

# Angina in stable ischaemic heart disease

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## **Abstract**

The placebo effect describes the natural human tendency to react positively to a healer. As the first placebo-controlled trial of percutaneous coronary intervention (PCI), the ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial was ground-breaking. After decades of routine use, ORBITA showed that PCI offered no significant angina relief compared to placebo on a background of maximally tolerated antianginal medications. Despite this finding, guidelines continue to recommend PCI as an additional therapy for persistent angina refractory to antianginal medication.

ORBITA left cardiologists with many questions. Central to the future of PCI as a treatment for angina was the question of whether PCI was simply ineffective, or whether the guideline directed antianginal medication used in ORBITA had attenuated all the observable benefit of PCI. I led the delivery of the ORBITA-2 Trial; designed to answer this question.

ORBITA-2 was a randomised, double-blind, placebo-controlled trial in patients with stable angina. To determine the unattenuated efficacy of PCI for angina relief, it was designed with the critical step of removing background antianginal medical therapy.

ORBITA-2 shows that PCI, under double-blind placebo-controlled conditions, without background antianginal medications, gives clear benefit across multiple endpoints: angina, quality of life and treadmill exercise time. The benefit is immediate and sustained, although not all symptoms are eliminated.

In this thesis, I present the primary and secondary results of the ORBITA-2 Trial. In addition, I present a systematic review and meta-regression of all placebo-controlled trials of procedural

therapies, designed to determine for which endpoints blinding matters most. Finally, I present the results of the *n-of-1* placebo-controlled ORBITA-STAR trial which tested whether independent symptom verification using anot at al placebo-controlled ischaemic stimulus could distinguish which patients achieve symptom relief from PCI.

## **Declaration of Originality**

The work presented in this thesis is original and my own, and all else is appropriately referenced.

Dr Christopher A Rajkumar

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## **Dedication**

I dedicate this thesis to my husband George who has supported me resolutely as we navigated the highs and lows of research, and who's patience was repeatedly tested as I set out for yet another day trip to a distant cath lab in 'a town beginning with B'. Your love, dedication, and ability to outsmart NEJM statistical editors made this happen!

To my Mum and Dad, Dianne and Raj, my sister, Anita and my Grandparents: Thank you for teaching me the value of hard work, setting me up for success and keeping me grounded... "but when are you going to be a normal doctor again?"

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# **I Introduction**

## **1.1 Stable coronary artery disease**

Coronary artery disease (CAD) is accumulation of atherosclerotic plaque within epicardial coronary arteries<sup>1</sup>. Acute presentations of CAD, namely unstable angina and acute coronary syndromes are characterised by sudden plaque rupture resulting in thrombosis and rapid occlusion of the arterial lumen. These abrupt plaque rupture events may cause infarction of the subtended myocardium because myocardial adaptation and collateralisation have not had time to develop. Emergency revascularisation reduces mortality in these settings.<sup>2</sup>

In the absence of acute plaque rupture, coronary atheroma is referred to as “stable” CAD. Stable CAD is most commonly clinically silent. For clinical manifestations to occur, deposition of atheroma must be in sufficient quantity and organised in an anatomical pattern capable of producing stenosis of the arterial lumen which is sufficient to restrict blood flow and, therefore, oxygen delivery below the metabolic requirement of the supplied myocardium.

When myocardial oxygen demand increases during periods of stress, restriction of blood flow due to stable CAD can be detected with dynamic electrocardiographic changes and focal wall motion abnormalities on provocative testing. This reversible stress-induced supply-demand imbalance is referred to as myocardial ischaemia.

Stable angina is a clinical syndrome associated with myocardial ischaemia that may present as exertional chest discomfort<sup>3</sup>. Stable angina only manifests if an individual patient is capable of

increasing their myocardial oxygen demand sufficiently to generate adequate ischaemia to be symptomatically perceptible.

Importantly, the presence of stable CAD does not imply the presence of myocardial ischaemia, and the presence of myocardial ischaemia does not imply the presence of angina. While stable CAD is a highly prevalent condition, the number of patients with reversible myocardial ischaemia is substantially smaller, and of these, the number who are symptomatic with angina diminishes again because progression between these distinct diagnostic entities is not inevitable.

It is imperative to accurately assess where an individual patient sits in this cascade from asymptomatic stable CAD, to myocardial ischaemia, to symptomatic angina as evidence-based treatments differ from level to level.

## **1.2 Epidemiology and prognosis**

Despite CAD being clinically quiescent in the majority, its high prevalence means that it remains the most common cause of mortality worldwide due to its acute manifestations<sup>4</sup>. In the United Kingdom, the annual death rate from CAD has fallen by more than half in the last 50 years, reflecting changing risk factor profiles, disease modifying therapies and the emergence of revascularisation therapies for myocardial infarction<sup>5</sup>. Nevertheless, CAD is still responsible for the second highest number of deaths in the United Kingdom after Alzheimer's dementia<sup>5</sup>. With improved detection and survival with CAD, more patients are living with the diagnosis for longer, estimated at 2.3 million patients in the United Kingdom at present<sup>5</sup>.

Of patients with stable CAD receiving medical therapy, the annualised risk of death or myocardial infarction is between 3-4%<sup>6,7</sup>. This risk is increased in patients who are symptomatic with angina<sup>8</sup> or have a larger burden of ischaemia on stress-perfusion imaging studies<sup>9</sup>. Whether ischaemia carries direct prognostic significance or is simply a confounding factor for greater atheroma burden remains a controversial question. Left ventricular dysfunction, however, carries the greatest prognostic relevance in stable CAD<sup>10</sup>.

### **1.3 Treatment of stable CAD**

#### **1.3.1 Goals of treatment**

There are two principal goals in the treatment of stable CAD. The first is to improve prognosis by preventing progression to myocardial infarction or death. This treatment goal applies to all patients in whom a diagnosis of CAD has been made, regardless of the presence of ischaemia or symptoms. Secondly, in patients with symptoms, an additional goal applies; namely treating angina to improve quality of life and functional capacity<sup>11</sup>.

#### **1.3.2 Treatments to improve prognosis**

##### *1.3.2.1 Lifestyle modification*

Evidence-based lifestyle modifications should be recommended for all patients. Lifestyle modifications with the strongest evidence for reduction of major adverse cardiovascular events in patients with stable CAD are smoking cessation<sup>12</sup>, adherence to a Mediterranean diet<sup>13</sup>, intentional weight loss<sup>14</sup> and regular physical activity<sup>15</sup>.

##### *1.3.2.2 Medical therapy for prognosis*

“Optimal medical therapy” (OMT) is a term often used to refer to a combination of medical therapies with proven cardiovascular risk reduction benefits in patients with established stable

CAD. Low dose aspirin<sup>16</sup> and statin<sup>17</sup> therapy are long established prognostic treatments for stable CAD. More recently, a range of additional medications have also been tested in randomised controlled trials and shown to independently reduce major adverse cardiovascular events through optimisation of risk factors. For lipid lowering, these include ezetimibe<sup>18</sup>, PCSK9 inhibitors<sup>19</sup> and icosapent ethyl<sup>20</sup>. Antihypertensive medications (targeting to a blood pressure <130/80mmHg) offer a 10% reduction in all-cause mortality for each 10mmHg reduction in systolic blood pressure<sup>21</sup>. For diabetic patients sodium-glucose transporter 2 (SGLT2) inhibitors<sup>22</sup> and glucagon-like peptide 1 (GLP1) receptor agonists<sup>23</sup> reduce major adverse cardiovascular events. Finally in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial, the addition of low dose rivaroxaban to aspirin in patients with stable CAD reduced the primary endpoint of myocardial infarction, stroke and cardiovascular death, albeit with an increase in major bleeding<sup>24</sup>.

#### *1.3.2.3 Revascularisation to improve prognosis*

- Coronary artery bypass grafting (CABG)

Coronary artery bypass grafting (CABG) predated percutaneous techniques for myocardial revascularisation. Trials of CABG are now long outdated as they were conducted before the introduction of modern medical therapy which is known to reduce cardiovascular risk. When the results of the Veterans Affairs Study<sup>25</sup>, Coronary Artery Surgery Study (CASS)<sup>26</sup> and the European Coronary Surgery Study<sup>27</sup>, performed in the 1970-1980's were pooled in a meta-analysis<sup>28</sup>, the results favoured CABG versus no revascularisation, with greater benefits seen in patients with left main stem disease or high risk 3-vessel disease. However, these trials were not only performed without contemporary risk reduction medical therapy but were conducted without even aspirin or statins. Therefore, whether CABG offers prognostic benefit in stable CAD in the modern era of highly effective medical therapy remains untested and unknown.

- Percutaneous Coronary Intervention (PCI)

The first percutaneous coronary intervention (PCI) was performed in 1978 with the principal aim of angina relief<sup>29</sup>. However, once CABG had been accepted as beneficial from a prognostic standpoint, myocardial revascularisation with PCI was tested in the hope of similar benefit. Early trials of PCI were of balloon angioplasty only (without stent implantation), and did not show benefit of angioplasty<sup>30,31</sup>.

## **COURAGE**

Without stent implantation, restenosis rates were high, and therefore hope remained that PCI could reduce death and myocardial infarction in a new era of revascularisation trials when use of intracoronary stents following angioplasty became accepted practice. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomised 2287 patients to PCI or conservative therapy, with a primary endpoint of death or non-fatal myocardial infarction<sup>32</sup>. At this point, it was accepted that trials of revascularisation should be performed on a background of aspirin and statin therapy, and almost all patients in COURAGE were treated with these agents. At 5-year follow up there was no difference in the primary endpoint between groups. The trial was criticised for randomising patients with insufficiently severe CAD, and not mandating ischaemia as an entry criterion. However, non-invasive evidence of ischaemia was available in all patients, and 88% were symptomatic with angina at enrolment.

## **BARI-2D**

The presence of diabetes is associated with a greater risk of adverse consequences from CAD. Therefore the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial set out to answer a similar question in a diabetic cohort<sup>33</sup>. Patients were first stratified according to

their anatomy, into those suitable for PCI or CABG. They were then randomised to that mode of revascularisation with intensive medical therapy or to intensive medical therapy alone. Within the subset deemed suitable for CABG, revascularisation was not associated with a mortality advantage, but did reduce the rate of myocardial infarctions. Within the group deemed suitable for PCI, there was no benefit of revascularisation for either endpoint.

## **FAME-2**

Following these disappointing results, it was hoped that more accurate patient selection, through better identification of ischaemic stenoses, would reveal the true benefit of PCI. By measuring a trans-stenotic pressure gradient, fractional flow reserve (FFR) was developed and validated as a surrogate of ischaemia that could be measured in the catheterisation laboratory. The Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation 2 (FAME 2) trial randomised patients with at least one stenosis with an FFR value  $\leq 0.80$  to either PCI + OMT or OMT alone<sup>6</sup>. There was no difference in death or myocardial infarctions between groups, but the trial was stopped early due to a high rate of “urgent revascularisation” in the conservatively managed arm. Importantly, these urgent revascularisation events were not triggered by ECG changes or troponin rises, but only by symptoms in unblinded patients in the OMT arm who had been told that they had an ischaemic stenosis that had been left “untreated”<sup>34</sup>. FAME-2 illustrated the pitfalls of unblinded trial design when incorporating endpoints which are subject to bias with knowledge of treatment allocation, often referred to as “soft endpoints”. When an intervention is routinely performed in clinical practice, withholding that intervention from patients in the control arm of clinical trials can be a cause of anxiety for both the patients and their physicians. That anxiety may be manifested as an enhancement of awareness of symptoms by the patient and increase the likelihood of a physician to trigger an “urgent revascularisation” event. This phenomenon has been termed “subtraction anxiety” and is reason to be sceptical of clinical trials which incorporate such results within a primary composite endpoint<sup>34</sup>.

## ISCHEMIA

One limitation of all preceding trials which attempted to determine if there was prognostic benefit of PCI in stable CAD was that they recruited patients after diagnostic coronary angiography. This is problematic, as this design incurs a selection bias in which those patients with the most severe CAD are systematically excluded from trials due to reluctance of cardiologists to randomise such patients.

The ISCHEMIA trial was designed to overcome this limitation by recruiting and randomising patients before invasive coronary angiography<sup>7</sup>. Patients entered the trial following positive ischaemia testing and then eligibility was confirmed with a CTCA examination, the results of which were kept blinded from the patient and their cardiologist. This ensured that the trial population was enriched with patients with severe CAD, who may not have been offered recruitment into the trial by their cardiologist, had their coronary anatomy been known prior to enrolment.

ISCHEMIA randomised 5,179 patients to an initial invasive approach of coronary angiography and subsequent revascularisation (CABG or PCI) versus a conservative approach in which patients did not undergo coronary catheterisation. There was no significant difference in the primary composite endpoint of cardiovascular death, MI, hospitalisation for unstable angina, heart failure or resuscitated cardiac arrest at median follow up of 3.2 years<sup>7</sup>.

As the largest trial to date, ISCHEMIA was not only helpful in confirming that revascularisation of stable CAD does not improve prognosis, but it also helped to clarify our understanding of ischaemia as a marker for outcomes. Although ischaemia was already known to be associated with poorer outcomes in stable CAD<sup>35,36</sup>, what remained unclear, was whether this was due to a direct causal link or whether the presence of ischaemia was simply a confounding factor representative of a greater burden of atherosclerosis. By selecting patients based on ischaemia testing, and not on anatomic characteristics, the negative result of the ISCHEMIA trial showed that the driver of

coronary events is the overall atheroma burden throughout the coronary tree and not the presence of focal severe stenoses capable of causing ischaemia during stress testing<sup>37</sup>.

#### *1.3.2.4 Summary*

All the aforementioned trials have been subject to criticism, and the results of these trials can only be applied to patient cohorts representative of the subjects recruited to them. Select subgroups have been systematically excluded from recent trials (left main disease, severe left ventricular impairment, “unacceptable” angina at baseline). Nevertheless, pooling the data in meta-analyses of trials of revascularisation in stable CAD, show a consistent finding of prognostic neutrality between revascularisation and conservative strategies<sup>2</sup>. Medical therapy alone is so effective in reducing cardiovascular events in stable CAD because it has the advantage of being equally effective across the totality of atherosclerotic disease within the coronary tree. This is an advantage over revascularisation, which can only target the lesions perceived to be most severe; but which are not necessarily the lesions most likely to cause coronary events. All patients with stable coronary artery disease should be treated with optimal risk reduction medical therapy. The success of modern medical therapy has been to drive cardiovascular event rates ever lower, and it is upon this background of low event rates that it is now increasingly difficult to demonstrate any additional prognostic effect of revascularisation in stable CAD.

### **1.4 Angina Pectoris**

The first description of angina is attributed to William Heberden in 1772. He described ‘a disorder of the breast marked with strong and peculiar symptoms... [with a] sense of strangling and anxiety’. Individuals affected are ‘seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if

it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes<sup>33</sup>.

Two and a half centuries have elapsed since Heberden's initial account of angina pectoris. Despite exponential advancement in diagnostic testing and therapeutic ability, Heberden's vivid portrayal of angina continues to hold a central position in the practice of contemporary cardiologists. This enduring relevance serving as a reminder that human symptomatology is a steadfast constant in a world characterised by rapid and continuous evolution.

Angina is the principal symptom associated with obstructive coronary artery disease. With few physical signs on examination, the diagnosis of this symptom is based exclusively on accurate history taking. The probability of discovering CAD then depends on the typicality of these symptoms elicited and the patient's risk factor profile. Diamond and Forrester set out the original criteria for which chest pain is judged as typical angina, which continue to be used widely, from medical school teaching to national clinical guidelines<sup>38</sup>:

- Typical (definite angina):
  - Substernal discomfort with characteristic quality (dull, heavy or aching) and duration (minutes, not seconds or hours)
  - Provoked by exertion or emotional stress
  - Relieved by rest or short acting nitrate drug
- Atypical (probable angina) meets two off the above criteria
- Non-cardiac chest pain meets one or none of the above criteria

As such, angina is a syndrome, and its diagnosis depends on the typicality of the presenting symptoms. Tests of coronary anatomy and ischaemia to confirm flow limiting potential are helpful to improve the pre-test probability that a patient presenting with chest pain does indeed have

angina. However, such tests can never truly confirm that a patient's symptom is truly angina, since coronary artery disease and ischaemia may be present in a patient whose chest pain is caused by an alternative pathology.

