17).

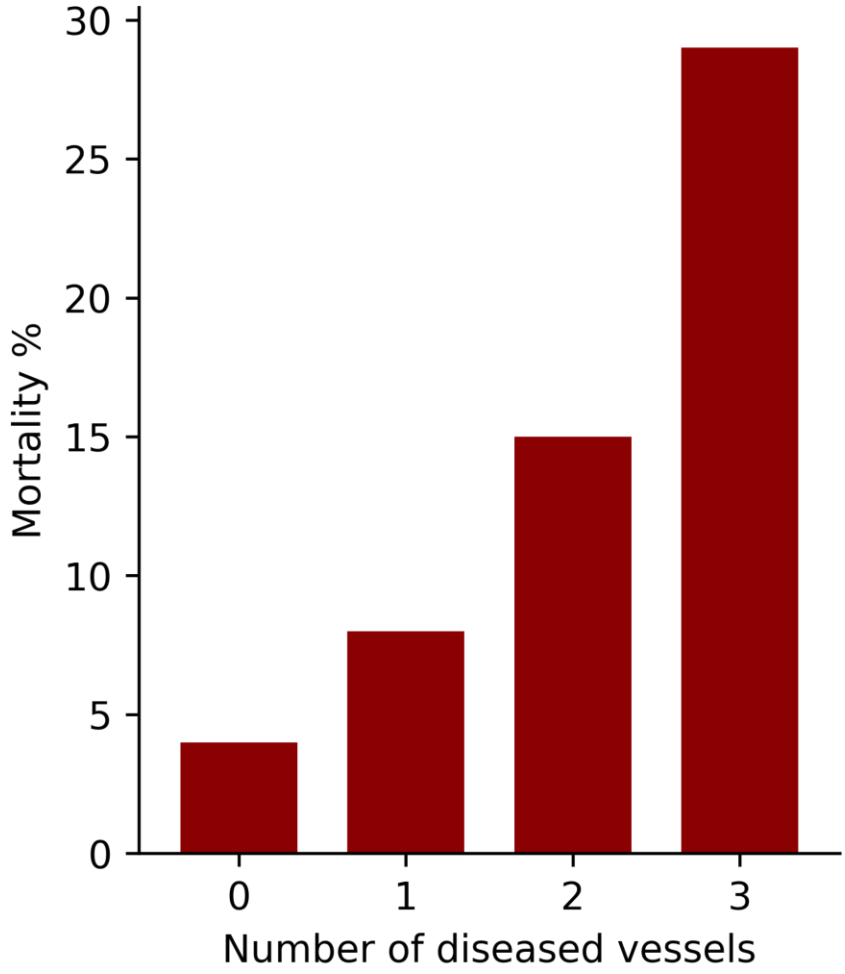

Figure 1.2 Number of diseased coronary arteries and mortality: data from the CASS registry(18). Adapted from Nowbar et al(17).

Elective coronary revascularisation for angina

Guidelines can still recommend elective revascularisation for relief of angina as there is extensive evidence that it relieves anginal symptoms(19). Unfortunately, all of this evidence is unblinded(4,6–8,20). Unblinded evidence was accepted until recently because there was an assumption of prognostic benefit, with symptom relief merely an incidental bonus. However, as the case for prognostic benefit has been challenged, it has become more important to test symptom relief properly.

The ORBITA trial randomised 200 patients to PCI or a placebo procedure on a background of multiple anti-anginal medications(9). The patients had severe (≥70%) single-vessel stenoses. 105 patients were assigned to PCI and 95 to the placebo procedure. The primary endpoint was difference in exercise time increment between groups. It showed no statistically significant improvement in exercise time beyond placebo (PCI minus placebo 16·6 s, 95% CI –8·9 to 42·0, p=0·200)(21). This was despite clear resolution of ischaemia on stress echocardiography.

When patients are aware that they have had PCI, they have clear reduction in angina and improved quality of life(10,20,22,23). However, not all angina is eliminated. In routine clinical practice doctors report that 5 to 15% of patients with stable CAD continue to have angina(24,25). In trials this proportion is even higher. This could reflect more meticulous documentation of residual symptoms in a trial protocol.

A key difference between ORBITA and other trials of PCI is that participants in ORBITA were blinded. Blinding enables assessment of the placebo-controlled effect size. Unblinded trials of intervention are susceptible to bias(26) and invasive treatments have a larger placebo effect than non-invasive treatments(27). The same standards for evidence for pharmacotherapy should be applied to invasive procedures i.e. blinded data.

ORBITA was powered to detect a between-group difference in the exercise time increment of 30 seconds with 80% power at the 5% significance level assuming a standard deviation of change of 75 seconds. In reality the variability in exercise time increments was larger so in retrospect ORBITA could be considered to be powered by a 34 second effect size as described in original manuscript(9).

It is possible that ORBITA was affected by type 2 error i.e. the null hypothesis of no effect was accepted when the null hypothesis may in reality be false (there is an effect), particularly in view of the symptom benefit seen in the much larger study, ISCHEMIA(28). In ISCHEMIA 2295 participants were randomised to an invasive treatment strategy and 2322 to a conservative strategy. At 3 months the Seattle Angina Questionnaires (SAQ) summary scores were 4.1 points higher (higher scores represent a better health status in angina) with the invasive strategy compared with the conservative strategy (95% credible interval, 3.2 to 5.0). This was sustained at 1 year and at 3 years when the SAQ summary score was still 2.9 points higher with the invasive strategy (95% credible interval, 2.2 to 3.7).

However, it is also worth noting that aside from lack of blinding, many of the patients in ISCHEMIA received CABG whereas ORBITA participants only had PCI and had to have only single-vessel disease. Symptom assessment in ISCHEMIA was by SAQ which was measured in ORBITA but was not the primary endpoint for which it was powered.

Another key difference between ORBITA and unblinded clinical experience or trials is that all ORBITA participants received maximally tolerated anti-anginal medication.

Several criticisms have been made of the ORBITA design and how its results should be interpreted(29). The design of ORBITA-2 will address some of these issues and provide the next test of the placebo-controlled efficacy of PCI in reducing angina. The design and rationale of this trial is described in Chapter 5. In brief, ORBITA-2 will randomise people with single- or

multi-vessel disease, off regular anti-anginal medications, looking at the impact on symptoms assessed on an ordinal clinical outcome scale over a 12 week follow-up period. The ORBITA-2 dataset will permit evaluation of the time-course of symptom relief because symptoms are reported daily on a smartphone app. The app design is described in Chapter 6. A two-week symptom assessment phase has been introduced to ensure that no asymptomatic patients are randomised. This bias-resistant trial is needed to evaluate the true physical effect of PCI because the procedure is costly and is associated with small but non-negligible short and long term risks compared to medical therapy.

Patient and public involvement was fundamental in the design of ORBITA-2. My aims with involvement of patients were to:

- To design a trial with patient-centred outcomes that is safe and feasible to deliver
- To select a primary outcome measure and timepoint for measurement that would be patient-centred
- To test the smartphone application used for the primary outcome
- To review and revise all patient-facing and general-practitioner facing trial documentation
- To aid data interpretation and trial result dissemination

Revascularisation and the ischaemia paradigm

PCI is intended to re-establish normal coronary blood flow by restoring the lumen of the vessel to match a reference segment. There is particular uncertainty in treating “intermediate” lesions based on angiographic appearance. A more sophisticated way to determine whether a coronary stenosis should be treated with PCI is to measure the pressure drop across a lesion using FFR.

It is defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow(30). In other words, FFR assesses whether a lesion is responsible for a reduction in flow, i.e. whether it is physiologically significant, and therefore gives an indication of whether restoring the lumen would improve flow. In an early study of 60 patients, all the values of FFR associated with inducible ischaemia (defined as a positive exercise test that normalised after angioplasty) were ≤ 0.74(30).

To evidence that FFR was an adequate measure of ischaemia, it was mapped against stress echo, thallium scintigraphy and exercise testing in 45 patients treated dichotomously. By "dichotomous" I refer to the plotting of patients' results of the three tests (stress echo, thallium and exercise) as either positive or negative as a black filled dot or unfilled dot across all the values of FFR in Figure 2 of Pijls et al(31). A threshold of ≤ 0.75 was chosen as significant. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FFR in detection of ischaemia was reported as 88%, 100%, 100%, 88%, and 93% respectively.

To evidence that FFR was a useful discriminator, its use was tested in randomised trials. The DEFER trial randomised people with an FFR ≥ 0.75 to PCI or conservative management(32). There was no difference in death and MI between groups suggesting deferral of PCI is "safe" in intermediate coronary lesions with FFR ≥ 0.75. This supported the idea that these lesions are not "significant" by which they mean there is no prognostic benefit from PCI.

The FAME trial randomised people to FFR-guided (using a threshold of ≥ 0.8 for deferral) treatment or angiography-only guided treatment(33) and found a benefit in the FFR group. There were fewer deaths, Mis, or urgent revascularisations in the FFR group and no difference in rates of freedom from angina. These results can be interpreted as establishing that doing fewer stents by using an index that enables some lesions to be deferred is prognostically beneficial.

The FAME-2(20) trial was intended to further establish the role of FFR using a threshold of 0.8. It randomised people with FFR ≤ 0.8 to either PCI or medical therapy alone. It found that PCI reduced the rate of the deaths, myocardial infarctions, and repeat revascularisation, which was driven by the rate of repeat revascularisation. These results could be interpreted as FFR usefully identifying lesions that would benefit from PCI. However, the trial design assesses the effect of PCI, not the effect of using FFR.

iFR was subsequently introduced and found to be an independent measure of ischaemia, and noninferior to FFR in guiding revascularisation in the DEFINE-FLAIR(34) and iFR-SWEDEHEART(35) trials. It has the advantage of not requiring hyperaemia so can be performed without adenosine, thus lowering the barriers to making the measurement.

Despite invasive angiography having been the original reference standard for stress echo which, in turn, was the reference for FFR, which in turn was the reference for iFR, the role for anatomical testing is unclear. Guidelines now recommend CTCA as the first-line investigation in stable chest pain(36). This was supported by evidence from the SCOT-HEART trial(37). SCOT-HEART randomised 4146 people with stable chest pain who had been referred to a cardiology clinic to CTCA and standard care or standard care alone. The primary end point was death from coronary heart disease or nonfatal myocardial infarction at 5 years. Rates of the primary endpoint were lower in the CTCA and standard care group compared to standard care alone (2.3% vs. 3.9%, hazard ratio, 0.59; 95% confidence interval, 0.41 to 0.84). This may have been due to the imitation of more preventative therapy in the CTCA group as rates of angiography and revascularisation were not significantly higher. CTCA was associated with less marked symptomatic improvement compared to standard care alone(38). This may be attributable to the detection of moderate non-obstructive coronary artery disease.

This contrasts with the results of the PROMISE trial which randomised 10003 patients to CTCA or functional testing(39). The primary endpoint was death, myocardial infarction, hospitalisation for unstable angina, or major procedural complication. There was no difference in events between the two groups at 2 years. However the functional testing strategy in this US trial was not the same as the UK standard of care during SCOT-HEART.

The idea is that these indices will identify who will have better outcomes with revascularisation. One of the expectations of ORBITA was that it would identify a threshold below which PCI would provide angina relief. In Chapter 4, I explore the inter-relationships between FFR and other ischaemia tests when treated dichotomously rather than continuously, building on the previously reported findings that iFR and FFR predicted the placebo-controlled benefit of PCI on stress echo score but not the effect on exercise time or other symptom endpoints(40). I also evaluate the association between anatomy, assessed by quantitative coronary angiography (QCA), and the placebo-controlled benefit of PCI in ORBITA.

Patient reported outcome measures

Common angina trial endpoints

Most clinical trials in stable angina use exercise time as the primary endpoint. One advantage of exercise testing as an endpoint is that it can be standardised within a participant, across participants within a trial and across trials. Another major advantage is that it is a continuous variable which increases statistical power compared to a binary variable. However, it can be dependent on the supervising staff and limited by non-anginal symptoms or pathology e.g. knee pain. Furthermore, achieving an improvement in exercise time in a controlled environment is not necessarily relevant to all patients.

There has been a movement towards using quality of life as a primary endpoint in clinical trials in stable angina. Symptoms and quality of life can be reported indirectly by the physician or directly by the patient. There is growing recognition that only the patient can assess their symptoms, function and quality of life. Physicians significantly under-estimate angina in comparison to the patient's report(41). Traditionally patient-reported assessments are done with paper questionnaires at the end of a follow-up period. They can be generic e.g. EuroQol-5D (EQ5D) or disease-specific e.g. Seattle Angina Questionnaire (SAQ). These questionnaires also deliver standardisation but can be burdensome to participants to complete frequently. They are also limited by being based on participant recall which can be inaccurate.

Validation of angina questionnaires

Validation can refer to a number of concepts. Particularly in the design of questionnaires or symptom assessment tools, validation methods can be considered as a hierarchy (Figure 1.3) of how well the tool achieves its aim. Other aspects of validation outside of this hierarchy are acceptability (for patient use) and responsiveness to change over time. Validation can be established directly through validation studies and indirectly through respective reviews of published data in which a group of patients has completed multiple simultaneous assessments. These indirect data can be from randomised trials or observational studies.

SAQ is the most commonly used questionnaire for angina. The International Consortium for Health Outcomes Measurement (ICHOM) CAD working group recommends using SAQ as part of the set for outcome measurement in coronary artery disease(42).

From a systematic search of the literature in 2020, the different domains of SAQ have been validated primarily using construct validation (Figure 1.4). The majority of validation work was for SAQ angina frequency, for which there were studies using all five methods from the hierarchy. Examples include:

- “Gold-standard” Validation: strong correlation with angina and anti-anginal diaries(43)
- Criterion Validation: strong correlation with anti-anginal prescriptions(43) and moderate correlation with Canadian Cardiovascular Society (CCS) class(44)
- Convergent Validation: strong correlation with Coronary Revascularization Outcome Questionnaire (CROQ)(45,46)
- Construct Validation: strong correlation with mortality(47)
- Internal Consistency: strong correlation with SAQ physical limitation(48)

In this thesis I consider all the above forms of validation, especially acceptability because the burden of questionnaires is a recognised barrier to participation. Enhancing the patient experience may help in expanding randomised trials to a broader range of patients than those that usually say yes to participation.

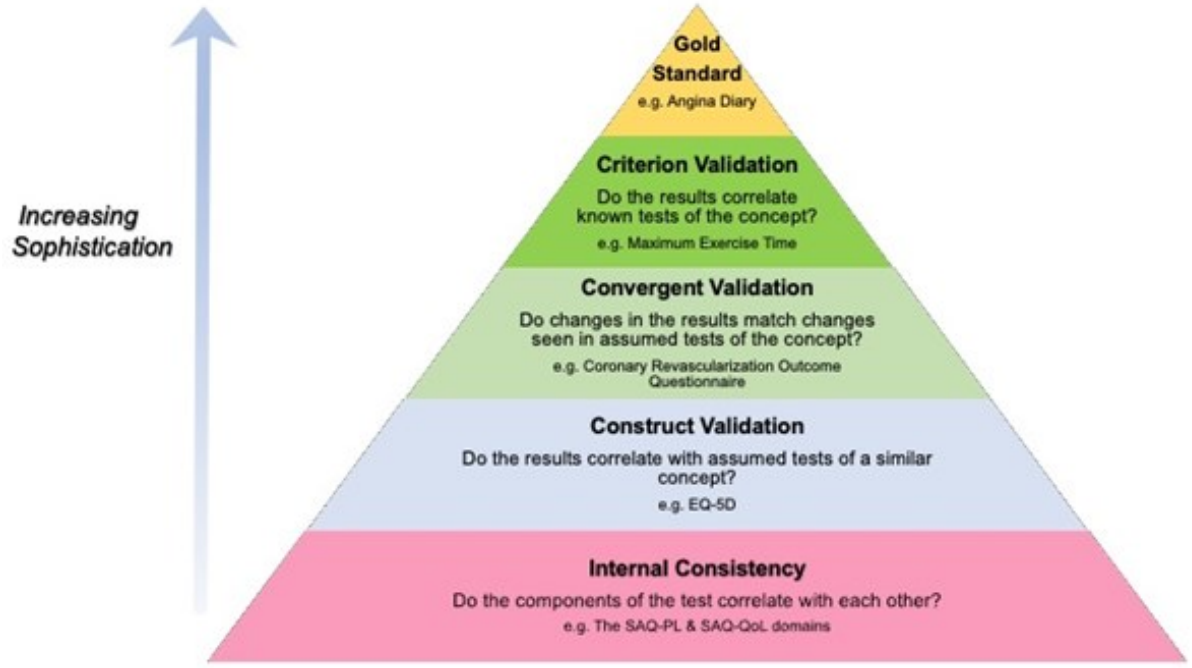

Figure 1.3 Hierarchy of validation evidence with examples for the assessment of stable angina(49).

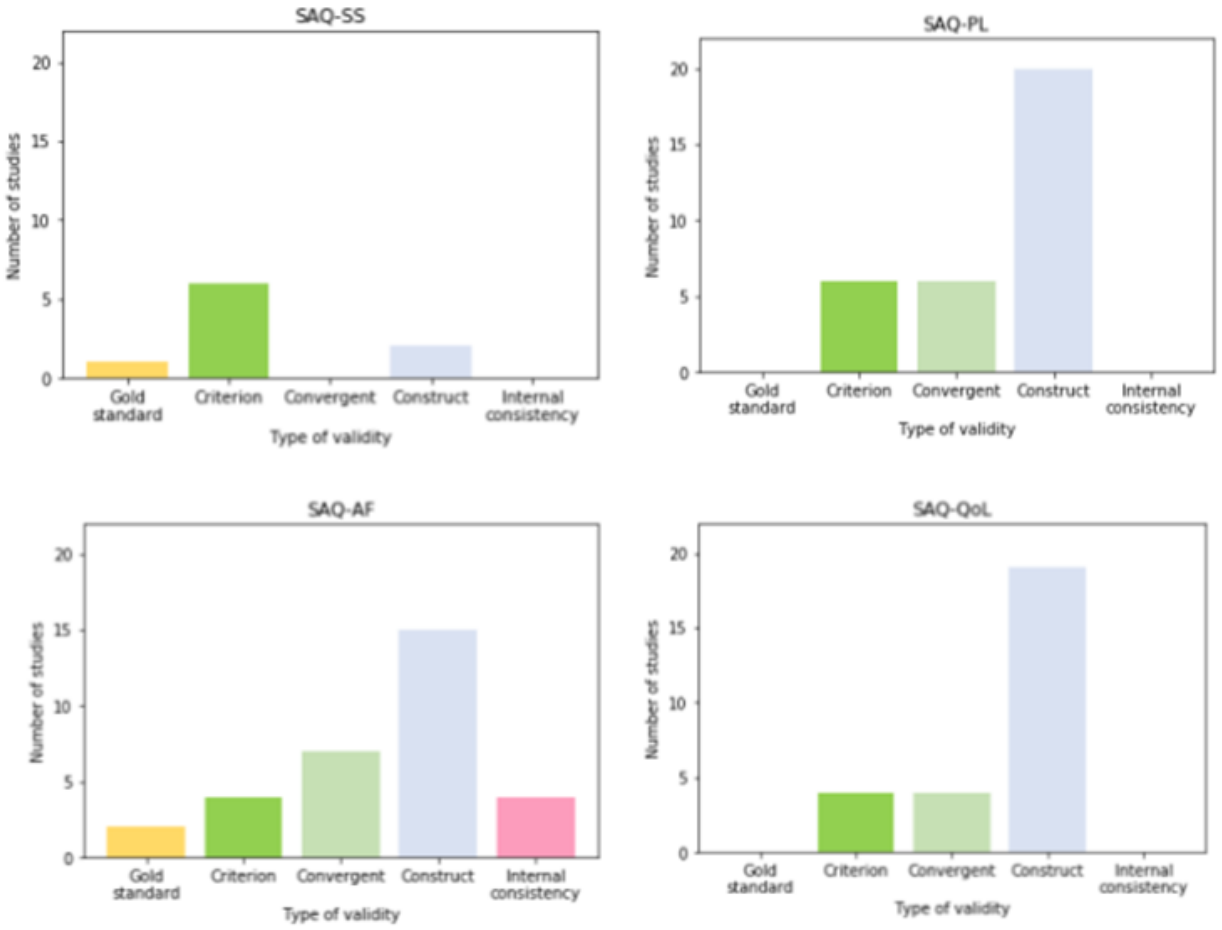

Figure 1.4 The quality of validation evidence for each SAQ domain. The x-axis indicates the quality of validation evidence, decreasing left to right, with gold standard considered the strongest, and internal consistency the weakest. The y-axis represents the number of studies in each category of validation.

Electronic patient-reported outcome measures

The ubiquity of smartphones means patients can frequently and contemporaneously report their symptoms. Symptom apps are widely available for other chronic pain conditions such as migraines. There is increasing use of electronic patient-reported outcome measures (ePROMS) in trials. For example, the TERISA trial recorded daily anginal episodes and nitroglycerin use with an electronic diary(50).

I searched 3 app stores: Android Google Play Store, Apple App Store and the Amazon Appstore for apps seeking to monitor angina. I identified the following three apps: Angina Control (Google Play), Angina Recorder (Apple) and Heartkeeper (Google Play). I also explored apps for other chronic pain conditions: Sora, Migraine Buddy and RheumaBuddy for endometriosis, migraines and rheumatoid arthritis respectively. These apps showed a range of functionality for self-monitoring but were not suitable for research purposes. While diverse features such as diagrams allowing the site of pain to be marked, scales of severity, and the ability to record associated symptoms, permit a complete picture of the symptom experience to be recorded, this is better suited for an assessment at a single point in time. Too many features are challenging for statistical analysis and patients may find that many questions burdensome to answer regularly over a follow-up period. Apps for monitoring pain are discussed further in Chapter 6.

An ordinal clinical outcome scale for angina

Angina is typically triggered by exertion. This means that recordings of angina are dependent on the frequency and degree of exertion. Thus a count of angina episodes may not fully reflect an individual's underlying health status. For some, a more relevant measure might be how limited they are in their activities of daily living because they may have limited their activities to avoid painful symptoms. In this case, an angina count might go down when the individual's underlying

health state is worse not better. An angina count would also mislead when an individual is no longer having angina because they have started anti-anginal medications, not because the underlying condition had improved. Some trials use GTN diaries to reflect the severity of the condition but again this is limited by the dependence on how much activity the patient does, the level of angina at which the patient uses GTN, and whether they even use it prophylactically.

I aimed to design an endpoint that would address these limitations as well as being patient-centred and relevant. The type of endpoint was chosen to be an ordinal clinical outcome scale because of the additional granularity of information it collects, therefore increasing the statistical power achieved with a given sample size.

For any pain outcome, more statistical power is achieved from a given sample size by using multiple levels of pain severity. This permits detection of a smaller effect size if present. So the main benefit of an ordinal scale (over binary scales) is that it has several levels. Of course, a continuous variable, e.g. exercise time, would optimise for this but no single variable can account for all the factors influencing the health status in angina, and is usually only measured at a single time point.

I aimed to address the following factors in the scale specifically:

- Performance of activities that trigger angina
- Collecting longitudinal time-course data
- Health states that would reduce angina but reflect a poorer health status such as having a myocardial infarction or starting anti-anginal medications
- The spectrum of patients' and clinicians' views on what is regarded as a better or worse health state in angina

Participant experience

Beyond the scientific value of the endpoint and its relevance to patients, it was equally important for data collection to be practical and tolerable in the trial. It is not sufficient to design a trial requiring a rich dataset if obtaining data accurately and completely is impossible. The participant's overall experience not only affects retention in the trial but is critical to their wellbeing. Ethically, it is necessary to avoid intrusion and overburdening even the most willing and helpful participants. The design of the primary endpoint, data collection tool (a symptom smartphone app) and trial, therefore, has a particular focus on usability, feasibility and personalisation.

In Chapter 2 I describe the formation of Focus Groups to involve patients with lived experience of angina and of trials in research design. I describe how their involvement altered the design of the trial (Chapter 5), the primary endpoint (Chapter 5), and the symptom smartphone app (Chapter 6).

Aims of this thesis

This thesis aims to test the following hypotheses:

1. The nature, severity and frequency of symptoms can predict the placebo-controlled efficacy of PCI.

I will test this hypothesis by performing a symptom-stratified analysis of ORBITA (Chapter 3). In ORBITA, symptoms were assessed pre-randomisation by the physician and reported by the patient. I expect that the typicality of symptoms i.e. central exertional pain will predict the placebo-controlled efficacy of PCI as there is greater certainty that typical symptoms are

attributable to the coronary disease and therefore there is a greater chance that PCI will lead to resolution.

2. FFR, used as a binary variable, does not agree well with non-invasive ischaemia tests.

The original validation of FFR was performed dichotomously in 45 patients. I will test the agreement of FFR, treated dichotomously, with non-invasive ischaemia tests performed pre-randomisation in ORBITA (Chapter 4).

3. FFR, used as a continuous invasive measure of physiology, correlates with non-invasive ischaemia tests.

I will test this hypothesis by assessing the relationship between FFR, treated continuously, and non-invasive ischaemia tests performed pre-randomisation in ORBITA (Chapter 4). I expect to find a correlation between FFR and stress echo score.

4. Coronary stenosis severity measured by quantitative coronary angiography (QCA) can predict the placebo-controlled efficacy of PCI.

I will test this hypothesis by performing a QCA-stratified analysis of ORBITA (Chapter 4). In clinical practice, more severe stenoses are assumed to be more likely to be the cause of symptoms and therefore there is a greater chance that PCI will lead to resolution. I would therefore expect that QCA would predict symptom benefit in ORBITA. In the physiology-stratified analysis(40), invasive haemodynamics predicted the placebo-controlled effect of PCI on stress echo score so I would expect QCA to have similar predictive ability.

5. Angina symptom reporting on a smartphone app for a clinical trial is feasible.

I will test this hypothesis by assessing app completion rates, app reminder rates and participant feedback in ORBITA-2 (Chapter 6).

6. Symptom recall becomes rapidly inaccurate after a few days, especially when angina is experienced.

I will test this hypothesis by comparing symptom recall with daily documentation of angina on a symptom smartphone app by ORBITA-2 participants over a 7 day period (Chapter 6).

In parallel this thesis describes the development of the ORBITA-2 protocol in partnership with patients (Chapter 5), in particular the rationale for an ordinal clinical outcome scale as the primary endpoint (Chapter 5) and the design of the ORBITA-2 symptom smartphone app (Chapter 6).

Chapter 2 Methods

Participant recruitment

ORBITA

Design

ORBITA randomised patients with stable angina and severe single vessel coronary disease to PCI or placebo (Figure 2.1). The design has been described previously(9). The study was approved by the London Central Research Ethics Committee (reference 13/LO/1340). Written consent was obtained from all patients.

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.

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 CABG, 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.

After enrolment, participants entered a 6-week medical optimisation phase, which focused on the initiation and up-titration of guideline directed anti-anginal therapy. This involved telephone consultations with a consultant cardiologist one to three times per week, supported by home measurements of pulse and blood pressure, aiming for at least two anti-anginal therapies per patient. All patients received dual antiplatelet therapy until the final (unblinding) visit. Participants then had baseline pre-randomisation assessment, followed by the randomised blinded procedure. They then entered the second phase which was the 6-week.

The pre-randomisation and follow-up assessments included a cardiopulmonary exercise test and stress echo. The physician and physiologist conducting the assessments were blinded to the allocation.

The primary endpoint was the between-arm difference in change in exercise time from pre-randomisation to 6-week follow-up.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed using the QUARK CPET breath-by-breath metabolic measurement system. The test was stopped when any of the following occurred: limiting symptoms, heart rhythm or blood pressure abnormalities, or marked ST-segment deviation (≥ 0.2 mV associated with typical angina or in the first stage of exercise).

Dobutamine Stress Echocardiography

Stress echo was performed using SonoVue contrast administered in 0.3ml boluses for each image acquisition followed by 1-2ml of saline flush(21). Intravenous dobutamine was infused at a starting dose of 10 mcg/kg/min rising to 20, 30 and 40 mcg/kg/min at 3 minute intervals. If 85% of maximum predicted heart rate was not achieved, intravenous atropine was administered in 300 mcg boluses up to a maximum of 1200 mcg. Images were acquired in the apical 2-

chamber, 3-chamber, 4-chamber and parasternal short-axis views at 4 timepoints: baseline, low-dose stress, high-dose stress, and recovery. Scans were analysed by multiple reported using a 17-segment model as described previously(21).

Invasive assessment, randomisation and blinding

Participants had coronary angiography via a radial or femoral arterial approach with auditory isolation throughout the procedure using over-the-ear headphones playing music. Invasive physiology assessment was performed including FFR and iFR. The operator was blinded to the physiology measures and therefore did not use them to guide treatment. After physiological assessment, participants were sedated and randomised to PCI or placebo in a 1:1 ratio. For the intervention, drug-eluting stents were used. Invasive physiology assessment was repeated post-PCI but again the operator was blinded to these values. For the placebo procedure, participants were kept sedated on the catheter laboratory table for 15 minutes before withdrawing the catheters.

Details of the procedure were not conveyed from catheter laboratory staff to the recovery staff. Participants and subsequent medical caregivers were kept blinded to the allocation.

Participant characteristics and data availability

230 patients were enrolled and entered the medical optimisation phase between 2013 and 2017. 195 (98%) of participants were Canadian Cardiovascular Society Class II or III at enrolment. 138 (69%) of participants had lesions in the left anterior descending artery. 105 were randomised to PCI and 95 to placebo.

For exercise time there were pre-randomisation and follow-up data for 104 participants in the PCI group and 90 participants in the placebo group.

For stress echo there were pre-randomisation data for 183 participants.

For Seattle Angina Questionnaire (SAQ) and the Rose Angina Questionnaire (Rose), there were pre-randomisation data for 197 patients.

For CCS class, there were pre-randomisation data for all 200 patients.

Chapter 3 analyses ORBITA stratified by symptoms. Chapter 4 analyses ORBITA stratified by quantitative coronary angiography (QCA) and compares the results of ischaemic tests from ORBITA to understand the inter-relationships between tests.

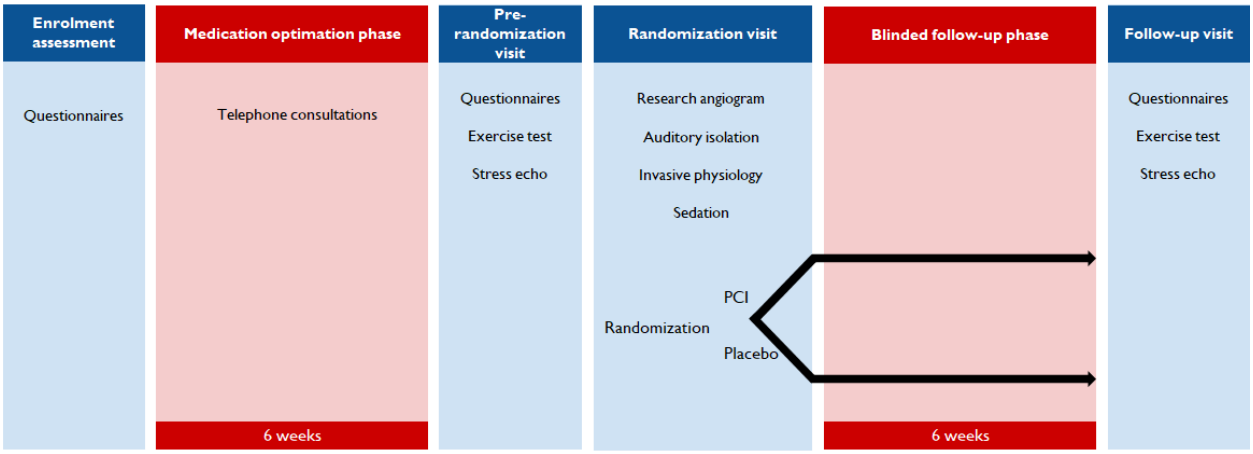

Figure 2.1 ORBITA Study Design. Adapted from Al-Lamee et al(9).