### **1.4.1 Treatments to improve symptoms**

#### *1.4.1.1 The placebo effect*

The term “placebo” (Latin: “I will please”) describes a positive physiological response to a stimulus perceived to be healing. The neurobiological basis of placebo effects are likely to lie in classical conditioning and are modulated by the effects of expectation, which itself is influenced by verbal cues and social learning<sup>39</sup>. Although the placebo effect is most commonly referred to in the context of a beneficial observed effect of an inert substance in a clinical trial, it is important to recognise that active treatments which are known to be effective also exert a placebo effect. Therefore, the measured efficacy of any treatment can be expressed as the sum of its real biological and placebo effects. Placebo effects are therefore not just important in clinical trials but can be an important part of day-to-day clinical practice.

Nevertheless, for treatments with symptomatic endpoints, placebo control should be considered mandatory in clinical trial design so that the total measured efficacy of the active treatment can be corrected for the size of the placebo effect to determine whether the real biological component of benefit justifies the cost and risks of the treatment.

#### *1.4.1.2 Antianginal medical therapy*

In patients deemed to be symptomatic with angina, clinical guidelines recommend that the first line approach to treat symptoms is antianginal medication<sup>1</sup>. Short acting sublingual nitrates are recommended for immediate angina relief and can also be used pre-emptively before exertion in patients with reproducible and predictable symptoms. A requirement for licencing of any new

pharmaceutical agent to treat symptoms is a placebo-controlled trial. Multiple classes of medications have proven antianginal properties in randomised placebo-controlled trials<sup>40</sup> and the optimal choice of medication is usually based on patient characteristics and potential side effects. Beta-blockers or calcium channel blockers are a standard approach to first line therapy, with dihydropyridine calcium channel blockers preferred for patients with a low resting heart rate, and beta blockade preferred for patients with left ventricular impairment or a history of MI<sup>1</sup>. Guidelines recommend reviewing response with dose up titration or addition of a second agent when angina has not been sufficiently suppressed after 4 weeks. Second line agents with proven efficacy in placebo-controlled trials for angina relief include ranolazine<sup>41</sup>, nicorandil<sup>42</sup>, ivabradine<sup>43</sup> and trimetazidine<sup>44</sup>.

#### *1.4.1.3 Unblinded evidence for PCI as a therapy for angina*

Unlike pharmaceutical therapies, procedural treatments for angina have often been considered exempt from the requirement for placebo-controlled trials prior to becoming accepted therapy and even entering clinical guidelines. The reason for this is that adding placebo-control into a trial of a procedural therapy has often been considered either unfeasible or unethical to perform.

For decades, most trials of revascularisation in stable CAD were performed to determine whether there was a prognostic benefit offered by PCI or CABG. For the principal endpoints of death and MI, an unblinded design was entirely reasonable since knowledge of treatment allocation would be unlikely to bias these results. However, with disappointing results for reduction of death and MI, trial authors have often placed increasing focus instead on their secondary endpoints of symptom relief in these unblinded trials.

The RITA-2<sup>45</sup>, BARI-2D<sup>33</sup> and ISCHEMIA<sup>7</sup> trials are three examples of trials in which there was no impact of revascularisation on mortality, but nevertheless the trials reported favourable

symptomatic benefits from revascularisation. Many other examples exist and a full list of unblinded trials which compared revascularisation with medical therapy alone for treatment of angina is shown Table 1.1. Whilst these trials formed a consistent message that revascularisation did not improve mortality, but did improve symptoms, one important factor was being overlooked. All these trials were unblinded and hence could not determine whether the observed symptom improvement was attributable to revascularisation, or whether it was a placebo effect.

Perhaps the clearest evidence of the pitfalls of unblinded symptom assessment comes from the FAME-2 trial. The most remarkable result from this trial were not from the randomised cohort, but instead from the patients withdrawn from the trial when they were found to have no significant ischaemia. In these patients, there was a 77% relative risk reduction in CCS class II-IV angina within 30 days of telling them that their stenosis was non-significant, and nothing further needed to be done<sup>6</sup>. This reduction in angina was achieved with no change in medical therapy and no revascularisation. Reassurance alone had achieved excellent symptom relief. These findings underscored the vulnerability of symptom assessments when disease status and treatment allocation are not blinded from patients and physicians.

#### *1.4.1.4 Blinded evidence for PCI as a therapy for angina*

The concept of performing a placebo-controlled procedural trial for angina relief is not new to cardiology. Following unblinded experience appearing to show benefit, internal mammary artery ligation was routinely performed in the 1950s with a view to relieving angina. Unfortunately, the first placebo controlled trial of this therapy revealed this benefit to be solely a placebo effect and the technique was quickly abandoned<sup>46</sup>. Similarly, initial unblinded trials of laser myocardial revascularisation stimulated interest in the procedure as it seemed to be effective<sup>47,48</sup>. However, this benefit was later dismissed as placebo when a blinded trial was latterly conducted<sup>49</sup>.

Despite this history of procedural therapies failing to deliver placebo-resistant benefits in blinded clinical trials, many considered that a placebo-controlled trial was not necessary for PCI. The benefits of PCI for symptom relief had already been seen in multiple unblinded trials and PCI was already approved for use as an antianginal therapy in clinical guidelines. Perhaps for these reasons, some considered it “unethical” to conduct a placebo-controlled trial. However, the truth remained that unblinded clinical trials were unable to determine what proportion of the observed clinical benefit of PCI was a physical effect and how much was placebo. This was an important question for a therapy which carries significant cost to healthcare providers and a small, but not insignificant risk to patients.

ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) was the first placebo-controlled trial to test angina relief from PCI<sup>50</sup>. ORBITA tested the incremental efficacy of PCI versus a placebo procedure on a background of maximally tolerated antianginal medical therapy. In this way, it was a test of clinical guidelines which place antianginal medications as first line therapy, with PCI reserved as an add-on therapy for patients who remain symptomatic.

The primary endpoint of ORBITA was change in treadmill exercise time. This was chosen to reflect the US Food and Drug Administration and European Medicines Agency recommendations on assessment of antianginal therapies. The sample size calculation was informed by the unblinded, but otherwise comparable, Angioplasty Compared to Medicine (ACME) Trial<sup>51</sup>. In ACME, plain balloon angioplasty offered a 96 second larger increment in treadmill exercise time when compared to medical therapy alone. In ORBITA, it was likely that use of a placebo comparator would attenuate the difference between arms, however, ORBITA also had the benefit of almost 2 decades of procedural enhancements in PCI and the arrival of drug eluting stents, which should have augmented the antianginal effect. With these factors in mind, ORBITA was powered

conservatively, and designed to be able to detect a difference in treadmill exercise time increment of just 30 seconds.

ORBITA enrolled patients with severe single-vessel coronary artery disease (CAD) who had presented with angina symptoms. Initially, patients underwent a six-week phase of medication optimisation, during which antianginal medications were initiated and their doses progressively uptitrated. By the time of randomisation, the median number of antianginal medications was three. Patients underwent pre-randomisation invasive physiological assessments, including fractional flow reserve (FFR) to estimate the burden of ischaemia. The randomisation procedure involved administration of intravenous opiates and benzodiazepines to achieve deep conscious sedation. The patient wore over-the-ear headphones of auditory isolation. Once sedation was confirmed, patients were randomly assigned to either percutaneous coronary intervention (PCI) with drug-eluting stents or a placebo procedure. Following the randomisation procedure, patients, all medical caregivers, and outcome assessors remained blinded to the treatment allocation until the conclusion of the six-week follow-up period.

To much surprise, in the ORBITA trial, percutaneous coronary intervention (PCI) did not provide greater relief from angina than the placebo procedure. The primary endpoint, the between-group difference in treadmill exercise time increment, was not significant, with a mere 16.6-second larger improvement in the PCI group<sup>50</sup>. Similarly, there was no significant difference between PCI and medical therapy alone in angina status, as measured by the Canadian Cardiovascular Society (CCS) score or the angina frequency derived from the Seattle Angina Questionnaire.

After many years of unblinded data supporting the commonly accepted view that PCI was effective for alleviating symptoms, the primary findings of the ORBITA trial were so astonishing to the

interventional cardiology community that prominent experts across the globe promptly rejected the results as inconceivable<sup>52–55</sup>.

It would be logical that the patients with the most ischaemic stenoses at baseline would have the most to gain symptomatically through PCI. However, the findings of a pivotal secondary analysis also defied expectations. This analysis stratified ORBITA's results based on the degree of ischaemia determined by invasive coronary physiology, specifically pre-randomisation FFR and iFR values<sup>56</sup>. Surprisingly, it revealed that the initial severity of ischaemia, as gauged by these invasive measures, did not correlate with the extent of angina relief provided by PCI. Instead, the modest placebo-controlled benefit of PCI was more closely, though weakly, associated with the impact on wall motion abnormalities during stress, as evaluated by dobutamine stress echocardiography<sup>57</sup>.

These findings challenged our core understanding of the link between anatomical stenosis, its haemodynamic effects, and the resulting symptoms. The anticipated straightforward linear relationship between ischaemia and symptoms was revealed to in fact, be far more complicated. In hindsight, these surprising results should not have been entirely unexpected. Our prior understanding was built on decades of unblinded data, which continuously reinforced the existing beliefs. Each piece of data was constrained by the inherent limitations of an unblinded study design.

Every clinical trial has its limitations, and ORBITA is no exception. The study was adequately powered but nevertheless had a modest sample size. Participants were on high doses of guideline recommended antianginal drugs which may have attenuated the observed effect of PCI, and patients with multivessel disease were excluded. This raises questions about how broadly the results apply. Some critics argued that the participants had too few symptoms or insufficient

ischaemia at baseline<sup>52</sup>, despite comparisons with real-world data. Although PCI provides immediate correction of haemodynamic parameters of ischaemia, some questioned whether the six-week follow-up period was sufficient to see the full benefits of PCI<sup>58</sup>.

Nevertheless, ORBITA provided some unequivocal insights: the placebo effect of PCI is large and proving this, for the first time, has rendered previous unblinded evidence of the symptomatic benefits of PCI questionable, and likely unreliable. More broadly, ORBITA established that use of a placebo procedure for trials of PCI was safe, acceptable to patients and a new necessary reference standard for clinical trial design when assessing symptomatic endpoints in trials of revascularisation in stable CAD.

#### **1.4.2 Unanswered questions**

The ORBITA trial generated as many questions as it answered. Strict inclusion criteria raised legitimate questions regarding the generalisability of the trial's result. Would the result have been different in patients with multivessel disease, and therefore a greater burden of ischaemia? If the patients had been taking fewer antianginal medications, would a benefit of PCI have emerged against placebo? Would extended follow up offer a larger effect?

Some questioned whether a different result would have been yielded if evidence of ischaemia had been mandatory, rather than guideline directed, in all patients, or if the patients had been more severely symptomatic at baseline? Perhaps a different primary endpoint would have been more sensitive to the physiological changes of PCI which were clearly smaller than many had expected.

More fundamentally, ORBITA raised deeper questions regarding our primary understanding of the biophysiological basis of angina. PCI was immediately effective in reversing the anatomic and physiological substrate for myocardial ischaemia, as demonstrated by post-PCI pressure wire

assessments and follow up dobutamine stress echocardiography. Why then, did this eradication of ischaemia not translate to a symptomatic benefit? Of all the questions ORBITA raised, understanding this paradox would be the critical step to unlocking how best to treat patients with stable angina.

Table 1.1: Unblinded clinical trials comparing revascularisation to medical therapy alone for angina relief.

| Trial       | Inclusion Criteria                                                                              | Mode of Revascularisation                                       | Antianginal Medical Therapy                                             | n   | Placebo control | Symptom endpoints                                                                         | Follow up duration | Result                                                                                                                                                                                                                                                                   |
|-------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------|-----|-----------------|-------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ACME 1992   | Men with 1VD and exercise induced myocardial ischaemia                                          | Balloon angioplasty only                                        | ISDN, GTN, Beta-blockers, CCB or a combination in medical therapy group | 212 | No              | Angina freedom, angina frequency, exercise time increment                                 | 6 months           | PCI superior for angina freedom ( $p<0.01$ ) and exercise time increment, $p<0.0001$ ). Trend to superiority for angina frequency ( $p=0.06$ )                                                                                                                           |
| MASS 1995   | Single vessel, severe proximal LAD stenosis                                                     | 33% balloon angioplasty<br>33% CABG<br>33% No revascularisation | Beta-blockers, CCB and nitrates                                         | 214 | No              | Angina freedom, $\geq$ CCS II angina                                                      | 3 years            | Angina freedom superior with CABG (98%) > PCI (82%) > No revascularisation (32%), ( $p<0.01$ ) for all comparisons. No patients had $\geq$ CCS2 angina.                                                                                                                  |
| ACME 2 1997 | Men with single (n=227) or two-vessel (n=101) disease and exercise induced myocardial ischaemia | Balloon angioplasty only                                        | Nitrates, beta-blockers and CCB in progressive stepped approach         | 328 | No              | Angina frequency, angina freedom exercise time increment, quality of life score increment | 6 months           | No difference between balloon angioplasty and no balloon angioplasty in patients with 2VD (Angina frequency $p=0.75$ , freedom $p=0.09$ , exercise time increment $p=0.89$ , quality of life $p=0.32$ ). Larger benefits of no balloon angioplasty in patients with 1VD. |

|                              |                                                        |                          |                                         |      |    |                                                  |                               |                                                                                                                                                                                                                                                                |
|------------------------------|--------------------------------------------------------|--------------------------|-----------------------------------------|------|----|--------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| RITA-2 1997                  | Single and multivessel disease patients                | Balloon angioplasty only | Beta-blocker, CCB, long-acting nitrates | 1018 | No | ≥CCS II angina, exercise time increment          | 3 months (symptom endpoint s) | Balloon angioplasty reduced ≥CCS II angina by 16.5% (p<0.001) over conservative therapy. Exercise time increment of 35s in favour of balloon angioplasty at 3 months (p<0.001)                                                                                 |
| ACME extended follow up 1998 | Men with 1VD and exercise induced myocardial ischaemia | Balloon angioplasty only | Not specified                           | 175  | No | Angina freedom, exercise time increment          | 3 years                       | Balloon angioplasty superior for angina freedom (62% vs 47%, p<0.05), and exercise time increment (+79.8s vs -16.8s, p<0.04).                                                                                                                                  |
| AVERT 1999                   | Stable CAD, asymptomatic or mild-moderate angina       | 52% PCI<br>48% No PCI    | Not protocol specified                  | 341  | No | Change in CCS class, SF-36 quality of life score | 18 months                     | PCI superior for change in CCS class (p=0.009). No significant difference in SF-36 quality of life score between groups.                                                                                                                                       |
| RITA-2 7 year 2003           | Single and multivessel disease patients                | Balloon angioplasty only | Beta-blocker, CCB, long-acting nitrates | 1018 | No | ≥CCS II angina, exercise time increment          | 7 years (median)              | Treatment difference attenuated to 6.4% in favour of balloon angioplasty for ≥CCS II angina at 5 years (p=0.011). Exercise time increment also reduced, but still in favour of balloon angioplasty at 3 year follow up (+25s mean difference, 95% CI 6 to 44s) |

|                 |                                    |                                                    |                                                                                                            |      |    |                                                         |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------|------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------|------|----|---------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MASS II<br>2003 | Prox<br>2VD/3V<br>D/LAD<br>disease | 33% CABG<br>33% PCI<br>33% No<br>revascularisation | Nitrates, beta-<br>blockers,<br>CCB                                                                        | 611  | No | Angina<br>freedom, CCS<br>>2, positive<br>exercise test | 1 year    | Angina freedom superior with<br>either CABG (59%) or PCI (52%)<br>in comparison to no<br>revascularisation (36%),<br>( $p<0.0001$ , and $p<0.001$ ,<br>respectively. No significant<br>difference between PCI and<br>CABG ( $p=0.16$ ). No patient had<br>CCS>2 in any group at follow up.<br>Significant reduction in rate of<br>positive ETT following CABG<br>(36%, $p<0.0001$ ) or PCI (18%,<br>$p=0.0005$ ), but not no<br>revascularisation group (5%,<br>$p=0.45$ ) |
| COURAGE<br>2007 | 1VD,<br>2VD or<br>3VD              | 50% PCI<br>50% No PCI                              | Long-acting<br>metoprolol,<br>amlodipine<br>and<br>isosorbide<br>mononitrate<br>alone or in<br>combination | 2287 | No | Angina<br>freedom                                       | 4.6 years | At 5 years, no significant<br>difference in freedom from<br>angina between patients in the<br>PCI or no PCI groups (74% vs<br>74%, $p=0.35$ )                                                                                                                                                                                                                                                                                                                              |
| JSAP 2008       | 1VD or<br>2VD                      | 50% PCI<br>MT 50% No<br>PCI                        | Antianginal<br>therapy                                                                                     | 384  | No | Change in CCS<br>class                                  | 3 years   | Overall change in CCS class<br>significantly better in the<br>PCI+MT group ( $p<0.0001$ )                                                                                                                                                                                                                                                                                                                                                                                  |

|                                          |                                                                                       |                                                                                                              |                                                                |      |    |                                            |                  |                                                                                                                                                                                                            |
|------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|------|----|--------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MASS II<br>extended<br>follow up<br>2010 | Prox<br>2VD/3V<br>D/LAD<br>disease                                                    | 33% CABG<br>33% PCI<br>33% No<br>revascularisation                                                           | Titrated<br>approach of<br>nitrates, beta-<br>blockers,<br>CCB | 611  | No | Angina<br>freedom,<br>refractory<br>angina | 10-years         | Freedom from angina at 10-year<br>follow up was 64% for CABG,<br>59% for PCI and 43% with no<br>revascularisation. No patients<br>had refractory angina in any arm.                                        |
| FAME II<br>2012                          | 1VD,<br>2VD or<br>3VD and<br>FFR $\leq$<br>0.80                                       | 50% PCI<br>50% No PCI                                                                                        | Beta-blocker,<br>CCB, long-<br>acting nitrate                  | 78*  | No | CCS $\geq$ 2                               | Mean<br>213 days | Non-significant reduction in CCS<br>$\geq$ 2 angina in PCI group at 12<br>months in comparison no PCI<br>(2.4% vs 16.2%, $p=0.07$ ). *Data<br>only available for 78/888 patients<br>randomised.            |
| ISCHEMIA<br>2020                         | Single or<br>multi-<br>vessel<br>disease<br>and<br>moderate<br>to severe<br>ischaemia | 50% Initial<br>invasive<br>strategy (PCI<br>74.2%, CABG<br>25.8%)<br>50% Initial<br>conservative<br>strategy | Beta blocker,<br>CCB                                           | 4617 | No | Seattle angina<br>questionnaire            | 48<br>months     | Significantly greater increase in<br>SAQ summary score in the group<br>randomised to revascularisation<br>(difference in increment of 4.1,<br>4.2 and 2.9 points at 3, 12 and 36<br>months, respectively). |

|              |                                                                                        |                                                                                        |                   |     |    |                              |                  |                                                                                                       |
|--------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------|-----|----|------------------------------|------------------|-------------------------------------------------------------------------------------------------------|
| ISCHEMIA-CKD | Single or multivessel disease, moderate to severe ischemia and advanced kidney disease | 50% Initial invasive strategy (PCI 85%, CABG 15%)<br>50% Initial conservative strategy | Beta blocker, CCB | 705 | No | Seattle angina questionnaire | Median 2.2 years | No significant difference in SAQ summary score between revascularisation and conservative strategies. |
|--------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------|-----|----|------------------------------|------------------|-------------------------------------------------------------------------------------------------------|

*Table 1.1: Summary of unblinded clinical trials assessing symptom relief from revascularisation compared with medical therapy alone. Adapted from Al-Lamee et al. BMJ 2022; 377: e067085*

## **2 Research Aims and Objectives**

The purpose of this research is to define the role of percutaneous coronary intervention for treatment of stable angina. The specific aims and hypotheses of each study are detailed below.

### **2.1 Does blinding matter? The impact of placebo-control on randomised trials of procedural interventions: a systematic review and meta-regression**

#### **2.1.1 Background**

Placebo-control is often omitted from randomised trials of procedural interventions which report symptom endpoints. The commonest stated justifications for this are that it may be unfeasible or unethical to perform a placebo surgical procedure. Previous studies have shown procedural interventions do have a significant placebo effect; however, the magnitude of this effect has not been quantified, and we do not know which endpoints are most vulnerable to this bias in trials of procedural interventions.

#### **2.1.2 Aims**

The aim of this systematic review and meta-regression was to quantify the magnitude of the placebo effect for procedural interventions in medicine and surgery by comparing the observed effect sizes from matched blinded and unblinded clinical trials. The hypothesis of this study was that the magnitude of the placebo-effect would vary and be dependent on the characteristics of the endpoint being reported. The overarching aim of this study was therefore to clarify for which endpoints placebo-control should be considered mandatory for unbiased reporting in clinical trials.

## **2.2 Percutaneous coronary intervention for stable angina (ORBITA-2): a randomised, placebo-controlled trial**

### **2.2.1 Background**

PCI is often performed to treat stable angina. Guidelines recommend PCI as an additional therapy for angina that persists despite antianginal medication. Under placebo-controlled conditions, PCI was seen to have surprisingly little additive benefit when used in this way. We do not know whether this smaller than anticipated effect size is because antianginal medication had attenuated all the potential benefit of PCI, or if PCI is simply ineffective for stable angina when compared to placebo.

### **2.2.2 Aims**

ORBITA-2 was designed to determine the effect of PCI compared to placebo without background antianginal medication in patients with single or multivessel coronary artery disease and evidence of ischaemia over 12 weeks of blinded follow up. The aim of this trial was to determine whether the removal of antianginal medications would reveal the underlying effect of PCI, and therefore test PCI as a monotherapy approach for stable angina.

## **2.3 Systematic Trial of Angina Assessment prior to Revascularisation: an n-of-1 placebo-controlled study in stable coronary artery disease (ORBITA-STAR)**

### **2.3.1 Background**

Despite effective reduction of ischaemia, up to 60% of patients continue to report symptoms following successful PCI for stable angina. The reasons for this are unknown. One possibility is that symptoms which persist following revascularisation may have an alternative aetiology. There

is no evidence-based method to objectively verify whether a symptom has an ischaemic origin or not, and for that reason, patients commonly undergo revascularisation for “atypical angina” or “angina equivalent” syndromes. Cardiologists often provoke symptoms of ischaemia during balloon occlusion across a coronary stenosis. Some patients report a precise replication of their usual pain during these episodes of ischaemia, but many patients do not. We do not know the significance of this, nor what this means for the success of subsequent PCI.

### **2.3.2 Aims**

ORBITA-STAR was designed to test whether independent placebo-controlled symptom verification during an ischaemic stimulus could predict which patients would respond to PCI. The hypothesis of this study was that patients with reproducible symptoms during experimental episodes of ischaemia would derive the greatest symptomatic benefit from PCI.

## **2.4 The role of the collateral circulation in stable coronary artery disease: an invasive placebo-controlled study**

### **2.4.1 Background**

In stable coronary artery disease, revascularisation decisions are based upon physiological tests to identify surrogates of ischaemia. However, little correlation exists between burden of ischaemia and severity of symptoms. This is poorly understood, and of major significance for treatment decisions in stable angina. The collateral circulation is an adaptive physiological response whereby neo-angiogenesis provides an alternative source of oxygenated blood to ischaemic myocardium. We do not know how the collateral circulation impacts upon symptoms of stable angina.

### 2.4.2 Aims

This study was designed to answer the following questions: Firstly, in patients with severe single vessel CAD without antianginal therapy, does more severe ischaemia result in more severe day-to-day angina? Second, in patients with stable angina, does the collateral circulation develop as a response to ischaemia? Finally, does the collateral circulation have functional relevance in attenuating the severity of ischaemic chest pain? We also investigated whether progressive collateral recruitment was a mechanism for ischaemic preconditioning.

### **3 Materials and Methods**

The methods described here relate principally to the ORBITA-2 Trial. The methods for chapters 4 (Systematic review and meta-analysis), 6 (ORBITA-STAR) and 7 (Coronary collateral sub-study) are detailed in their respective chapters.

#### **3.1 Design**

ORBITA-2 was an investigator initiated, prospective, multi-centre, randomised placebo-controlled trial of PCI in patients with stable angina and single or multivessel ischaemia without antianginal medical treatment. The study design is shown in Figure 3.1.

#### **3.2 Ethical approval**

Ethical approval was granted by the London Central Research Ethics Committee (reference 18/LO/1203). Each participant provided written informed consent. The ORBITA-2 consent form is available in the supplementary appendix.

#### **3.3 Setting**

ORBITA-2 was conducted at 14 trial sites in the United Kingdom. A list of trial sites and principal investigators is provided in Table 3.1.

#### **3.4 Population**

Subjects were enrolled following diagnostic invasive coronary catheterisation or computed tomography coronary angiography (CTCA). A full list of inclusion and exclusion criteria are available in Table 3.2 and Table 3.3, respectively.

### **3.5 Study Interventions**

#### **3.5.1 Enrolment**

At enrolment, baseline assessments included Quality of Life Questionnaire (European EQ-5D-5L), Seattle Angina Questionnaire (SAQ), MacNew Heart Disease Health-related Quality of Life Questionnaire, Canadian Cardiovascular Society (CCS) angina class, MRC Dyspnoea score and the McGill Pain Questionnaire.

Antianginal medications were suspended at enrolment. All changes to medications throughout the trial were performed in line with the ORBITA-2 medication prescribing standard operating procedure (See Appendix - Section 10.11).

#### **3.5.2 Pre-randomisation symptom assessment phase**

All patients were provided with a smartphone application and began daily scoring of symptoms using a visual analogue scale for a 2-week symptom assessment phase. If they were asymptomatic during this period, they would exit the trial and routine medical care would resume. If they reported intolerable anginal symptoms during this period, antianginal medications would be initiated from a pre-specified panel by the trial team and this information would be recorded in the case report form.

#### **3.5.3 Pre-randomisation visit**

Any antianginal medications started during the pre-randomisation symptom assessment phase were stopped for 72 hours prior to pre-randomisation visit. At this visit, repeat symptom questionnaires were performed. Blood testing for lipid profile and HbA1c were performed. Patients then underwent an exercise treadmill test (ETT) using the modified Bruce protocol and a dobutamine stress echocardiogram (DSE).

#### **3.5.4 Invasive assessment**

To maintain blinding, participants wore over the ear headphones playing music for the duration of the invasive procedure to achieve auditory isolation. Radial or femoral arterial access was obtained at the operator's discretion. Coronary angiography was performed, and pre-randomisation pressure wire assessments made including Fractional Flow Reserve (FFR) and instantaneous wave-free ratio (iFR) for each vessel with a  $\geq 70\%$  stenosis. An intravenous infusion of adenosine at 140mcg/kg/min was used for hyperaemic measurements. In each case the wire was placed  $> 3$  vessel diameters distal to the most distal stenosis. Normalisation was documented for each measurement along with a drift check. Repeat measurements were required in the presence of drift greater than  $\pm 0.02$  units.

Following completion of pressure wire assessment, the operator identified vessels suitable for treatment and the selection was recorded in the case report form prior to randomisation. If no vessels were suitable for PCI, based on non-invasive or invasive assessment of ischaemia the patient would not proceed to randomisation and would exit the trial at this stage.

#### **3.5.5 Sedation, Randomisation and Blinding**

Before sedation, patients were informed that they may experience pain or shortness of breath during the procedure. Patients were sedated using incremental doses of intravenous benzodiazepines and intravenous opiates to a deep level of conscious sedation such that they were unresponsive to verbal or tactile stimulus, but that airway, ventilation and cardiovascular function are maintained. Once sedation was confirmed, patients were randomised 1:1 to PCI or placebo procedure using an online randomisation tool. Any deviation from the random treatment allocation was treated as a protocol violation.

- **PCI**

Patients randomised to receive PCI were treated with angioplasty and implantation of any second-generation drug eluting stents, at the operator's discretion, to all vessels with demonstrable ischaemia which were suitable for PCI. Complete revascularisation at the index procedure was mandated. Post dilation of stents and use of intravascular imaging was encouraged. Following PCI, repeat pressure wire studies were performed to ensure that treatment had resulted in normalisation of haemodynamic parameters to non-ischaemic values.

- **Placebo procedure**

Patients randomised to placebo remained sedated on the catheter laboratory table for a minimum of 15 additional minutes with no intervention performed.

All documentation in the catheter laboratory was managed using a standardised protocol. Nursing staff were only permitted to document that the patient had been randomised in the ORBITA-2 trial. They were not permitted to document the randomisation arm or any further details of the procedure in the clinical notes. All clinical documentation was instead made in the patient's research notes by the unblinded research fellow.

After the procedure, the patient's handover to the recovery room medical team included only access sites and medication given. This was identical between arms as even those patients randomised to placebo received heparin for the invasive physiological protocol. Handover did not include the treatment allocation. Instead, recovery ward staff were instructed to care for all participants in the ORBITA-2 trial as if they had undergone PCI for monitoring and post procedural care. Catheter laboratory staff were not permitted to have any further contact with the patient for the duration of their hospital stay.

A standardised discharge letter was given to all patients and their GPs which informed the reader that a blinded procedure had taken place, that this procedure was a coronary angiogram +/- angioplasty, that all medications should remain unchanged, including continuation of dual antiplatelet therapy, until trial follow-up is complete. The letter stated that they should receive standard post-angioplasty care until full details of the procedure are provided after unblinding at 12 weeks.

All contact with the patient following the randomisation visit was made by members of the research team who were also blinded to the patient's treatment allocation.

The fidelity of blinding was assessed at two timepoints in this trial (See blinding index assessment below).

### **3.5.6 Follow up assessment phase**

Following the randomisation visit, any antianginal medications started during the pre-randomisation symptom assessment phase were suspended. Patients then continued to score their symptoms daily using the smartphone app for a blinded follow up period of 12 weeks. Patients were able to restart antianginal medications if symptoms required, in accordance with the pre-specified protocol, as directed by a blinded member of the research team. Each medication change was documented in the case report form.

### **3.5.7 Follow up assessment visit**

At the end of the 12 week follow up assessment phase, participants returned to the hospital for repeat symptom questionnaires, exercise treadmill test and dobutamine stress echocardiogram.

### **3.5.8 Unblinding and study end**

At the end of the follow up assessment visit, patients were informed of their treatment allocation. Patients who were randomised to placebo were offered PCI at the discretion of their clinician. Dual antiplatelet therapy was stopped for patients in the placebo arm who did not wish to proceed to PCI.

## **3.6 ORBITA-2 smartphone application**

The primary endpoint of ORBITA-2 was a novel clinical endpoint based on daily reporting of symptoms by the patient, with data collected using a smartphone application. At enrolment, the participant would define their angina in their own words, and this would be saved within the app. Participants would then report the number of episodes of this symptom for each day of the trial. Participants were also required to report each week if they experienced angina with 2 activities that were pre-selected by the participant at enrolment as likely to trigger their symptoms. Screenshots from the smartphone application are available in Figure 3.2.

The symptom application approach permitted not only a quantitative assessment of the time-course of angina evolution during the blinded period, but also a time-to-event analysis of occurrence of first angina episode. Other benefits of this approach were that it eliminated recall bias, improved the power of the trial, and it allowed a patient centred approach to symptom description, unlike previous patient reported outcome measures for angina which required the patient to assess their symptoms according to fixed descriptions of angina.

The development, use and validation of the application have previously published.<sup>59,60</sup>

The smartphone application was only available in the English language and was intentionally designed to be very simple. An culturally and gender diverse patient focus group with lived experience of coronary artery disease assisted in the design of the smartphone application. For the minority of patients who were not able to read, write or speak English, a contact who was capable of translating assisted them. If participants did not have a contact who could offer this help, a blinded member of the research team arranged daily data entry using a translator service.

At enrolment, participants completed a training module, with a test component, which demonstrated and documented their ability to understand the app and input data.

Participants had 24/7 access to a blinded member of the trial team for any queries about the smartphone application.

### **3.7 Derivation of the ordinal scale primary end point**

The primary end point of ORBITA-2 was the angina symptom score measured daily for each participant in the trial. This is an ordinal clinical outcome scale of angina health status, ranging from 0 to 79. The daily score is calculated from the number of episodes of angina reported by a patient on a given day via the smartphone application, the units of antianginal medication prescribed on that day, and high-level category overrides for unblinding due to intolerable angina, acute coronary syndrome, and death.