ORBITA-2

Design

ORBITA-2 is a multi-centre double-blind randomised placebo-controlled trial to assess the efficacy of PCI for relief of stable angina in single- and multi-vessel coronary artery disease. The London Central Research Ethics Committee (reference 18/LO/1203) approved the study. Written consent is obtained from all patients. The rationale and design are described further in Chapter 5.

Participants are randomised at least 2 weeks after the symptom assessment phase and followed up for 12 weeks as shown in Figure 2.2.

ORBITA-2 is being conducted at fourteen study sites: Imperial College Healthcare NHS Trust, Royal Berkshire NHS Foundation Trust, the Essex Cardiothoracic Centre, University Hospitals Dorset NHS Foundation Trust, Buckinghamshire Healthcare NHS Trust, Portsmouth Hospitals NHS Trust, Royal Free London NHS Foundation Trust, Worcestershire Acute Hospitals NHS Trust, University Hospital of Wales, St George's University Hospitals NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, Sandwell and West Birmingham Hospitals NHS Trust, Salisbury NHS Foundation Trust, and Royal Brompton & Harefield NHS Trust.

As of 30th July 2021, 176 participants were enrolled and 104 randomised as shown in Figure 2.3.

The primary endpoint is 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.

Figure 2.2 ORBITA-2 Study Design.

Site	Enrolled	Withdrawal (pre-rand)	Randomised
Hammersmith Hospital	81	33	45
Essex CTC	26	7	18
Bournemouth Hospital	24	6	17
Queen Alexandra Hospital	14	4	7
Royal Berkshire Hospital	9	2	7
Worcestershire Royal	5	1	4
St George's Hospital	6	2	2
Cardiff & the Vale UHB	3	1	2
Royal Free Hospital	4	2	1
Wycombe Hospital	3	2	1
Harefield Hospital	0	0	0
University Hospital Southampton	1	1	0
Total	176	61	104

Figure 2.3 Recruitment to the ORBITA-2 across sites as of 30th July 2021. Essex CTC = Essex Cardiothoracic Centre, Basildon, Cardiff & the Vale UHB = Cardiff and the Vale University Health Board.

Symptom assessment

The aim of ORBITA-2 is to assess the impact of PCI on symptoms, therefore the most likely cause of the participants' symptoms must be stable angina. At enrolment participants undergo a clinical assessment including CCS class and Medical Research Council (MRC) Dyspnoea Scale. They complete quality of life questionnaires (EuroQol-5D and MacNew), the Seattle Angina Questionnaire (SAQ), the McGill Pain Questionnaire and the Rose Angina Questionnaire (Rose).

Participants are provided with a symptom smartphone app and trained to use it via a practice module. The app is personalised to the participant's own symptoms and activities that trigger their angina. Participants start completing the app every day the day after enrolment. Once a week, participants enter whether they had angina when they undertook their preset 2 activities. If at any stage participants need further information, they can refer to the Help page of the app. If participants do not complete the app for three days, they are sent text reminders. If they still have not completed their entries, they are contacted by a member of the research team.

Exercise Testing

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).

Dobutamine 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 10μg/kg/min followed by 20μg/kg/min, 30μg/kg/min and 40μg/kg/min in 3 minute stages. In participants who have an "inadequate" heart rate response to dobutamine, atropine may be administered in 300mcg increments to a maximum dose of 1200mcg.

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.

Invasive assessment, randomisation and blinding

For the invasive procedure, participants will wear over-the-ear headphones with auditory isolation. Radial or femoral vascular access will be used at operator's discretion. Coronary angiography including pressure wire assessment with FFR and iFR will be performed. Operators will be unblinded to the measurements.

Participants will be sedated. They will then be randomised 1:1 to PCI or placebo procedure. 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.

Blinded analyses in ORBITA-2

I have used data from ORBITA-2 participants in two analyses. The first analysis is from the Completion Assessment Group consisting of ORBITA-2 participants who had their final visit

before the end of April 2021 (n=142). The second analysis is from the Recall Assessment Group consisting of ORBITA-2 participants who had their final visit between August 2020 and April 2021 (n=29). These data were collected by blinded researchers while participants were blinded.

Focus Groups

Participants from ORBITA were invited to attend a research presentation evening held in January 2018. Attendees were asked to sign up if they were happy to be contacted about being involved in future research. Those who signed up were contacted and invited to attend focus group meetings in October 2018. They were told they could bring a friend or family member if they wished.

Those who attended two meetings relating specifically to the design of ORBITA-2 and the symptom app are referred to as the Design Focus Group. Details of the involvement of the Design Focus Group are provided in Chapter 5. Figure 2.4 shows photos from these meetings.

I also regularly contacted focus group members via phone call, email and video calls. For example, they reviewed patient-facing literature and grant applications. One focus group member has been a grant co-applicant and sits on the Trial Steering Committee for ORBITA-2. He is supported in this role with open phone, email and video communication to discuss concepts. Focus group members have also been consulted on the other cardiovascular research projects within our National Heart and Lung Institute Section (Cardiovascular Trials and Epidemiology). The focus group body has since grown to include ORBITA-2 participants (who had completed their participation) and people with heart failure without clinical trial experience.

Focus group member opinions were collected through verbal feedback and written surveys.

Figure 2.4 Photographs of meetings of the Design Focus Group. The individuals shown are previous ORBITA participants, their family members and medical student and doctor facilitators. Taken with permission.

Software

Electronic Case Report Form

Study data was collected using the open source electronic data capture system, OpenClinica (Version 3.15.2). This is hosted on a central server.

Analyses

Summary statistics are presented using mean (standard deviation) or median (interquartile range) as appropriate. ORBITA analyses were performed on an intention-to-treat basis, i.e. participants were analysed based on allocated arm not based on treatment actually received.

The open-source statistical environment, R (Version 4.1.0) was used for all analyses except the initial processing of symptom app data, for which I used Python (Version 3.8.3).

Regression analyses, including ordinary least squares linear regression and logistic regression, were performed using the “rms” package in R. Graphs were created using the “ggplot2” package in R.

For symptom app data I used “pandas” and “JSON” in Python. “pandas” is a tool for data frame manipulation. “JSON” is a tool for working with json (JavaScript Object Notation) data which is the format of the symptom app data.

Symptom Smartphone App

Design

The process is shown in Chapter 11 Appendices. The app was designed to be available on any smartphone, tablet or computer. To avoid charges from the App Store and the cost of designing

multiple apps for different platforms, the app was a progressive web app written in JavaScript, in other words a singular website that could provide the appearance and functionality of an app across all platforms.

The following components were developed and verified to function as per the specification:

- User on-boarding supervised by a study investigator on Android and iOS
- Logging in procedures
- Blinded and unblinded investigator profiles
- Date stamping for daily and weekly questions
- Error messages e.g. not connected to the internet
- Data storage

Regulatory considerations

A data protection impact assessment was carried out and a General Data Protection Regulation statement was prepared in line with the Data Protection Act 2018(51). Users are required to agree to a privacy policy during onboarding. Key issues included:

- Increasing transparency with a statement in the patient information sheet and within the app itself
- Explicitly stating the purpose of the data collection i.e. for the purpose of research within the ORBITA-2 trial
- Collecting adequate and relevant data limited to only what is necessary i.e. medications, date of birth and other information are not collected as this is collected through the electronic case report form

- Keeping data only for as long as needed i.e. in line with Imperial College London policy on research data
- Maintaining security through encryption and hierarchical access controls
- Ensuring data quality through extensive testing of the algorithms prior to deployment

The app is not being used to make decisions about clinical care. It is a tool to collect data for research purposes. According to Medicines and Healthcare Products Regulatory Agency Guidance: Medical device stand-alone software including apps (including IVDMDs) v1.08, it is not a medical device(52).

Chapter 3 Patient-reported and Physician-assessed Symptoms as Predictors of the Placebo-Controlled Response to PCI in ORBITA

Abstract

In clinical practice it is widely assumed that the nature and severity of symptoms predicts the likelihood of benefit from PCI. I test this hypothesis using patient-reported and physician-assessed symptoms from the ORBITA trial.

Patient-reported and physician-assessed symptoms were recorded at three time points: enrolment, pre-randomisation and follow-up. I tested whether symptom typicality (Rose Angina Questionnaire and Diamond), and intensity (SAQ and CCS Class) predicted clinical responses, using regression modeling.

82 (42%) patients were Rose grade 1 or 2 (i.e. typical angina). 147 (75%) patients had typical or atypical chest pain based on Diamond criteria. Median pre-randomisation SAQ angina frequency was 70 (IQR 50-90). Five (3%) patients had CCS class I symptoms, 118 (59%) CCS class II, and 77 (39%) CCS class III.

There was no evidence for interaction between enrolment CCS Class and the effect of PCI on exercise time ($P_{interaction}$=0.411). There was no evidence for interaction between enrolment SAQ angina frequency ($P_{interaction}$=0.87) or SAQ physical limitation ($P_{interaction}$=0.406) and the effect of PCI on exercise time. There was no evidence for interaction between enrolment Rose grade and the effect of PCI on exercise time ($P_{interaction}$=0.301). There was no evidence for interaction

between enrolment Diamond grade and the effect of PCI on exercise time ($P_{interaction}$=0.749). There was also no evidence of an interaction between CCS Class, SAQ, Rose or Diamond and the following endpoints: stress echocardiography score, SAQ angina frequency or freedom from angina.

The nature and severity of symptoms did not predict the placebo-controlled response to PCI in patients with severe single vessel disease. This contrasts with the unblinded experience of clinical trials prior to ORBITA and of clinical practice.

Introduction

In suspected CAD, symptoms are routinely assessed to diagnose angina and to determine whether revascularisation is indicated. The validity of this latter aim is supported by decades of clinical experience but does not appear to have been prospectively tested under placebo-control. ORBITA provides a platform to assess the link between symptoms and benefit from PCI.

ORBITA assessed symptoms before randomisation in 4 ways: (i) patient-reported intensity, using the Seattle Angina Questionnaire (SAQ), (ii) patient-reported nature of symptoms, using the Rose Angina Questionnaire (Rose), (iii) physician-assessed intensity, using CCS, and (iv) physician-assessed nature of symptoms, using the Diamond-Forrester criteria (Diamond).

SAQ assesses physical limitation, angina stability, angina frequency, treatment satisfaction, and quality of life(43). It is designed for patients with confirmed angina to report their symptoms without the overlay of physician interpretation. It does not distinguish between types of symptoms (i.e. typical or atypical). It quantifies the intensity of symptoms by asking how limited the patient is in certain activities, how often the symptoms occur and how often short-acting nitrates are used.

The Rose questionnaire is designed for patients with suspected angina, to directly report the nature of their symptoms(53). It was originally developed using physician interpretation of symptoms at interview as the reference standard. In ORBITA, participants completed the Rose questionnaire, unfiltered by physician interpretation.

CCS Class(54) is a physician-assessed metric of symptom severity that focuses exclusively on the level of activity needed to bring on angina: 0 for no angina, 1 for angina with strenuous/rapid/prolonged exertion only, 2 for angina slightly limiting ordinary physical activity

e.g. angina with climbing stairs rapidly or walking uphill, 3 for angina markedly limiting ordinary physical activity e.g. angina with walking 1-2 blocks on level ground or climbing 1 flight of stairs at normal pace, and 4 for inability to carry on any physical activity without discomfort.

The Diamond-Forrester criteria are a physician-assessed system focusing exclusively on the nature of the symptom. They count features of typicality: (a) presence of substernal discomfort, (b) precipitation by exertion, and (c) prompt relief by rest or nitroglycerin. Patients with all 3 are classified as “typical angina”, those with 2 as “atypical angina”, those with 1 as “non-cardiac chest pain”, and 0 is asymptomatic(55). These criteria are said to be validated against angiography, with ≥50% diameter narrowing in at least one major coronary artery considered positive. Guidelines generally use a version of the Diamond. For example, the NICE guideline, Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (CG95)(36), updated in 2016, states:

“Assess the typicality of chest pain as follows:

- Presence of three of the features below is defined as typical angina.
- Presence of two of the three features below is defined as atypical angina.
- Presence of one or none of the features below is defined as non-anginal chest pain.

Anginal pain is:

- constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms
- precipitated by physical exertion
- relieved by rest or GTN within about 5 minutes.”

Exactly how location of pain is classified varies between Rose, Diamond, and clinical practice. Diamond specifically requires substernal pain (accepting no other alternatives) but the Rose

also accepts the combination of left chest together with simultaneous left arm pain as an alternative. Clinical practice is more inclusive: most clinicians would consider isolated exertional left arm pain, isolated exertional left chest pain, or even exertional jaw pain as “typical angina” even though Rose and Diamond would not.

In this chapter I examine the ability of patient-reported and physician-assessed symptoms to predict the placebo-controlled response to PCI. I hypothesised that the placebo-controlled response to PCI would be greater in those with more severe symptoms or more typical symptoms.

Methods

The methods of ORBITA are described separately(9) and summarised in Chapter 2.

Symptom assessment instruments

Symptoms were assessed at enrolment, pre-randomisation and follow-up. Between enrolment and pre-randomisation, participants underwent a 6 week medical optimisation phase of introduction and uptitration of anti-anginal and risk prevention medication.

At the pre-randomisation visit, patients underwent cardiopulmonary exercise testing and dobutamine stress echo. At the invasive randomisation procedure, invasive physiological assessment was performed using FFR and iFR. Patients received sedation and auditory isolation and were randomly allocated to receive PCI or placebo. Patients and all subsequent medical caregivers and the research team were blinded to treatment allocation.

Patient-reported intensity was assessed with SAQ which covers 5 domains: physical limitation, angina frequency, angina stability, quality of life, and treatment satisfaction. Patient-reported nature of symptoms was assessed with the 7 angina questions in the Rose questionnaire. Physician assessment of symptoms was assessed with CCS class for effort-dependence and Diamond for nature.

Statistical analysis

All participants with at least one pre-randomisation symptom questionnaire completed were included in the analysis. Summary statistics are presented using mean (standard deviation) or median (interquartile range) as appropriate. Regression models were used to test the interaction

of SAQ angina frequency, SAQ physical limitation, Rose, CCS Class, Diamond grade and placebo-controlled efficacy of PCI.

Rose was graded as 0 if any of the following features were not present:

- Pain or discomfort in location including sternum, or left chest and left arm
- Provoked by going uphill or hurrying
- Response to pain is to stop or slow down
- Pain relieved within 10 minutes of stopping

Rose was graded as 1 if the answers indicated all of the following:

- Pain or discomfort in location including sternum, or left chest and left arm
- Provoked by going uphill or hurrying
- Stop or slow down in response to pain
- Pain relieved within 10 minutes of stopping
- Not provoked by walking on the flat

Rose was graded as 2 if the answers indicated all of the following:

- Pain or discomfort in location including sternum, or left chest and left arm
- Provoked by going uphill or hurrying
- Stop or slow down in response to pain
- Pain relieved within 10 minutes of stopping
- Provoked by walking on the flat

In other words, to be classed as Rose grade 1 or 2 the pain has to be sternal, exertional, and quickly relieved by rest, otherwise the symptoms are grade 0. Rose grade 1 and 2 differ by whether the pain is only provoked by going uphill and not on the flat (1) or provoked by both (2).

Diamond grade was assessed using answers collected from the Rose. It was classified as “asymptomatic” if none of the following features were present, “non-cardiac chest pain” if only one was present, “atypical” if only 2 were present and “typical” if all 3 features were present:

- Pain or discomfort in location including sternum
- Precipitated by exertion
- Pain relieved within 10 minutes of stopping

Four endpoints from ORBITA were selected to define placebo-controlled efficacy from PCI: exercise time, freedom from angina, SAQ angina frequency and stress echocardiography score. Freedom from angina was calculated using the SAQ.

Models were fitted for each endpoint. Linear models were used for the continuous variables: exercise time, stress echocardiography score and SAQ angina frequency. Proportional odds ordinal logistic models were used for ordinal variables: freedom from angina. For SAQ angina frequency and freedom from angina, a higher score represents a better health state; therefore, an odds ratio >1 suggests that a better health state was achieved with PCI over placebo.

For both continuous and categorical outcome variables, I modeled the follow-up value conditioned on the enrolment value transformed by a restricted cubic spline with 3 parameters and randomisation arm. A model was then fitted for each outcome variable with enrolment SAQ, Rose, CCS Class or Diamond grade interacting with the randomisation arm and the enrolment value of the outcome variable with a restricted cubic spline with 3 parameters, ie, the shape of effect was allowed to vary over treatments(56). Graphs of the end points against SAQ, Rose,

CCS and Diamond grade and the contrast between the arms were generated adjusting for the median value of the enrolment value.

Analyses were performed using the open-source statistical environment “R”(57) using the “rms” package for regression modeling and “ggplot2” package for graphs.

Results

200 patients were randomised in ORBITA (Table 3.1). SAQ and Rose data were available for 197 patients. CCS class was available for 200 patients. The distribution of the nature and intensity of symptoms reported by patient and by physician, is shown in Table 3.2 and 3.3.

Only 82 patients met the strict criteria for Rose grade 1 or 2 (indicating typical angina). The Sankey diagram in Figure 3.1 shows the flow of patients though the Rose questions.

To be classified as Rose grade 1 or 2 requires specific answers to the first 5 multiple choice questions, and, most challengingly, particular locations for the chest pain. Of the 112 patients who answered “yes” to chest pain or discomfort, then “yes” to uphill or hurry, then “yes” to goes away on standing still, then “slow down” or “stop” as their response to pain, then “less than 10 minutes” for offset time, only 79 marked the sternal region and none marked both left arm and left chest. All other patients are classified by Rose as not angina. The distribution of pain locations are shown in Table 3.4.

On the broader Diamond criteria, 147 (75%) patients had typical or atypical chest pain (Table 3.3).

	PCI group n=105	Placebo group n=95	Complete group n=200
Age in years	69 (10)	66 (8)	66 (9)
Male	74 (70%)	72 (76%)	146 (73%)
Hypertension	72 (69%)	66 (69%)	138 (69%)
Hypercholesterolaemia	81 (77%)	62 (65%)	143 (72%)
Diabetes mellitus	15 (14%)	21 (22%)	36 (18%)
Previous MI	5 (5%)	7 (7%)	12 (6%)
Previous PCI	10 (10%)	15 (16%)	25 (13%)

Table 3-1 Demographics of ORBITA participants at enrolment

	PCI group n=105	Placebo group n=95	Complete group n=200
CCS class I	2 (2%)	3 (3%)	5 (3%)
CCS class II	64 (61%)	54 (57%)	118 (59%)
CCS class III	39 (37%)	38 (40%)	77 (39%)
CCS class IV	0 (0%)	0 (0%)	0 (0%)

Table 3-2 CCS Class of ORBITA participants at enrolment. CCS = Canadian Cardiovascular Society.

	PCI group n=103	Placebo group n=94	Complete group n=197
Rose grade 0	61 (59%)	54 (57%)	115 (58%)
Rose grade 1	17 (17%)	19 (20%)	36 (18%)
Rose grade 2	25 (24%)	21 (22%)	46 (23%)
SAQ angina frequency	60 (50-80)	70 (43-90)	70 (50-90)
SAQ physical limitation	67 (45-89)	67 (44-78)	67 (44-86)
Diamond asymptomatic	10 (10%)	6 (6%)	16 (8%)
Diamond non-cardiac chest pain	21 (20%)	16 (17%)	37 (19%)
Diamond atypical	62 (60%)	52 (55%)	114 (58%)
Diamond typical	12 (12%)	21 (22%)	33 (17%)

Table 3-3 Symptoms of ORBITA participants at enrolment measured by Rose, SAQ and Diamond. Values indicate n (%) or median (IQR).

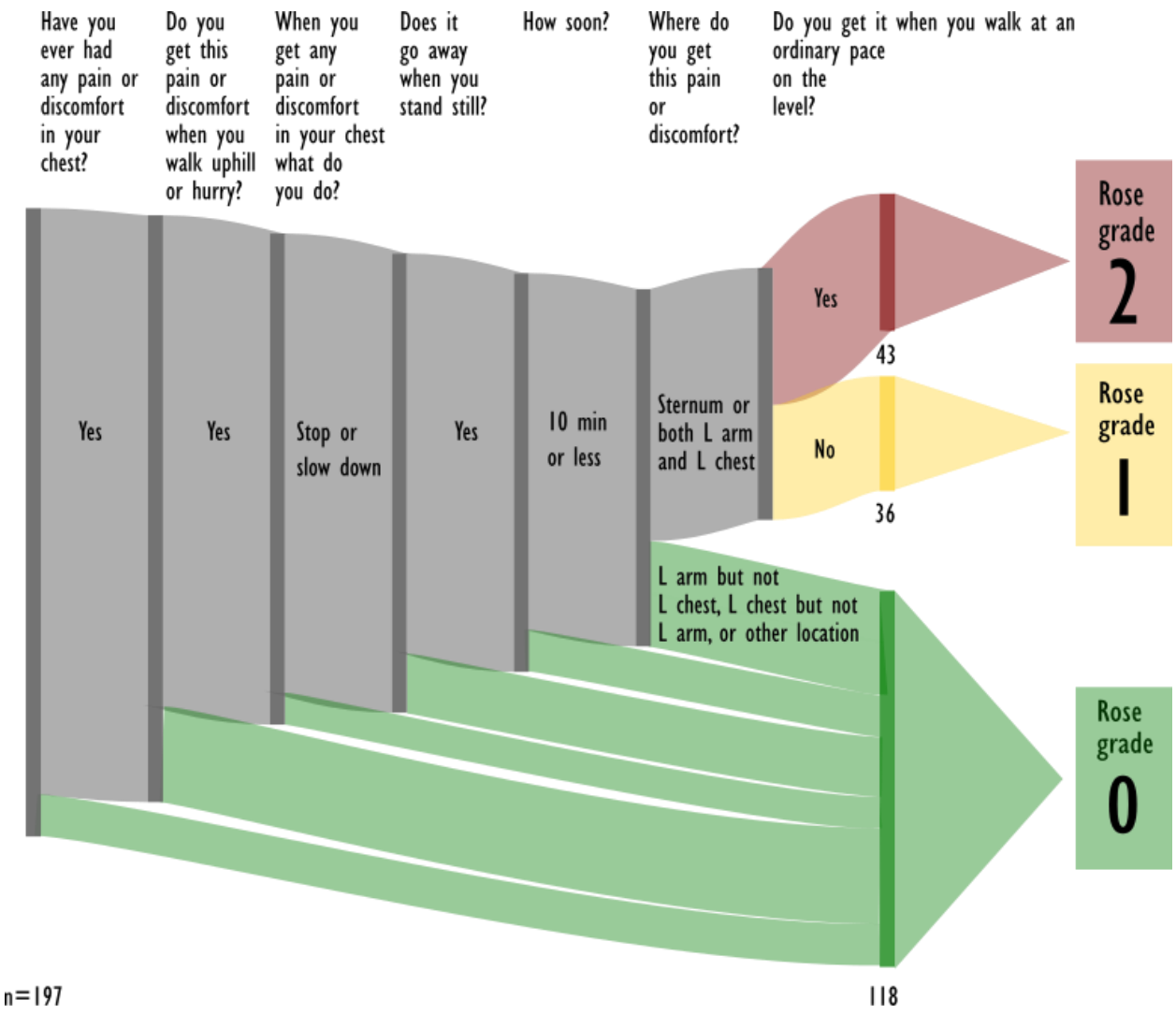

Figure 3.1 Flow of patients through the Rose questions.

	Complete group n=197
Includes sternum	130 (66%)
Includes left chest	104 (53%)
Sternum only	48 (24%)
Left chest only	30 (15%)
Neck only	3 (2%)
Left arm only	3 (2%)
Right chest only	1 (1%)
Right arm only	0 (0%)

Table 3-4 Locations of chest pain in ORBITA participants. Values indicate n (%).

Association between symptoms and change in exercise time

Noting that absence of evidence is not evidence of absence(58) in what follows, by “no interaction” I mean low statistical evidence against the supposition of no interaction, loosely translated as low evidence to support existence of interaction effects.

There was no interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on exercise time ($P_{interaction}$=0.411, $P_{interaction}$=0.87, $P_{interaction}$=0.406, $P_{interaction}$=0.301 and $P_{interaction}$=0.749 respectively) (Figure 3.2). Figure 3.2 with data points depicted is shown in Chapter 11 Appendices.

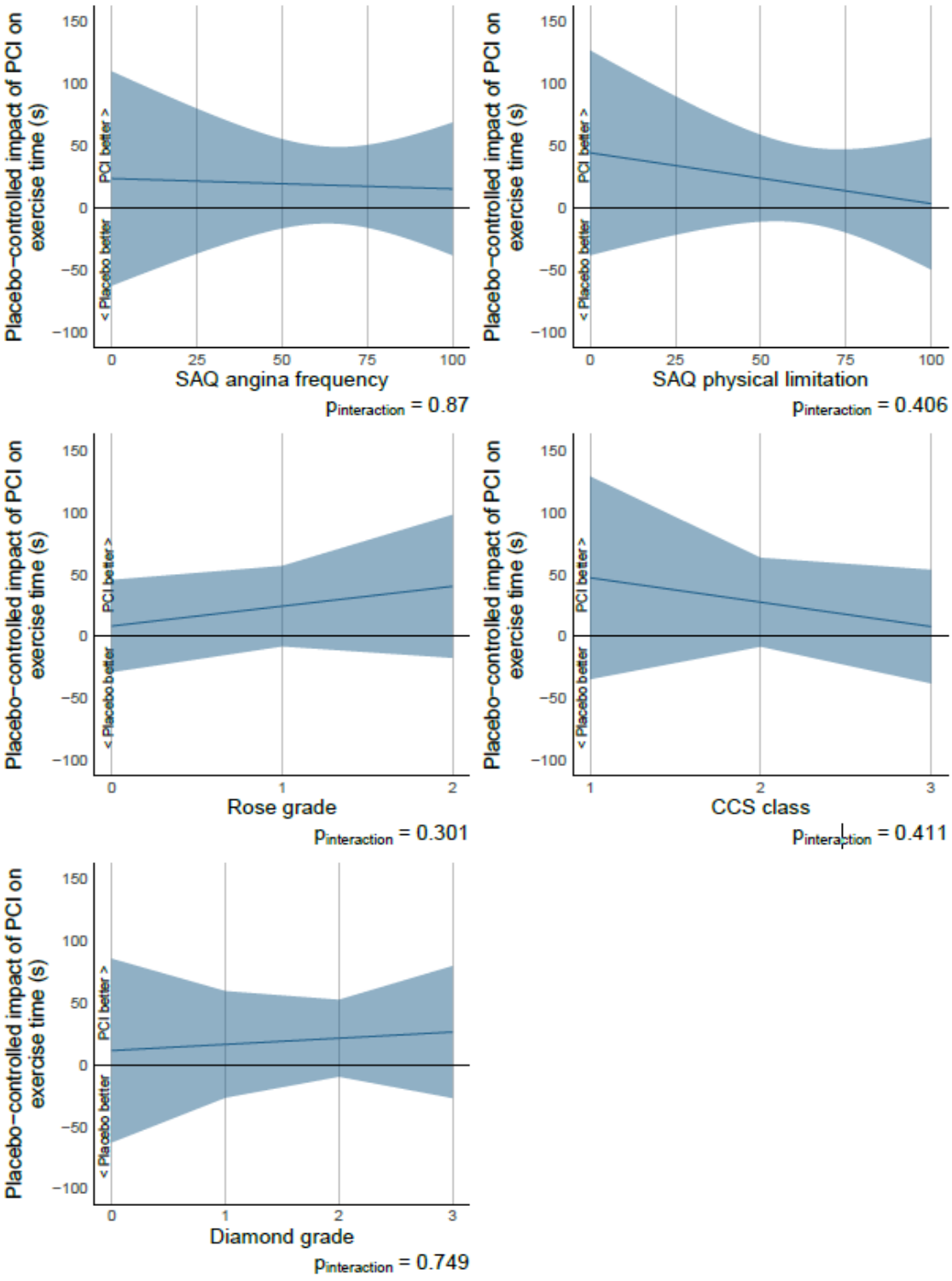

Figure 3.2 Interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on exercise time. Enrolment = prior to medical optimisation phase.

Association between symptoms and angina freedom

There was no interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on angina freedom ($P_{interaction}$=0.765, $P_{interaction}$=0.523, $P_{interaction}$=0.091, $P_{interaction}$=0.357 and $P_{interaction}$=0.739 respectively) (Figure 3.3).

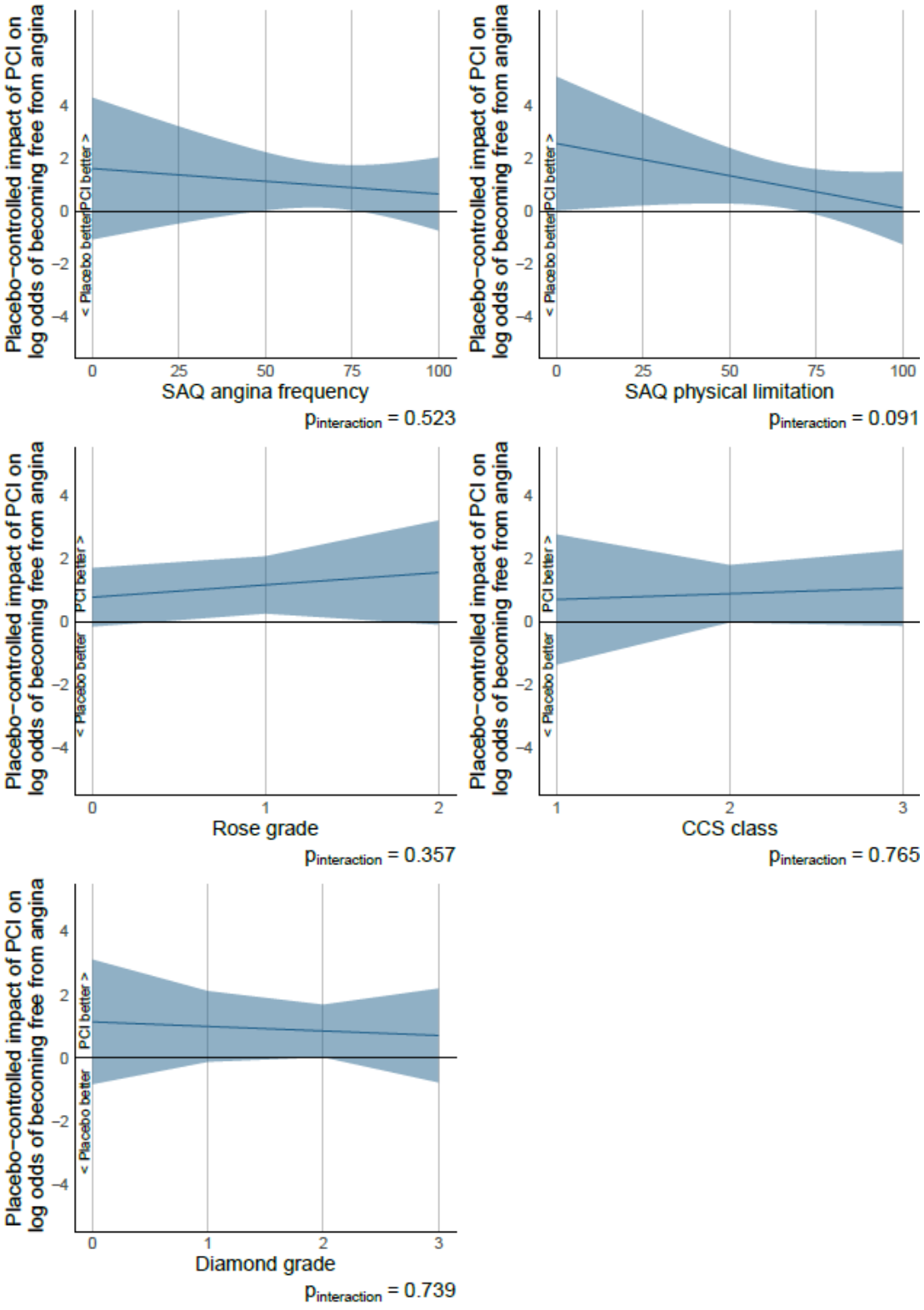

Figure 3.3 Interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on freedom from angina.