The total daily dosage of commonly prescribed antianginal medications considered to be 1 unit is reported in Table 3.4. Full details of the calculation of the primary end point have been published previously<sup>61</sup>.

### **3.8 Mechanisms of blinding**

Mechanisms to ensure fidelity of blinding are reported in Table 3.5.

Our protocol assessed for accidental leakage of information to staff and to patients. The ward clinical staff were asked to guess the treatment allocation at the time of discharge from the blinded procedure. The blinded research staff were asked to guess the treatment allocation from all information available to them at the follow-up visit prior to speaking to the patient.

Patient blinding was assessed at the time of discharge from the randomised blinded procedure. For completeness the same question was also asked when they attended for final follow-up. However, it should be noted that at this timepoint, the patient had benefit of knowing their own symptomatic response and therefore this was no longer strictly a valid measure of blinding.

Patients and staff were asked to guess one of the following: (1) PCI, (2) Placebo, (3) Don't know. Patients and medical staff were asked to state the certainty of their answers, graded 1-5 with 5 being most certain.

Statistical analysis of the blinding index was performed using published methods<sup>62</sup>.

Table 3.1: ORBITA-2 Trial sites

| Centre                                                                                 | Principal Investigator             | Coinvestigators                                                                                                                                                                                                                                                                                          | Support team                                                                                                        | Patients enrolled |
|----------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------|
| Hammersmith Hospital<br>(Imperial College Healthcare NHS Trust)                        | Dr Rasha Al-Lamee                  | Professor Darrel Francis<br>Dr Sayan Sen<br>Dr Sukhjinder Nijjer<br>Dr Punit Ramrakha<br>Dr Raffi Kaprielian<br>Dr Iqbal Malik<br>Dr Amarjit Sethi<br>Dr Masood Khan<br>Dr Ramzi Khamis<br>Dr Rodney Foale<br>Dr Christopher Rajkumar<br>Dr Michael Foley<br>Dr Fiyyaz Ahmed-Jushuf<br>Dr Henry Seligman | Denise Rouse<br>Hawa Amadu                                                                                          | 163               |
| Essex Cardiothoracic Centre<br>(Mid and South Essex NHS Foundation Trust)              | Dr Thomas Keeble                   | Dr John Davies<br>Dr Gerald Clesham<br>Dr Reto Gamma<br>Dr Jason Dungu<br>Dr Kare Tang<br>Dr Shah Modh Nazri<br>Dr Alamgir Kabir                                                                                                                                                                         | Raiji Koothoor<br>Michael Galinato<br>Craig Robertson<br>Joanne Turton<br>Ellie Gudde<br>Joanne Hall<br>Karen Lyons | 70                |
| Royal Bournemouth Hospital<br>(University Hospitals of Dorset NHS Foundation Trust)    | Dr Peter O’Kane                    | Dr Jehangir Din<br>Dr Jonathan Hinton                                                                                                                                                                                                                                                                    | Stephanie Horler<br>Annette Fraine<br>Tanith Changuion                                                              | 55                |
| Queen Alexandra Hospital<br>(Portsmouth Hospitals University NHS Trust)                | Dr Peter Haworth                   | -                                                                                                                                                                                                                                                                                                        | Charlotte Turner                                                                                                    | 32                |
| St George’s Hospital<br>(St George’s University Hospitals NHS Foundation Trust)        | Professor James Spratt             | Dr Rupert Williams<br>Dr Claudia Cosgrove<br>Dr Pitt Lim                                                                                                                                                                                                                                                 | Stavroula Kazagli<br>Giovanna Bonato                                                                                | 25                |
| Worcestershire Royal Hospital<br>(Worcestershire Acute Hospitals NHS Trust)            | Dr Helen Routledge                 | Dr Lal Mughal<br>Dr Jasper Trevelyan                                                                                                                                                                                                                                                                     | Angela Doughty                                                                                                      | 23                |
| Royal Free Hospital<br>(Royal Free London NHS Foundation Trust)                        | Dr Tushar Kotecha                  | -                                                                                                                                                                                                                                                                                                        | Nina Arnold<br>Felicity Picton<br>Tarik Mustafa<br>Leoni Bryan<br>Alejandra Perez<br>Rodriguez<br>Valene Cadden     | 21                |
| Southampton General Hospital<br>(University Hospital Southampton NHS Foundation Trust) | Professor Nick Curzen              | Dr James Wilkinson<br>Dr Alison Calver<br>Dr Rohit Sirohi<br>Dr John Rawlins<br>Dr Richard Jabbour                                                                                                                                                                                                       | Karen Banks<br>Zoe Nicholas                                                                                         | 15                |
| Royal Berkshire Hospital<br>(Royal Berkshire NHS Foundation Trust)                     | Associate Professor Neil Ruparelia | -                                                                                                                                                                                                                                                                                                        | Mark Brunton                                                                                                        | 11                |
| Salisbury District Hospital                                                            | Dr Manas Sinha                     | -                                                                                                                                                                                                                                                                                                        | Fiona Trim                                                                                                          | 10                |

|                                                                                |                        |   |                                        |   |
|--------------------------------------------------------------------------------|------------------------|---|----------------------------------------|---|
| (Salisbury NHS Foundation Trust)                                               |                        |   |                                        |   |
| University Hospital of Wales<br>(Cardiff and Vale University Health Board)     | Professor Tim Kinnaird | - | Elizabeth Hodges<br>Elizabeth Thompson | 7 |
| Wycombe Hospital<br>(Royal Berkshire NHS Foundation Trust)                     | Dr Ricardo Petraco     | - | Mari Kononen<br>Josephine Chaplin      | 6 |
| Birmingham City Hospital<br>(Sandwell and West Birmingham Hospitals NHS Trust) | Dr Fairoz Abdul        | - | Sibet Joseph                           | 1 |
| Harefield Hospital<br>(Royal Brompton and Harefield NHS Foundation Trust)      | Dr Vasileios Panoulas  | - | -                                      | 0 |

Table 3.2: Inclusion Criteria

| Inclusion Criteria                                                                 | Evidence                                                                                                                                                          |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Angina or angina-equivalent symptoms                                            | As judged by referring cardiologist and research team                                                                                                             |
| 2. Anatomical evidence of a severe coronary stenosis in at least 1 vessel, either: | Invasive diagnostic coronary angiography indicating $\geq 70\%$ stenosis                                                                                          |
|                                                                                    | Computerised tomography coronary angiography (CTCA) indicating severe stenosis                                                                                    |
| 3. Evidence of ischaemia, on any of the following tests:                           | Positive dobutamine stress echocardiography                                                                                                                       |
|                                                                                    | Positive stress perfusion cardiac magnetic resonance imaging (MRI)                                                                                                |
|                                                                                    | Positive nuclear medicine myocardial perfusion scan                                                                                                               |
|                                                                                    | Invasive pressure wire assessment suggestive of ischaemia, as judged by the interventional cardiologist, at the time of clinical or research coronary angiography |

*Table 3.3: Exclusion Criteria*

| <b>Exclusion Criteria</b>                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Age younger than 18                                                                                                                              |
| Recent acute coronary event (within last 6 months)                                                                                               |
| Previous coronary artery bypass graft surgery                                                                                                    |
| Significant left main stem coronary disease                                                                                                      |
| Chronic total occlusion in the target vessel                                                                                                     |
| Contraindication to percutaneous coronary intervention or drug-eluting stent implantation                                                        |
| Contraindication to antiplatelet therapy                                                                                                         |
| Severe valvular disease                                                                                                                          |
| Severe left ventricular systolic impairment (ejection fraction $\leq 35\%$ )                                                                     |
| Severe respiratory disease (requiring long term oxygen or symptoms deemed by investigator to be more likely attributable to respiratory disease) |
| Life expectancy less than 2 years, pregnancy, inability to consent                                                                               |

*Table 3.4: Antianginal medication quantification.*

| Medication                | Total daily dose in mg that<br>constitutes 1 unit |
|---------------------------|---------------------------------------------------|
| 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                                                 |

Common antianginal medications were classified as 1 unit based on the above total daily dosages.

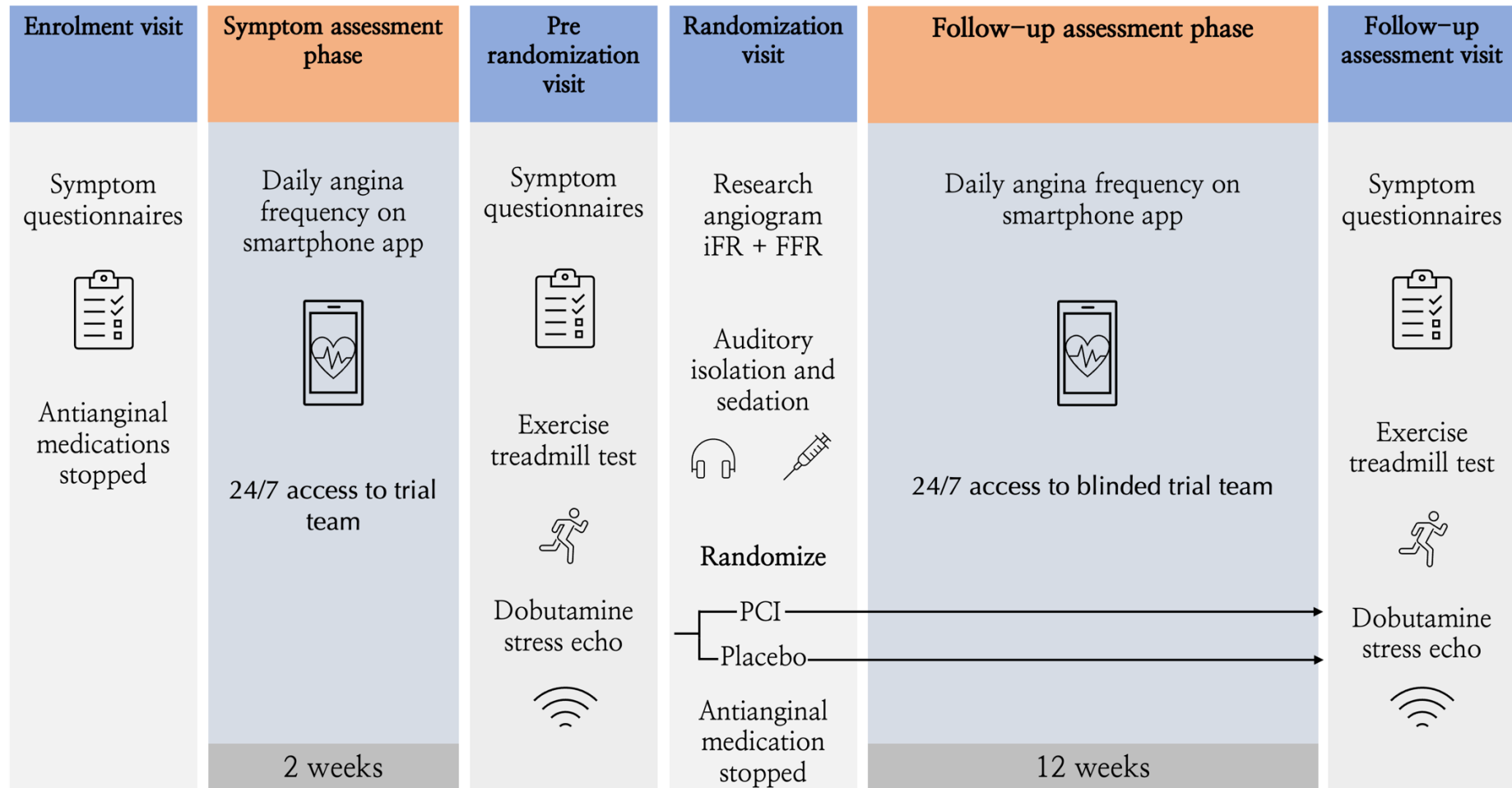
All antianginal medication changes, including cases when it was clinically necessary to prescribe an alternate medication to the above list, were adjudicated by the Data Safety Monitoring Board.

Table 3.5: Blinding optimisation strategies in ORBITA-2

| Domain                                                                 | Blinding optimisation strategy in ORBITA-2 Trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Sensory Manipulation</b>                                            | Patients received incremental doses of intravenous opiate and benzodiazepine to achieve a deep level of conscious sedation such that the patient was unresponsive to verbal or tactile stimulus, with maintained airway, ventilation and cardiovascular function. Physiological support with oxygenation and intravenous fluids was administered as necessary. Additional steps for sensory manipulation are detailed below.                                                                                        |
| <i>Visual Masking</i>                                                  | Positioning of the patient meant that the operator screen was not visible to them.                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Verbal cues</i>                                                     | Patients were not able to hear any verbal cues due to sedation and auditory isolation. Treatment allocation was communicated from the research team to the operator away from the patient to prevent inadvertent leakage of information. During placebo procedures, catheter laboratory staff mimicked language used during PCI procedures.                                                                                                                                                                         |
| <i>Auditory cues</i>                                                   | Auditory isolation and sedation minimised any possible auditory difference between PCI and placebo procedures.                                                                                                                                                                                                                                                                                                                                                                                                      |
| <i>Physical cues</i>                                                   | Before the procedure began, patients were counselled that they may experience some pain or shortness of breath during the procedure.                                                                                                                                                                                                                                                                                                                                                                                |
| <i>Visual cues</i>                                                     | Although subjects were sedated, the operator screen was also positioned so that it was not visible to the patient.                                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Auditory masking</i>                                                | Patients wore over-the-ear headphones playing music throughout the invasive procedure to provide auditory isolation. These were worn prior to sedation and randomisation to prevent the patient hearing any communication between the clinical team.                                                                                                                                                                                                                                                                |
| <b>Use of devices to optimise blinding</b>                             | In both the PCI and placebo groups, the catheterisation laboratory table and equipment table were set up for PCI. All patients underwent angiography and pressure wire studies as part of the randomisation procedure; therefore, patients all underwent vascular access using devices which did not differ between treatment groups.                                                                                                                                                                               |
| <b>Mimicked Timings</b>                                                | The invasive procedure consisted of angiography and pre-randomisation coronary physiological assessments. This meant that the procedure was significantly longer than a standard diagnostic coronary angiogram. Patients subsequently randomised to placebo remained on the catheter laboratory table for a minimum of 15 additional minutes following randomisation to mimic the time required for PCI. Benzodiazepines utilised for sedation had a secondary effect of amnesia regarding the procedural duration. |
| <b>Restricting interaction between blinded and unblinded personnel</b> | The blinded ward staff managed all patients as if they had undergone PCI for post procedural monitoring and care. The catheter laboratory staff involved in the procedure were not permitted any contact or communication with the patient after handover.                                                                                                                                                                                                                                                          |

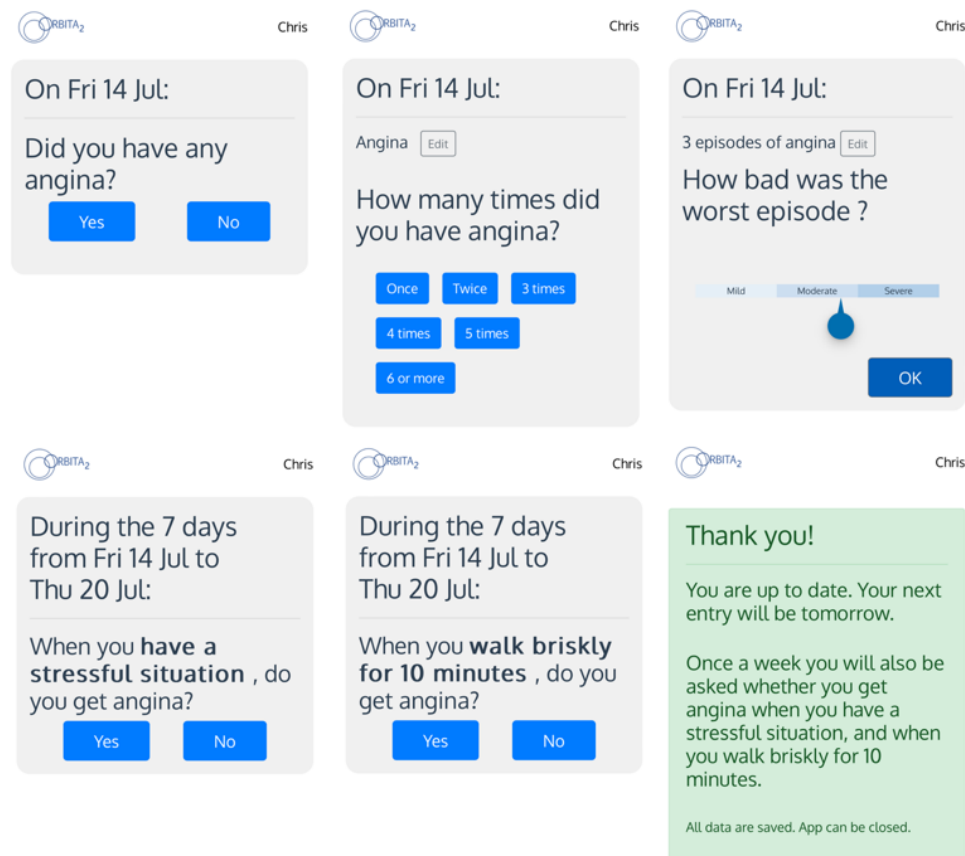
|                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Omission of intervention details in trial paperwork</b>     | <p>The unblinded fellow entered the treatment allocation to a pre-allocated page of the online case reporting form to which none of the other members of the research team had access.</p> <p>A blinded fellow performed all the communication with the patient after discharge and performed all the follow-up tests. At the 12-week point the blinded fellow contacted the unblinded fellow to confirm that all the assessments had been performed, only at that time did the unblinded fellow communicate the treatment allocation. From that time, the patient, the research team, and the clinical team became unblinded.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Intervention not specified in patient notes</i>             | <p>A standardised protocol was used for the management of all documentation in the catheter laboratory in all centres. During the procedure, the nurses documented that the patient had participated in the ORBITA-2 trial. They did not document treatment allocation or any details of PCI in the medical notes. After the procedure, the handover between the catheter laboratory staff and ward nursing staff was carefully managed to include only location of access sites and medication given (which was identical for the two randomised arms, as all patients required heparin for physiological assessment and all patients received sedation). The handover did not indicate the treatment allocation and therefore did not indicate whether a PCI was performed. Additionally, during the handover process patients continued to have auditory isolation with music via headphones.</p> <p>The unblinded fellow prepared a standardised discharge letter at the end of the procedure which informed the reader that a blinded procedure had taken place, that this procedure was a coronary angiogram +/- PCI, that all medications should remain unchanged, including continuation of dual antiplatelet therapy, until trial follow-up was complete. The letter stated that they should receive standard post-angioplasty care until full details of the procedure were provided after unblinding at 12 weeks. This standardised letter was approved by the local ethics committee and was given to all patients and their general practitioners on discharge.</p> |
| <b>Unblinded operator delivering component of intervention</b> | <p>The unblinded operator who performed the procedure was not permitted to attend to the patient after completion of the interventional procedure. This meant that the unblinded operator was not able to review or have any communication with the patient in recovery. Furthermore, the unblinded operator was not permitted to have any contact with the patient during the 12-week blinded follow-up period, until the patient had completed the trial and been unblinded to treatment allocation.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Figure 3.1: ORBITA-2 Trial Design



ORBITA-2 Trial design. PCI = percutaneous coronary intervention, iFR = instantaneous wave-free ratio, FFR = fractional flow reserve.

Figure 3.2: Screenshots from the ORBITA-2 smartphone application



When you joined ORBITA-2, you told us:  
My angina is **tight pain across my chest.**

Use this App every day throughout the trial to report the symptoms you had the day before. Once a week, the App will additionally ask whether you get angina when you have a stressful situation and when you walk briskly for 10 minutes. The App will say when you are up to date with data entry.

#### What happens if I miss a day?

If you miss a day, for example from lack of internet access, you can enter the data later. Our team will phone you if there is too much delay.

#### Do I count episodes of angina I get when I have a stressful situation or walk briskly for 10 minutes?

Yes, include such episodes within your daily angina counts. Then at the weekly question about angina during those specific activities, please answer yes. When we process the data, we know not to double-count the answers to the weekly questions as extra episodes.

#### How do I use the mild-moderate-severe slider?

Use the slider to record your personal opinion on the severity of the angina you had on the day being asked about. This is a personal judgement for you to make at the time you are asked. We expect the way you make these judgements may naturally change over the course of the study. We are asking your independent view on how you feel each day.

#### What happens if I make a mistake?

Make a note of what you intended to enter and then call our helpline.

#### Why can't I see my previous entries?

During the trial we need your independent answers from the separate days and therefore the app does not show previous entries. After you finish the trial, we can show you all your entries.

#### What if the app isn't working properly?

Please call our helpline.

#### What should I do if I don't feel well?

If you want to discuss this with us, please call our helpline at any time.

#### Helpline number

#### Advanced Tools

ORBITA staff may ask you to click this button

[Advanced Tools](#)

[Close Help](#)

#### 4 Does blinding matter? The impact of placebo-control on randomised trials of procedural interventions: a systematic review and meta-regression

Parts of this chapter have been published as:

**Placebo Control and Blinding in Randomized Trials of Procedural Interventions: A Systematic Review and Meta-Regression.**

**Rajkumar CA**, Thomas KE, Foley M, Ganesanathan S, Evans H, Simader F, Syam S, Nour D, Beattie C, Khan C, Reddy RK, Ahmed-Jushuf F, Francis DP, Shun-Shin M, Al-Lamee RK.

**JAMA Surg. 2024 Jul 1;159(7):776-790.**

PMID: 38630462

## **4.1 Abstract**

### **4.1.1 Background**

Unlike medications, procedural interventions are rarely trialed against placebo prior to becoming accepted in clinical practice. When blinded trials are eventually conducted, procedural interventions may be less effective than previously believed. We investigated the importance of blinding in trials of surgical and interventional procedures by comparing the effect size from blinded and unblinded trials of the same procedure.

### **4.1.2 Methods**

A structured search identified all randomised controlled trials (RCTs) assessing any surgical or interventional procedure against placebo-control. A secondary search then identified corresponding unblinded RCTs assessing the same intervention, disease and endpoint, permitting a paired comparison. Endpoints were examined in pre-specified subgroups: physician or patient reported, quality of life, pain, blood pressure, exercise tolerance, rebleeding rates, and all-cause mortality (PROSPERO: CRD4202020663).

### **4.1.3 Findings**

Ninety-seven endpoints from 24 interventions were matched from 72 blinded and 55 unblinded trials, including 111,500 individual-patient endpoints.

Unblinded trials had larger standardised effect sizes than blinded trials for exercise capacity (0.59, 95% CI 0.29 to 0.89,  $p=0.0001$ ), quality of life (0.32, 95% CI 0.11 to 0.53,  $p=0.003$ ) and endpoints assessed by healthcare professionals (0.4, 95% CI 0.18 to 0.61,  $p=0.0002$ ). The placebo effect accounted for 88.1%, 55.2% and 61.3%, respectively, of the observed effect size of these endpoints in unblinded trials.

There was no significant difference in standardised effect sizes between unblinded and blinded trials for patient-reported endpoints (0·31, 95% CI -0·02 to 0·64,  $p=0\cdot067$ ), blood pressure (0·26, 95% CI -0·10 to 0·62,  $p=0\cdot15$ ), all-cause mortality (0·23, 95% CI -0·26 to 0·72,  $p=0\cdot36$ ), pain (0·03, 95% CI -0·52 to 0·57,  $p=0\cdot91$ ), and recurrent bleeding events (-0·12, 95% CI -1·11 to 0·88,  $p=0\cdot88$ ).

#### **4.1.4 Interpretation**

The magnitude of the placebo effect depends on the characteristics of the endpoint. Placebo-control in trials of interventional and surgical procedures has the greatest impact on exercise performance, quality of life and physician-assessed endpoints.

## 4.2 Introduction

An unblinded trial of a new medication may find an improvement that is not replicated when a placebo arm is included. For this reason, the gold standard design for a trial of a new medication, and a regulatory authority prerequisite, is a trial that is not merely randomised, but placebo-controlled. This is not yet an established standard for trials of interventional or surgical procedures.

The commonest justifications offered for lack of blinding are that it is impractical to perform or unethical to expose research volunteers to potential harm<sup>63</sup>. Therefore, invasive therapies typically become established treatments and enter guidelines without a placebo-controlled trial. This is despite evidence that the placebo effect may actually be larger for invasive, compared to non-invasive treatments<sup>64,65</sup>, and therefore even more problematic.

In reality, it is ethical to conduct placebo-controlled research with informed volunteers, and has been demonstrated to be practical for a range of interventions including coronary angioplasty for stable angina<sup>50</sup> and vertebroplasty for osteoporotic vertebral fractures<sup>66,67</sup>.

Although previous systematic reviews have demonstrated the safety and necessity of placebo-controlled trials of surgical and interventional procedures<sup>68–70</sup>, what is not known is the size of the impact of blinding on the observed effect of the intervention as they examined only the blinded trials.

This study quantifies the effect of blinding on the observed effect size of procedural interventions in medicine and surgery by comparing matched blinded (i.e. placebo-controlled) and unblinded randomised trials in a systematic review and meta-regression. We test this effect of blinding for each category of endpoints.

### 4.3 Methods

This meta-analysis was registered on the PROSPERO database (CRD4202020663), and performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement<sup>71</sup>. The structured search consisted of two phases: (1) identification of placebo-controlled trials for procedural therapies, and (2) identification of matched unblinded trials assessing the same condition, intervention, and endpoint.

#### 4.3.1 Phase 1: Identification of placebo-controlled trials

We sought to identify all placebo-controlled trials for procedural interventions in any specialty of medicine and surgery. We developed search strategies for two databases: Medline and Embase. The databases were searched from their inception to 31<sup>st</sup> March 2019. The search terms are documented in Table 4.1. Relevant systematic reviews and reference lists were manually inspected.

Any interventional procedure requiring a skin incision, or the use of endoscopic techniques was eligible. The intervention was required to be anatomically site specific; intravenous injections and the addition or removal of products to the bloodstream were excluded.

We defined placebo as a surgical placebo, often referred to as a “sham” procedure designed to mimic the active intervention without the patients being able to distinguish whether they had an intervention. Endoscopic procedures were included. All studies were published randomised controlled trials.

We excluded studies of anaesthetics or other medications, dental studies (including periodontal procedures) but not procedures that required maxillofacial surgery (such as palatal procedures). We excluded studies of only 2 patients, patients under the age of 18, non-humans, and non-English

language, single blind studies, and studies in which patients in the placebo arm crossed over to the intervention arm in an unplanned manner.

Two reviewers (KET and CAR) independently performed the primary search and reviewed all eligible publications. A third independent investigator (RA-L) adjudicated when consensus was not reached. Eligible trials were then grouped by condition and intervention.

#### **4.3.2 Phase 2: Identification of matching unblinded trials**

For each placebo-controlled trial from the primary search, a secondary search was conducted to identify matching unblinded trials. An unblinded trial was considered a match if it examined the same intervention, for treatment of the same condition, and reported at least one identical endpoint and where there were multiple matches, all were included.

Eight authors (CAR, KET, MF, CB, CK, SS, DN, HE) performed literature searches for each intervention and inspected the references of relevant publications to provide a list of unblinded trials. Trials with no unblinded match were excluded.

##### *4.3.2.1 Assumptions regarding pairing of publications:*

To permit fair comparison between paired blinded and unblinded RCTs, restrictions on the degree of heterogeneity were pre-specified. These limits were set by consensus agreement between CAR, KET, MSS and RA-L. Adequacy of pairing of blinded and unblinded RCTs was reviewed by CAR and KET. MSS adjudicated any dispute.

- Heterogeneity of follow up duration

To account for heterogeneity of follow up duration, prespecified criteria were set. For categorical endpoints such as death, rebleeding or syncope, the number of events was examined. If the event

occurred in <25% of patients, matching could occur for any pair within 5 years follow up. Otherwise, pairing was deemed acceptable if the two time periods were no further apart than 50% (using the longer time point as the reference).

If the endpoint examined symptoms (such as quality of life scores, exercise times or pain), then endpoints could be paired if they were reported within six months. Where multiple matches of timepoints were made, the primary timepoint of the trial was taken if possible. If this was not possible, the closest possible match to the primary timepoint was made.

- Limits on derivations of similar endpoints:

Several studies examined derivations of the same endpoint (for example, weight loss as absolute reduction in weight or as a percentage of BMI; FEV1 as % predicted or litres). Variations in reporting such as these were permitted for inclusion. For each endpoint, a hierarchy was constructed for order of pairing. Where multiple matches of the same endpoint derivation occurred, the highest endpoint in the hierarchy was taken.

### **4.3.3 Data extraction**

Data were extracted from all primary manuscripts (and appendices where relevant), including primary author, year, characteristics of participants, intervention, and all outcomes. The effect size and confidence intervals for matched endpoints were extracted. We did not limit by primary outcome measure; any matched endpoint between blinded and unblinded studies was eligible. Any studies where no endpoints could be matched were excluded.

Data for intention-to-treat were used where this was available.

Two investigators (CAR and KET) grouped endpoints into categories according to their characteristics. Disagreements were resolved by a third author (RA-L). Endpoints were categorised as either patient assessed (such as a self-administered questionnaire e.g. Seattle Angina Questionnaire) or healthcare professional (HCP) assessed (e.g. Canadian Cardiovascular Society Class). Endpoints were further grouped by all-cause mortality, recurrent bleeding events, pain, exercise tolerance, blood pressure measurement, and quality of life. These subgroups were chosen as they were the most prevalent categorisations within the sample.

#### **4.3.4 Risk-of-bias assessment**

The risk of bias was assessed according to the revised Cochrane risk-of-bias tool for randomised trials (RoB 2)<sup>72</sup>. Risk of bias was assessed at outcome level. Two reviewers (SG and RR) completed the risk of bias assessment.

#### **4.3.5 Statistical analysis**

For each endpoint for each trial, the between group (intervention vs. control) effect size and standard error were either directly abstracted or calculated from the provided data. For dichotomous endpoints (such as all-cause mortality) the number of patients and events in each arm were extracted and the log odds ratio with associated error were calculated. We performed a similar analysis for repeatable events such as bleeding or number of syncopal episodes.

For continuous endpoints (such as treadmill distance or FEV1 measurements) we abstracted or calculated the mean difference between arms. This ideally would have been adjusted for baseline values (ANOVA) or calculated through the difference of the differences. If such data was not available or not in a format that could be used, we used the follow up data alone. For these endpoints, we then calculated the population estimate of the characteristic at baseline from all studies that contributed to that endpoint weighted by study size. This was then used to standardize

these continuous outcome effect sizes so they could be compared on an equal footing. Finally, we standardised the direction of each endpoint so that a positive number indicates an improvement in the intervention group.

The endpoints were categorised into different classes. All-cause mortality, recurrent bleeding events and blood-pressure each contained an individual endpoint. Quality of Life, exercise associated, pain, healthcare-professional assessed, and patient reported classes contained multiple endpoints standardised by the baseline population standard deviation. A random-effects meta-regression, with blinding as a fixed-effect and the intervention and the endpoint grouping as a random effect was used to calculate the impact of blinding on trial results within each endpoint “class” (e.g. healthcare-professional assessed or pain scores).

The statistical environment “r”<sup>73</sup> was used with the “metafor” and “tidyverse” set of packages.

## 4.4 Results

### 4.4.1 Study characteristics

The phase 1 search identified 222 eligible blinded trials following full text review (Figure 1). Their interventions formed the search criteria for matching unblinded trials in phase 2, which found 132 unblinded trials matching the condition and intervention.

There were 72 blinded and 55 unblinded trials with matched endpoints meeting full inclusion criteria and sufficient data for analysis (Table 1). These totalled 111,500 patient-endpoint results: 51,688 in blinded trials and 59,812 in unblinded trials. Details of all trials included in this analysis have been published previously<sup>74</sup>.

### 4.4.2 Impact of blinding on clinical trial endpoints

Unblinded trials had a larger standardised effect size than blinded trials for exercise-related endpoints (0.59, 95% CI 0.29 to 0.89,  $p=0.0001$ ), healthcare professional-assessed endpoints (0.40, 95% CI 0.18 to 0.61,  $p=0.0002$ ) and quality of life endpoints (0.32, 95% CI 0.11 to 0.53,  $p=0.003$ ), (Table 4.2, Figure 4.2).