Association between symptoms and change in stress echo score

There was no interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on stress echo score ($P_{interaction}$=0.799, $P_{interaction}$=0.618, $P_{interaction}$=0.278, $P_{interaction}$=0.421 and $P_{interaction}$=0.15 respectively) (Figure 3.4).

Association between symptoms and enrolment stress echo score

Enrolment CCS class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade and enrolment Diamond grade were not correlated with enrolment stress echo score (rho = -0.055, p = 0.46; rho = -0.078, p = 0.3; rho = -0.11, p = 0.16; rho = -0.086, p = 0.24 and rho = 0.069, p = 0.36).

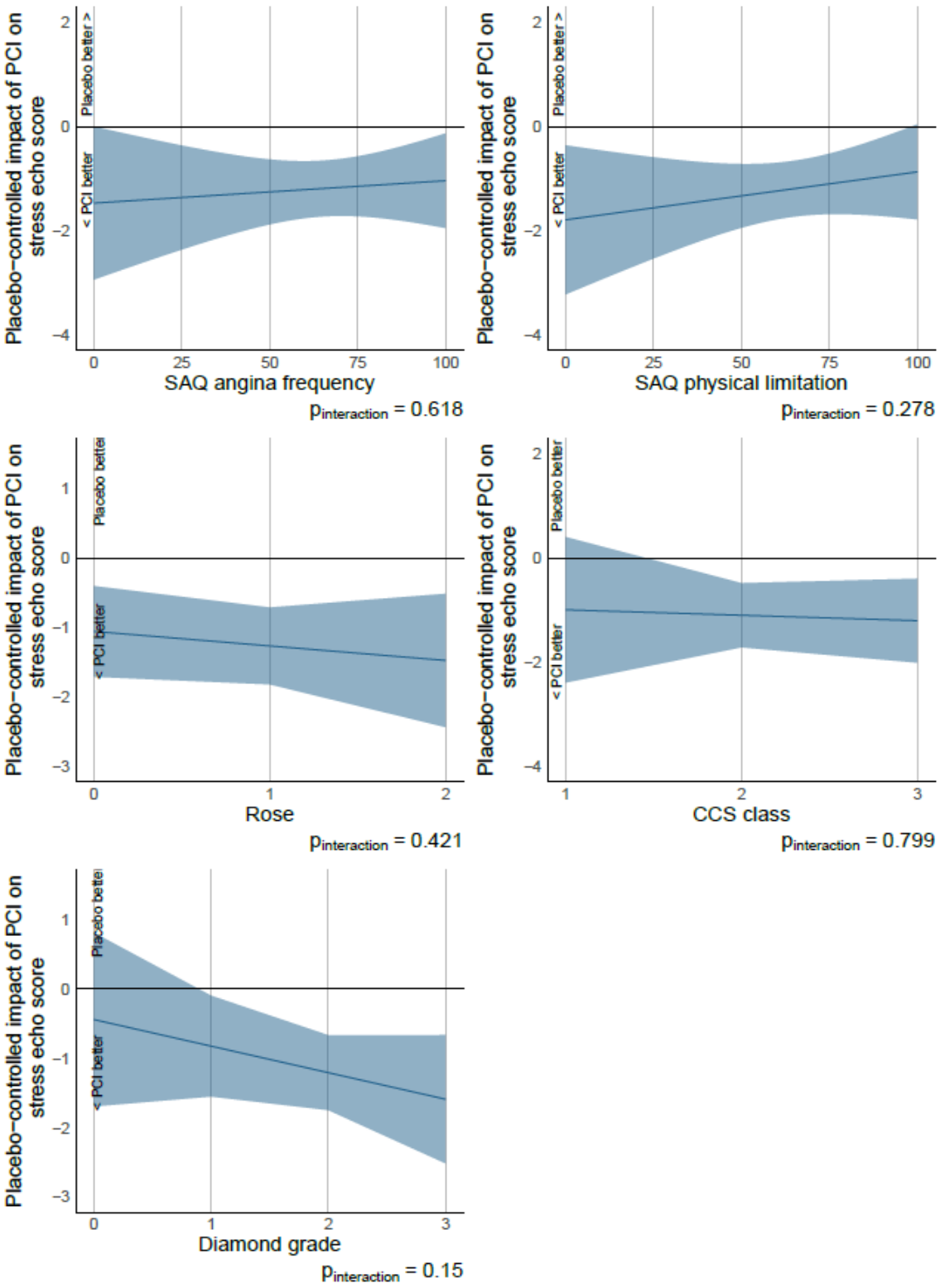

Figure 3.4 Interaction between enrolment CCS Class, enrolment SAQ angina frequency, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on stress echo score.

Association between symptoms and change in angina frequency

There was no interaction between enrolment CCS Class, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on angina frequency ($P_{interaction}$=0.696, $P_{interaction}$=0.874, $P_{interaction}$=0.29 and $P_{interaction}$=0.353 respectively) (Figure 3.5).

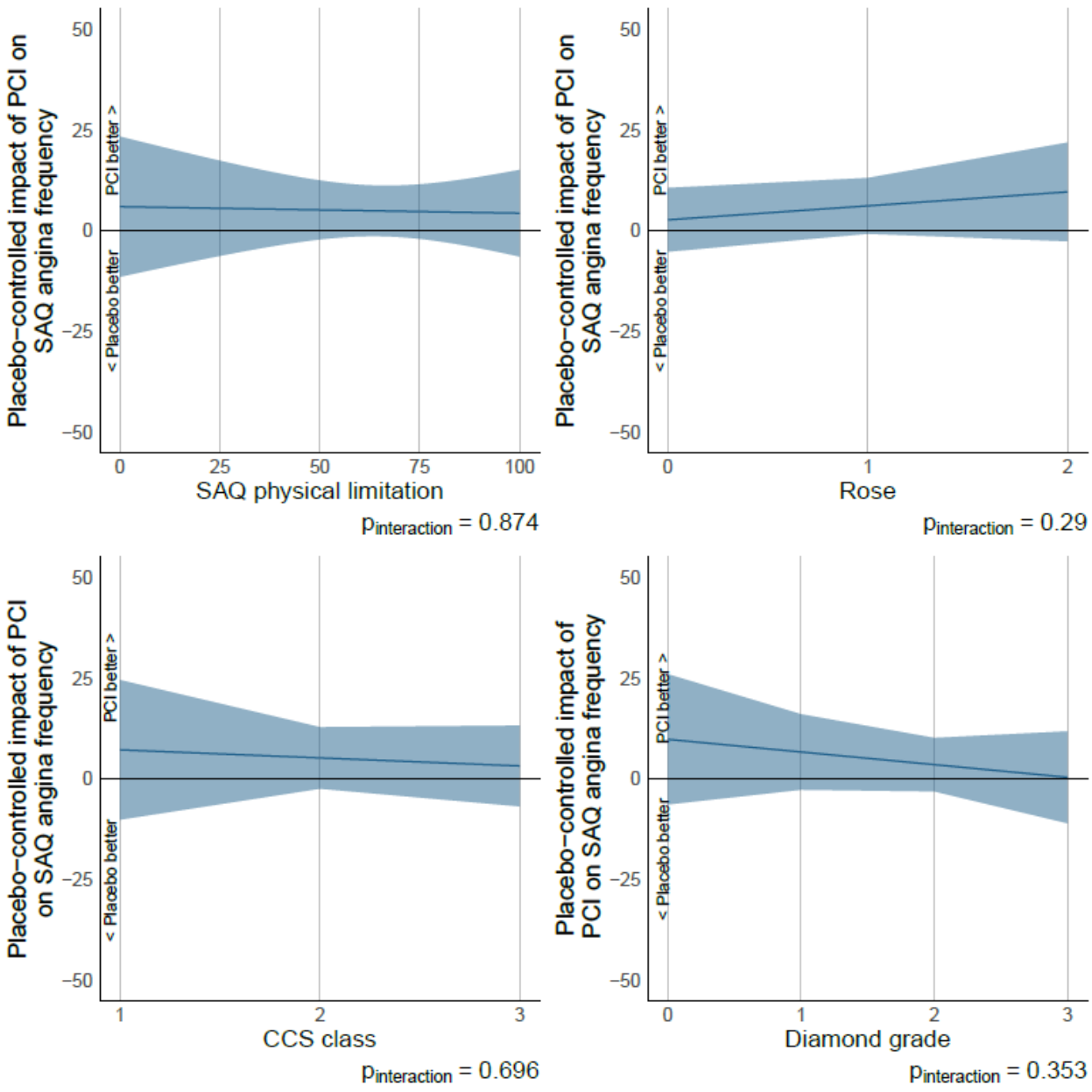

Figure 3.5 Interaction between enrolment CCS Class, enrolment SAQ physical limitation, enrolment Rose grade, enrolment Diamond grade and the effect of PCI on SAQ angina frequency.

Association between enrolment symptoms and change in symptoms

The enrolment SAQ angina frequency predicted the change in SAQ angina frequency (rho = -0.58, $p < 0.000001$, Figure 3.6). The enrolment CCS predicted the change in CCS (rho = -0.38, $p < 0.000001$, Figure 3.7). These regression to the mean effects are expected.

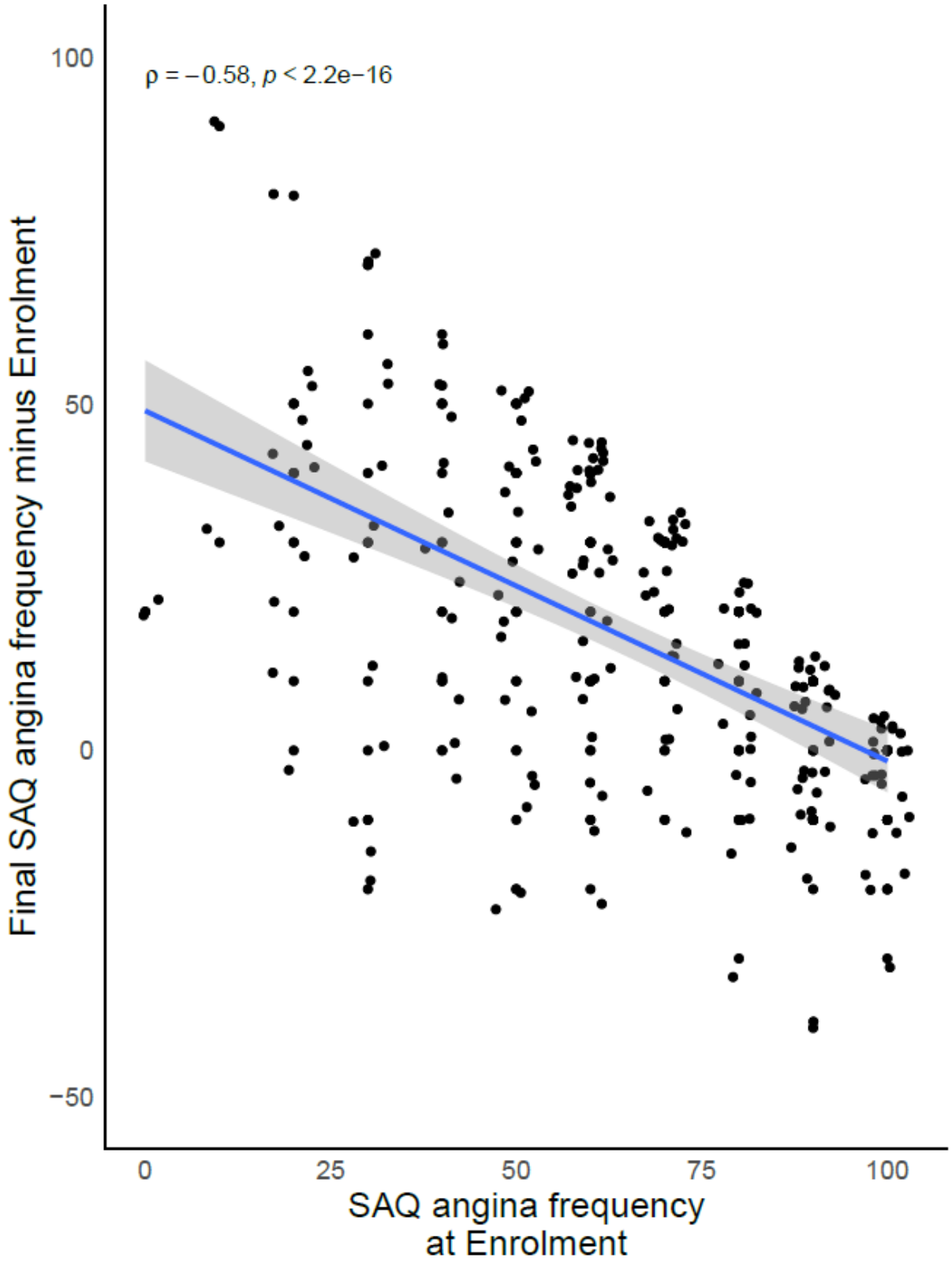

Figure 3.6 Association between Enrolment SAQ angina frequency and change in SAQ angina frequency in ORBITA

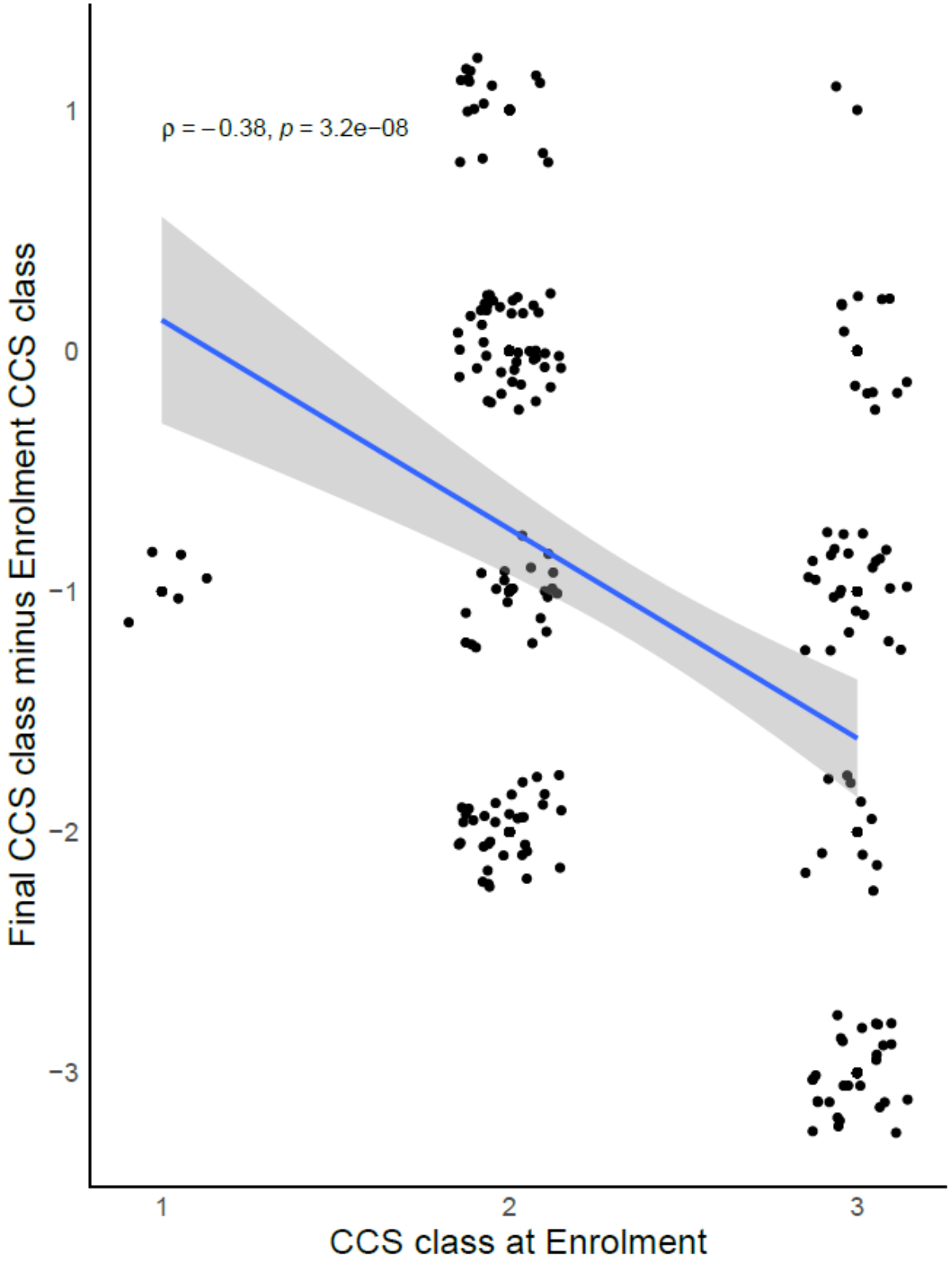

Figure 3.7 Association between Enrolment CCS Class and change in CCS Class in ORBITA

Discussion

These are novel placebo-controlled data looking at the relationship between the nature and intensity of symptoms and the efficacy of PCI in single-vessel coronary artery disease. Unexpectedly there was no convincing evidence for an interaction between more severe symptoms (the patient-reported SAQ or the physician-assessed CCS) or more typical symptoms (the patient-reported Rose or physician-assessed Diamond) and the placebo-controlled response to PCI (by the primary endpoint or three other endpoints).

The possible exception was SAQ physical limitation score which showed weak evidence for an interaction with the placebo-controlled impact of PCI on angina freedom.

Integration with the ISCHEMIA Trial

ISCHEMIA showed no difference in the primary endpoint of death from cardiovascular causes, MI, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest, but it showed an improvement in angina with an invasive strategy(6). In the conservative arm, SAQ angina frequency improved by approximately 11 units over 4 years of follow-up. The corresponding improvement in the invasive arm was approximately 14 units. The difference between these values represents the combination of the physical and placebo effects of the invasive strategy.

While both ORBITA and ISCHEMIA enrolled patients with stable coronary artery disease, ORBITA enrolled patients after angiography with single-vessel disease suitable for PCI, while ISCHEMIA enrolled patients before angiography and the revascularisation (received by 79% in the active arm) was either CABG or PCI. In general, more invasive procedures give larger placebo effects(27), and therefore it is likely that the placebo effect in ISCHEMIA was enhanced by CABG in the 26% of patients in the invasive arm who underwent revascularisation.

Spertus et al report that those with more angina at baseline in ISCHEMIA had a greater improvement in angina-related health status. This does not specifically represent symptoms being a predictor of benefit due to regression to the mean effects.

Integration with other stratified analyses of ORBITA

FFR and iFR did not predict symptom relief(40) measured by exercise time, angina freedom or SAQ. Stress echo score did not predict symptom relief measured by exercise or angina freedom but there was evidence of an interaction with the impact of PCI on SAQ angina frequency(21). Here I have shown that the nature of symptoms and intensity of symptoms were not predictors of symptom relief although there was weak evidence for SAQ physical limitation predicting the placebo-controlled effect of PCI on freedom from angina.

Taken together, these results do not provide a consistent narrative about different measures of angina. Stress echo score, exercise time, angina freedom, angina frequency and physical limitation should be intimately related to one another and therefore if there is an association with one (either as a predictor or an endpoint), associations would be expected with the others. However, this consistency was not observed.

Implications for assessment of symptoms in clinical trials

Symptoms are an expression of an experience by the patient. They are variable(59). The actual symptoms can be affected by physical activity, other medical conditions, emotions and mental health. Then the reporting of the symptoms can be affected by language, culture, and other social factors. Then the physician interprets this expression. Measuring or grouping symptoms that arise in this multi-level pathway is challenging.

The SAQ uses five domains to assess angina. It has been extensively validated as described in Chapter 1. However, in clinical practice it is not only angina frequency or severity that is used to judge whether to advise intervention: it is the nature of symptoms too.

Trials can assess the nature of symptoms by the Rose questionnaire and the Diamond criteria. The Rose questionnaire assesses several features of angina (Figure 3.1) but its most challenging hurdle is the location. To be acceptable in the Rose grading as even “possible angina”, symptoms must be present in either the sternal area, or in both the left arm and left chest(53). In clinical practice, it is conventional to consider a much wider array of symptoms to be angina, including heaviness or pressure (rather than only pain or discomfort). More importantly, as long as symptoms are exertional, clinical practice accepts a much wider array of locations as typical angina, including left arm alone, left chest alone and neck or jaw alone: all of these would be rejected as “no angina” in the Rose system. It is not known in other trials such as COURAGE and ISCHEMIA, what the distribution of Rose and Diamond results would have been, had they been evaluated.

There are many other ways to assess and classify symptoms as well as more sophisticated methods especially now that technology such as video and audio recording and analysis is so readily available. However, it is not clear what type of assessment will provide the most useful information pertaining to the role of intervention.

Clinical implications

PCI is invasive and expensive so it would be useful to be able to know the likelihood of benefit for symptom relief. This would provide information for patients and clinicians to make decisions about intervention.

The data presented in this chapter indicate that neither nature, frequency or severity of symptoms predicted the placebo-controlled efficacy on any of the endpoints in patients with symptoms, a severe coronary artery lesion and (in 94%) one or more positive ischaemic test. Therefore it is unlikely that in clinical practice that these parameters could be used to judge whether intervention on such a lesion would provide a benefit beyond placebo. Clinical experience will often contradict this, in part because this experience is unblinded. Clinical experience lacks a placebo comparison so cannot separate a physical benefit from placebo effect, spontaneous regression, or improvement due to other interventions e.g. medication, increase in fitness, changes in activity, treatment of anaemia.

Study limitations

The placebo-controlled effect on exercise time in ORBITA was small. This may limit the power of these analyses to detect variation in exercise time effect between the strata of symptoms. However, if a two hundred patient study does not find a clear link between symptoms and benefit then it is unlikely that the common clinical experience that response is linked to symptoms is reflecting the actual physical effect of PCI (as opposed to the placebo effect).

This study was restricted to patients with single vessel coronary artery disease. One could argue that an association between symptoms and effect of PCI would be revealed in a study including patients with greater SAQ physical limitation scores, for example in mutli-vessel disease. This will be assessed in the ongoing ORBITA-2 study(60).

Assessment of the nature of symptoms was limited to Rose and Diamond. In the ongoing ORBITA-STAR study(61) the nature of symptoms will be explored through additional assessments including the McGill Pain Questionnaire and audio and visual descriptions by patients in a semi-structured interview format.

Symptoms were assessed at enrolment and at pre-randomisation. Between these 2 timepoints, patients underwent a 6 week medical optimisation phase with anti-anginal medication introduction and uptitration. This had an impact on the mean CCS class, and SAQ and Rose (Table 3.5 and 3.6). The data at enrolment were used for this analysis as they are more representative of patients that are encountered in clinical practice. For completeness, we repeated the analyses using the pre-randomisation data and found no significant difference in results (Table 3.7).

Microvascular physiology was not measured in the ORBITA trial. Patients with significant epicardial disease commonly have concomitant microvascular disease and this may have contributed to the symptoms reported. However, randomisation, placebo-control and blinding should have distributed this effect equally between groups.

	Enrolment (n=200)	Pre-randomisation (n=200)
CCS class I	5 (3%)	22 (11%)
CCS class II	118 (59%)	25 (13%)
CCS class III	77 (39%)	97 (49%)
CCS class IV	0 (0%)	56 (28%)

Values indicate n (%). CCS = Canadian Cardiovascular Society

Table 3-5 CCS class at enrolment and after 6-week optimisation phase.

	Enrolment (n=197)	Pre-randomisation (n=200)
Rose grade 0	115 (58%)	119 (60%)
Rose grade 1	36 (18%)	52 (26%)
Rose grade 2	46 (23%)	29 (15%)
SAQ angina frequency	70 (50-90)	80 (60-90)
SAQ physical limitation	67 (44-86)	72 (56-89)
Diamond asymptomatic	16 (8%)	13 (7%)
Diamond non-cardiac chest pain	37 (19%)	47 (24%)
Diamond atypical	114 (58%)	107 (54%)
Diamond typical	33 (17%)	33 (17%)

Values indicate n (%) or median (IQR). IQR = Interquartile Range, Rose = Rose Angina Questionnaire, SAQ = Seattle Angina Questionnaire

Table 3-6 Rose, SAQ and Diamond at enrolment and after 6-week optimisation phase.

	Exercise time	Angina freedom	Stress echo	SAQ angina frequency
CCS class	$P_{interaction}$=0.487	$P_{interaction}$=0.578	$P_{interaction}$=0.485	$P_{interaction}$=0.109
SAQ angina frequency	$P_{interaction}$=0.870	$P_{interaction}$=0.808	$P_{interaction}$=0.585	N/A
SAQ physical limitation	$P_{interaction}$=0.665	$P_{interaction}$=0.868	$P_{interaction}$=0.391	$P_{interaction}$=0.349
Rose grade	$P_{interaction}$=0.899	$P_{interaction}$=0.532	$P_{interaction}$=0.428	$P_{interaction}$=0.621
Diamond grade	$P_{interaction}$=0.190	$P_{interaction}$=0.739	$P_{interaction}$=0.151	$P_{interaction}$=0.100

Table 3-7 Pre-randomisation symptoms and the impact of PCI on exercise time, angina freedom, stress echo and SAQ angina frequency.

Conclusions

There was no apparent evidence that either the nature or intensity of symptoms predicted the placebo-controlled efficacy of PCI in single-vessel coronary artery disease. These data do not support the use of these symptom features to guide treatment. The link between coronary stenosis and symptoms of angina requires further study.

Chapter 4 Inter-relationships between Ischaemic Tests and Prediction of Placebo-controlled Response to PCI in ORBITA

Abstract

FFR is recommended in guidelines for decision-making in PCI. The original mapping of FFR was based on multiple ischaemic tests in 45 patients treated dichotomously. The ORBITA dataset provides an opportunity to compare FFR to multiple ischaemic tests within a larger sample of patients under rigorous conditions.

194 randomised participants in the ORBITA study had an FFR measurement. In this analysis I examine the association between intracoronary pressure indices and results of exercise testing and stress echocardiography, treated both dichotomously and continuously.

In the dichotomous assessment, one or both of the noninvasive tests detected ischaemia in 78/112 (70%) of participants with FFR <0.75, versus 40/82 (49%) of those with FFR ≥ 0.75. On this basis, the sensitivity of FFR in identifying ischaemia was 64%, specificity 56%, positive predictive value 70%, negative predictive value 43%, and accuracy 62%.

In the continuous assessment, FFR was correlated with iFR ($r = 0.9$, $p < 0.0001$), stress echo score ($r = -0.3$, $p < 0.0001$), exercise time ($r = -0.25$, $p = 0.00037$), and QCA area ($r = -0.6$, $p = p < 0.0001$). These continuous markers all predicted the placebo-controlled impact of PCI on stress echo score. However, only stress echo score was a significant predictor of placebo-controlled efficacy of PCI on SAQ angina frequency.

Under blinded conditions, a dichotomous classification of FFR is not as closely associated with non-invasive ischaemia tests as previously assumed. The associations are much clearer when variables are treated continuously. While there is considerable commonality between ischaemia tests, their association with placebo-controlled efficacy of PCI is surprisingly weak.

Introduction

Ischaemic heart disease remains the top cause of death in the UK and worldwide(62). Percutaneous coronary intervention (PCI) prevents death in acute coronary syndrome but its role in stable coronary artery disease is under scrutiny.

Invasive assessment of ischaemia is growing in use for the immediate assessment of the physiological significance of coronary stenoses seen at angiography. The landmark study calibrating Fractional Flow Reserve (FFR) against standard non-invasive ischaemia tests was carried out in only 45 patients.

The initially reported sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FFR in detection of ischaemia were 88%, 100%, 100%, 88%, and 93% respectively.

Myocardial ischaemia is defined as insufficient blood flow to the myocardium. Most tests for ischaemia do not directly measure this reduction in blood flow(63). Instead they measure a proxy for ischaemia such as a pressure drop (FFR) or a consequence of ischaemia (e.g. perfusion abnormalities on MRI, or regional wall motion abnormalities on stress echo). Absolute coronary flow can be measured invasively in the cath lab but this is not routinely performed.

Stress echo was originally calibrated against the presence of stenoses on invasive coronary angiography. It was established as a technique for detecting coronary artery disease, rather than a measure of ischaemia per se. This raises the question of what to use as a reference standard for assessing these different measurements. Even though imaging was used to validate FFR originally, FFR has also been used in the COMPRESS trial as a reference standard to assess stress echo and SPECT(64) and in a meta-analysis comparing SPECT, stress echo, invasive coronary angiography, CTCA, CTFFR, and MRI(65).

FFR is the ratio of mean distal coronary pressure to mean aortic pressure during pharmacologically induced coronary vasodilatation(63). FFR is known to correlate moderately well with dobutamine stress echocardiography in moderate coronary stenoses(66). However clinical practice often finds discrepancies between FFR and other ischaemic tests(67). Not all patients undergo non-invasive imaging prior to attendance to the cath lab so FFR carries a key advantage of providing an assessment of severity of a stenosis prior to intervention. Some have argued that it is costly and time-consuming. iFR correlates with FFR and has been found to be non-inferior in predicting events(35) and has the advantage of not requiring pharmacological vasodilation which saves time and is often more comfortable for the patient. In a 129-patient study, FFR, iFR, and Pd/Pa had a similar performance compared with PET imaging(68).

A hybrid approach using a combination of anatomical and functional assessment has been assessed (either SPECT and CTCA or PET and CTCA) but this did not enhance overall diagnostic accuracy(69).

In this Chapter I look at how indices of ischaemia, symptoms and anatomy relate to each other. Making decisions based on thresholds in measured biological variables may be flawed(70). I use data from the 194 participants in ORBITA to re-assess the diagnostic performance of FFR in the modern era. I take the opportunity to handle the ischaemia tests not only as dichotomous variables but also as continuous variables.

Methods

Participants

This Chapter describes a substudy of ORBITA, the first placebo-controlled trial of PCI in stable single-vessel coronary artery disease. It addresses all ORBITA participants who had a pre-randomisation FFR measurement.

Assessed variables

Before randomisation, participants underwent FFR, iFR and QCA as previously described(9). Before randomisation and at follow-up, participants underwent questionnaires, exercise testing(9) and stress echo. Stress echo score was calculated as previously described(21).

Continuous analysis

FFR, iFR, QCA and SAQ, were available for analysis as continuous variables.

From the exercise test I extracted two continuous variables: exercise time and Duke Treadmill Score which incorporates exercise time, degree of ST depression and a symptom score(71).

Stress echo score is a continuous variable as described previously(21). This uses 6 observers each reporting the case twice, blinded to the other reports and to the arm and timepoint. The 12 independent reports are each on a scale which begins at 0 for normal. 1 represents 1 hypokinetic segment. 2 represents 2 hypokinetic segments or 1 akinetic segment, and so on. This means that the score is approximately the number of hypokinetic segments, although akinetic and dyskinetic segments count double or treble. The 12 independent values are then

averaged to form the stress echo score. A value of 1 indicates that on average the 12 reports rated it as having 1 hypokinetic segment.

Dichotomous analysis

FFR was dichotomised as positive if ≤0.75, iFR if <0.9, QCA area if <90%, and stress echo score if ≥1. Exercise testing was considered positive if there was ST depression of ≥0.2mV.

Statistical Analysis

Summary statistics are presented using mean (standard deviation) or median (interquartile range) as appropriate.

The association between pre-randomisation variables was measured using Spearman's rank correlation coefficient rho.

The ability of QCA to predict placebo-controlled efficacy of PCI was tested using the non-linear regression approach as previously described(21,40) and applied to iFR, FFR and stress echo.

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for FFR were calculated in the standard manner against the other ischaemia tests.

Results

Of the 200 randomised participants in ORBITA, 194 had an FFR measurement. Of the remaining 6, the lesion could not be crossed with the pressure wire in 3, crossing of the lesion with the pressure wire caused intimal disruption requiring immediate PCI in 1, and a hyperemic response with intravenous or intracoronary adenosine could not be elicited in 2. In 191 of the 194, the pre-randomisation exercise test was available for analysis. 183 of the 194 had a pre-randomisation stress echo. All 194 had an iFR measurement.

Association between dichotomised pre-randomisation variables and FFR

In the dichotomous assessment, one or both of the noninvasive tests detected ischaemia in 78/112 (70%) of participants with FFR <0.75, versus 40/82 (49%) of those with FFR ≥ 0.75.

Figure 4.1 shows the range of FFR values at which 4 variables (iFR, exercise test, stress echo, and QCA) are positive and negative. iFR is the only variable in which there is an apparent threshold of FFR below which very few patients have a negative iFR. For the other variables, there is no apparent threshold of FFR below which patients are unlikely to have a negative result.

The sensitivity of FFR in identifying ischaemia (seen on either exercise test, stress echo or both) was 64%, specificity 56%, positive predictive value 70%, negative predictive value 43% and accuracy 62%.

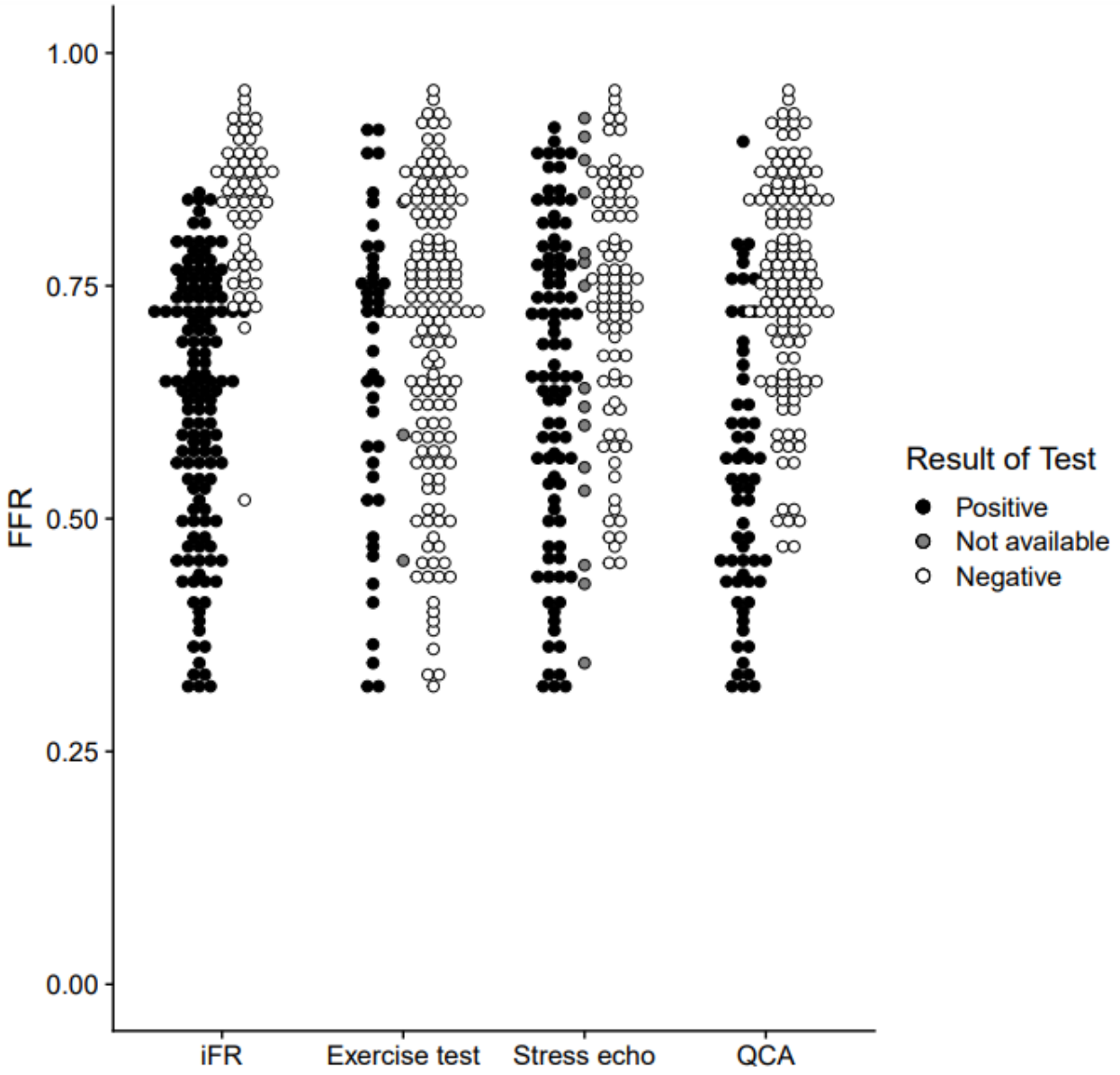

Figure 4.1 Relationship between dichotomised pre-randomisation variables and FFR.

Association between continuous pre-randomisation variables and FFR

In the continuous assessment (Figure 4.2), FFR was correlated with iFR (rho = 0.9, $p < 0.0001$), stress echo score (rho = -0.3, $p < 0.0001$), exercise time (rho = -0.25, $p = 0.00037$), and QCA area (rho = -0.6, $p < 0.0001$). FFR was not correlated with any variables relating to symptoms: Duke Treadmill Score, SAQ angina frequency and SAQ physical limitation (rho = -0.012 $p = 0.86$, rho = -0.043 $p = 0.55$, rho = -0.062 $p = 0.39$).

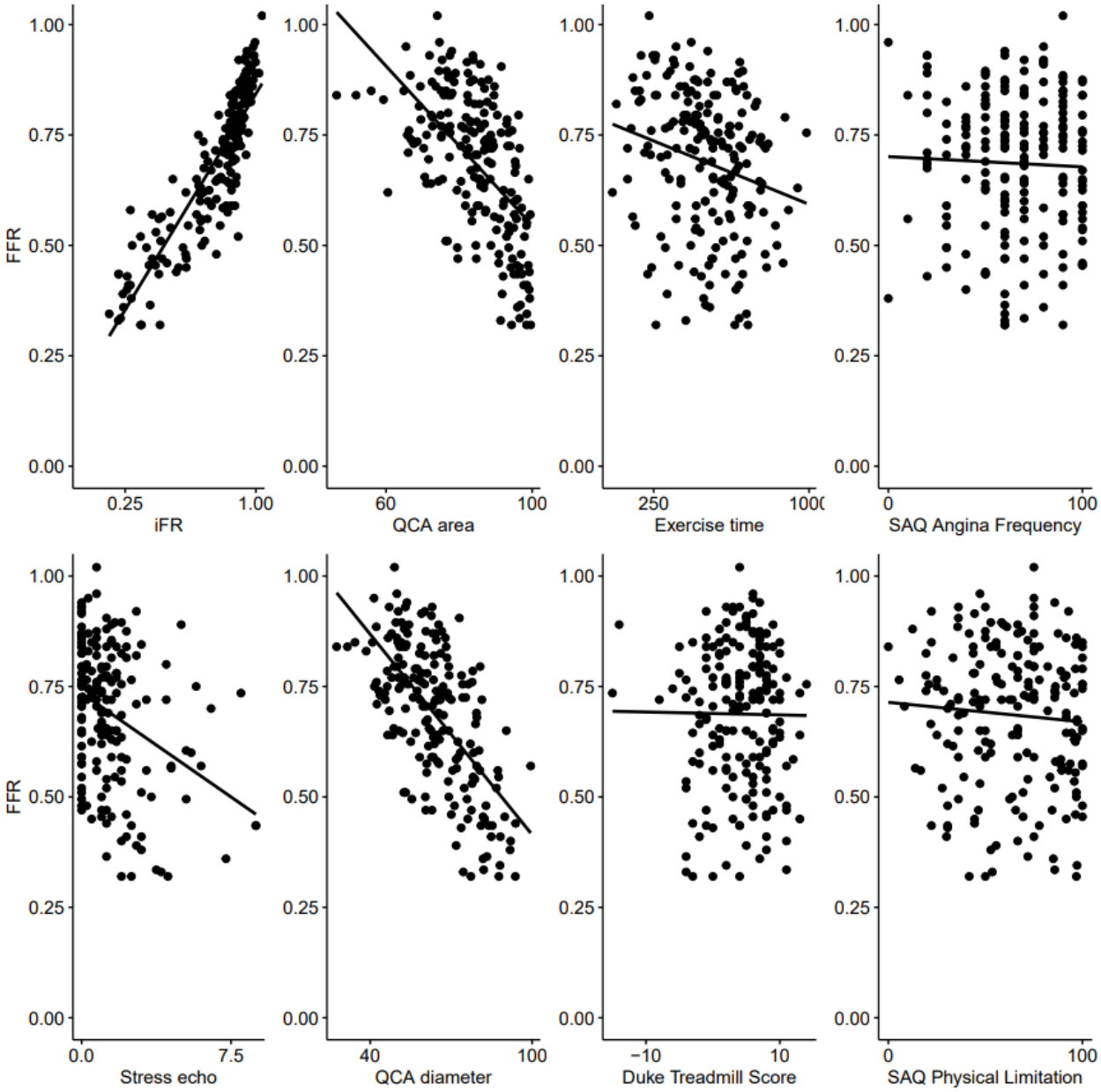

Figure 4.2 Relationship between pre-randomisation variables and FFR.

Association between continuous pre-randomisation variables and the placebo-controlled impact of PCI on clinical response variables

The associations between FFR, iFR, stress echo and response variables (including function, ischaemia and symptoms) in ORBITA have been published previously(21). The association between QCA and five clinical response variables are shown for the first time in Figure 4.3 - 4.7. FFR, iFR, and QCA all strongly predicted the placebo-controlled impact of PCI on stress echo, but not on any other response variables.

Pre-randomisation stress echo score(40) but not iFR or FFR(40) predicted the placebo-controlled impact of PCI on SAQ angina frequency. The relationship between QCA and the placebo-controlled impact of PCI on SAQ angina frequency is shown for the first time in Figure 4.5. There was no significant prediction.

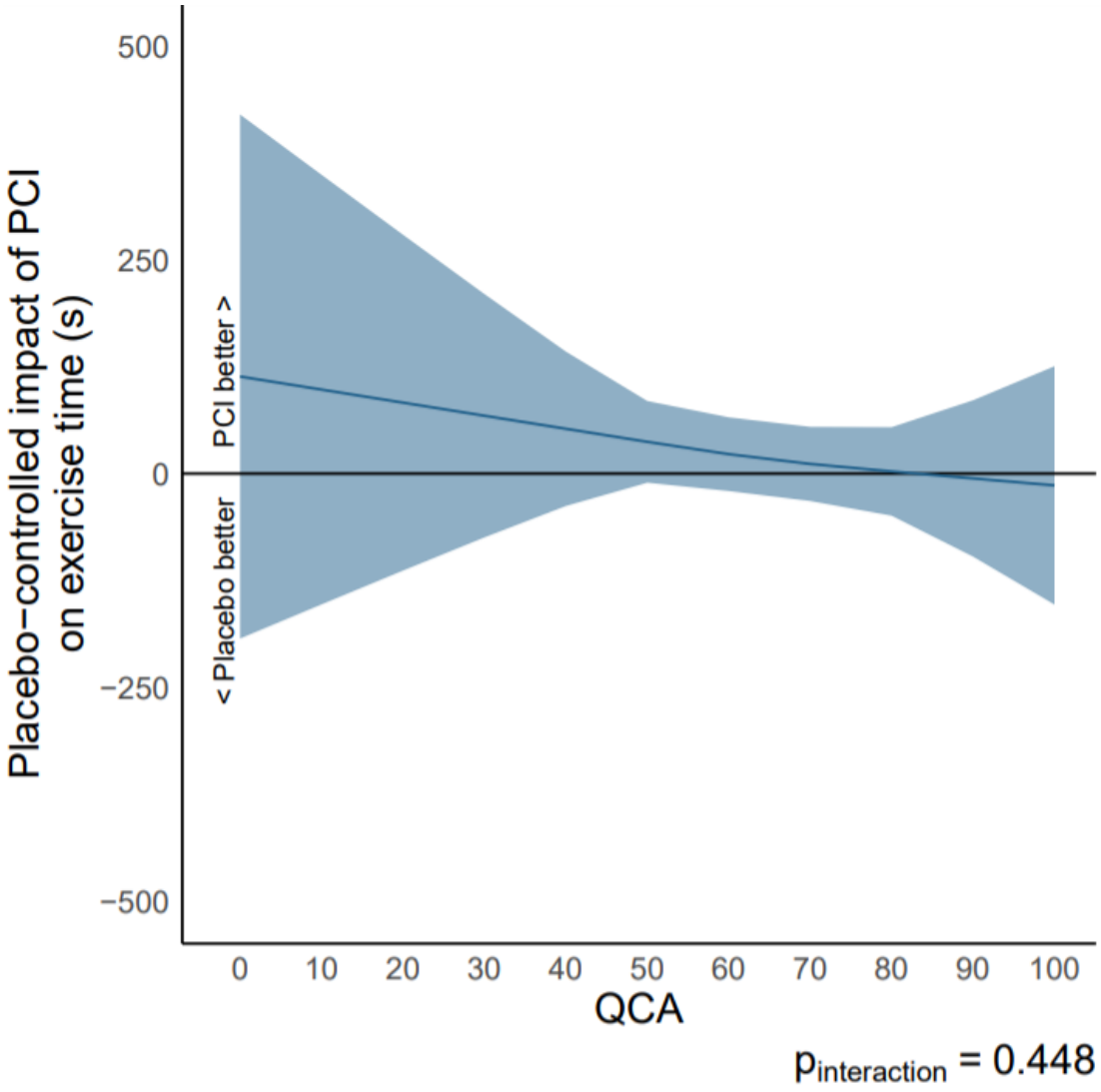

Figure 4.3 Relationship between QCA and placebo-controlled effect of PCI on exercise time.

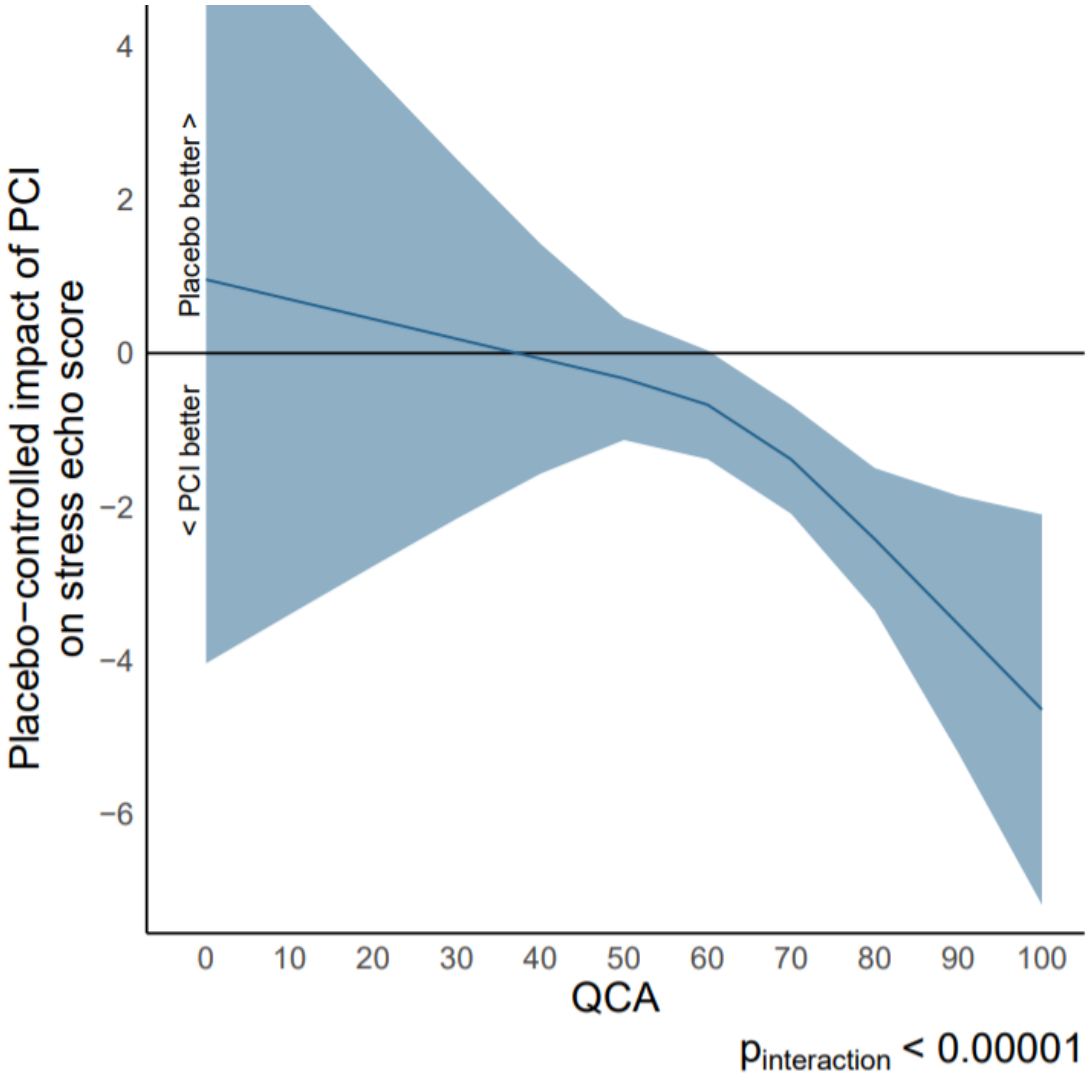

Figure 4.4 Relationship between QCA and placebo-controlled effect of PCI on stress echo score.

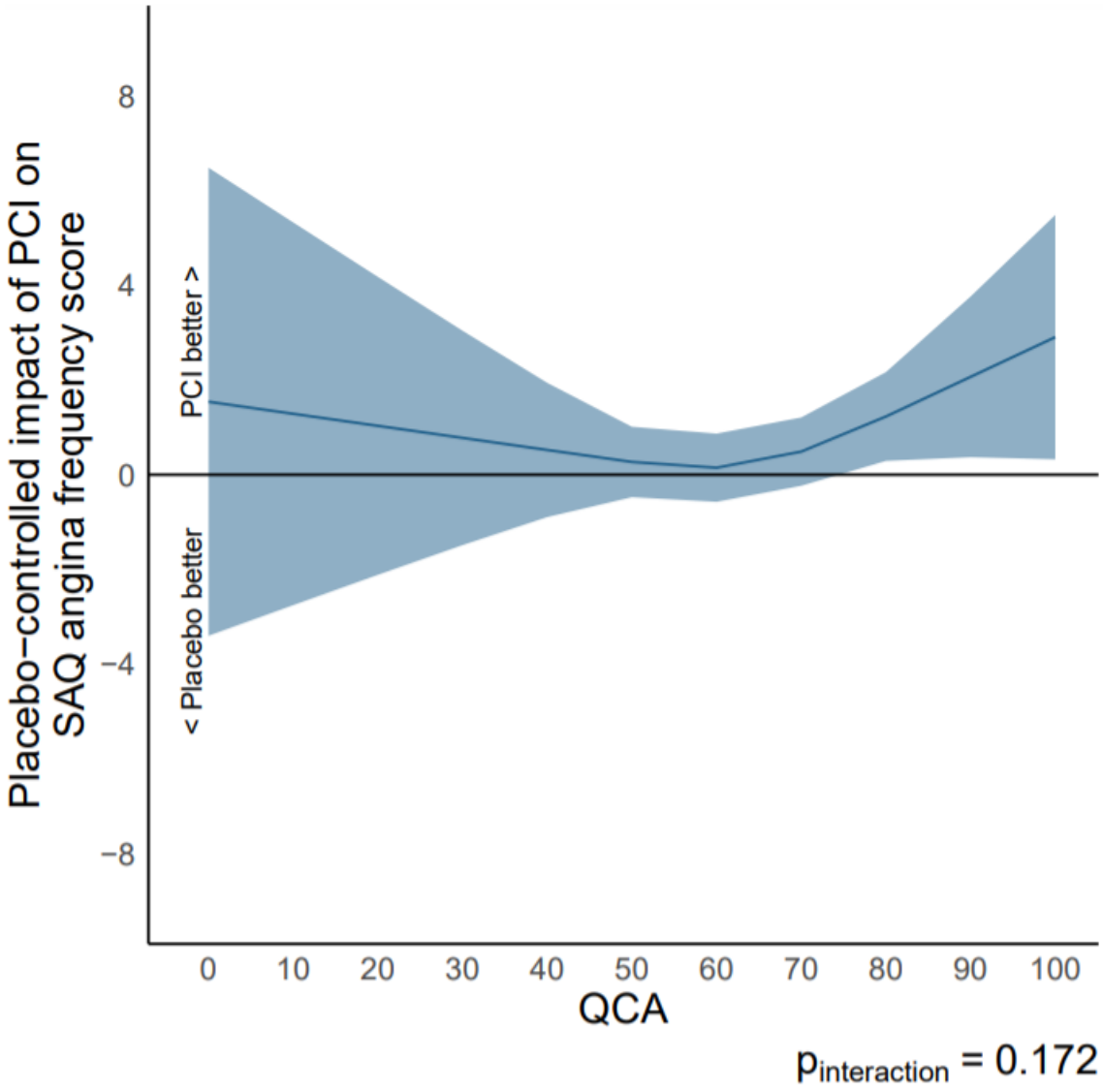

Figure 4.5 Relationship between QCA and placebo-controlled effect of PCI on SAQ angina frequency.

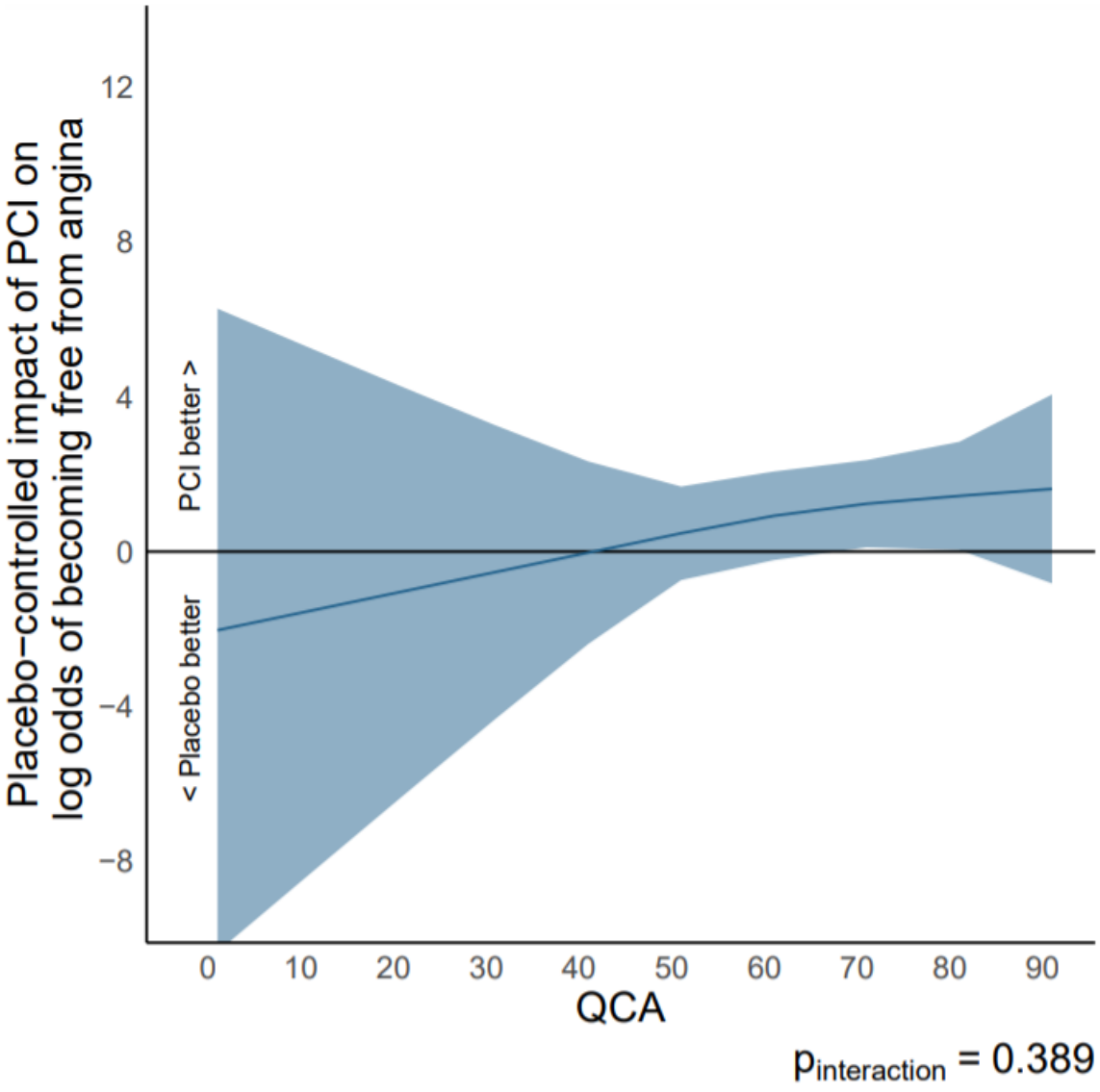

Figure 4.6 Relationship between QCA and placebo-controlled effect of PCI on freedom from angina.

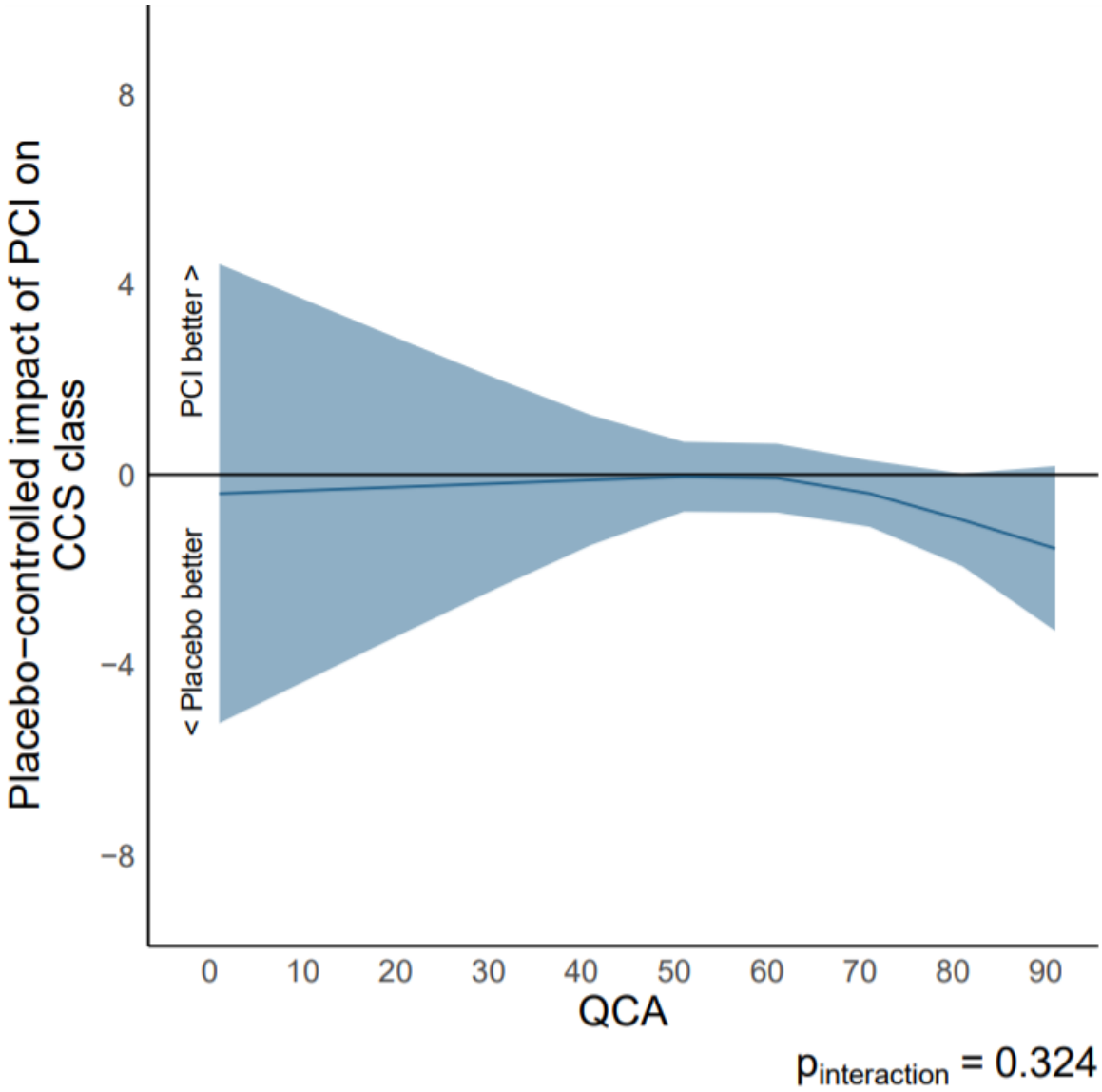

Figure 4.7 Relationship between QCA and placebo-controlled effect of PCI on CCS class.