For exercise-related endpoints, 88.1% of the observed effect size in unblinded trials was attributable to the placebo effect. For healthcare-assessed endpoints, 61.3% of the observed effect size in unblinded trials was placebo and finally, for endpoints reporting quality of life, 55.2% of the observed effect size was placebo.

We detected no significant differences between standardised effect sizes in blinded and unblinded trials for patient reported endpoints (0.31, 95% CI -0.02 to 0.64,  $p=0.067$ ), blood pressure endpoints (0.26, 95% CI -0.10 to 0.62,  $p=0.15$ ), all-cause mortality (0.23, 95% CI -0.26 to 0.72,  $p=0.36$ ), endpoints reporting pain (0.03, 95% CI -0.52 to 0.57,  $p=0.91$ ), and recurrent bleeding events (-0.12, 95% CI -1.11 to 0.88,  $p=0.88$ ), Table 4.2.

#### 4.4.3 Risk of bias

In unblinded trials, 69·4% (125/180) of all endpoints were deemed high risk for bias, 15·0% (27/180) had some concerns and 15·6% (28/180) were deemed low risk.

Conversely, for the blinded trials, 4·0% (9/227) trial endpoints were high risk for bias, 35·2% (80/227) trial endpoints had some concerns, and 60·8% (138/227) were considered low risk of bias.

## 4.5 Discussion

The clinical effect of a procedure will combine both a true physical and a placebo component. The placebo component is amplified in surgical procedures<sup>75</sup>. However, while placebo-controlled trials are the gold standard for medical therapies, they are rarely performed for surgical procedures.

This is the first analysis to quantify the effect of blinding on the observed efficacy of interventional procedures through systematic comparison of matched blinded and unblinded trials. The results highlight that for many endpoints the placebo effect of interventions is powerful and may be much greater than the underlying biological effect.

More specifically, our results indicate that endpoints adjudicated and reported by healthcare-professionals are highly vulnerable to bias in unblinded trials. Endpoints of exercise tolerance and quality of life metrics were also found to be significantly more likely to show a larger effect size in unblinded trials when compared to matched placebo-controlled trials, suggesting that they too, are significantly biased when the reporter, be it patient or physician, has knowledge of treatment allocation.

Conversely, we found no significant difference between blinded and unblinded trials in the pooled standardised effect sizes for endpoints which were patient reported, or endpoints reporting blood pressure, all-cause mortality, pain, or recurrent bleeding events. However, the small numbers of events in some of these categories may limit certainty.

It was unsurprising that quality of life reporting was significantly influenced by placebo. A patient who anticipates benefit from an intervention is more likely to report improvement in symptoms during follow up assessments. Irrespective of whether true physical benefit was conferred by the

intervention, patients may subconsciously seek to validate the effort and resource investment of their physician or surgeon: an example of the sunken-cost fallacy in action.

Importantly, clinician evaluation was also vulnerable to the placebo effect. This is recognised to be influenced by treatment characteristics, health-care setting, clinician and patient characteristics and patient-clinician interaction<sup>76</sup>. For example, a patient, with hope for a new treatment, anticipates cure for a disease, relief of a pain or an improvement in functional capacity. They hold this hope because of confidence and trust placed in their physician or surgeon who has recommended a particular course of action. This confidence and trust in turn naturally leads to a responsibility of the physician or surgeon to deliver the proposed benefits of a procedure through technical success. Indeed, the way in which a clinician communicates information to a patient can affect the size of the placebo component. Our data demonstrate that physicians and healthcare professionals assessing endpoints in unblinded trials have difficulty separating the responsibility to deliver favourable technical results from their ability to provide unbiased reports of clinical endpoints in clinical trials.

Most surprisingly, the objective variable of exercise performance was exceptionally vulnerable, with a placebo effect that was 6 times the size of the true physical effect. Quantitative assessment of exercise capacity may be considered an objective measurement; however, termination of the test is subject to the decision of the patient and the healthcare professional. Exercise time may be particularly vulnerable because the decision to stop the test depends on the interaction between patient and physician, both of whom are likely to be influenced in the same direction by knowledge of treatment allocation. Not only may patients perceive their symptoms differently when they know they have had the intervention, but they may also feel safer to push themselves further. Clinicians too may feel confident to provide more encouragement in the knowledge that treatment has been delivered. The unifying remedy is rigorous blinding of the subject and assessor.

A clear example was observed in trials of percutaneous coronary intervention for stable angina. In 1992, the unblinded Angioplasty Compared to Medicine (ACME) trial reported a 90 second improvement in treadmill exercise time with balloon angioplasty compared to conservative therapy in patients with stable angina<sup>51</sup>. Some twenty-five years later, despite decades of technical innovation, the placebo-controlled Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial reported a much smaller effect size of just 16.6 seconds; a result that was met with shock and disbelief<sup>50</sup>. The results of the present meta-analysis indicate that the 6-fold amplification of exercise performance increment in unblinded trials could have been predicted.

Of all procedural interventions, the importance of placebo-control has perhaps been most clearly demonstrated in the setting of radiofrequency-based renal denervation for hypertension. Early unblinded trials reported a marked anti-hypertensive action of denervation therapy<sup>77</sup>; effect sizes which were substantially diminished in latterly conducted placebo-controlled trials<sup>78</sup>. Physicians measuring blood pressure in the office may be surprised when a blood pressure measurement is much higher than expected after intervention. They may suspect that they had not sufficiently relaxed the patient, and therefore remeasure in the hope of a more representative value. They may be less motivated to do this in the control group since they are not expecting a blood pressure reduction. Additionally, patients may change their behaviour including diet and medication adherence after undergoing an invasive procedure that highlights to them the seriousness of their condition<sup>79</sup>.

Given this knowledge, it may appear surprising that in the present analysis we found no significant difference between standardised effect sizes in trials of denervation therapy between blinded and unblinded trials. We hypothesise that this may be due to the effect of examining the totality of data

from a complex field in which multiple iterations of devices have been used. Contemporary double-blind trials use the latest derivation of renal denervation catheters which may indeed be more effective than those used for earlier unblinded trials. Moreover, contemporary double blind trial protocols in this field require medication adherence monitoring with analysis of urine drug concentrations which removes any Hawthorne effect which could have been present in early unblinded data. Finally, we have grouped all endpoints which report blood pressure together, both office and ambulatory blood pressure assessments. A different result may have been observed if these subgroups of endpoints were analysed separately.

Importantly, there are endpoints that are more resistant to the implications of unblinded trial design. For example, our meta-analysis confirmed that re-bleeding rates after endoscopic therapies did not show evidence of biased reporting in unblinded trials<sup>80</sup>. We also found no evidence of a placebo effect on mortality. However, even mortality is not immune to the placebo effect because patients may change their behaviour, and physicians may change their management when they know a procedural intervention has taken place. Notably, the median follow-up of the placebo-controlled survival trials was only 9 months which may have limited the ability to detect a difference from the unblinded trials.

Another common misconception is that the introduction of a blinded endpoint adjudication committee can mitigate for the omission of a placebo-control arm. However, their role is merely to standardise the interpretation of endpoints. This does not make the trial blinded, since this committee will be interpreting documentation provided by unblinded staff and unblinded patients with the inherent magnification of perceived treatment effect<sup>34</sup>.

#### 4.5.1 Clinical Implications

If quality of life metrics are measured in a trial it is almost inevitable that they will be reported. Since they are so vulnerable to the placebo effect, the decision to include them may not only contribute misleading information to the literature but add unnecessary inconvenience to the patient and cost to the trial. Quality of life is certainly important, if measured blinded.

The potential for harm is commonly cited as a reason to avoid placebo-controlled trials of intervention. However, harm also occurs to patients who have complications or simply costs from a clinical procedure that has become widely adopted based on unblinded trials whose positive effects are largely placebo. It should be remembered that the numbers of clinical patients outside of trials might be orders of magnitude larger than the number of patients needed to volunteer to participate in a placebo-controlled trial. There is far greater harm to future patients that results from failing to promptly discover which treatments are beneficial, neutral, or harmful. This leads to three kinds of harm affecting orders of magnitude more patients. Harmful treatments become adopted as standard. Second, effective treatments are not adopted or even developed because ineffective treatments have become entrenched. Finally, practice of medically neutral therapies has an economic cost. Importantly, the introduction of placebo control in procedural trials has been shown to be safe when trials are well designed to include account for risk, feasibility and placebo optimisation<sup>68,81</sup>.

The principal aim of many treatments is relief of symptoms. This analysis underlines that RCTs testing new treatments for improvements in symptoms or quality of life, or physician assessed endpoints, or even objective exercise capacity, need to be blinded to give meaningful results.

Omitting blinding from early trials can easily lead to inappropriate adoption of ineffective treatments into clinical practice and guidelines. Enthusiasm for procedures such as vertebroplasty and renal denervation reached a peak prior to the publication of blinded data. Unfortunately, by the time this data had been provided, many patients had already been subjected to procedures, with inherent risk, that did not have the unblinded promised treatment effect.

Moreover, it is wrong to assume that even on the background of risk of harm from the operative procedure, the active intervention itself can only be beneficial or neutral. A sobering reminder was the Echo CRT trial in which the patients in the active arm experienced a doubling of mortality<sup>82</sup>. This would have been falsely attributed to the operative risks, were it not for the fact that this trial was placebo-controlled. All patients received the same device implant; it was merely switched off in the control arm.

#### **4.5.2 Study limitations**

Our study deliberately encompassed a wide range of interventions. Interventions may well vary in the size of the placebo effect they elicit.

We could only address endpoints that had sufficient appropriately reported blinded and unblinded trial data on the same intervention. We cannot exclude the possibility that trial authors were selective in the endpoints they reported.

Unfortunately few of the blinded trials reported the statistical fidelity of blinding<sup>62</sup>, which is of paramount importance in trials of procedural interventions where the potential for unblinding is large.

## **4.6 Conclusions**

Omitting blinding in trials of procedural intervention significantly inflates the magnitude of efficacy, not only in quality of life assessments but also healthcare professional-assessed endpoints and even objective measurements of exercise capacity. It is time for the major stakeholders: physicians, researchers, funders, regulators, healthcare systems, and of course patients, to recognise this and mandate the necessity for placebo-controlled trials when these endpoints are reported.

Table 4.1: Search Terms

|                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------|
| 1. Randomized controlled trial.pt.                                                                                           |
| 2. placebo\$.tw.                                                                                                             |
| 3. sham.tw.                                                                                                                  |
| 4. imitation.tw.                                                                                                             |
| 5. blinding.tw.                                                                                                              |
| 6. double-blind.tw.                                                                                                          |
| 7. 2 or 3 or 4 or 5 or 6                                                                                                     |
| 8. surgery.tw.                                                                                                               |
| 9. surgical.tw.                                                                                                              |
| 10. arthroscopy.tw.                                                                                                          |
| 11. endoscopy.tw.                                                                                                            |
| 12. endoscopic.tw.                                                                                                           |
| 13. transplantation.tw.                                                                                                      |
| 14. laparoscopic.tw.                                                                                                         |
| 15. laparoscopy.tw.                                                                                                          |
| 16. denervation.tw.                                                                                                          |
| 17. coronary intervention.tw.                                                                                                |
| 18. stent\$.tw.                                                                                                              |
| 19. angioplasty.tw.                                                                                                          |
| 20. pacing.tw.                                                                                                               |
| 21. pace?maker.tw.                                                                                                           |
| 22. ablation.tw.                                                                                                             |
| 23. ligation*.tw.                                                                                                            |
| 24. laser*.tw.                                                                                                               |
| 25. radiofrequency\$.tw.                                                                                                     |
| 26. palatal.tw.                                                                                                              |
| 27. balloon\$.tw.                                                                                                            |
| 28. bubble.tw.                                                                                                               |
| 29. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 |
| 30. acupuncture.tw.                                                                                                          |
| 31. acupressure.tw.                                                                                                          |
| 32. scar.tw.                                                                                                                 |
| 33. infection.tw.                                                                                                            |
| 34. pre\$medication.tw.                                                                                                      |
| 35. pre?operative.tw.                                                                                                        |
| 36. post?operative.tw.                                                                                                       |
| 37. post?surgical.tw.                                                                                                        |
| 38. animal\$.tw.                                                                                                             |
| 39. dose\$.tw.                                                                                                               |

|                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 40. meta analy\$.tw.                                                                                                                                                                             |
| 41. metaanaly\$.tw.                                                                                                                                                                              |
| 42. dental.tw.                                                                                                                                                                                   |
| 43. oral\$.tw.                                                                                                                                                                                   |
| 44. antibiotic\$.tw.                                                                                                                                                                             |
| 45. hormone\$.tw.                                                                                                                                                                                |
| 46. growth factor\$.tw.                                                                                                                                                                          |
| 47. topical.tw.                                                                                                                                                                                  |
| 48. concentration.tw.                                                                                                                                                                            |
| 49. pre-treatment.tw.                                                                                                                                                                            |
| 50. anaesthesia.tw.                                                                                                                                                                              |
| 51. anesthesia.tw.                                                                                                                                                                               |
| 52. anaesthetics.tw.                                                                                                                                                                             |
| 53. anesthetics.tw.                                                                                                                                                                              |
| 54. post-surgical.tw.                                                                                                                                                                            |
| 55. pre?surgical.tw.                                                                                                                                                                             |
| 56. pre-surgical.tw.                                                                                                                                                                             |
| 57. dosage.tw.                                                                                                                                                                                   |
| 58. drug therapy.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]                                                                                             |
| 59. biomarker.tw.                                                                                                                                                                                |
| 60. periodontal.tw.                                                                                                                                                                              |
| 61. antagonist.tw.                                                                                                                                                                               |
| 62. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 |
| 63. procedure.tw.                                                                                                                                                                                |
| 64. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 63                                                               |
| 65. 1 and 7 and 64                                                                                                                                                                               |
| 66. 65 not 62                                                                                                                                                                                    |

Table 4.2: Effect of blinding on effect sizes of procedural interventions stratified by endpoint classification

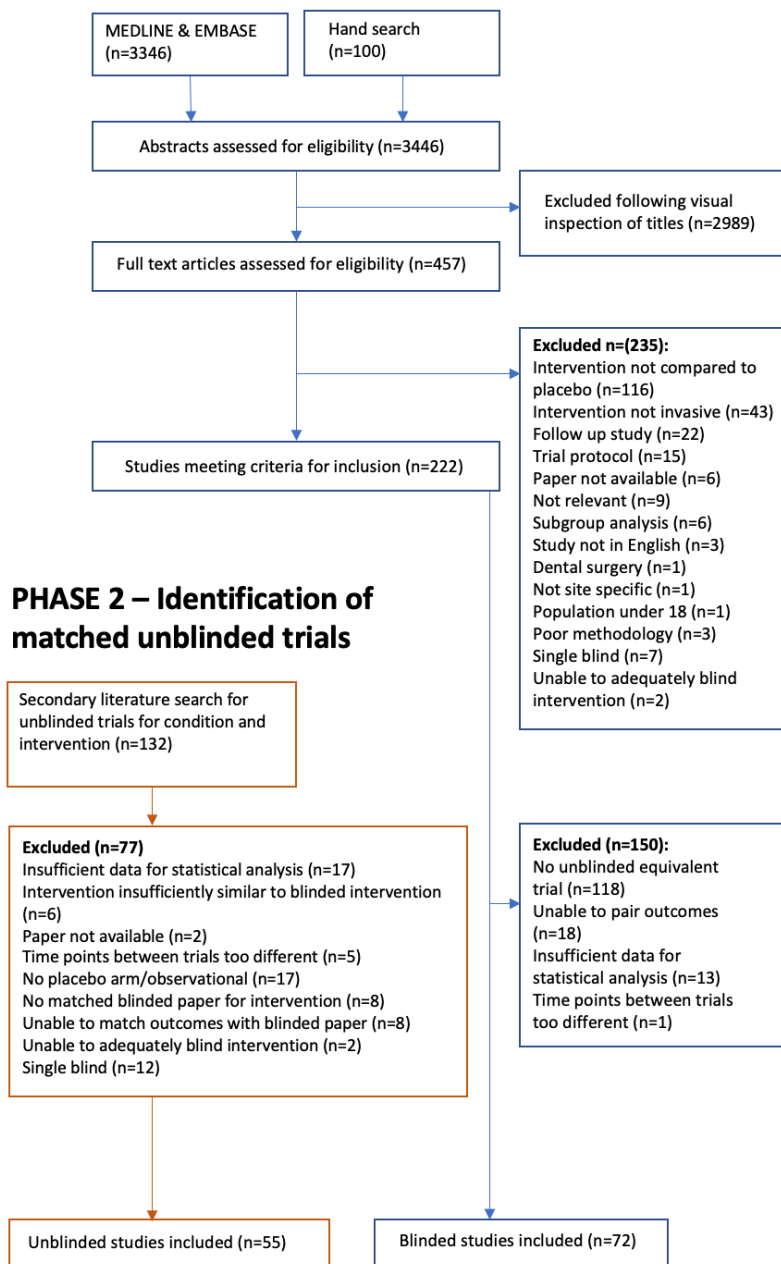
| Endpoint Domain           | Arm               | Coefficient<br>(Positive values are an improvement) | p-value         |
|---------------------------|-------------------|-----------------------------------------------------|-----------------|
| Exercise-related endpoint | Unblinded         | 0.67 (0.48 to 0.87)                                 | <b>P=0.0001</b> |
|                           | Blinded           | 0.08 (-0.15 to 0.32)                                |                 |
|                           | <b>Difference</b> | <b>0.59 (0.29 to 0.89)</b>                          |                 |
| HCP-assessed endpoint     | Unblinded         | 0.65 (0.41 to 0.89)                                 | <b>P=0.0002</b> |
|                           | Blinded           | 0.25 (0.01 to 0.50)                                 |                 |
|                           | <b>Difference</b> | <b>0.40 (0.18 to 0.61)</b>                          |                 |
| Quality of Life           | Unblinded         | 0.58 (0.33 to 0.83)                                 | <b>P=0.003</b>  |
|                           | Blinded           | 0.26 (0.01 to 0.51)                                 |                 |
|                           | <b>Difference</b> | <b>0.32 (0.11 to 0.53)</b>                          |                 |
| Patient Reported          | Unblinded         | 0.51 (0.24 to 0.78)                                 | <b>0.067</b>    |
|                           | Blinded           | 0.20 (-0.05 to 0.45)                                |                 |
|                           | <b>Difference</b> | <b>0.31 (-0.02 to 0.64)</b>                         |                 |
| Blood Pressure            | Unblinded         | 0.50 (0.19 to 0.81)                                 | <b>P=0.15</b>   |
|                           | Blinded           | 0.24 (0.05 to 0.43)                                 |                 |
|                           | <b>Difference</b> | <b>0.26 (-0.10 to 0.62)</b>                         |                 |
| All-cause mortality       | Unblinded         | -0.13 (-0.84 to 0.58)                               | <b>P=0.36</b>   |
|                           | Blinded           | -0.36 (-1.13 to 0.41)                               |                 |
|                           | <b>Difference</b> | <b>0.23 (-0.26 to 0.72)</b>                         |                 |
| Pain                      | Unblinded         | 0.21 (-0.26 to 0.68)                                |                 |
|                           | Blinded           | 0.18 (-0.15 to 0.52)                                |                 |

|                          |                   |                              |               |
|--------------------------|-------------------|------------------------------|---------------|
|                          | <b>Difference</b> | <b>0·03 (-0·52 to 0·57)</b>  | <b>P=0·91</b> |
| Recurrent bleeding event | Unblinded         | 1·09 (0·33 to 1·85)          |               |
|                          | Blinded           | 1·21 (0·39 to 2·02)          |               |
|                          | <b>Difference</b> | <b>-0·12 (-1·11 to 0·88)</b> | <b>P=0·88</b> |

*Difference in standardised effect size between matched blinded and unblinded trials arranged according to endpoint subclassifications. HCP = Healthcare professional.*

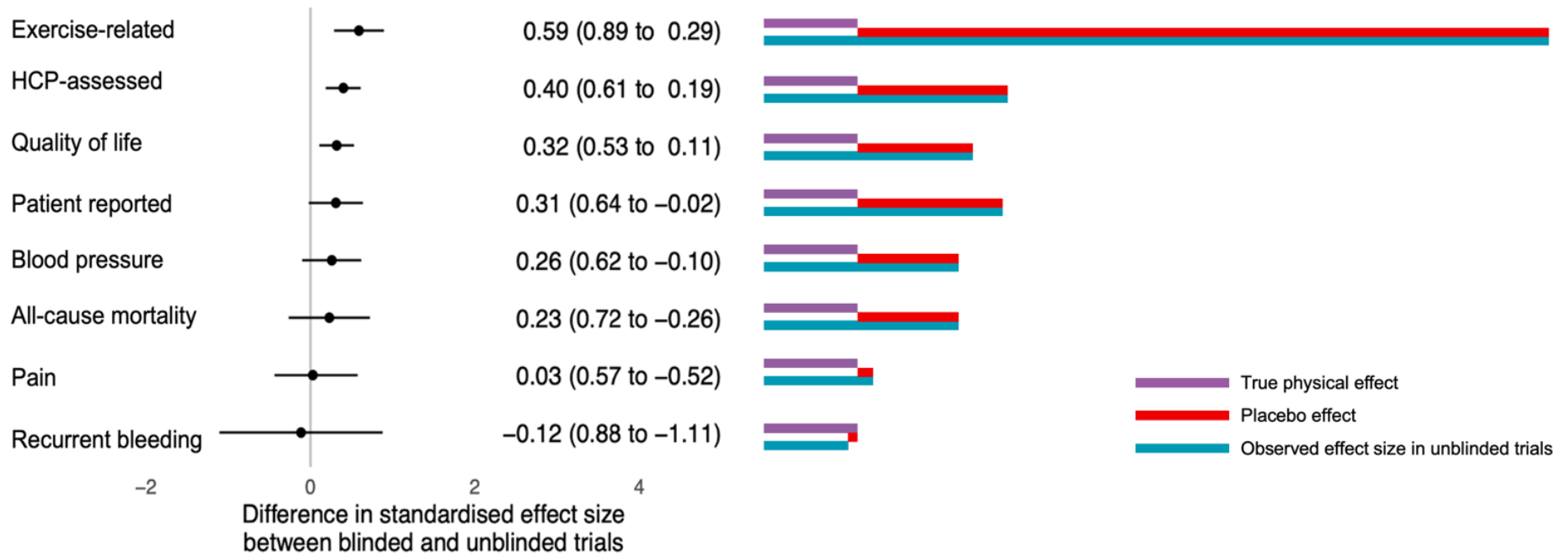
Figure 4.1: Consort diagram

## PHASE 1 – Identification of placebo-controlled trials



Consort Diagram. Phase 1 consisted of identification of randomised placebo-controlled trials. Phase 2 consisted of identification of RCTs examining the same intervention for the same condition and reporting the same endpoint, but with an unblinded design.

Figure 4.2: Forest Plot



Forest plot showing the difference in standardized effect sizes between blinded and unblinded trials for different endpoint categories. HCP = healthcare professional



## 5 Percutaneous coronary intervention for stable angina (ORBITA-2): a randomised, placebo-controlled trial

Parts of this chapter have been published as:

### **A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina (ORBITA-2).**

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## **5.1 Abstract**

### **5.1.1 Background**

Percutaneous coronary intervention (PCI) is frequently performed for stable angina. The first placebo-controlled trial found PCI did not increase treadmill exercise time on guideline-directed antianginal medication. Whether PCI without antianginal medication relieves angina beyond placebo remains unknown.

### **5.1.2 Methods**

ORBITA-2 was a randomised, double-blind, placebo-controlled trial in patients with stable angina. It consisted of antianginal medication cessation, 2-week pre-randomisation symptom assessment phase, randomisation to PCI or placebo, and 12-week follow-up. The primary endpoint was the ORBITA Score: calculated daily from angina episodes, antianginal medication restarts, unblinding for intolerable angina, acute coronary syndrome, and death.

### **5.1.3 Results**

Three hundred and one patients were randomised. Ischaemia was present in one territory in 242 (81%), two in 49 (16%) and three in 7 (2.3%). Median fractional flow reserve was 0.63 (0.49 to 0.75) and instantaneous wave-free ratio 0.78 (0.55 to 0.87).

PCI compared to placebo improved ORBITA Score from the start of follow-up (OR 1.54, 95% CrI 1.32 to 1.81, Pr(Benefit)>99.9%) to the end (OR 1.88, 95% CrI 1.57 to 2.27, Pr(Benefit)>99.9%). Over 12 weeks, PCI resulted in 27.7% (95% CrI 23.7 to 31.5, Pr(Benefit)>99.9%) more days free of angina and antianginal medication than placebo.

PCI increased treadmill exercise time (+52s, 95% CrI 12 to 92s, Pr(Benefit)=99.5%) and improved Canadian Cardiovascular Society class (-0.72, 95% CrI -0.95 to -0.49, Pr(Benefit)≥99.9%) compared to placebo.

#### **5.1.4 Conclusions**

In patients with stable angina and objective evidence of ischaemia, on little or no antianginal medication, PCI improved ORBITA Score, reduced angina and increased exercise capacity compared to placebo.

ClinicalTrials.gov: NCT03742050

## 5.2 Introduction

Angina relief is the primary reason that percutaneous coronary intervention (PCI) is carried out in stable coronary artery disease (CAD).<sup>2,7,32</sup> Evidence for angina reduction comes from unblinded trials<sup>6,32,51,83</sup> with the effect composed of both physical and placebo components.<sup>84</sup> The size of the physical component, calculated with placebo control, is essential knowledge in clinical decision-making, especially for procedures with non-negligible risk and cost.<sup>85</sup>

The first placebo-controlled trial of PCI, ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina), mandated guideline-directed antianginal medication, and found no significant effect.<sup>50</sup> It proved the feasibility of conducting placebo-controlled trials of established interventional procedures, and made it possible to design subsequent research applied to a wider population of patients and clinical practice. To quantify the true physical effect of PCI without placebo and the attenuating effect of background antianginal medication, required a new trial design.

ORBITA-2 was designed to tackle a more comprehensive question, without background antianginal medication. It enrolled a larger sample size, included single and multi-territory ischaemia, required symptoms during the pre-randomisation run-in-phase, and assessed efficacy with a longer duration of follow-up. Importantly, the primary endpoint is the first of its kind, based on daily patient symptom reports and need for antianginal medication, analysed using Bayesian methodology.

## **5.3 Methods**

### **5.3.1 Trial design and oversight**

ORBITA-2 was an investigator-initiated multicentre, double-blind, randomised, placebo-controlled trial performed at 14 sites in the United Kingdom. The study was approved by the London Central Research Ethics committee (reference 18/LO/1203). Written informed consent was obtained from each patient. The trial steering committee retained overall supervision of the trial, led by an independent chairperson. An independent data safety monitoring board (DSMB), blinded to treatment allocation, adjudicated all adverse events, and had the ability to terminate the trial at any point. The trial was subject to independent data monitoring. The sponsor and the funders had no role in the design, collection, analysis, or interpretation of the data, or writing of the report. The first and last authors had full access to all data and had final responsibility for the decision to submit for publication.

### **5.3.2 Patients**

Patients were eligible for enrolment if they were considered clinically suitable for PCI by their referring heart teams and met the inclusion criteria: (i) angina or equivalent symptoms, (ii) anatomical evidence of a severe coronary stenosis in at least one vessel from invasive diagnostic coronary angiography or computerised tomography coronary angiography and (iii) evidence of ischaemia on non-invasive imaging testing (dobutamine stress echocardiography (DSE), stress perfusion cardiac magnetic resonance imaging, nuclear medicine myocardial perfusion scan) or invasive physiological assessment during clinical or research coronary angiography. Exclusion criteria were age <18 years old, acute coronary syndrome in last six months, previous CABG, 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,

severe valvular disease, severe left ventricular systolic impairment (ejection fraction  $\leq 35\%$ ), severe respiratory disease, life expectancy less than 2 years, pregnancy and inability to consent.

### **5.3.3 Enrolment**

The full trial protocol<sup>61</sup> consisted of cessation of antianginal medication at enrolment, a 2-week pre-randomisation symptom assessment phase, randomisation to either PCI or placebo, and a 12-week blinded follow-up period. The study design is shown in Figure 5.1.

At enrolment, symptom and quality of life questionnaires (including Seattle Angina Questionnaire (SAQ) and EuroQOL 5 dimensions (EQ-5D-5L)) were performed. Patients were taught to use a dedicated smartphone application for daily angina symptom reporting. The design and features of the smartphone application<sup>60</sup> are described in Materials and Methods Section 3.6.

All medications prescribed for angina relief were suspended at enrolment. Risk-reduction medications were continued. Antihypertensive medications with antianginal properties were replaced with antihypertensives with no antianginal effects. Patients were provided with blood pressure monitors and home readings were monitored by the research team. Patients were prescribed dual antiplatelet medication, proton pump inhibitor, and high-intensity statin. Medications with antianginal properties required for other clinical indications e.g. heart failure or atrial fibrillation rate control, were continued as necessary.

### **5.3.4 Pre-randomisation symptom assessment phase**

Patients then began a 2-week pre-randomisation symptom assessment phase and reported daily angina frequency via the ORBITA-2 smartphone application. The research team issued prompts when patients had failed to report symptoms.

Patients could contact the trial team directly 24 hours a day. Where needed, antianginal medications were introduced and uptitrated for angina as determined by patient preference and symptom severity. Prescribing followed a pre-specified protocol, with blinded DSMB oversight (Appendix 10.11).

Patients were eligible to progress to randomisation if they reported at least one angina episode during the symptom assessment phase. Asymptomatic patients were withdrawn.

### **5.3.5 Pre-randomisation assessments**

Patients attended Imperial College London for pre-randomisation assessments, including treadmill exercise test (ETT) using the modified Bruce protocol.<sup>61</sup> Patients also underwent DSE. The images were double-reported by three imaging consultants (JS, GDC, DPF) blinded to treatment allocation and timepoint using an online reporting tool and previously reported methodology.<sup>57</sup>

### **5.3.6 Invasive protocol**

Coronary angiography was performed with auditory isolation using over-the-ear headphones with music playing. Pre-randomisation invasive physiological assessments were performed in each vessel, with  $\geq 50\%$  visual stenosis, considered a target for revascularisation using fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). The operator was not blinded to these values. When iFR was not available, an alternative non-hyperaemic pressure ratio was measured.

After physiological assessment, operators selected and documented the vessels they considered suitable for treatment; these were defined as the target vessels. For randomisation, evidence of ischaemia was required in at least one territory from invasive assessment, or any non-invasive

ischaemia test performed in pre-enrolment clinical evaluation. Non-ischaemic patients were withdrawn. Operators did not have access to the research ETT or DSE data to preserve the utility of these as stratifiers in future analyses.

### 5.3.7 **Invasive protocol**

Eligible patients were administered incremental doses of intravenous benzodiazepines and opiates to achieve a deep level of conscious sedation until they were unresponsive to verbal and tactile stimuli. Auditory isolation was continued throughout the procedure.

Patients were then randomised 1:1 to PCI or placebo procedure using computer generated randomisation with block size between 8 and 16 and no stratification. Allocation was communicated to catheter laboratory staff.

### 5.3.8 **Interventions**

For the PCI group, angiographic and physiological complete revascularisation of target vessels was mandated, and intravascular imaging encouraged. In multivessel disease, all vessels were treated during the index procedure.

After PCI, invasive physiological assessment was repeated with physiological optimisation encouraged.

The placebo group remained sedated for at least 15 minutes after randomisation. Coronary catheters were withdrawn without any intervention having taken place.

### **5.3.9 Blinding procedures and blinding index**

There was no transfer of information regarding the treatment allocation from catheter laboratory to recovery staff, who received a standardised handover and remained blinded. All subsequent medical caregivers were also blinded to treatment allocation. The operator and research staff present during the randomisation procedure had no further patient contact.

Each patient and the recovery team underwent a blinding test prior to discharge. All patients were discharged with standardised discharge documentation and dual antiplatelet medication. Patients were discharged on the day of randomisation unless otherwise clinically indicated. The blinding framework<sup>81</sup> is available in Section 3.8.

### **5.3.10 Follow-up evaluation**

On the day of randomisation, all antianginal medications initiated in the pre-randomisation period were stopped. Patients then entered the 12-week blinded follow-up phase, with continued daily smartphone application symptom reporting. During this period, antianginal initiation and up-titration for angina was triggered by patient contact and managed by staff blinded to treatment allocation, using an identical standardised protocol to the pre-randomisation phase.