Discussion

In this examination of the inter-relationships of ischaemic indices, symptoms and anatomy, there were three main findings. First, the dichotomous relationship between FFR and other ischaemia tests is not as close as previously suspected. Second, continuous interpretation of FFR correlates with noninvasive indices of ischaemia (stress echo and exercise time) and anatomical stenosis (as assessed by QCA). Third, the continuous markers FFR, iFR, stress echo, and QCA did not predict the placebo-controlled benefit of PCI on exercise time or any of the symptom endpoints except for stress echo score predicting the SAQ angina frequency benefit (results published previously(21)). However, the continuous markers, FFR, iFR, exercise time and QCA, each predicted the placebo-controlled impact of PCI on stress echo score.

Utility of FFR as a measure of ischaemia

FFR is richly informative as a continuous variable, accessible immediately within the catheter laboratory. The correlations show it to be a bridge between, on the one hand, anatomical lesion severity (QCA, rho = -0.6, $p < 0.0001$) and, on the other hand, impact on function of the organ (stress echo score, rho = -0.3, $p < 0.0001$) and the whole body (exercise time, rho = -0.25, $p = 0.00037$). It is convincingly on the causal path of ischaemia since it predicts the placebo-controlled impact of PCI on stress echo score ($p_{interaction} = 0.03$).

Applying a threshold, however, dramatically weakens the informativeness of FFR. Dichotomous FFR shows a surprisingly weak agreement with non-invasive ischaemia tests. Accuracy was 62%, some distance from the values reported from the various analyses of the landmark 45 patient dataset(31), which were 93%, 99%(72) and approaching 100%(73).

Dichotomisation of any biological variable tends to have two undesirable effects(74). First, it trims even a very rich information source down to a single binary digit. Second, the trimmed

result forces the management of a patient with an FFR of 0.79 to be driven by results in patients with an FFR of 0.5 and not by patients with an FFR of 0.80.

The best way to identify a true threshold for treatment is to randomise patients across a spectrum of values and measure the ability of that value to predict the treatment effect(75). Even when there is a strong biological plausibility for a test to predict treatment effect, the true gradient of that relationship is often surprisingly weak. None of the expected predictors of benefit predicted placebo-controlled increment in exercise capacity in ORBITA. On an endpoint which was more local to the heart, namely stress echo score, all of them provided significant predictions: FFR and iFR as previously reported(40) and QCA as reported here. Nevertheless, while the slope of the prediction was statistically significant (i.e. distinctly beyond chance) it was weak.

Clinical implications

This study confirms FFR as an index, accessible immediately in the catheter laboratory, of the impact of a lesion on the function of the heart and of the patient. However, the power of FFR comes from the wide range of values it can distinguish. Very low values give useful information that the stress echo and exercise test are likely to show large abnormalities. More importantly they give a powerful indication that the stress echo score is likely to be markedly improved by PCI. Cropping the richness of FFR to a single bit destroys most of its informativeness, because it can no longer highlight extreme values as distinct from the far more numerous middling values(75).

Study limitations

This analysis only addresses the 194 patients who had an FFR measurement in ORBITA. There is potential for bias if the remaining 6 patients differ in some way. It is also possible that 6 weeks

of follow-up was insufficiently long to observe the impact of PCI on symptoms. However, when PCI is conducted, anatomical relief and normalisation of FFR and iFR is immediate and normalisation of the stress echo had already occurred by 6 weeks. ORBITA did not use nuclear stress testing. This is because in the UK, almost all stress testing is conducted without radionuclides.

The results of ORBITA have been presented stratified by symptoms and QCA in this thesis and by FFR, iFR, and stress echo previously. Simultaneous within patient measurement of these variables also allows the ORBITA participants to be classified by the concordance between these variables. Defined as positive FFR, iFR, QCA, stress echo and exercise test, only 9 participants were concordant. Therefore I did not perform an ischaemia-concordance-stratified analysis of the effect of PCI on the outcome measures in ORBITA. The low proportion of patients with fully concordant tests does not imply that the participants did not have ischaemia. Instead it highlights the loss of power of the ischaemic tests when classified as positive or negative as is often done in clinical practice and in head to head comparisons of multiple ischaemic tests.

Conclusions

FFR is a richly continuous measure of ischaemia and is accessible immediately in the catheter laboratory. However when trimmed to a dichotomy, its agreement with other indicators is surprisingly poor. This may be because most patients are close to the middle of the range, and therefore being grouped with either the very low values or the very high values, based solely on the accident of being on one or other side of a threshold.

Chapter 5 Design and Rationale of a Placebo-controlled Trial of PCI for the Relief of Stable Angina without Anti-anginal Medications (ORBITA-2)

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 anti-anginal therapy. ORBITA-2 will assess the placebo-controlled efficacy of PCI on angina health status, in patients with single or multivessel disease, at 12 weeks, on no anti-anginal 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 ischemia, (iv) single or multivessel disease, and (v) clinical eligibility for PCI.

At enrolment, anti-anginal medications will be stopped and angina questionnaires completed. Participants will record their symptoms on a smartphone application daily throughout the trial and undergo exercise treadmill testing and stress echocardiography prior to randomisation. They will 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 questionnaire, exercise testing and stress echocardiography assessment. If angina becomes

intolerable, anti-anginal medications will be introduced using a pre-specified medication protocol.

The primary outcome is 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.

Introduction

For stable coronary artery disease, PCI is principally performed to relieve angina. More than 500,000 PCI procedures are performed annually worldwide for stable coronary artery disease(76). The results of over 14,000 patients randomised to an invasive versus a conservative strategy, followed up for 4.5 years, show no evidence of net reduction in mortality(3,6,7,77). ORBITA did not find a placebo-controlled benefit of PCI on exercise time. This was in contrast with unblinded clinical experience and trials. The contrasting results may be due to placebo effects, because the true physical efficacy of PCI may be smaller than expected, and because the link between stenosis, ischaemia, symptoms and exercise time is likely to be more complex than previously thought.

However, there are several reasons why ORBITA may not have provided the definitive picture. In this Chapter I will describe the development of a trial protocol for a subsequent randomised controlled trial of PCI to address these issues ORBITA-2(60).

ORBITA enrolled patients with single vessel disease, to allow the effect size to be later regressed(40) against the severity of the lesion. It is not known whether symptom relief would have been greater in patients with multi-vessel disease. ORBITA-2 will enrol patients with both single and multi-vessel disease. ORBITA excluded many patients with multi-vessel disease who were eligible for PCI. Including this broader range of patients has three advantages. It will increase the relevance of the findings to the general population of patients with angina, it will enable stratification of results based on disease characteristics, and more patients will be eligible to participate which will help recruitment rates.

ORBITA participants received maximally tolerated anti-anginal medication. 97.5% were taking at least two anti-anginal medications(78). The ORBITA protocol mandated this anti-anginal strategy to test the guideline-directed incremental effect of PCI on a background of anti-anginal

therapy. This may have attenuated the potential benefit of PCI. Additional therapies in medicine often show diminishing returns. This was seen in anti-anginal therapy trials; as additional therapies were added to treatment, the symptomatic benefit decreased. For example, in the MARISA trial, ranolazine monotherapy increased exercise time by up to 55 seconds above placebo(79). In the counterpart CARISA trial, where ranolazine was added to another anti-anginal, the incremental benefit was only 24 seconds(80). ORBITA-2 will measure the placebo-controlled effect of PCI off regular anti-anginal medications with a protocol for managing subsequent stopping and starting of agents. The need to restart medications could influence angina frequency and severity even though randomisation and blinding should limit any bias. ORBITA-2 will deal with this by strict adherence to the protocol, explaining and agreeing the medications protocol with participants at enrolment, and using an ordinal clinical outcome scale including anti-anginal medications as part of the assessment of angina-related health status. Medications and doses will be counted in units that were agreed upon by members of the Focus Group, Trial Steering Committee and surveyed cardiologists.

ORBITA enrolled patients based on clinically indicated PCI, with 94-96%(40,81) of patients having evidence of ischemia before randomisation. ORBITA-2 will require patients to have at least one test suggestive of ischaemia to enrol, including FFR, iFR or any non-research noninvasive tests, regardless of anatomical severity.

While patients needed to have symptoms prior to enrolment in ORBITA, there was no additional requirement to have angina episodes immediately before randomisation. 88% were in CCS class I to III at randomisation. This proportion was 89% in FAME-2 and 88% in COURAGE(7,82). ORBITA-2 will include a symptom assessment phase between enrolment and randomisation. Participants must have one or more documented angina episodes in a 2-week symptom assessment phase to be eligible for randomisation.

ORBITA prespecified treadmill exercise time as the primary endpoint as in the unblinded ACME (Angioplasty Compared to Medicine) trial of balloon angioplasty(8) and to mirror US Food and Drug Administration and the European Medicines Agency requirements for trials of anti-anginal therapy, but in retrospect the effect may have been larger on symptoms than on exercise time. Exercise time may not have been sensitive enough. ORBITA-2 will include treadmill exercise time as a secondary endpoint. The primary endpoint will be angina symptom score measured daily using a novel ordinal clinical outcome scale designed for assessing health status in angina.

ORBITA used a 6 week follow-up period as long enough for resolution of ischemia and short enough to be ethical and practical for the first placebo-controlled trial of PCI. ORBITA-2 will use a 12 week follow-up period with procedures to mitigate potential risks.

Finally, ORBITA pre-specified paired t-test methodology, as used by the positive unblinded ACME trial. This was not the most powerful statistical method for detecting treatment effect. In ORBITA-2, analysis is prespecified to 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.

The differences between the two trials are summarised in Table 5.1. ORBITA-2 was designed in partnership with the ORBITA Focus Group consisting of previous ORBITA participants. They were involved in the development of the visit schedule, medications management protocol, the primary endpoint and symptom smartphone app.

Feature	ORBITA	ORBITA-2	Rationale
Coronary disease	Single vessel	Single and multi-vessel	More representative of patients referred for clinical PCI, only half of whom have single vessel disease
Enrolment	Only after invasive angiography	After either CT or invasive angiography	Representative of modern patient pathways
Requirement for symptoms	Originally referred for angina. Anti-anginals 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 pre-specified narrow window of time ***after*** enrolment
Requirement for ischemia evidence	As per clinical guidelines and FAME-2, only required for lesions of moderate anatomical severity.	Regardless of anatomical severity, required to have one or more tests suggestive of ischemia, including	In ORBITA, 94% or 96% had one or more positive pre-randomisation ischemia tests. In

		FFR, iFR or any non-research noninvasive tests	ORBITA-2 this will be 100%
Primary endpoint	Exercise treadmill time	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 anti-anginals	Stop anti-anginals.and 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 anti-anginals
Duration of follow-up	6 weeks	12 weeks	Even more certain to be long enough to demonstrate effect

Table 5-1 Comparison of features of ORBITA and ORBITA-2.

Aims of ORBITA-2

- To investigate whether PCI incrementally improves symptoms and exercise time of patients with stable angina with a wider range of coronary artery anatomy compared with a placebo procedure
- To investigate whether non-invasive tests of ischaemia can be used to predict the efficacy of the improvement in symptoms and exercise time following PCI.
- To evaluate the effect of PCI on health-related quality of life
- To evaluate the cost-effectiveness of using PCI to relieve angina

The hypothesis is that PCI improves symptoms of angina in people off anti-anginal medications. I also hypothesise that the nature of symptoms will predict the size of symptom benefit and that ischaemia will not because ischaemia does not necessarily mean that the epicardial lesion is responsible for the symptoms.

Study Design

ORBITA-2 is a double-blind randomised controlled trial of PCI for stable angina without anti-anginal medications. Participants will be enrolled and undergo a 2-week symptom assessment phase prior to randomisation. They will then be randomised to either PCI or placebo in a 1:1 ratio. Participants and staff outside the catheter lab will be blinded to the study arm. Participants will be unblinded at 12 weeks. Throughout the study, participants will complete a daily symptom smartphone app.

Study Population

Rationale

Participants are required to be suitable for PCI and for dual antiplatelet therapy. If CABG is deemed to be a more appropriate therapy for the patient then these patients will not be recruited i.e. if there is severe triple vessel disease and/or significant left main stem coronary disease. The anatomy also has to be such that PCI could be delivered in one procedure rather than a staged procedure to preserve masking.

If symptoms are more likely to have an alternative cause e.g. respiratory disease, these participants will not be recruited. If intervention is needed for alternative indications such as LV dysfunction, these participants will not be recruited.

It is important to ensure that the recruited population have stable angina as the indication for PCI i.e. no recent acute coronary syndrome. People who have undergone previous CABG will be excluded because non-native coronary PCI may be indicated.

Eligibility Criteria

To enrol participants are required to meet all of the following criteria:

- Symptoms of angina
- Anatomical evidence of significant coronary stenosis is at least one vessel on either invasive coronary angiography or on computerised tomography coronary angiography (CTCA)
- Evidence of ischaemia defined as one or more of the following tests being suggestive of ischaemia

- Stress echo
- Cardiac magnetic resonance imaging (MRI) stress perfusion scan
- Nuclear medicine myocardial perfusion scan
- Invasive pressure wire assessment (at the time of diagnostic or research invasive angiography

To be randomised, participants are required to additionally meet all of the following criteria:

- Reported at least one episode of angina during the 2-week symptom assessment phase
- Invasive coronary angiogram indicating ≥ 70% stenosis in at least one vessel
- Clinical eligibility for PCI

Participants who do not meet the criteria for randomisation e.g. asymptomatic will be withdrawn.

By design, some participants will be eligible for enrolment, but will not meet criteria for randomisation at the time of the research angiogram. For example, a participant may have a severe stenosis on a CTCA but will be found, at research angiography, to have non flow-limiting disease on invasive physiology, 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.

The inclusion and exclusion criteria are designed to encompass all patients in the NHS who would be eligible for PCI in current practice. There will be no upper age restriction. The aim of this study to assess the impact of PCI on symptoms, therefore the most likely cause of the participants' symptoms must be stable angina.

The exclusion criteria have been divided up by their rationale as follows:

Not suitable for PCI:

- Significant left main stem coronary disease
- Chronic total occlusion in the target vessel
- Contraindication to PCI or drug-eluting stent implantation
- Contraindication to antiplatelet therapy
- Pregnancy

Alternative cause of symptoms more likely:

- Severe valvular disease
- Severe LV systolic impairment
- Severe respiratory disease

Indication for PCI not stable angina:

- Recent acute coronary event (last 6 months)

Possible non-native coronary PCI indicated:

- Previous coronary artery bypass graft surgery

Not suitable for trial participation:

- Unable to consent

Intervention

PCI with drug-eluting stents

Primary Outcome

The primary endpoint is 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 Table 5.2. The numbers represent a relative ranking without any assumption related to category spacing. It comprises the number of episodes of angina, units of anti-anginal medications, and high-level category overrides for unblinding due to intolerable angina, acute coronary syndrome and death. Table 5.3 shows the total daily dose of common anti-anginal medications considered to be one unit.

Participants will be asked once a week whether they had angina during 2 activities that were chosen by the participant as activities currently provoking 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 general consensus in use of an ordinal outcome scale, the components of the scale, the ranking of relative worsening of health status in the sequence shown in Table 5.2 and the counting of units of anti-anginal medications shown in Table 5.3.

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

Grade	Number of angina episodes in a day	Units of anti-anginal 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

Table 5-2 Ordinal Clinical Outcome Scale for Angina

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

Table 5-3 Total daily dose of anti-anginal medication considered to be one unit

Secondary Outcomes

- Exercise treadmill time
- Angina severity as assessed by CCS Class
- Angina frequency measured by the symptom smartphone app
- Physical limitation, angina stability, quality of life, angina frequency, freedom from angina as assessed with 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
- Stress echo score
- Need for anti-anginal medication introduction and up-titration
- Unblinding due to intolerable angina
- Admission for acute coronary syndrome
- Death

Exploratory Outcomes

- Frequency of angina episodes rated as moderate or severe
- Freedom from angina measured by the symptom app
- Freedom from severe angina measured by the symptom app

- Presence of angina on personalised activities measured by the symptom app

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 SAQ, EQ-5D-5L, the McGill pain questionnaire, MacNew heart disease health-related quality of life questionnaire and 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 Chapter 6. Lack of a smartphone is not an exclusion criterion. 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 assessment

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

Participants will then attend for the pre-randomisation visit when they will have an exercise treadmill test, stress echo, and symptom and quality of life assessment. Exercise testing and stress echo methods are described in Chapter 2.

Physician-assessed symptoms

The physician assessment of symptoms will include CCS Class and the MRC dyspnoea scale.

Patient-reported symptoms

Participants will report their symptoms via the smartphone app, the Rose Angina Questionnaire, the McGill Pain Questionnaire and the SAQ.

Quality of life assessment

Participants will report their quality of life using EQ-5D-5L and MacNew.

Medications

Dual antiplatelet therapy:

Standard loading doses will be used. Thereafter, aspirin 75mg once daily and clopidogrel 75mg once daily or ticagrelor 90mg twice daily or prasugrel 5-10mg 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, 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 80mg once daily will be preferred.

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

Anti-hypertensives:

Anti-hypertensives with anti-anginal 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 it is not adequate, anti-hypertensives will be added; agents without anti-anginal properties will be preferred.

Anti-anginal medication:

Regular anti-anginal medications will be stopped on enrolment. All participants will be given glyceryl trinitrate spray to be used when necessary. The need for starting regular anti-anginals will be determined by participant preference and patient reported symptoms. An individualised protocol for potential introduction of anti-anginal medications will be prepared for each participant by the research team. This protocol will be based on their 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

Nifedipine MR is preferred over amlodipine where possible because it has a shorter half-life so the effect will not last as long after stopping. Anti-anginal medications 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 operator's discretion. Coronary angiography including pressure wire assessment with FFR and iFR will be performed for each coronary stenosis deemed anatomically suitable for PCI, 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, the operators must be satisfied with the evidence of ischemia available to them, which comprises the FFR, iFR and/or any non-invasive ischemia testing that has been performed on clinical grounds prior to randomisation. The operators will not have access to the results of research pre-randomisation stress echocardiography and exercise testing. This arrangement preserves the utility of these measures as baseline stratifiers against which effect size can later be regressed(21,40).

Randomisation and blinding

Participants are allocated to PCI or placebo in a 1:1 ratio with randomly varying block sizes using a secure central online, computer-generated random number system (Randi - opensource clinical trials software) immediately prior to delivery of the intervention (or placebo).

Before randomisation participants will be counselled that they might experience pain and shortness of breath. They will receive headphones playing music that ensure auditory isolation and prevent hearing of communication between staff. Participants will be sedated using incremental doses of intravenous benzodiazepines and intravenous opiates 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.

Participants randomised to placebo will be kept in the catheter laboratory for a minimum of 15 minutes post-randomisation.

A standardised protocol will be used for the management of all documentation in the catheter laboratory, the handover, post-procedural care and discharge documentation.

The blinded team will perform all the communication with the participant after discharge and will perform all the follow-up tests.

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 grade 1-5 with 5 being most sure.

Follow-up assessment

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

Unblinding will be performed once all follow-up assessment has been completed. Patients could be unblinded early due to intolerable angina, withdrawal of consent or by accident.

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. 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 and had discussed having PCI with their cardiologist and 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 handling

Data management

Data will be entered onto an electronic case report form(eCRF) (OpenClinica). I designed and tested the eCRFs with particular regard to ensuring data integrity of demographics, medications and symptoms. 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, in line with Imperial College London policies.

Data monitoring

Source data will be made available to the Data Monitor.

Sample size calculation

The sample size calculation was based on a frequentist approach for simplification.

ORBITA-2 is designed to detect a difference between arms in the change of angina symptom score units of 2 with a standard deviation of 6 angina symptom score units. Using a 2 sample t-test with an alpha of 0.05 and 80% power, 284 participants need to be randomised across the active and control arms. 396 participants accounts for a dropout rate of 7% between enrolment and randomisation (through either withdrawal of consent or becoming ineligible) and a cross-over rate of 10% from the control arm and 2% in the active arm (rates based on the experience of ORBITA). The aim is therefore to enrol 400.

The primary outcome was affirmed in 2021 following a survey of patients and cardiologists, as being a longitudinal ordinal outcome scale incorporating number of episodes of angina per day, units of antianginal medications per day and whether one of the following events has occurred (1) unblinding due to intolerable angina, (2) acute coronary syndrome, or (3) death.

A longitudinal ordinal outcome provides several-fold greater power than a time to event analysis as it has many levels and is measured daily.

Recruitment status

ORBITA-2 recruitment began in November 2018. It was paused from March 2020 to May 2020 due the COVID-19 pandemic.

The trial was resumed at sites where possible, in line with local COVID-19 policies, with the following protocol amendments as clinically necessary:

- Omission of exercise testing and of stress echo 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

The patient-centred and app-delivered primary endpoint is well-suited to being maintained regardless of COVID-19 precautions.

Statistical analysis plan

Analysis of the Primary Outcome

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. The analysis 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(83). The statistical model extracts maximum information from the outcome data's severity and timing of events to maximise power.

Sensitivity analyses will be performed and reported for a range of possible prior distributions, especially using a flat prior for the treatment effect.

Interim analyses

The primary objective of interim analyses is to ensure the safety of the participants enrolled in the trial and will only include Serious Adverse Events (which includes acute coronary syndrome

and death), not efficacy data. This will be performed at 6-monthly intervals or when 10 serious adverse events have occurred since the last analysis (whichever is sooner).

Missing data

When data is missing for the number of angina episodes and units of anti-anginal medications, the score will be considered to be <77. When data is additionally missing for acute coronary syndrome, the score will be considered to be <79. When all post-randomisation data is missing for a participant, they will not be included in the analysis. However, missingness of all post-randomisation data is not expected to occur.

Stratified analyses

Clinicians use heuristics to speculate on whether PCI will improve angina in individual participants. Importantly, these heuristics are conveyed to students and staff as part of their training and are included in guidelines. For example, it is believed 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. This trial has the potential to assess this by recruiting a broad range of patients clinically eligible for PCI, and not restricting eligibility to any one of those parameters. If eligibility was restricted, it would be impossible to test whether the parameter predicted benefit.

Information to permit baseline stratified analyses will include 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 echo 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 echo 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 ischemia. 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 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).

Trial management

Local site management

Training for local sites will be provided at informal meetings via video call and formally at the Site Initiation Visit. Further training, support and engagement with local site investigators will be delivered by site visits, webinars and a quarterly newsletter.

Safety monitoring

All adverse events will be reported to and reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB will also review clinically-driven withdrawals and protocolised starting and uptitration of antianginal medications. The DSMB will report their findings to the independent chair of the Trial Steering Committee.

Potential barriers to success

Criteria for success are:

- To recruit to time and target with dropout rates no higher than predicted
- To obtain complete data for the primary endpoint
- To maintain blinding (measured by blinding indices)
- To maintain data integrity (with independent verification by the trial monitor)

Table 5.4 describes risks and their corresponding mitigation strategies.

Risk	Strategy to mitigate risk
Slow recruitment	Planning a realistic target
	Monitoring monthly recruitment
	Quarterly newsletter
	Website to track site progress and stimulate competitiveness between sites
	Easy referral pathway
	Frequent visits to site from central research team
	Adding more sites
Incomplete follow-up	Providing easy access to a doctor
	Providing free and convenient transport
	Offering a reliable, prompt and responsive service e.g. timely responses to patient requests and queries
	Offering flexibility in visit scheduling
Missing data	Robust investigator training and regular training updates
	Statistical methods such as imputation
	Monitoring documentation for protocol adherence
Discrepancies in data	Regular data monitoring
	Robust case report form design

Loss of investigators	Website to support and engage investigators
	Involving multiple senior staff at each site so that loss of individuals is unlikely to affect completion
Accidental unblinding	Using a blinding index
	Clear verbal and written documentation and procedures that are repeatedly reinforced
	Robust investigator training and regular training updates

Table 5-4 Risk mitigation strategies in the ORBITA-2 trial.

Participant retention strategy

I chose to implement the following measures after discussions with the ORBITA Focus Group and Trial Steering Committee:

- Instant access to study team member by phone and email.
- Easy access to in-person appointment with study team member if needed.
- Encouraging involvement of the participant's family members.
- Taxis to all appointments arranged and paid for by the central site.
- Detailed, timely communication with GP/ relevant healthcare professionals.
- Empowering participants to be the master of their own care by education and frequent information exchange.

Results

Table 5.5 shows baseline characteristics of the first 101 participants randomised in ORBITA-2. The majority were male. There was a high prevalence of hypertension and hyperlipidaemia. Almost all participants had either CCS Class II or III symptoms, and predominantly Class II. The baseline characteristics are very similar to that of the ORBITA participants and ISCHEMIA participants (although CCS class was not reported in ISCHEMIA)(6,9). ORBITA and ORBITA-2 participants had more severe symptoms than FAME-2 participants (3%, 2% and 25% had CCS Class I symptoms). However, ORBITA and ORBITA-2 participants lower risk factor prevalence than FAME-2 participants(20).

	n=101
Mean age (SD)	67(9)
Male (%)	79 (78%)
Hypertension (%)	61 (60%)
Hyperlipidaemia (%)	64 (63%)
Diabetes (%)*	29 (30%)
Current smoker (%)*	13 (13%)
Ex-smoker (%)*	55 (56%)
Previous PCI (%)	13 (13%)
No LV impairment (%)*	94 (93%)
Mild LV impairment (%)	2 (2%)
Moderate LV impairment (%)	2 (2%)
CCS Class I (%)*	2 (2%)
CCS Class II (%)	65 (64%)
CCS Class III (%)	31 (31%)
CCS Class IV (%)	0
Mean duration of angina in months (SD)**	14 (12)

*Table 5-5 Baseline characteristics of patients randomised until April 2021. SD = standard deviation. *Values for 3 participants are missing. **Values for 9 participants implausibly long (likely recorded in wrong units) so excluded.*

Discussion

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 been confirmed to show a correlation coefficient of -0.64 with the gold standard of daily documentation of symptoms(84). However, it is limited by recall bias and, more importantly, patients' modifications to their activity that lead to reduced symptom frequency.

ORBITA-2 takes 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(50). Daily reporting provides the opportunity 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 2 activities, that the participant pre-specified as causing angina, are still causing angina. Chapter 6 explores the advantage of the app further.

The third challenge facing trials of angina treatment was exemplified by Saxon et al, who found that amongst patients who themselves reported no angina, the clinician documented CCS class II, III or IV in 20 to 46% of cases(85). 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 DEFER (Deferral of PTCA Versus Performance of

PTCA), 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%(32,86). 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%(20,86). ORBITA dealt with this by blinding both the participant and the staff member assessing the symptoms at follow-up. ORBITA-2 will do the same.

Conclusions

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 in both single and multi-vessel disease. The participants randomised so far have a similar baseline cardiovascular risk profile to ORBITA and ISCHEMIA participants. Novel features include the use of an ordinal clinical outcome scale for angina and daily symptom reporting using a smartphone app. It will provide a further opportunity to look for predictors of the placebo-controlled effect of PCI.

Chapter 6 Daily Angina Documentation on a Smartphone App versus Subsequent Recall

Abstract

The traditional approach to documenting angina outcomes in clinical trials is to ask the patient to recall at the end of a week, a month, or longer period. With ubiquitous availability of electronic devices such as smartphones and tablets, daily contemporaneous documentation might be possible.

I developed the ORBITA-2 symptom smartphone app with a user-centred iterative design and testing cycle involving a focus group of previous ORBITA participants and a competitive analysis of existing angina apps and apps for other chronic pain conditions. Feasibility and acceptability were assessed in an internal pilot of participants in the ongoing ORBITA-2 trial. Seven days of app entries by ORBITA-2 participants were compared to subsequent participant recall at the end of the seven day period.

The Design Focus Group (10 previous ORBITA participants) tested a prototype app and iterations with major modifications. They reported that the final version captured their symptoms to their satisfaction and was easy to use.

In the Completion Assessment Group (the first 142 participants in ORBITA-2) 141 (99%) completed the app in full, 47/141 (33%) without reminders. 22 participants required one reminder, 19 two, 13 three, 6 four, 18 five to nine, 15 ten to twenty and 1 more than twenty with 31 reminders.

In the Recall Assessment Group (ORBITA-2 participants finishing between August 2020 and April 2021) 100% of participants said they could recall the previous day's symptoms, and 82% of them recalled correctly. For 2 days ago, 88% said they could recall and of those, 87% recalled correctly. The proportion saying they could recall fell progressively thereafter: 89%, 67%, 61%, 50% and at 7 days, 55% ($p<0.0001$ for trend). The proportion recalling correctly also fell progressively to 55% at 7 days ($p=0.01$ for trend). Only 79% said they could recall the total number of episodes in the past 4 weeks, of whom 43% recalled correctly and of those 80% had no symptoms.

Episode counts of angina are often difficult to recall (and very difficult to recall accurately) after a few days. For trials focusing on angina, such as ORBITA-2, daily symptom collection via a smartphone app will increase the validity of the results.

Introduction

The emphasis on symptom relief in stable angina has increased since the value of coronary revascularisation for reducing cardiovascular outcomes like MI and death was questioned(6,7). It is important that symptom relief is measured in an accurate, reliable and patient-centred manner.

Modes of assessment include exercise time, angina frequency e.g. SAQ, and quality of life e.g. EQ-5D. Symptoms can be self-reported or physician-assessed, but both rely on patients recalling their symptoms over a period of time.

The TERISA trial used an electronic device for patients to keep a diary of angina episodes(50).

The primary endpoint of ORBITA was exercise time. ORBITA-2 was designed in line with feedback from ORBITA participants and the clinical and scientific cardiology community. ORBITA-2 recruits people with symptoms of stable angina, evidence of ischemia, and significant coronary stenosis in at least one vessel. In particular the endpoint is an ordinal clinical outcome scale for angina which contains daily angina frequency.

In this Chapter I describe the development of the smartphone application used for documenting daily symptoms, including a feasibility and acceptability assessment, and a comparison with subsequent recall.

Methods

Development Overview

The app was developed using a user-centred iterative design and testing cycle as shown in Chapter 11 Appendices. This involved a focus group of people with lived experience of stable

angina and of participation in clinical trials. They were asked what elements would adequately cover their symptoms for reporting to researchers. Their feedback was recorded as notes during the meetings. They were each given a prototype of the app to try recording symptoms, and again their feedback was recorded. The app was iteratively improved and retested by members of the focus group.

The first prototype of the app was based on feedback from ORBITA participants and investigators regarding the limitations of other angina assessments such as exercise testing and the SAQ. The next iteration incorporated the results of a competitive analysis of other apps (in angina and other chronic pain conditions).

Feasibility was assessed in two ways: first by focus group members using the prototype app, second with pilot data from actual ORBITA-2 participants. The pilot data included completion rates of daily symptom app entries, the proportion of participants requiring reminders to complete the app and how many reminders were required.

Acceptability was also assessed by focus group members using the prototype app and with pilot data from actual ORBITA-2 participants. Focus group member opinions were collected through verbal feedback and a written survey. ORBITA-2 participants feedback was collected verbally at the end of their involvement in the study.

Participants

The **Design Focus Group** participants were participants from the previously completed ORBITA trial. All participants from ORBITA who agreed to subsequent contact were invited to focus group meetings.

The **Recall Assessment Group** was a substudy of ORBITA-2, composed of ORBITA-2 participants who had their final visit between August 2020 and April 2021 inclusive.

The **Completion Assessment Group** were all participants in ORBITA-2 who had their final visit before the end of April 2021.

Technical aspects

The app design team created a progressive web app, designed to be available on any smartphone, tablet or computer. Usability was tested across these platforms.

The user interface was tested and iteratively improved by focus group members who could try it on their phones and iPads available during focus group meetings.

Maintenance of data integrity was tested by the app design team, including ensuring adequate logging of dates, times, users and changes.

User experience

This phase focused on optimisation of features such as font, readability, the onboarding process, error messages e.g. for lack of internet connection, and the frequently asked questions section, with input from the focus group members.

Competitive Analysis

The aim of the competitive analysis was to critically appraise the range of existing pain app features to inform the design of the symptom app for ORBITA-2.

Android Google Play Store, Apple App Store and the Amazon Appstore were searched for apps that monitored symptoms of angina over time in English. The search terms used were: “angina”, “angina management”, “angina symptoms”, “heart pain”, “heart pain monitoring”, “chest pain”, “chest pain monitoring”, “symptom” and “symptom tracker”.

Apple App Store was searched for highly rated (based on reviews and numbers of downloads) symptom monitoring apps for each of three other common chronic pain conditions (endometriosis, migraines and rheumatoid arthritis).

Statistical Analysis

Data are summarised as n (%) and median (interquartile range) for skewed data. Differences in proportions were assessed using the Chi squared test for trend in proportions. Differences in means were assessed using an unpaired t-test. The association between continuous baseline variables and recall and reminders was measured using Spearman's rank correlation coefficient rho. Associations between baseline variables and app completion were not assessed as the app completion rate was too high.

Analyses were performed using the open-source statistical environment "R" Version 4.1.0.

Results

A working prototype web-based app was developed and tested across various Android smartphones, iPhones, tablets, and computer platforms.

Participants

The Design Focus Group was composed of 10 participants of the previous ORBITA trial, of whom one was female.

The Recall Assessment Group consisted of 29 ORBITA-2 participants who had their final study visit between August 2020 and April 2021, of whom 5 were female. The mean age was 65 (standard deviation 9) in the Recall Assessment Group. The mean angina duration was 14

months (standard deviation 14). 17 had CCS Class II symptoms and 12 had CCS Class III symptoms.

The Completion Assessment Group consisted of the 142 ORBITA-2 participants who had their final study visit by the end of April 2021, of whom 34 were female. The mean age was 67 (standard deviation 9) in the Completion Assessment Group.

Data on the socio-economic status and ethnicity of these individuals are not available.

Competitive analysis

The following apps for angina met the criteria: Angina Control (Google Playstore), Angina Recorder (Apple App store), and Heart Keeper (Google Playstore). Features of these apps included the ability to track angina episode duration, angina episode severity, and GTN usage. A literature search did not identify any studies evaluating angina apps.

I identified the following apps for other chronic pain conditions: Sora, Migraine Buddy and RheumaBuddy for endometriosis, migraines and rheumatoid arthritis respectively. These apps had features for reporting the location of pain on a diagram, tracking the severity of symptoms, recording the duration of pain and had the ability to record other symptoms e.g. nausea. Migraine Buddy also enabled activities affected by the pain to be recorded.

Existing apps can provide a comprehensive assessment of the nature of symptoms, e.g. site and duration of pain. However, to monitor the impact of a therapy on symptom relief, the key feature is the ability to monitor episodes of pain, and to use an app for research purposes, it has be quick and easy to use. Clinical experience and the experience of the Design Focus Group indicates a wide inter-patient variety of symptoms. Therefore the Design Focus Group settled on a personalised approach to defining symptoms and choosing reference activities.

Design Focus Group and app design

The Design Focus Group had meetings during October 2018. They reviewed prototype apps on their phones and/or iPad tablets which were available for their use during the meetings. They tried out the onboarding process. Table 6.1 shows their comments and the resulting changes made to the app and the participant onboarding process.

Feedback from focus group	**Researcher Comments**	**App modification**
There is a practice on an imaginary patient named Bob. Can there be a practice on oneself as well?	The reason that the practice module refers to an imaginary patient was (a) to cover a wide range of possible answers, (b) create no possible confusion between the patient's genuine symptom status and the practice process, and (c) minimise the duration of the practice session. All participants were able to enter their data after a single practice session.	Onboarding process is mandated to be done one-to-one with a researcher so that any queries can be resolved immediately
Can you add a Help button?	During the prototype design, whenever there was a possible need for a Help button, the design was changed to become more obvious.	Added a button with reference information and contact phone number
Why can we not describe our symptoms in more detail?	The app is to document symptoms numerically in all participants for each day. It was paramount in the design of the app that the burden on participants should be minimal. Descriptions of the symptoms are obtained via separate questionnaires.	A freetext box for description of symptoms was added to the onboarding process only. The app team decided not to invite additional freetext description in the daily entries because this would be burdensome, inconsistently entered and not usable as an endpoint.

Shouldn't the app include instructions for use?	Every extra sentence in an app can make it look complicated to some participants and thereby reduce completion rates.	The participant workflow was modified, with additional concisely worded instructions shown but only at the precise stage that they are required. The onboarding process was augmented with data entry on an imaginary patient for a series of days of pre-specified symptoms that cover the full range of possibilities. A Help button was added to provide additional instructions and a contact phone number.

Table 6-1 Recommendations from the Design Focus Group

Design Focus Group and angina induction by personalised reference activities

Discussion with the Design Focus Group highlighted that people may modify their activity to avoid episodes of angina. I therefore wanted ORBITA-2 to include questions about symptom responses to reference activities that were stable during trial participation but were individually tailored to the participant at enrolment.

The Design Focus Group completed a written survey of activities that triggered their angina episodes. Their responses are shown in Table 6.2. The Design Focus Group advised that changes in symptom response to these stimuli would be the best indicator of whether the treatment had worked, since it was relevant to their life and was the reason they originally sought medical help.

I used their responses to provide a list of activities in the ORBITA-2 app. During onboarding, participants select two activities that currently cause angina. The list also contains an option for participants to enter an unlisted activity in free text form. This is shown in Figure 6.1. Subsequently every week during the trial, participants are asked whether they had angina during the two activities they specified.

Respondent	I always have angina with:	I sometimes have angina with:	Other activities causing angina
1	Running 5 to 10km	Walking up hill	No response
2	Cycling up hill	Walking up hill	Very cold weather
3	Walking up hill	Walking quickly	No response
4	Walking far	No response	No response
5	Walking up hill	No response	No response
6	Cycling	Walking	No response
7	Walking fast up hill	Stress	No response
8	Walking up hill with cold weather	Walking up hill	No response
9	No response	Walking up hill	No response
10	Walking up stairs	Walking 2.5km	No response

Table 6-2 Design Focus Group responses to survey of angina triggers

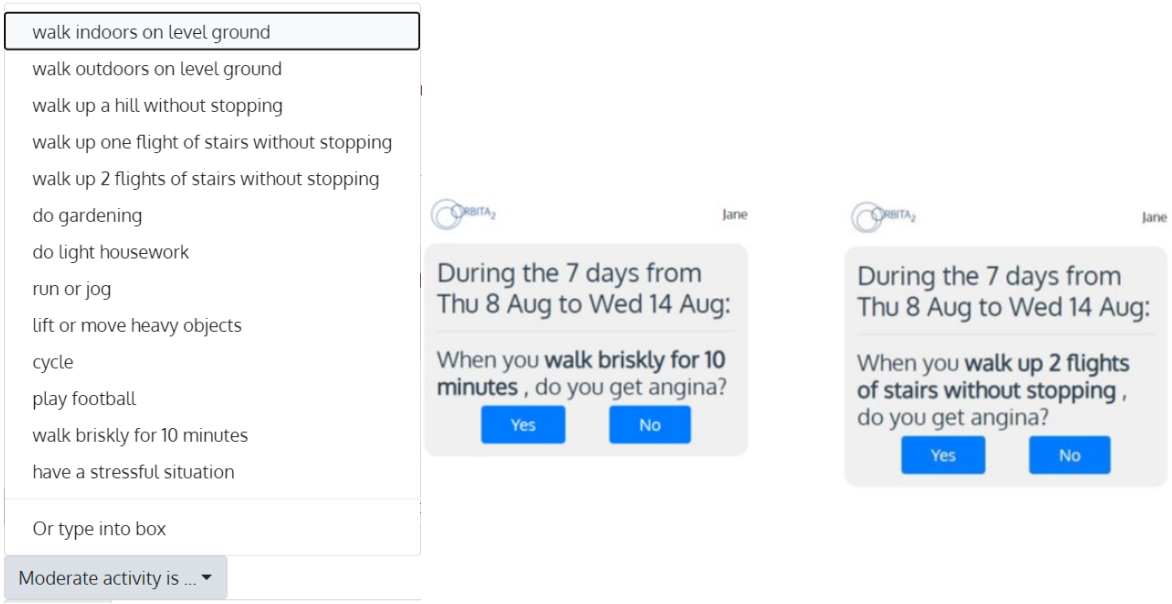

Figure 6.1 Options for weekly provocation questions on smartphone app [left] and examples of the questions as shown to the participant [right].

Completion Assessment Group

Of the 142 ORBITA-2 participants in the Completion Assessment Group, 141 (99%) provided complete data on the app, i.e. answers to every question for every day for the duration of their participation.

The single participant who did not complete the app in full stopped entering data part way through the follow-up period, despite confirming that the app was working and receiving encouragement to use it. On telephone calls she advised she was keeping paper records instead, because her lifestyle was busy. At her final visit, she had not brought these paper records. It was unreasonable to delay unblinding until receiving the paper records and therefore continued with the unblinding and asked for the records to be mailed or emailed in. Despite several further contacts, she did not do so.

Total number of reminders required across the 142 participants of the Completion Assessment Group during the 14 weeks of participation (totalling 9935 participant-days) was 463. 47 participants required 0 reminders, 22 one, 19 two, 13 three, 6 four, 18 five to nine, 15 ten to twenty, 1 more than twenty with 31 reminders. The participant requiring 31 reminders participated in the trial for 232 days because his randomisation was delayed by the COVID-19 pandemic. The one non-completer required 18 reminders. The distribution is shown in Figure 6.2. This is 0.01 reminders per participant per day.

Reminders required over the duration of participation were not specific to the time period within the trial (Figure 6.3). There was no association between the number of reminders required and age (Figure 6.4), or gender (men required a mean of 4.1 reminders and women required a mean of 3.5 reminders ($p = 0.64$)).

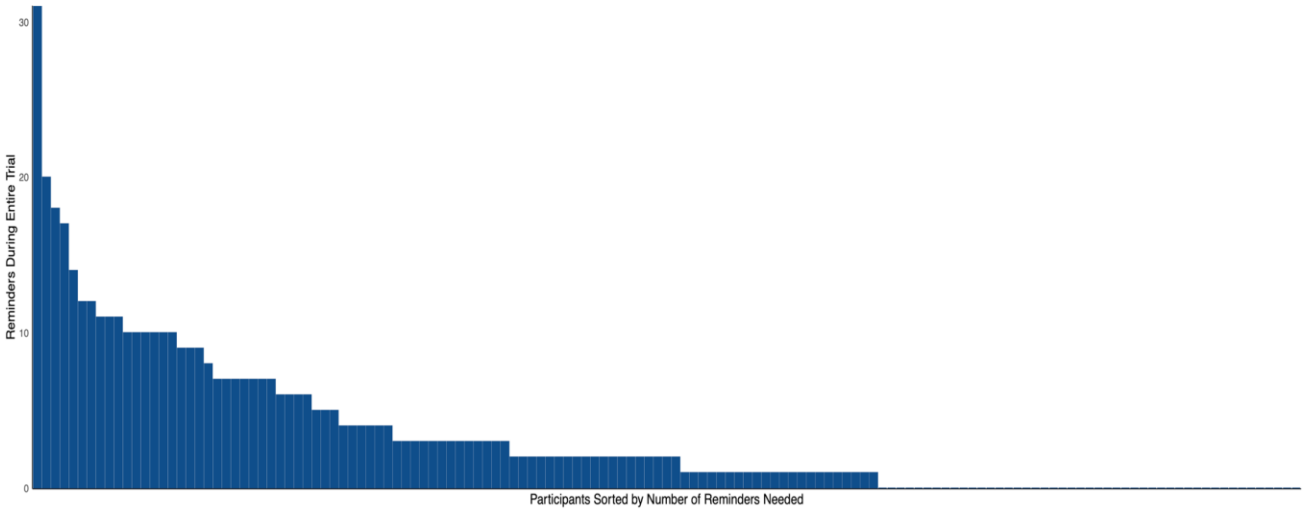

Figure 6.2 Distribution of number of reminders needed in Completion Assessment Group sorted from highest to lowest number of reminders required from left to right.

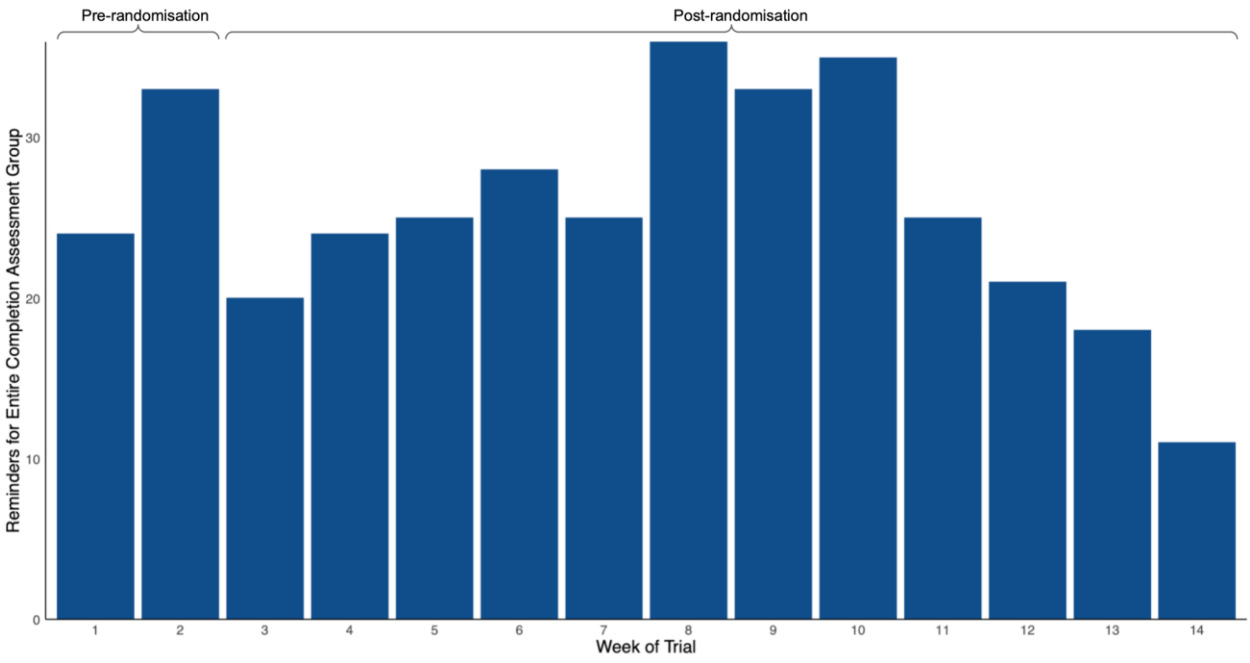

Figure 6.3 Reminders by week of trial in Completion Assessment Group

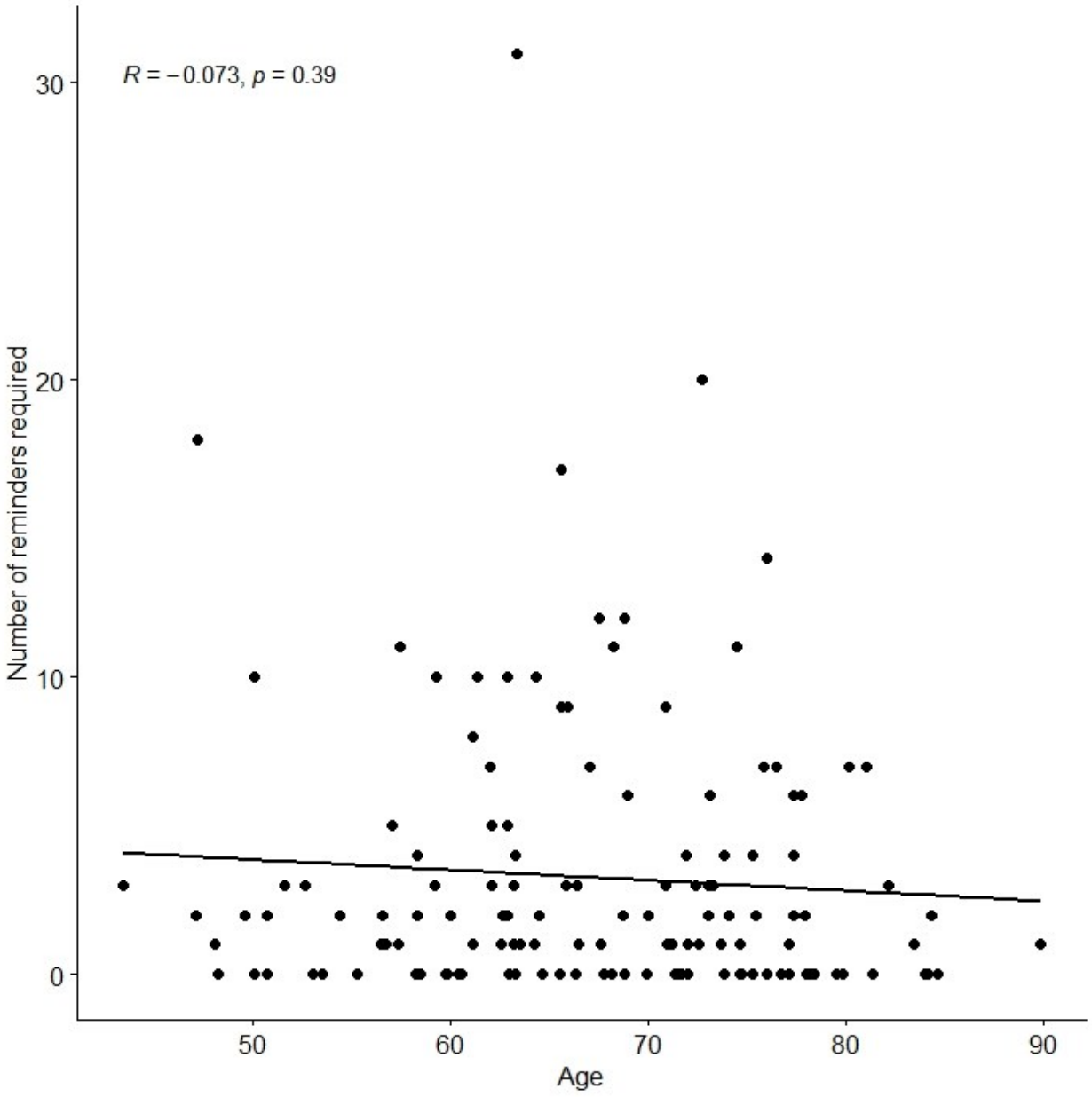

Figure 6.4 Relationship between age of participant and number of reminders required shown with Spearman's rank correlation coefficient rho.

Recall Assessment Group

The Recall Assessment Group were asked at the end of their participation to recall their number of episodes in each of the seven previous days individually. All said they could recall the previous day's symptoms, but the proportion declined for each day before that, reaching 10/18 (55%) for 7 days previously (Figure 6.5, $p<0.0001$ for trend).

Recollections did not always match what they had entered in the app. For the previous day, 14/17 (82%) were able to give a correct recollection. This proportion declined for each day before that, reaching 55% for 7 days previously (Figure 6.5, $p=0.01$ for trend).

Rates of correct recall were lower in those who had had at least one episode (Figure 6.6).

The Recall Assessment Group were also asked to recall the total number of episodes in the past 4 weeks. 6/29 (21%) said they could not recall. The remaining 23 participants reported a total of 157 episodes in the past 4 weeks, median 2 (IQR 0 to 12). 10/23 (43%) recalled correctly, of whom 8/10 (80%) had had no episodes.

There was no association between ability to recall correctly and age, duration of angina (Figure 6.7), or CCS class (Table 6.3). Being male was associated with higher rates of correct recall (Table 6.3) but this may be because many of these participants had zero episodes (which were found to be easier to recall). With relatively few women and people having non-zero numbers of episodes in a modestly sized sample, this finding is unlikely to be robust.

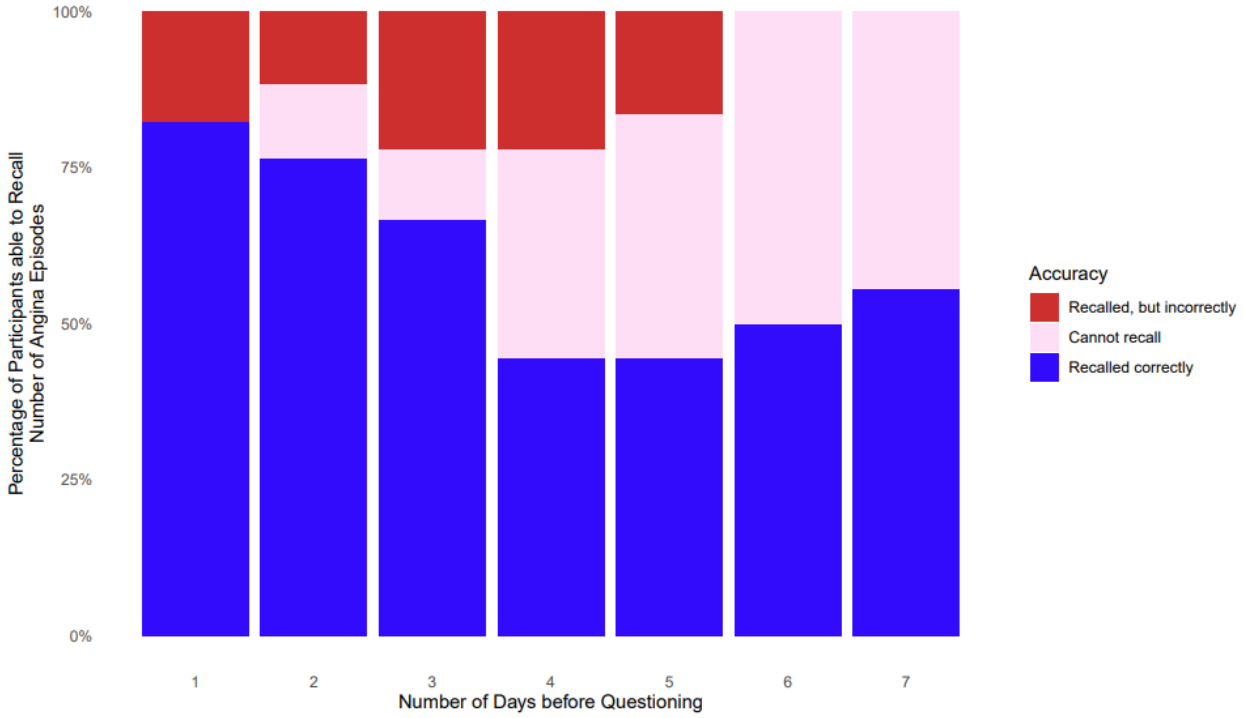

Figure 6.5 Stated ability and actual ability to recall numbers of angina episodes.

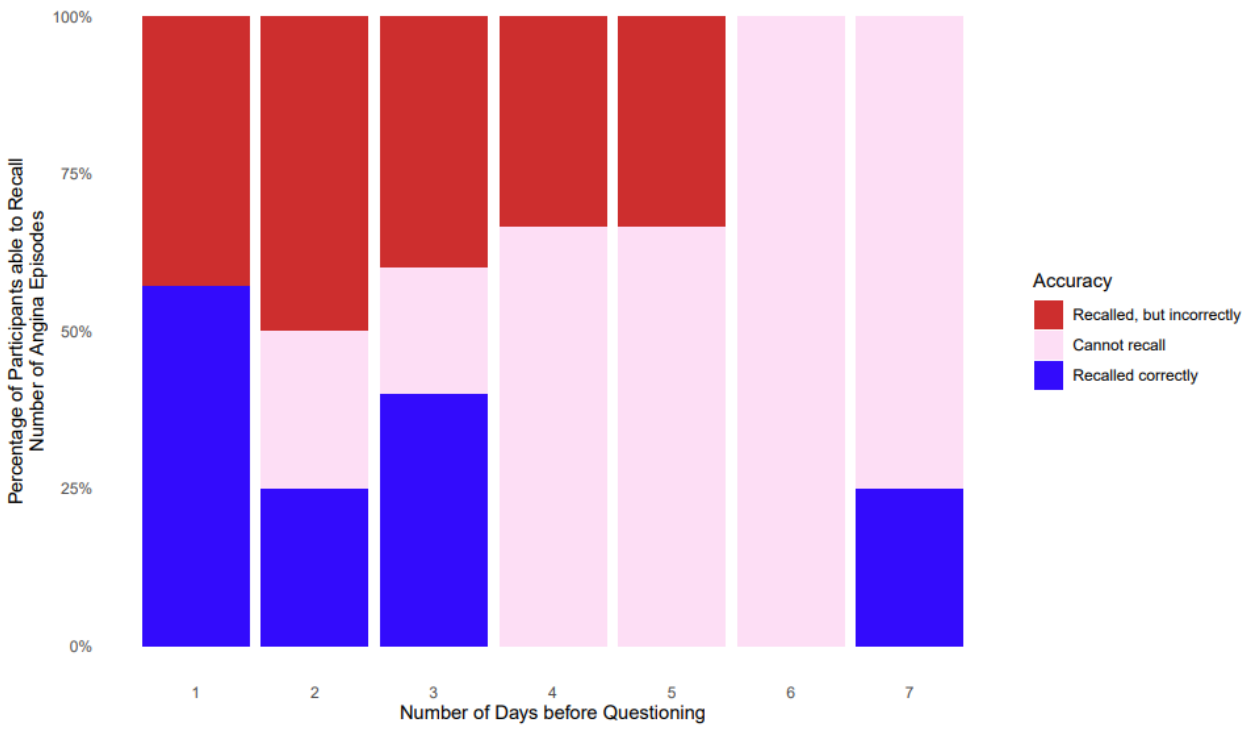

Figure 6.6 Stated ability and actual ability to recall numbers of angina episodes when at least one episode was recorded.

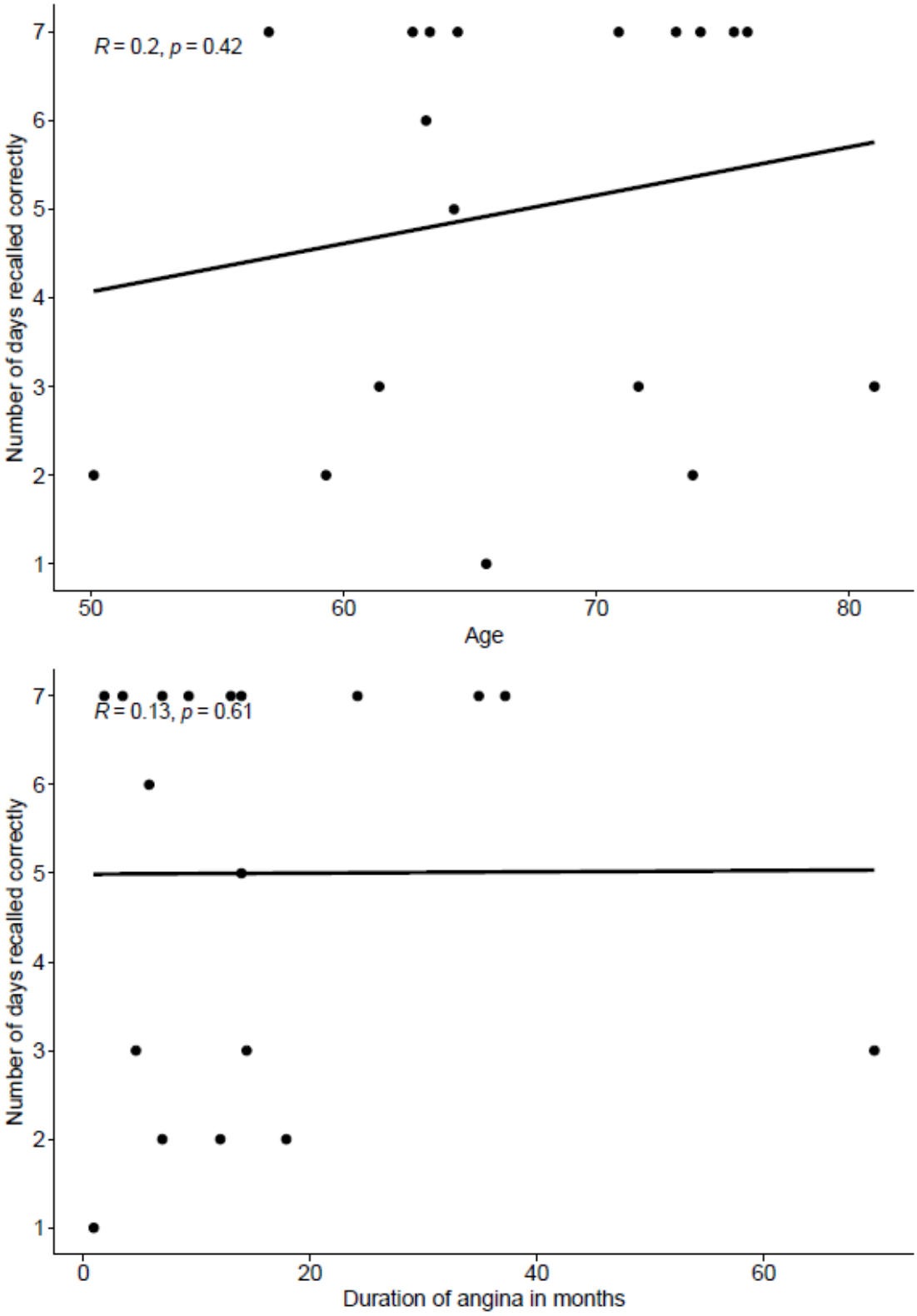

Figure 6.7 Relationship between ability to recall and age (upper panel) and duration of angina (lower panel), shown with Spearman's rank correlation coefficient rho. n=18 as participants with incomplete data on recall were excluded.

Characteristic	Mean number of days correctly recalled
CCS Class II CCS Class III	4.9 5.1 p = 0.8326
Male Female	5.4 2 p < 0.00001

Table 6-3 Relationship between ability to correctly recall and CCS Class and gender.

Discussion

These data show that recalling numbers of episodes of angina is difficult or impossible after a few days unless that number is zero. For patients who experienced angina, episodes that occurred more than one day ago were only 14% likely to be correctly recalled, while they were 29% likely to be incorrectly recalled, with the remainder stating that they could not recall.

The sample size of the recall assessment group was limited for assessment of predictors of ability to benefit.

The ORBITA-2 symptom app was developed with patients who had completed the first ORBITA trial, because they recommended symptoms be the primary focus of ORBITA-2. In the Completion Assessment Group, 99% completed data entry in full.

Avoiding confounding by patients limiting activity to avoid angina

The Design Focus Group advised that simply counting episodes would understate the impact of the condition because they reported adapting their activity patterns to avoid experiencing angina. ORBITA-2 therefore asks each participant at enrolment to identify two reference activities which characteristically caused them angina and which they would continue to carry out at least weekly throughout their participation. Separate from the main assessment which was daily episode count, the app asked them weekly whether they experienced angina on each of the two personalised reference activities.

Personalising the nature of angina

Members of the Design Focus Group, during their discussions, noticed that their individual experiences of angina were different although generally stereotyped within an individual. They

wanted this to be formally documented somehow in ORBITA-2. Repeatedly asking large numbers of categorical questions could be burdensome and still leave the participant with the feeling that their individual symptom has not been adequately described. Certainly repeating the process regularly during the study would impair the goodwill of participants on which the trial depends.

ORBITA-2 therefore asks participants to describe their symptoms in their own words at enrolment. This personal definition of angina is available on the app for them to refer back to. This allows a single daily question to cover the participant's own angina without the excessive wordiness of listing all possible variants.

Ability to recall

Ability to recall (correctly or incorrectly) episodes of angina declines progressively within a few days to reach only 55% at 7 days. Even this limited recall is bolstered by those who actually had zero episodes. For those with one or more episodes to recall, ability to recall (correctly or incorrectly) reached only 25% at 7 days.

The rapidity of decline in these proportions was surprising. Incorrect recall was only a problem in the very recent past: further back, participants would simply say they could not recall. Recall was not associated with age, duration of angina, or CCS Class. Recall was higher in women compared to men but this may represent type 1 error given the small sample size with few women.

ORBITA-2 collects daily data via the symptom app so that its angina episode counts can be as representative as possible.

Study limitations

The Design Focus Group only admitted patients who participated in ORBITA. Thus it does not include people who would not agree to participate in a trial or would not agree to undergo a randomised blinded procedure. It is therefore not representative of the general population of patients with angina. However, this work was intended for application to the ORBITA-2 trial and therefore the Design Focus Group is suitably qualified to advise.

The Recall Assessment Group did not include all participants in ORBITA-2 but rather all recruited within a particular time window. There is no reason to believe that these participants were any different from the generality of ORBITA-2 participants.

For the reference measurement I used the daily reports from participants via the symptom app, rather than making daily phone calls, or asking them to keep a separate paper diary. Therefore I cannot exclude the possibility that they entered incorrect information on the app. On the other hand, telephone calls would be unnecessarily burdensome for participants, jeopardising retention in the trial. With paper diaries there is no way to tell that entries are made contemporaneously rather than just before a subsequent visit. Therefore daily entries on the app were considered to be a suitably contemporaneous reference dataset.

Multiple different protocols for reminding participants, for example starting when they are only one day late, were not attempted. The Design Focus Group settled on a pattern that they considered acceptable to participants.

A limitation of reporting symptoms via an app is that it relies on the individual being able to read, use the technology and comply with daily entries. This could exclude participants with a lower literacy level, lower dexterity or who do have access to a device or internet connection. To mitigate these factors, the wording is short and simple, questions are answered using multiple

choice buttons so no typing is required and it takes less than one minute to complete per day, one-to-one training is provided to all participants and they are encouraged to access help over the phone at any time. Family and friends were permitted to help participants complete the app entries and were involved at the time of training. None of those screened for ORBITA-2 declined due to inability to use the app but it is not possible to exclude the possibility that the app was a deterrent to participation in some individuals. The majority of those approached had their own devices.

Conclusions

As time passes, it becomes increasingly difficult to recall episodes of angina accurately. When patients have had angina, accurate recall falls to 25% even within one week. For clinical trials focusing on angina endpoints, daily documentation is therefore advisable. All participants found a smartphone app easy to use. One third of patients entered all their data without needing reminders, and the other two thirds required a mean of 0.4 reminders per week of participation. Overall, data collection was 99% complete.

Chapter 7 Synthesis

In this thesis I have investigated the nature of angina symptoms, their placebo-controlled response to PCI, the relationships between ischaemia tests, and the documentation of daily symptoms. I then show how the findings inform the design of the ORBITA-2 trial.

The commonly taught paradigm for the origin of angina is that anatomical stenosis reduces flow to the myocardium and this insufficient flow causes pain which the patient expresses, which limits exercise tolerance, and which the clinician interprets as angina. In this paradigm, relief of the anatomical stenosis is the obvious way to relieve the angina.

The lack of substantial angina relief observed under placebo-control in ORBITA, despite elimination of the anatomical stenosis and the objective ischaemia, calls this paradigm into question. ORBITA-2 will help establish whether the disappointing effect size is due to lack of effect of PCI or other factors, such as background anti-anginal therapy, length of follow-up and the choice of endpoint.

Of the ORBITA outcomes directly observable by the patient, the one that was closest to be improved by PCI was angina. The ORBITA patients were keen for ORBITA-2 to focus on angina. Together, this was the basis for the complete overhaul of the primary endpoint between ORBITA and ORBITA-2. I developed a symptom smartphone app and a reminder system to enable daily reporting of symptoms. We also took the opportunity to increase the statistical power of ORBITA-2 by not simply counting angina episodes but adding additional levels of refinement so that individuals would spread out on a spectrum to maximise the information gained.

ORBITA's neutral result was not due to low symptom burden

Critics speculated that the result was due to inclusion of CCS Class I patients in the study(29).

In Chapter 3, I tested this hypothesis. If low symptom burden was the cause of a weak average effect of PCI on exercise time, the lower the symptom burden, the lower should be the effect of PCI. My finding was that symptoms did not predict the placebo-controlled effect of PCI on any of the endpoints.

During my research, I noticed that interventional cardiologists use the term "asymptomatic" to refer to patients who have come to the catheter laboratory after coronary disease and ischaemia have been picked up from testing not driven by chest pain. To them, it is obvious that the remaining patients whose tests were driven by chest pain are the other group, namely "symptomatic". Although simple, this categorisation is open to abuse, because those statistics can be misrepresented as though they refer to ongoing recurrent chest pain symptoms. Critics of ORBITA hastened to point out that most elective PCI in the UK is done for symptomatic coronary artery disease, while many patients in ORBITA were not symptomatic. That statement is only true for different meanings of the word "symptomatic": "ever had chest pain", "having chest pain recently". This led me to realise the importance of not using a classification vulnerable to misrepresentation. It encouraged me to design with ORBITA participants a method of capturing symptom burden that would be acceptable to future trial participants and provide good data validity and completeness.

Anatomy does matter after all

For decades, anatomical stenosis was the gold standard against which ischaemia tests were calibrated. So intense was this belief that the community accepted anatomical stenosis to be

dichotomously and unambiguously present versus absent, so that ischaemia tests could be correct or incorrect and therefore have measurable sensitivity, specificity etc.

Anatomy was dethroned in 1996 when noninvasive ischaemia tests (which had been built on anatomy) were used as the reference to enthrone a new gold standard, invasive pressure measurement with FFR(31). The invasive physiology movement arising from this landmark study and the subsequent DEFER, FAME and FAME-2 trials, argued that only FFR and not anatomical stenosis, could be trusted to guide management.

In Chapter 4, I performed a study which has not been carried out since the original 45 patient study in 1996. I used the data from the 200 patients of ORBITA to assess the interplay between the ischaemia tests. I discovered that in the modern era the association between dichotomous FFR and the other ischaemia tests was far less strong than reported in 1996.

Because ORBITA was placebo-controlled and systematically measured an index of ischaemia at follow-up (stress echo), I was able to go on and test the relative abilities of FFR, iFR and anatomy (QCA) as predictors of the placebo-controlled impact of PCI. As expected, these markers did not predict the patient-facing endpoints of exercise time and symptoms.

Surprisingly, however, QCA turned out to be just as effective in predicting placebo-controlled reduction of stress echo ischaemia by PCI, as FFR and iFR. This is curious because FFR and iFR are themselves indices of ischaemia and therefore should have a better opportunity to match stress echo than anatomy, assessed by the simplest possible index.

Angina is not always due to obstructive epicardial disease

There are several possible reasons why PCI did not improve angina as much as expected under placebo-controlled conditions when it appears so effective in clinical practice and unblinded trials(3,6,7,77).

One reason is that the presence of a stenosis and ischaemia does not necessarily mean that the angina symptoms are caused by the stenosis(12). This could be explained by microvascular dysfunction. Microvascular dysfunction frequently co-exists with obstructive epicardial disease(87). Vasomotor disorders(88) could also contribute to the lack of benefit observed in this blinded trial of PCI. These factors were not formally assessed in ORBITA. There is a strong argument for further research into personalising angina therapy depending on the results of vasomotor and microvascular dysfunction testing in the catheter laboratory. This has shown to be beneficial in angina with ischaemia but no obstructive coronary artery disease(89).

There is an argument that most angina in clinical practice must have a major microvascular contribution because most angina in clinical practice is responsive to anti-anginal medications which cannot have any effect on the macrovascular stenosis. It is possible that the macrovascular stenosis, on which we have become fixated because it is easy to visualise on coronary angiography, is in fact a minority contributor to the burden of clinical angina. This would explain why all licensed anti-anginal medications have been demonstrated against placebo-control to reduce angina but this has been surprisingly difficult to demonstrate for relief of even very obvious macrovascular stenosis in ORBITA.

Other cardiac dysfunction could also be contributing to symptoms (and therefore explain the lack of benefit with PCI which can only target relief of an epicardial obstruction), such as left ventricular hypertrophy, valvular disease, and heart failure with preserved or reduced ejection fraction(90). Interestingly, in many of these cases, particularly left ventricular hypertrophy, the mechanism of angina induction could be argued to be microvascular.

Not all chest pain symptoms in people with coronary disease and ischaemia are necessarily angina (in the sense of being caused by ischaemia). I hypothesised that within ORBITA, the participants with the most convincingly cardiac angina symptoms would preferentially benefit

from PCI. Disappointingly, in Chapter 3, I found no evidence of such an association. This could be because there is no association between the nature of symptoms and the likelihood that a stenosis is responsible for symptoms, because the classification of symptoms was insufficiently granular to detect a difference, or because the trial was underpowered for this. In ORBITA-2, additional symptom assessment will be performed.

This indicated to me that distinguishing cardiac origin for chest pain, even in patients with confirmed coronary stenosis and ischaemia, is more difficult than we supposed. I searched the literature and found observational studies describing methods to distinguish angina from non-anginal chest pain but no experimental studies that deliberately induced ischaemia so that the description of the angina could be documented formally. This has led to the development of a specific protocol to identify experimentally the exact pattern of chest pain produced by ischaemia. The study, ORBITA-STAR(61), is using experimental balloon occlusion of coronary arteries and asking participants to report their symptoms. Some of the balloon inflations are placebo so that the nocebo element can be subtracted. It will show if it is possible to establish whether a coronary stenosis is responsible for the symptoms that a patient experiences day-to-day. The implications of finding a method for confirming whether a stenosis is responsible for a patient's symptoms are that revascularisation could be targeted at such lesions and deferred if not. Invasive assessment of vasomotor and microvascular dysfunction could also help to understand whether symptoms are attributable to a stenosis and help to better target therapies.

The value of FFR as a continuous measure of ischaemia

The data presented in Chapter 4 confirm FFR as an index of the impact of a lesion on the function of the heart and of the patient. However, the power of FFR comes from the wide range of values it can distinguish, rather than being dichotomised as "positive" or "negative" by a threshold. Very low values give useful information that the stress echo and exercise test are

likely to show large abnormalities. More importantly, they give a powerful indication that the stress echo score is likely to be markedly improved by PCI. Cropping the richness of FFR to a single dichotomy destroys most of its informativeness, because it can no longer highlight extreme values as distinct from the far more numerous middling values(75).

Can there really be a gold standard for ischaemia?

Ischaemia is a state of insufficient blood flow. However, the tissues can survive with insufficient blood flow: they just manage a little less well and the patient may have symptoms. Even if there was a practical direct measure of tissue blood flow, it would be difficult to define when blood flow is “sufficient”, because the amount required varies with workload and may even vary with types of metabolic fuel being consumed (e.g. carbohydrates versus fats).

Moreover, this begs the question, “sufficient for what?” If one is monitoring wall motion abnormalities on stress echo, one is likely to think that blood flow is sufficient if the heart is able to produce a normal looking pattern of contraction. On the other hand, if one is observing perfusion on MRI, one may think that a rise in flow meeting one’s expectations is a reasonable definition of sufficient. If one was measuring intracardiac biochemicals, one might define sufficient as indicating that there is no adverse change in pH, pO2, ATP, etc. Each of these definitions is individually reasonable and when measured in a range of patients will generally give a conflicting result with the other definitions.

Invasive pressure measurements such as FFR are convenient in the catheter laboratory as an immediate method of totalling up the haemodynamic impact of atheroma, which has been difficult to do by eye. However, there is no reason for a particular fractional pressure to trigger particular downstream consequences across all patients because individuals are likely to have a wide variety of different levels of pressure loss at which any particular process starts to show

abnormality and certainly an even wider variety when all the processes are taken into consideration. Nevertheless, it should be expected that in general worse values on any index of ischaemia should be associated to some extent with worse values on any other index. I certainly saw this within ORBITA.

Given the consistent performance of anti-anginal medications in placebo-controlled trials, it is likely that the presence of an average of three anti-anginal medications in ORBITA greatly limited the ability of PCI to show a symptomatic benefit. When ORBITA was designed, it was assumed that the benefit of relieving such tight lesions would be so large that inevitably angina would be reduced and exercise capacity increased.

The main innovation in ORBITA-2 is removal of anti-anginal medications. This should give PCI a full opportunity to manifest angina reduction. It also introduces multi-vessel disease and lengthens the follow-up period although I do not believe these are as important as removing the anti-anginal medications.

The second important way it differs is in its strong focus on symptoms documented daily by the participants rather than an exercise test at the end.

ORBITA-2: an improved trial

ORBITA-2 will be the first trial to use an ordinal clinical outcome scale for angina. The scale includes number of episodes (including episodes that occurred with reference activities done at least once a week), number of and dose of anti-anginal medications, and need for unblinding and PCI due to intolerable angina, MI and death.

Symptoms will be documented using the symptom smartphone app designed hand in hand with patients who had completed ORBITA.

I expect ORBITA-2, with the advantage of no background anti-anginal medications, a larger sample size, and an explicit focus on reliably acquiring symptoms and analysing them sensitively on the ordinal scale, will have a good chance of finding a benefit of PCI.

If ORBITA-2 is positive when ORBITA was neutral, the key difference may be the absence of anti-anginal medications in ORBITA-2. This might mean that the conventionally recommended approach for angina which is to try anti-anginal medications first and then only use PCI when this in unsuccessful, may not in fact be the ideal approach. People whose angina is not improved by anti-anginal medications, each of which has been licensed through placebo-controlled trials, would suggest that the pain may not be due to myocardial ischaemia which might make them less rather than more liable to benefit from PCI.

An ordinal clinical outcome scale for the primary endpoint

To develop the ORBITA-2 protocol and the symptom smartphone app, I collected feedback from previous ORBITA participants (members of the ORBITA Focus Group) about the ORBITA endpoint and what would be a more relevant endpoint to them. They identified a key challenge in measuring angina outcomes: under-estimation of the impact of angina on a patient's health status by counting only the number of episodes (as patients may restrict their activities to avoid pain or start medication that reduces the angina. With advice from statistician Frank Harrell, I devised an ordinal clinical outcome scale that addresses this issue with the ORBITA Focus Group and sent it to a group of cardiologists for peer review.

Ordinal clinical outcome scales in randomised trials, such as the COVID Outcomes scale(91), are growing in popularity for several reasons. First, they add information beyond a binary endpoint like mortality, thus increasing the power for a given sample size. Second they can combine multiple factors that are part of a patient's overall health status but not measurable as a single continuous variable. For example, duration of symptoms is a continuous variable but an

ordinal scale could combine symptoms with return to work and readmission to hospital and so on.

For angina, the following factors were considered most relevant and were included in the scale for the primary endpoint of ORBITA-2: number of episodes (including episodes that occurred with reference activities done at least once a week), number of and dose of anti-anginal medications, need for PCI due to intolerable angina, myocardial infarction and death. The following factors were not included in the scale: severity of episodes, ability to carry out activities of daily living and other symptoms such as breathlessness, dizziness and fatigue.

When ORBITA-2 is complete, the utility of the ordinal clinical outcome scale can be assessed further through comparison with other measures, especially looking at how the treatment effect differs using different elements of the scale. For example, it will be useful to explore how different methods of counting anti-anginal medications affect the outcome. It may also be possible to identify whether any elements of the scale were redundant.

Delivering placebo-controlled trials of interventional procedures

Placebo-controlled trials of interventional procedures present additional recruitment challenges compared to placebo-controlled drug trials and unblinded interventional trials. This is related to the additional risks a placebo-intervention might pose to patients without any potential for physical therapeutic benefit. Patient reluctance to participate can lead to difficulty in recruiting to target and time in these important clinical trials.

My experience of recruiting patients to a placebo-controlled interventional trial has taught me that there are ways to potentially improve recruitment rates and patient experience. For any trial, participation relies on the researcher-participant relationship. There is a link between recruitment rates and the nature of the trial. For example, an internet survey may have a high

participation rate despite the researchers developing no relationship with the participants. The more invasive or intrusive the study, with more study visits, or greater procedural risk, the more critical this relationship becomes. When the placebo-intervention can carry risks which extend as far as death, the participant places a lot more trust in the research team.

Both clinicians and patients often cite desire for the patient to receive the active treatment as reason not to participate because the idea of deferral of an intervention is not palatable to them. Of course, it is understandable for participants and their clinicians to prefer to be in the intervention arm because of the possibility of therapeutic benefit but we rely on their altruism to accurately assess interventions, without bias, in order to better treat the patients of the future.

I found many patients understood the concept of placebo and were interested in it. Ideally I would approach patients in person as it was more effective for building rapport and offer to involve a friend or family member. Sham and placebo are synonymous terms that can equally be applied to medications or procedures. However, the term sham tends to be used in relation to procedures to highlight to the reader or listener that the placebo arm involves an intervention that mimics the real procedure(92).

I found the phrase “sham procedure” could be associated with “deception” in the minds of both patients and their clinicians so I focused on the word “placebo”. There is increasing receptiveness to the concept of placebo-interventions in the same way that placebo medications have become acceptable to the public.

Symptom smartphone app

The primary endpoint of ORBITA-2 quantifies a patient’s symptomatic response to therapy using daily documentation on a smartphone app. This form of documentation has two key advantages. First, reporting is directly from the patient; it is unfiltered by the physician who may

inadvertently influence the patient in a particular direction and/or include additional factors in their assessment. Second, reporting is frequent; this is more accurate as I found recall of symptoms to be very poor after only 2 days, especially if there had been at least one episode of angina, as opposed to no episodes. Questionnaires based on recall are likely to be a measure of the patient's impression of their condition rather than a reflection of actual episodes experienced. This impression is valuable and relevant but potentially misleading in an unblinded setting.

I found that people were willing and able to use this app. Most participants had their own smartphone, tablet or computer on which to use the app, and the rest were provided with smartphones for the duration of the study. Entries were generally completed in full with a simple reminder protocol and in some cases, family support and encouragement.

Conclusions

ORBITA found that people with stable angina and single-vessel coronary disease who are taking anti-anginal medications were unlikely to receive a benefit from PCI beyond placebo. This thesis aimed to explore this surprising finding. One proposed explanation was that ORBITA participants had disease that was too mild. However, neither coronary physiology, nor anatomical severity, nor the nature of symptoms, predicted benefit from PCI.

ORBITA-2 will provide placebo-controlled data on the efficacy of PCI in people off anti-anginal medications. An ordinal clinical outcome scale for angina was designed in partnership with patients to be a relevant, powerful and inclusive primary endpoint. This endpoint incorporates daily documentation of angina episodes on a novel smartphone app. This larger trial, with longer follow-up, will more definitively establish which patient, if any, will benefit from PCI.

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Chapter 9 Publications arising from this PhD (2018-2021)

First author peer-reviewed publications

Mortality From Ischemic Heart Disease. **Nowbar AN**, Gitto M, Howard JP, Francis DP, Al-Lamee R. Circ Cardiovasc Qual Outcomes. 2019 Jun;12(6):e005375. doi: 10.1161/CIRCOUTCOMES.118.005375. Epub 2019 Jun 4.

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. **NOWBAR AN**, Rajkumar C, Foley M, Howard JP, Seligman H, Petraco R, Sen S, Nijjer S, Shun-Shin M, Keeble T, Sohaib A, Collier D, McVeigh P, Harrell FE, Francis DP, Al-Lamee RK. EuroIntervention. 2022 Feb 11;EIJ-D-21-00649. doi: 10.4244/EIJ-D-21-00649.

Under review at *European Heart Journal – Digital Health*:

Daily angina documentation versus subsequent recall: development of a symptom smartphone app. **NOWBAR AN**, Howard JP, Shun-Shin M, Rajkumar C, Foley M, Basu A, Goel A, Patel S, Adnan A, Beattie CJ, Keeble TR, Sohaib A, Collier D, McVeigh P, Harrell FE, Francis DP, Al-Lamee RK.

First author invited reviews

Controversies in revascularisation for stable coronary artery disease. **NOWBAR AN**, Rajkumar C, Al-Lamee RK, Francis DP. Clin Med (Lond). 2021 Mar;21(2):114-118. doi: 10.7861/clinmed.2020-0922.

Quality of Life Assessment in Trials of Revascularization for Chronic Stable Angina: Insights from ORBITA and the Implications of Blinding. **NOWBAR AN**, Francis DP, Al-Lamee RK. Cardiovasc Drugs Ther. 2021 Aug 21. doi: 10.1007/s10557-021-07198-8.

Co-author publications

1. The Placebo-Controlled Effect of Percutaneous Coronary Intervention on Exercise Induced Changes in Anti-Malondialdehyde-LDL Antibody Levels in Stable Coronary Artery Disease: A Substudy of the ORBITA Trial. Hartley A, Shun-Shin M, Caga-Anan M, Rajkumar C, **NOWBAR AN**, Foley M, Francis DP, Haskard DO, Khamis RY, Al-Lamee R. Front Cardiovasc Med. 2021 Oct 11;8:757030. doi: 10.3389/fcvm.2021.757030. eCollection 2021.

2. Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. Howard JP, Wood FA, Finegold JA, **NOWBAR AN**, Thompson DM, Arnold AD, Rajkumar CA, Connolly S, Cegla J, Stride C, Sever P, Norton C, Thom SAM, Shun-Shin MJ, Francis DP. J Am Coll Cardiol. 2021 Sep, 78 (12) 1210–1222.

3. Mechanical thrombectomy with retrievable stents and aspiration catheters for acute ischaemic stroke: a meta-analysis of randomised controlled trials. Rajkumar CA, Sashiananthan G, Ahmad Y, Seligman H, Thornton GD, Foley M, **NOWBAR AN**,

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4. Phasic Flow Patterns of Right versus Left Coronary Arteries in Patients Undergoing Clinical Physiological Assessment. Seligman H, Nijjer S, van de Hoef TP, de Waard GA, Mejía-Rentería H, Echavarría-Pinto M, Shun-Shin MJ, Howard JP, Cook CM, Warisawa T, Ahmad Y, Androshchuk V, Rajkumar CA, **NOWBAR AN**, Kelshiker MA, van Lavieren MA, Meuwissen M, Danad I, Knaapen P, Sen S, Al-Lamee R, Mayet J, Escaned J, Piek JJ, van Royen N, Davies J, Francis D, Petraco R. EuroIntervention. 2021 Aug 3:EIJ-D-21-00189. doi: 10.4244/EIJ-D-21-00189

5. Placebo-Controlled Efficacy of Percutaneous Coronary Intervention for Focal and Diffuse Patterns of Stable Coronary Artery Disease. Rajkumar CA, Shun-Shin M, Seligman H, Ahmad Y, Warisawa T, Cook CM, Howard JP, Ganesananthan S, Amarin L, Khan C, Ahmed A, **NOWBAR A**, Foley M, Assomull R, Keenan NG, Sehmi J, Keeble TR, Davies JR, Tang KH, Gerber R, Cole G, O'Kane P, Sharp ASP, Khamis R, Kanaganayagam G, Petraco R, Ruparelia N, Malik IS, Nijjer S, Sen S, Francis DP, Al-Lamee R. Circ Cardiovasc Interv. 2021 Aug;14(8):e009891. doi: 10.1161/CIRCINTERVENTIONS.120.009891. Epub 2021 Aug 3.

6. N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. Wood FA, Howard JP, Finegold JA, **NOWBAR AN**, Thompson DM, Arnold AD, Rajkumar CA, Connolly S, Cegla J, Stride C, Sever P, Norton C, Thom SAM, Shun-Shin MJ, Francis DP. N Engl J Med. 2020 Nov 26;383(22):2182-2184. doi: 10.1056/NEJMc2031173. Epub 2020 Nov 15.

7. Achieving Optimal Medical Therapy: Insights From the ORBITA Trial. Foley M, Rajkumar CA, Shun-Shin M, Ganesananthan S, Seligman H, Howard J, **NOWBAR AN,** Keeble

TR, Davies JR, Tang KH, Gerber R, O'Kane P, Sharp ASP, Petraco R, Malik IS, Nijjer S, Sen S, Francis DP, Al-Lamee R. J Am Heart Assoc. 2021 Feb 2;10(3):e017381. doi: 10.1161/JAHA.120.017381. Epub 2021 Jan 26.

8. Cost-effectiveness analysis of percutaneous coronary intervention for single-vessel coronary artery disease: an economic evaluation of the ORBITA trial. McCreanor V, Nowbar A, Rajkumar C, Barnett AG, Francis D, Graves N, Boden WE, Weintraub WS, Al-Lamee R, Parsonage WA. BMJ Open. 2021 Feb 9;11(2):e044054. doi: 10.1136/bmjopen-2020-044054.

9. Effects of Percutaneous Coronary Intervention on Death and Myocardial Infarction Stratified by Stable and Unstable Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. Chacko L, P Howard J, Rajkumar C, Nowbar AN, Kane C, Mahdi D, Foley M, Shun-Shin M, Cole G, Sen S, Al-Lamee R, Francis DP, Ahmad Y. Circ Cardiovasc Qual Outcomes. 2020 Feb;13(2):e006363. doi: 10.1161/CIRCOUTCOMES.119.006363. Epub 2020 Feb 17.

10. Dobutamine Stress Echocardiography Ischemia as a Predictor of the Placebo-Controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Stress Echocardiography-Stratified Analysis of ORBITA. Al-Lamee RK, Shun-Shin MJ, Howard JP, **NOWBAR AN**, Rajkumar C, Thompson D, Sen S, Nijjer S, Petraco R, Davies J, Keeble T, Tang K, Malik I, Bual N, Cook C, Ahmad Y, Seligman H, Sharp ASP, Gerber R, Talwar S, Assomull R, Cole G, Keenan NG, Kanaganayagam G, Sehmi J, Wensel R, Harrell FE Jr, Mayet J, Thom S, Davies JE, Francis DP. Circulation. 2019 Dec 10;140(24):1971-1980. doi: 10.1161/CIRCULATIONAHA.119.042918. Epub 2019 Nov 11.

11. Improving ultrasound video classification: an evaluation of novel deep learning methods in echocardiography. Howard JP, Tan J, Shun-Shin MJ, Mahdi D, **NOWBAR AN**, Arnold AD, Ahmad Y, McCartney P, Zolgharni M, Linton NWF, Sutaria N, Rana B, Mayet J, Rueckert D, Cole GD, Francis DP. J Med Artif Intell. 2020 Mar 25;3:4. doi: 10.21037/jmai.2019.10.03.

12. Gender-Related Differences in Clinical Presentation and Angiographic Findings in Patients with Ischemia and No Obstructive Coronary Artery Disease (INOCA): A Single-Center Observational Registry. Gitto M, Gentile F, **NOWBAR AN**, Chieffo A, Al-Lamee R. Int J Angiol. 2020 Dec;29(4):250-255. doi: 10.1055/s-0040-1709500. Epub 2020 May 14.

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15. Vascular Closure Devices for Transfemoral Angiography. Al-Lamee R, **NOWBAR AN**. Circ Cardiovasc Interv. 2018 Aug;11(8):e007085. doi: 10.1161/CIRCINTERVENTIONS.118.007085.

16. Percutaneous coronary intervention for stable coronary artery disease. Al-Lamee RK, **NOWBAR AN**, Francis DP. Heart. 2019 Jan;105(1):11-19. doi: 10.1136/heartjnl-2017-312755. Epub 2018 Sep 21.

Abstracts

NOWBAR AN, McBeath K, Keene D, Plymen C, Cole G, Francis DP. NIHR Academy Members' Conference 2020. "An app for people with Heart Failure: What have I done to be more inclusive?"

Ganesananthan S, Rajkumar C, Shun-Shin M, **NOWBAR A**, Foley M, Seligman H, Wensel R, Davies J, Francis D, Al-Lamee RK. Abstract 13124: "Exercise Capacity as a Predictor of the Placebo-controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Ventilatory Gas Exchange-stratified Analysis of ORBITA". AHA 2020. https://doi.org/10.1161/circ.142.suppl_3.13124

Ganesananthan S, Rajkumar C, Shun-Shin M, **NOWBAR A**, Foley M, Seligman H, Wensel R, Davies J, Francis D, Al-Lamee RK. Abstract 13116: "Ventilatory Gas Exchange in Stable Coronary Artery Disease". AHA 2020. https://doi.org/10.1161/circ.142.suppl_3.13116

Howard J, Wood F, Finegold J, **NOWBAR A**, Thompson D et al. "A Three-arm N-of-1 Trial With Statin, Placebo and Tablet Free Periods, to Verify Side Effects and Identify Their Cause: The SAMSON Trial." Late Breaking Science American Heart Association 2020.

NOWBAR AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. "Global and temporal trends in mortality from ischaemic heart disease: statistics from the World Health Organisation." British Cardiovascular Society May 2019 Heart (British Cardiac Society) 105(Suppl 6):A93.2-A93. DOI:10.1136/heartjnl-2019-BCS.109

McCreanor V, **NOWBAR A**, Rajkumar C, Barnett A, Francis D et al. "Economic Evaluation of the ORBITA Trial, in the Australian Context" November 2020. Heart, Lung and Circulation 29:S254. DOI:10.1016/j.hlc.2020.09.490

Chapter 10 Awards during this PhD

1. NIHR Doctoral Fellowship 2019 (£557,028)

2. ITMAT Push for Impact Scheme 2019-2021: Machine learning to support general physicians using hand-held echocardiography in acutely unwell patients: Leveraging Imperial's large scale outcome-linked, echocardiography dataset (£178,913) - co-applicant

3. Imperial College COVID-19 Research Fund 2020: Preventing Cardiac Complications of COVID-19 Disease with Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial (£50,000) - co-applicant

Chapter 11 Appendices

ORBITA-2 Patient Information Sheet

Version 1.9 19/08/2021

Imperial College London

Imperial College Healthcare NHS Trust

International Centre of Circulatory Health
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Patient Information Sheet A (Patients who have had an angiogram)

ORBITA-2: A placebo-controlled trial of percutaneous coronary intervention for the relief of stable angina
Chief Investigator: Dr Rasha Al-Lamee

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If you decide not to take part this will not affect your clinical care in any way. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?
You are suffering from chest pain or shortness of breath on exertion. This may be due to a narrowing of your heart arteries. These symptoms occur when you exert yourself. This is referred to as stable angina. Currently we are not sure whether this is best treated by coronary angioplasty (a procedure in which we open up the narrowings in your heart arteries using inflation of a balloon and a stent) or with medication.

In order to assess whether angioplasty really makes a difference to symptoms, exercise capacity and quality of life, we are conducting a study in which participants are randomly allocated to receive angioplasty or placebo (which will involve a procedure where no stent is inserted). Both groups will take medications for angina as needed. For a period of 12 weeks after the procedure both the participants and the medical team will not be told whether or not they received coronary angioplasty. The control group in this study is the group that will not receive angioplasty. This group will be offered angioplasty 12 weeks after the coronary procedure if it is still necessary.

The secondary purpose of the study is to investigate a new tool for assessment of stable angina, called ultrafast stress echo. The major advantage of ultrafast echo is that by using the same probe that is currently used in routine clinical practice, we can capture many more images of your heart over the same period of time. We expect that this will lead to better visualisation of the movement of the heart muscle and therefore greater ability to detect abnormalities. Ultrafast stress echo will be done alongside the conventional stress echo you will have during the study assessments. This will up to 5-10 minutes longer but carries no additional risk to you.

What are the findings and implications of previous trials?
This study follows on from the ORBITA-1 study which was published in the Lancet. ORBITA-1 was the first trial to assess the difference in exercise time with angioplasty compared a placebo procedure. ORBITA-1 showed that while the blood supply to the heart was improved by angioplasty, the ability of patients who had angioplasty to exercise on a treadmill was no better than those patients in the placebo group.

The ORBITA-1 results tell us there is more to learn about angioplasty for stable angina. We still do not know which of these treatments is best in improving symptoms, ability to exert oneself and quality of life. This study will have twice as many patients with a wider range of disease and will last twice as long as the first (ORBITA-1 – published in *The Lancet*). The results from this study

may help us to recommend the best treatment option for patients with your condition and therefore may affect how we treat patients in the future.

Why have I been chosen?
You have been chosen because you have symptoms of angina, had an angiogram showing a narrowing of your heart arteries and are now scheduled to have angioplasty.

Do I have to take part?
No. Your decision as to whether to participate in this study is entirely voluntary. You have the right to refuse as well as to withdraw your participation at any time (even if you agree today) without giving a reason. If you decide not to participate or to withdraw, it will not affect the quality of your care or treatment, nor the relationship you have with your doctor and nursing team.

What will happen to me if I take part?
A doctor will record your medical history and examine you. You will be asked to complete written questionnaires. If you agree, the doctor will record your voice talking about your symptoms and experience for a few minutes. This recording will be transcribed by a member of the research team and stored on a secure computer (transcripts will not include any personal identifiers such as name or address but will not be fully anonymous). You will be provided with a smartphone application and begin daily scoring of symptoms using a visual analogue scale for 2 weeks. You will receive training on how to use the application. (If you were to have no symptoms during this 2 week period you will no longer be included in the trial and routine medical care will continue.)

If you are taking antianginal medications, these will be stopped when you start the trial. This is to assess your symptoms off medication. You will be asked to record your symptoms daily on a smartphone application which will be monitored daily by the research team. If you experience angina, antianginal medication will be started. If you have high blood pressure you will be supplied with a home blood pressure monitor. We will monitor these readings and new medication will be started as required if your blood pressure is elevated. If the medications give you side effects they will be adjusted or stopped.

You will undergo the routine investigations required prior to angioplasty which includes a resting ECG (an electrocardiogram). This is a painless test that looks at the electrical activity of the heart. It involves placing stickers on your arms, legs and across your chest while you lie in a relaxed position. You will also undergo investigations that are often done prior to angioplasty (but are not always required as part of standard care) which includes an ultrasound of the heart (Dobutamine stress echocardiogram) and an exercise test. We are also researching a new way of acquiring and processing ultrasound images so we will take some additional images during your dobutamine stress echocardiogram with a different ultrasound probe. This means your test may take up to 10 minutes longer than a routine stress echo but there is no additional risk. The test will be stopped at any time if you are not happy to proceed or if it is making you unwell. You will also have a blood test which includes your cholesterol level. Together these tests last approximately 2 hours. If you are taking anti-anginal medications, you will need to stop them 72 hours before these tests. You will also be provided with a smartphone application to rate your symptoms on a daily basis throughout the duration of the study. You will then start taking 2 anti-platelet medications (aspirin and either clopidogrel, ticagrelor or prasugrel) unless you are already on them in which case you should continue taking them. Clumping of platelets in the blood can lead to formation of clot that can block stents or cause a heart attack. Anti-platelet medications are therefore used routinely to prevent blockage of stents and heart attacks. A possible side effect of these medications is bleeding in the stomach or intestines so your risk of this will be assessed and you may also start taking an anti-acid medication called lansoprazole.

A week later you will attend the catheter lab for your procedure. We will enter the artery in your wrist or at the top of your leg with a needle. Local anaesthetic will be used (by injection under the skin) and this should not cause any discomfort. A small plastic tube called a cannula will also be inserted into a vein. Wires and a balloon will then be passed into the heart arteries and

measurements taken with an adenosine infusion via the cannula. Adenosine is a drug which is routinely used to open up the small blood vessels within the heart muscle to simulate exercise. In total the process will add 10 minutes to the procedure. The measurements will not prolong your recovery from the procedure. Sometimes the disease will have changed. If the angiogram shows that having a stent is not suitable for you then you will not be randomised and routine medical care will resume. If you are suitable, you will randomly be assigned to have angioplasty (stent) or placebo.

You will receive sedation and music will be played to you through over the ear headphones. You will not be aware of what you have been assigned to. If you are allocated to placebo procedure the procedure will end at this stage. If you are allocated to receive stenting we will proceed to inflate a balloon within the narrowing in your coronary artery to widen the artery and will then place a coronary stent within the narrowing to keep the artery open. We will then repeat the pressure measurements both with and without an adenosine infusion. At the end of this procedure the wires and tubes will be removed.

You will then receive routine care on the cardiology ward. A key aspect of this study is that both you and the medical staff who will continue your care will not be told at this stage whether or not you received a coronary stent during the procedure. You will be monitored for a short period (whether you had stent or placebo) as you recover from the sedation and you will be discharged home later that day with medication.

If you develop chest pain at rest at any time during the trial, you should contact a member of the research team immediately (on 07885587409, 24 hours a day, 7 days a week). If necessary, urgent angioplasty will be performed. You may be withdrawn from the trial. This happened in 0.5% of patients in ORBITA-1.

You will then be invited to return to hospital 12 weeks later for a repeat Dobutamine stress echocardiogram, an exercise test, and questionnaires. If you are taking any anti-anginal medications, you will need to stop them 72 hours before these tests. After these tests we will reveal to you whether you had a stent or not. If not, then you will be offered a third procedure at which stage you will have coronary stenting in discussion with a cardiologist. This will be quite similar to the second procedure, however on this occasion no pressure measurements will be required. Therefore a tube will be passed into the artery in the leg or wrist. A wire will be passed through the narrowing in your coronary artery and coronary angioplasty will be performed with a balloon inflation and then stent implantation into your coronary artery. The wires and tubes will then be removed and you will have routine care on the cardiology ward and will be discharged with medications. You will then be followed up by the clinical team as normal.

If you do not have a stent the anti-platelet medications can be stopped unless you were already on them prior to the study.

You will be reimbursed for travel expenses.

What are the possible side effects, risks and disadvantages of taking part?
The anti-platelet medications (such as aspirin) routinely used in angioplasty can have serious side effects include gastrointestinal bleeding (if you feel dizzy, faint, have black tarry stool or vomit blood you should seek immediate medical attention) and haemorrhagic stroke (bleeding in the brain).

During the procedure we will administer a medication called adenosine. This is routinely used every day in the cardiac catheter laboratory and maybe used in the clinical stages of your procedure. The risk of using adenosine is very low, but, in some patients it may cause a short lived chest discomfort which usually disappears within 3-5 seconds of stopping the drug.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause any damage to your blood vessels. The risk of death, heart attack or stroke during pressure measurement is the same as your routine angiogram (less than 1 in 1000). If you are allocated to receive coronary angioplasty, the risk of the procedure will increase to that of routine coronary angioplasty (1 in 100 risk of major bleeding, death, heart attack or stroke following coronary angioplasty). There is a risk that the wire used to make the measurement could cause damage to your coronary arteries; if this happens, we will not proceed to randomisation as we will need to perform coronary stenting. This occurred in 2% of patients in ORBITA-1. This risk is minimised as the measurements are performed by an experienced senior consultant cardiologist. We will place the wires under x-ray guidance; the mean effective dose from this procedure is equivalent to 10.4 years of natural background radiation and carries an additional lifetime cancer risk to a health individual of 0.1%.

It is normal practice for patients with a significant coronary artery narrowing to have 2 procedures with a coronary angiogram first followed by a coronary angioplasty procedure. In this study, those patients who are allocated to the placebo group may require a third procedure in which they have coronary stenting. This will be an additional risk. The additional risk will be the same as that of routine coronary angioplasty (1 in 100 risk of major bleeding, death, heart attack or stroke following coronary angioplasty). All the angiogram procedures carry some exposure to radiation. In the catheter laboratory this is made up of routine imaging of the blood vessels, measurement of the severity of the stenosis, and the treatment of the disease with a stent. The patients who did not receive a stent will not have been exposed to the radiation associated with the stent procedure. However, they will undergo a third procedure. During this procedure, patients will receive some minor additional imaging, but most of the procedure will be limited to opening up the blocked vessel and inserting a stent. Whilst this will undoubtedly require an additional dose of radiation, the dosage will be extremely small.

There will be a time period between your diagnostic angiogram and treatment with a stent. This is routine for many patients after a diagnostic angiogram. The usual waiting time for PCI in routine practice can vary between approximately 2 and 4 months. If you are in the PCI arm of the study the stenting will be performed at the time of the research angiogram. If you are in the placebo arm of the study, you will wait a further 12 weeks after the research angiogram until the study follow-up is complete. You will be carefully monitored throughout this period.

As part of the study you will have a dobutamine stress echocardiogram at the start and end of the study. This involves having an ultrasound scan of your heart. We will then inject a medication called dobutamine which will speed up your heart rate while continuing to scan your heart. There is a very small risk of minor side effects such as chest pain, development of low or high blood pressure, irregular heartbeats, dizziness, nausea and fatigue. There is also a less than 1 in 1000 risk of heart attacks and ventricular arrhythmias.

What are the possible benefits of taking part?
You will not directly benefit from this study, but the information we gain will give us a much better understanding of how to treat your condition and may help develop a new way of assessing if the narrowing in your heart arteries is causing your chest pain.

What if something goes wrong?
Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of this study or your care then you should immediately inform the Investigator (Dr Al-Lamee (02075945735)). The normal National Health Service complaint complaints mechanisms are also

available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?
If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in a pseudonymised format and any information obtained from this investigation that can be identified will remain confidential. Relevant sections of your medical notes & data collected during the study may be looked at by individuals from Imperial College, from regulatory authorities or from Imperial NHS trust, where it is relevant to you taking part in this research. We will ask for your permission for these individuals to have access to your records. Your GP will be informed that you are participating in this study and will be requested to share information about any adverse events. While taking part in the study we may find something about your health that you were unaware of and we would inform your GP of this. Your data (including the audio recordings and transcripts) will be stored for 10 years after the end of the study in accordance with the Data Protection Act 2018.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time without having to give a reason. If you withdraw from the study, we will keep and continue to use all your previously collected data. We will, however not collect any further data about you.

What would happen if I lost the ability to consent during the study?
In the unlikely event that during the course of the study you were no longer able to give your consent because you had lost the capacity to do so, you would be withdrawn from the study and no further testing performed. However, any personal data collected previously would be retained and used for the purposes which you had already consented.

What will happen to the results of the research study?
This study will contribute to the theses of a number of PhD students at Imperial College London. Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you wish, we will give you a summary of the results.

Who is sponsoring the study?
The study will be sponsored by Imperial College London.

Who is funding the research?
The study will be funded by NIHR Imperial Biomedical Research Centre.

Who has reviewed the study?
This study has been reviewed and given a favourable ethical opinion by the London-Central Research Ethics Committee.

	Where
Visit 1	Hammersmith Hospital, London
Visit 2	St Mary's Hospital, Paddington, Imperial College Healthcare NHS Trust, London
Visit 3	Hammersmith Hospital, London
Visit 4	St Mary's Hospital, Paddington, Imperial College Healthcare NHS Trust, London

What protection is in place against COVID-19?
While it is deemed clinically necessary, you will have 1 hospital visit instead of 4. Visit 1 can be done on the telephone and Visits 2 and 4 will not be take place unless deemed safe to do so (i.e. you will not have stress echo or exercise tests).

When you attend the hospital, staff will take all necessary infection control precautions. Randomisation procedures will be performed according to local infection control guidelines. If you experience symptoms, please let a member of the research team know so that your procedure can be re-scheduled if needed.

If you have any further questions please do not hesitate to contact:
Dr Christopher Rajkumar or Dr Rasha Al-Lamee (0207 594 5735)
christopher.rajkumar@nhs.net

Thank you for taking the time to consider participating in this study

ORBITA-2 Informed Consent Form

Version 1.3

09/12/2019

Imperial College London

Imperial College Healthcare NHS
NHS Trust

International Centre of Circulatory Health
NHLI, 2nd floor B Block
Hammersmith Hospital
London W12 0NN

Tel No: 0207 594 5735

CONSENT FORM A

(Patients who have had an angiogram)
ORBITA-2 IRAS ID 242451
Chief Investigator: Dr Rasha Al-Lamee

		Please initial as applicable
1.	I have read the Patient Information Sheet (A Version ….).	☐
2.	I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.	☐
3.	I have spoken to Dr……	☐
4.	I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my medical or legal rights being affected.	☐
5.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust. I give permission for these individuals to access my records.	☐
6.	I agree to take part in this research study.	☐
7.	I agree to my GP being informed about my participation in this research study and I understand my GP will be asked to share adverse event information with the research team.	☐

Signature…… Date……

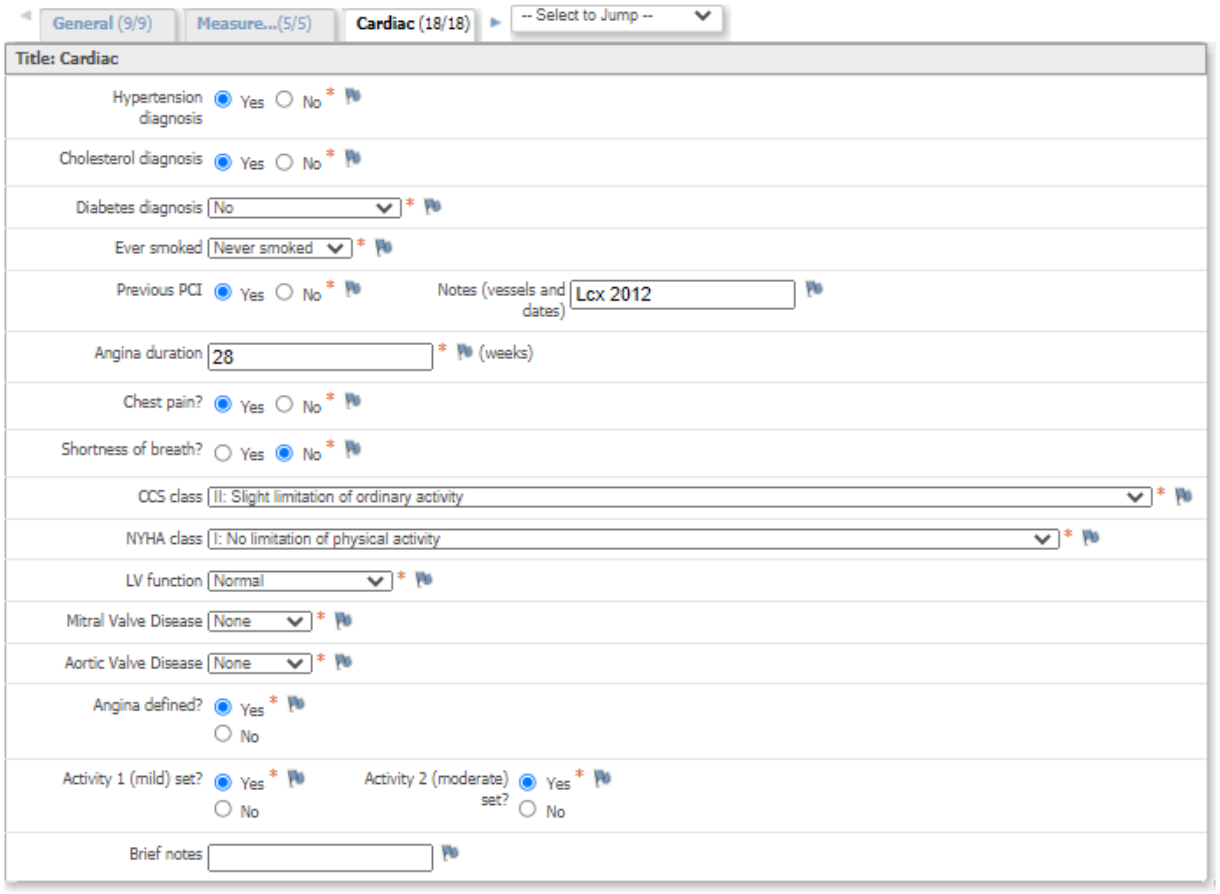
Name (block capitals)……

Signature of Study Investigator…… Date……

Name (block capitals)……

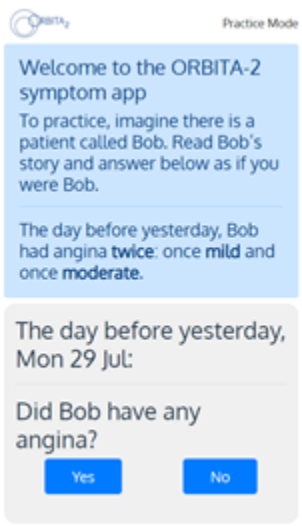
ORBITA-2 Excerpts from the Electronic Case Report Form

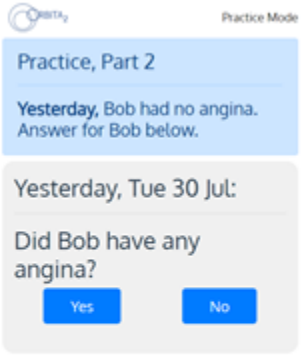
Follow-up Assessment	07-Sep-2019		completed	MacMRCMcG ORBITA2	1.0		
				Questionnaires ORBITA2	1.0		07-Sep-2019 (anowbar)
				Assessments ORBITA2	1.0		09-Sep-2019 (anowbar)
				FU CCS ORBITA2	1.0		09-Sep-2019 (anowbar)
				Adverse events ORBITA2	1.0		09-Sep-2019 (anowbar)
				Drugs change ORBITA2	1.0		09-Sep-2019 (anowbar)
Study End	04-Sep-2019		data entry started	Withdraw ORBITA2	1.1		
				Unblind ORBITA2	1.0		09-Sep-2019 (anowbar)
Pre-randomisation Assessment	17-Jun-2019		completed	MacMRCMcG ORBITA2	1.0		
				Pre-rand CCS ORBITA2	1.0		
				Angio Procedure ORBITA2	1.2		18-Aug-2019 (crajkumar)
				Bloods ORBITA2	1.1		09-Sep-2019 (anowbar)
				Adverse events ORBITA2	1.0		09-Sep-2019 (anowbar)
				Questionnaires ORBITA2	1.0		09-Sep-2019 (anowbar)
				Assessments ORBITA2	1.0		09-Sep-2019 (anowbar)
				Drugs change ORBITA2	1.0		09-Sep-2019 (anowbar)
Randomisation Procedure	17-Jun-2019		completed	Rand Procedure ORBITA2	1.0		18-Aug-2019 (crajkumar)
				Procedural complications ORBITA2	1.0		18-Aug-2019 (crajkumar)
Pre-randomisation Interval (2)	17-Jun-2019		completed	Drugs change ORBITA2	1.0		09-Sep-2019 (anowbar)
				Adverse events ORBITA2	1.0		09-Sep-2019 (anowbar)
Pre-randomisation Interval (1)	12-Jun-2019		completed	Drugs change ORBITA2	1.0		09-Sep-2019 (anowbar)
				Adverse events ORBITA2	1.0		09-Sep-2019 (anowbar)
Enrolment	28-May-2019		completed	MacMRCMcG ORBITA2	1.0		
				Enrolment ORBITA2	1.0		09-Sep-2019 (anowbar)
				Enrolment drugs ORBITA2	1.1		10-Jun-2019 (anowbar)
				Questionnaires ORBITA2	1.0		10-Jun-2019 (anowbar)
Screening visit	28-May-2019		completed	Inclusion and exclusion criteria ORBITA2	V1.0		10-Jun-2019 (anowbar)

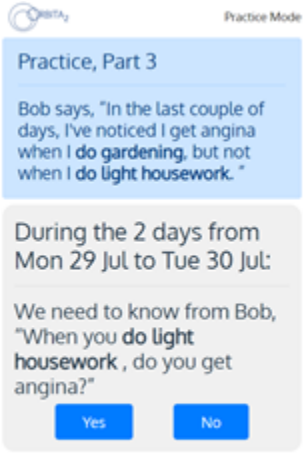

General (9/9)
Measure...(5/5)
Cardiac (18/18)
-- Select to Jump --
Title: Cardiac
Hypertension diagnosis
Yes
No
Cholesterol diagnosis
Yes
No
Diabetes diagnosis
No
Ever smoked
Never smoked
Previous PCI
Yes
No
Notes (vessels and dates)
Lcx 2012
Angina duration
28
(weeks)
Chest pain?
Yes
No
Shortness of breath?
Yes
No
CCS class
II: Slight limitation of ordinary activity
NYHA class
I: No limitation of physical activity
LV function
Normal
Mitral Valve Disease
None
Aortic Valve Disease
None
Angina defined?
Yes
No
Activity 1 (mild) set?
Yes
No
Activity 2 (moderate) set?
Yes
No
Brief notes

ORBITA-2 Symptom Smartphone App Screenshots

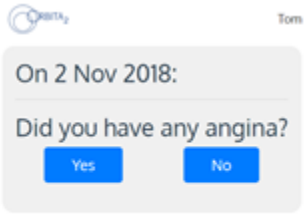
Practice module

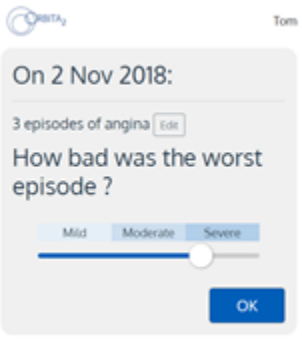






Daily symptom questions





Standard Operating Protocol for ORBITA-2 Randomisation

Angiography Procedure

1. Consent for ? proceed
2. Explain procedure including the following research elements (headphones, sedation, chest pain during FFR measurement)
3. Antecubital fossa cannula preferably green
4. Send bloods for fasting lipids
5. Ensure clopidogrel started appropriately
6. Reassure patient on entering lab
7. Put on oxygen with monitoring
8. Get radial access (femoral if necessary) – record this as start time using time on Volcano machine, use this clock to record each step with a time stamp on the case report form
9. Place headphones and music on
10. Ask nurses to prepare IV adenosine 140mcg/kg/min, midazolam and either fentanyl or morphine
11. Connect the ECG and BP cables from the s5 (if applicable) to the haemosystem (this is already done on an s5i).
12. Enter patient information on imaging system. (IVUS first, then switch to FFR)
13. Select iFR on the bottom right hand corner of the screen.

14. Select the Settings tab on the bottom of the screen. Make sure the ECG Trace box is ON.

15. Select the Pressure tab on the s5 or s5i. Make sure the s5 or s5i has the MAP reading at 3 beats.

16. Once the ECG trace is on and the MAP reading is at 3 beats, select the HOME tab on the bottom of the screen to go to the “LIVE” screen. Make sure there is an ECG signal on the top of the HOME screen.

17. Flush the guide wire with enough saline to fill the dispenser hoop and let sit for at least 2 minutes.

18. Plug the guide wire into the Volcano pimette and allow it to zero. It will take 10 to 15 seconds for the wire to “zero”. Once wire has zeroed, the machine will display a message at the bottom of the screen that states, “Wire Zeroed, ready to insert.” The wire can now be taken out of the dispenser hoop.

19. Administer 300 mcg IC Nitro through the guide catheter, per standard lab procedures.

20. Shape the guide wire (if needed), insert and advance transducer to the end of the guide catheter. Flush catheter with saline. Make sure guide catheter is coaxial with vessel and AO pressure is not damped. If the AO pressure trace appears damped, ideally disengage the guide catheter to ensure an optimum AO pressure trace. If this is - Remove wire introducer. Tighten Tuohy manually, even if the Tuohy has a haemostatic valve.

21. Wait 10 seconds, then press NORMALISE on the sS5 /S5i. Make sure Pd/Pa equals 1.00. If Pd/Pa does not equal 1.00, wait 10 seconds and then press NORMALISE again. If the Pd/Pa ratio still does not equal 1.00, then check the height of the AO transducer to

make sure it is midline to the patient and NORMALISE again. If Pd/Pa ratio still will not equal 1.00, then open new wire and contact the Volcano study team member to obtain instructions on returning the guide wire to Volcano. Press RECORD on the Volcano system to acquire 5-10 beats of normalisation in FFR mode. Fluoro record wire position.

22. Position the wire and pressure sensor at least 3 vessel diameters distal to the lesion to be evaluated. Flush the guide catheter with saline (to prevent pressure damping). Remove wire introducer. Close Tuohy manually, even if it is a Tuohy with a haemostatic valve. Turn transducer back on to pressure and make sure Pa pressure is not damped.

23. In FFR mode record PdPa 30 seconds

24. Press RECORD on the Volcano system and make an iFR measurement.

25. Select FFR on the bottom left hand corner of the screen.

26. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 20 seconds. Continue recording and make an FFR assessment at the same location using Adenosine infusion through a peripheral vein at 140 mcg/kg/min up to 3 minutes in duration or until stable hyperemia as determined by the physician. Make sure the recording is uninterrupted for the entire duration, no injection of contrast, or saline, or disruption to the aortic pressure transducer should be made during this recording phase. A 3 beat moving Pd/Pa average window will be used to obtain FFR. For patients greater than 100kg, but less than or equal to 220kg, please follow hospital protocol (found in pharmacy) for non-invasive cardiac stress testing using Adenosine and make note of it in the case report form. Data from patients greater than 441 pounds (200 kg) will be excluded.

27. Wait for PdPa to return to reading in step 20.

28. Make another iFR measurement.

29. iFR pullback

30. Drift check. Check normalisation. If Pd/Pa is outside of 1.00 ± 0.02, then re-NORMALISE and repeat steps 21-29 to obtain a drift-free comparison. Ensure that you record at least 5-10 beats of normalisation.

31. Repeat above steps again for each vessel as required.

32. Sedate using incremental doses of midazolam and opiate until asleep (monitor with eyelid palpation)

33. Randomise patient to PCI or placebo arm using Randi online tool (https://icch.med.ic.ac.uk/randi/login) Click randomize for ORBITA2-BLOCKS and enter 4 digit ID. Type the hospital site in the comments. Click randomise and then click again to confirm details of patient are correct. It will appear like nothing is happening. To reveal the arm the patient has been allocated to, click cancel and go to Trial in the panel down the lefthandside. Select ORBITA2-BLOCKS. Then click Own Randomization Data in the panel down the lefthandside. Find the current date and time and patient ID and in the Treatment column of that row you will see which arm the patient is allocated to. Inform operator.

34. If the patient is then randomised to PCI, pullback the wire, re-administer 300 mcg IC Nitro through the guide catheter and repeat steps 21-26 to repeat iFR and FFR post-PCI. Ensure distal wire position is identical to that in position 19.

35. Complete an entry on the Case Report Form for each Baseline/iFR/FFR comparison run.

36. Monitor lab staff to ward staff handover. Then remove patient's headphones.

37. Put front sheet on patient's notes to maintain team blinding.

38. Archive to memory stick to create CSV file, then put memory stick in + save csv/sdy/bmp images (v340Spgt)

39. Go to cath lab bookings administrator to grey out a PCI date in 12 weeks time (or up to 13 weeks) if patient had placebo explaining that you can't give them the name yet and that no letter should be sent out to the patient)

40. At point of discharge from ward perform blinding index test on patient and a member of ward staff who looked after patient. Give patient discharge letter including date of follow-up tests (at which time patient will also be unblinded) and date for next procedure (give a date regardless of which arm they were, this will be a dummy date for those who had PCI but patient and all blinded staff will not know that). These 2 dates go in the ORBITA-2 calendar.

41. Delay any cardiology follow-up appointments until after unblinding and remind patient to contact us if they receive letter about any appointments

42. Book taxi on Green Tomato app 2 hours prior to discharge (0208 568 0022)

43. Give discharge letter

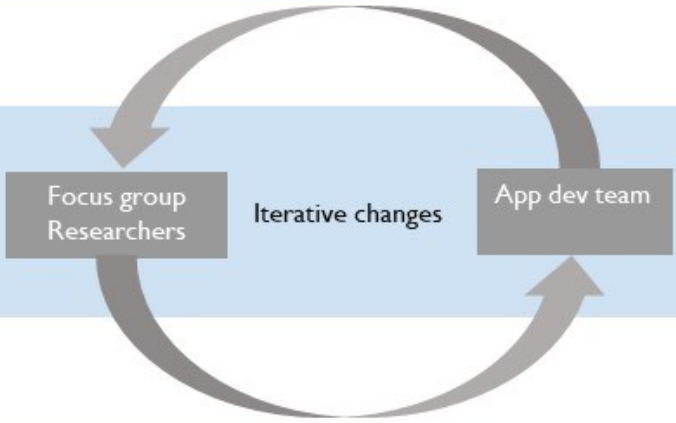
44. Remind patient to continue recording their symptoms every day on the smartphone app.

45. File copies of pre and post ECGs

46. File copy of trial consent form and original stress echo consent form in NHS notes

47. On ORBITA-2 app, enter the randomisation date and click fill down weekly dates

Phases of development for symptom smartphone app

Planning	Agree aims of project Chose platform Define timeline Survey of patients on angina triggers	• Focus group • Researchers AN, RAL
Design	Plan user access controls and hierarchy Choose fonts, layout, button types, slider types and colours Draft participant and researcher-facing wording	• Focus group • Researchers AN, RAL, DF
Development	Backend database structuring Error message design Software verification and validation e.g. date stamping	• App dev team
Testing		
Implementation	Write SOP for use of app in ORBITA-2 Create researcher user accounts Train staff how to onboard participants Troubleshooting with AN	• Researchers AN • Trial site staff

Association between enrolment symptoms and change in exercise time with individual data points shown