At the end of the 12-week blinded follow-up period, patients returned for repeat ETT, DSE and symptom and quality of life questionnaires, performed by a physician and physiologist blinded to treatment allocation. Once tests were completed, patients and the research and medical teams were unblinded. This marked the end of the research study and patients returned to usual clinical care. Patients initially randomised to placebo could undergo PCI as part of routine care. Any actions or decisions taken after unblinding did not contribute to endpoint data.

### 5.3.11 Trial end points

The pre-specified primary endpoint of ORBITA-2 was the between-group longitudinal difference in the ORBITA Score. This is an ordinal clinical outcome scale calculated daily from the number of angina episodes and the units of antianginal medication prescribed. More angina episodes and antianginal use leads to a higher score. A patient who has no angina and no antianginal medications scores zero. This ordinal scale also incorporates high-level category overrides so that the occurrence of unblinding for intolerable angina, acute coronary syndrome or death are rated as worse than maximal symptoms or medication.

The post-randomisation ORBITA Scores were calculated throughout the 12-week period after randomisation except for the day of randomisation and the day after (since some were still in hospital) and the final day (during which they became unblinded). Full details are available in Section 3.7.

Secondary endpoints include components of the ORBITA Score: self-reported angina frequency (smartphone application) and need for antianginal medication initiation and uptitration. They also include difference in treadmill exercise time increment, change in angina severity as assessed by Canadian Cardiovascular Society (CCS) class, angina frequency, physical limitation, and angina stability (SAQ), quality of life (SAQ and EQ-5D-5L), and change in stress echocardiography score.<sup>57</sup>

## 5.4 Statistical analysis

For all endpoints, evidence for efficacy was quantified with Bayesian posterior probabilities of a beneficial effect of PCI over placebo. This is the probability of an odds ratio  $> 1$  in an ordinal model, which for the primary outcome is identical to the probability of positive increase in days with improved symptoms.

### 5.4.1 Primary endpoint

The primary outcome is the daily odds ratio of transitioning to a better clinical state on the ORBITA Score. This was derived by constructing a Bayesian Markov longitudinal ordinal model. The model maximises power by utilising daily symptom assessment while accounting for clinical events. The model includes the previous daily score (a first order Markov model), mean score value during the pre-randomisation period, trial day number, and randomisation arm. The trial day number was allowed to interact with the treatment group to allow for differing treatment effect each day. Effects were allowed to be non-linear with restricted cubic splines, and partial proportional odds with constraints with respect to time. In addition to the daily odds ratio, clinically relevant estimates and contrasts can be drawn from the model. This is illustrated by deriving the number of days in a state (such as no angina, or no antianginal medication use) from the daily transition probabilities.

### 5.4.2 Components of the primary endpoint

In addition to the ORBITA Score, similar models were constructed for its components: the number of daily episodes of angina (irrespective of antianginal use), and number of standardised doses of antianginal medications. Only raw data is presented for high grade events (unblinding due to intolerable angina, acute coronary syndromes, and deaths).

### 5.4.3 Secondary endpoints

The secondary endpoints were measured at pre-randomisation and follow-up. For both continuous and categorical outcome variables, the ordinal (proportional odds) equivalent of the analysis of covariance described previously was used<sup>56</sup> within a Bayesian framework. The follow-up value was conditioned on the pre-randomisation value, transformed by a restricted cubic spline with 3 knots, and randomisation arm, with no interaction. For clinical interpretation, the contrast between the PCI and placebo groups are presented for a typical patient with the median baseline value, transformed to the original scale, along with the probability that the difference in benefit is greater than zero ( $\Pr(\text{Benefit}) > 0$ ). Further details including priors have been previously published<sup>86</sup>.

The blinding index for patients and staff at baseline and follow-up were calculated using published methods.<sup>62</sup>

All analyses were conducted using the statistical environment “R”,<sup>73</sup> using the package “rmsb” for Bayesian modeling<sup>87</sup> and “BI” for the blinding index.

## **5.5 Results**

### **5.5.1 Patients**

Between 12th November 2018 and 17th June 2023, 923 patients were assessed for eligibility. Of these, 439 were enrolled into the pre-randomisation symptom assessment phase, and 301 were randomised to PCI or placebo. The consort diagram is shown in Figure 5.2.

Baseline characteristics are described in Table 5.1. The majority were in CCS class II or III (290, 96%) at enrolment. The median number of antianginal agents at enrolment and before protocolled cessation was 1 (mean 1.39). This equated to 2 (mean 2.3) standardised antianginal units. The quantity of antianginal medication prescribed at each stage of the trial is described in Table 5.2.

Assessment of cardiovascular risk factors was performed at pre-randomisation: mean total cholesterol 3.88mmol/l (SD 1.22), mean HbA1c 44mmol/mol (SD 12) (Table 5.3).

### **5.5.2 Procedural characteristics**

Procedural characteristics are described in Table 5.4. Radial access was used in 288 (96%). Invasive physiological assessment was performed in a median of 1 (mean 1.6) vessel per patient. Coronary territories with ischaemia were identified through pre-randomisation invasive physiology and pre-enrolment non-invasive functional testing: 242 (81%) had one, 49 (16%) had two and 7 (2.3%) had three. The most common ischaemic territory was the left anterior descending artery (55%). Angiographic images of the first 12 randomised stenoses are shown in Figure 5.3.

By quantitative coronary angiography, the mean diameter stenosis was 61.2% (SD 17.7) and area stenosis was 81.0% (SD 15). Across all stenoses the median FFR was 0.63 (0.49 to 0.75) and iFR was 0.78 (0.55 to 0.87).

In the PCI group, median number of stents was 2 (1 to 2). Median stent length was 42mm (23 to 64), and stent diameter 3.0mm (2.5 to 3.5). Post-dilation was performed in 242/284 (86%). Intravascular imaging was used in 104/151 (69%). Post-PCI FFR was 0.89 (0.85 to 0.93) and iFR 0.93 (0.91 to 0.97). Complete revascularisation was achieved in all but two patients. In both, the pressure wire pullback and intravascular imaging demonstrated diffuse disease which was managed conservatively.

### **5.5.3 Primary endpoint: ORBITA Score**

The design of the primary endpoint ensured that status was calculable as an angina symptom score for every patient daily. Data were available for 99.7% of the 22,823 patient days in the trial.

In this placebo-controlled trial, in patients on no or limited antianginal medication, PCI resulted in an immediate improvement in the ORBITA Score (OR 1.54, 95% CrI 1.32 to 1.81, Pr(Benefit)>99.9%) that was sustained to the last day of follow-up (OR 1.88, 95% CrI 1.57 to 2.27, Pr(Benefit)>99.9%, Figure 5.4, Table 5.5). This reduction in ORBITA Score was driven by a similar reduction in angina episodes (Figure 5.5, Table 5.5), rather than differences in antianginal medication use (Figure 5.6, Table 5.5). It was also not driven by high grade events: 0 versus 1 unblinding for intolerable angina, 4 versus 6 acute coronary syndromes and 0 versus 0 deaths in the PCI and placebo groups respectively.

Over 12 weeks, PCI resulted in 27.7% more days free of angina and antianginal medication (ORBITA Score=0) than placebo (95% CrI 23.7 to 31.5,  $\text{Pr}(\text{Benefit}) > 99.9\%$ ).

#### 5.5.4 Secondary endpoints

The results of all secondary endpoints are reported in Table 5.5.

Treadmill exercise time increased with PCI as compared to placebo (+52.3s, 95% CrI 12.5 to 92.3s,  $\text{Pr}(\text{Benefit}) = 99.5\%$ ), Figure 5.7.

Physician-assessed CCS class was lower with PCI than placebo (-0.72, 95% CrI -0.49 to 0.95,  $\text{Pr}(\text{Benefit}) > 99.9\%$ ), Figure 5.8.

Patient-reported SAQ angina frequency score improved with PCI versus placebo (14.6, 95% CrI 9.5 to 19.5,  $\text{Pr}(\text{Benefit}) = 99.5\%$ ), as did physical limitation score (8.9, 95% CrI 5.0 to 12.8,  $\text{Pr}(\text{Benefit}) > 99.9\%$ ) and quality of life (10.0, 95% CrI 5.2 to 14.9,  $\text{Pr}(\text{Benefit}) > 99.9\%$ ). PCI increased the proportion of patients free from angina derived from the SAQ angina frequency at follow-up (41% vs 17%,  $\text{delta} = 24\%$ , 95% CrI 15% to 34%,  $\text{Pr}(\text{Benefit}) \geq 99.9\%$ ).

Quality of life was improved by PCI versus placebo, with both the EQ-5D descriptive system (0.07, 95% CrI 0.04 to 0.11,  $\text{Pr}(\text{Benefit}) \geq 99.9\%$ ) and EQ-5D visual analogue scale (6.1, 95% CrI 2.3 to 9.7,  $\text{Pr}(\text{Benefit}) = 99.9\%$ ) as compared to the placebo group.

Ischaemia, as assessed by stress echocardiography score, was reduced by PCI in comparison to placebo (-0.88, 95% CrI -1.25 to -0.52,  $\text{Pr}(\text{Benefit}) \geq 99.9\%$ ), Figure 5.9.

Further details including regression coefficients, chain mixing and density plots for the primary and secondary endpoints have been previously published<sup>86</sup>.

#### **5.5.5 Blinding Index**

The principal assessment of blinding was performed prior to discharge after the randomisation procedure. The blinding index for the PCI group was 0.01 (95% CI -0.05 to 0.06) and the placebo group was -0.09 (-0.15 to -0.03) demonstrating effective blinding. The index for blinded staff in the PCI group was 0.01 (95% CI -0.01 to 0.04) and in the placebo group was 0 (-0.03 to 0.03) demonstrating effective blinding.

At the end of follow-up, the reassessment values were: 0.19 (95% CI 0.05 to 0.34) in the PCI group and 0.24 (0.09 to 0.38) in the placebo group. For the corresponding staff groups, it was 0.01 (95% CI -0.01 to 0.02) and 0 (-0.02 to 0.02).

## **5.6 Discussion**

### **5.6.1 Summary of results**

In this placebo-controlled trial in patients with stable angina on little or no antianginal medication, with stenoses that were anatomically and physiologically severe, PCI improved the ORBITA Score through a reduction in daily angina episodes. The PCI group had 28% more days free of angina and antianginal medication over 12 weeks and showed a 52-second increment in treadmill exercise time. The angina reduction was observable immediately and persisted throughout the blinded follow-up period. This is the first trial demonstrating a benefit of PCI beyond placebo for angina in stable coronary artery disease.

### **5.6.2 Specific features of the ORBITA-2 design**

The headline results of ORBITA-2 differ from those of ORBITA because they had different designs to answer different questions. Crucially, ORBITA adhered to the recommended guidance of antianginal medication first, with PCI as an add-on therapy.<sup>1,88</sup> The small effect size of PCI was surprising in the context of larger effects seen in clinical practice and previous clinical trials. One plausible explanation for this contrast is that this previous unblinded experience was augmented by placebo. Another possibility is that the effect of PCI, as an antianginal procedure, is larger with less background antianginal medication. While guidelines recommend higher levels of antianginal medication, half of patients undergoing clinical PCI are on zero or one antianginal medication<sup>89</sup> and no other trial has achieved the high levels of antianginal medication of ORBITA.<sup>90</sup> Perhaps it is unrealistic in clinical practice to attain and maintain high dose antianginal medication. Indeed, the patients enrolled in ORBITA-2 were referred for clinical PCI on an average of 1 full dose of antianginal medication. Analogous to trials of renal denervation,<sup>79,91</sup> to measure the physical effect

of PCI free from both placebo and any attenuation of effect by background antianginal medication, a trial was required with the specific design of ORBITA-2.

There are other possible contributors to the contrasting results. Symptoms were required at enrolment in ORBITA but, at randomisation, only 88% of patients remained symptomatic. In ORBITA-2, 100% of patients were symptomatic at randomisation. In ORBITA, only 94% had one or more positive ischaemia tests at randomisation;<sup>50</sup> in ORBITA-2 this was 100%. In ORBITA, median FFR and iFR were 0.72 and 0.85 respectively; the corresponding values in ORBITA-2 were 0.63 and 0.78. The mean stress echocardiography score was 1.08 in ORBITA and 1.88 in ORBITA-2.

ORBITA-2 extended follow-up to 12 weeks. Nevertheless, it found that angina relief is immediate and independently visible on every day of the 12-week follow-up.

Of the numerous differences between ORBITA and ORBITA-2, the overwhelmingly important one is the removal of mandated antianginal medication. Under placebo-controlled conditions, PCI reduces angina, but only with no background antianginal medication. Nevertheless, despite decades of technical advances in PCI, including the introduction of stents, the effect on exercise time under blinded conditions is still 44 seconds lower than under unblinded conditions in 1994.<sup>51</sup>

ORBITA-2 also introduces a new patient-orientated endpoint informed by patient and public engagement and involvement. This is centred on contemporaneous documentation of daily angina data on a smartphone application. This approach has several advantages: high temporal fidelity of data, minimising recall bias and maximising data completeness, all of which increase the power of the trial to detect change. This tool is now being employed in several clinical trials (NCT05459051,

NCT04280575, NCT04892537). The ordinal ORBITA Score builds on these daily symptom data, incorporating antianginal medication and relevant clinical events.

ORBITA demonstrated the ethical basis, feasibility and necessity of placebo-controlled trials of established interventional procedures.<sup>81,85,92</sup> ORBITA-2 builds on this by demonstrating the ethical basis, feasibility, and necessity of testing a coronary intervention without background therapy that may attenuate its effect.

### 5.6.3 Clinical implications

Only by not mandating guideline-directed antianginal medication as a precondition for PCI,<sup>93</sup> could we test the unattenuated efficacy of PCI on angina. The two trials together reveal that the recommendation to restrict PCI to patients with inadequate response to antianginal medications may be inadvertently selecting the cohort with the least to gain.

Going forward, patients and medical teams embarking on shared decision-making now have the choice of two pathways. The first is antianginal medication, as recommended in guidelines. However, if this is ineffective, the guideline-recommended next step of PCI provides little additional benefit<sup>50</sup>. The alternative pathway is to have an antianginal procedure. Although it is neither risk nor cost-free, this pathway can now at least be considered evidence based.

However, both pathways do not resolve angina in the majority. In ORBITA, with multiple antianginal medications and additional PCI, 61% of patients still had residual angina. In ORBITA-2, with PCI and access to antianginal medications, if required, 59% of patients still had residual symptoms.

The similarity of the outcomes underlines the possibility that it is the first therapy, whether it be antianginal medication or PCI, that has the greatest chance of efficacy. Consistent with this, the effect of PCI as monotherapy in ORBITA-2 was a 52s increment in treadmill exercise time, similar to the 48-55s that can be achieved with a single antianginal medication.<sup>41,43</sup> Perhaps, angina resulting from epicardial coronary disease can be treated effectively by either PCI or antianginal medication, leaving residual symptoms which will be resistant to either treatment as an additional therapy.

#### 5.6.4 Limitations

One limitation of ORBITA-2 was the follow-up of 12 weeks. However, the daily data show no evidence of change in the effect size during follow-up and therefore there is little reason to suspect a marked change in subsequent weeks. Another limitation is that it removed antianginal medications against guideline recommendations. However, these are non-prognostic agents and only this design allowed PCI to be tested as an antianginal monotherapy procedure. While the trial enrolled both single and multivessel disease, when tested systematically using invasive physiology, 81% had single territory ischaemia. This is similar to routine clinical practice.<sup>94</sup> The majority of patients in the PCI group still had residual symptoms at the end of the trial, albeit with near normalised stress echocardiography ischaemia. This trial cannot ascertain the cause of the residual symptoms, be it microvascular disease, residual epicardial disease not amenable to PCI, or non-cardiac causes of chest pain.

## **5.7 Conclusion**

ORBITA-2 shows that PCI as an antianginal monotherapy is feasible and effective, compared to a placebo procedure, on angina, quality of life and treadmill exercise time. The angina relief is immediate and sustained for at least 12 weeks, but not perfect. ORBITA and ORBITA-2 combined give patients and medical teams a choice of evidence-based placebo-controlled pathways. The first therapy administered, antianginal medication or PCI, appears to deliver most of the available symptomatic benefit.

Table 5.1: Baseline characteristics

|                                           | <b>PCI,<br/>N = 151<sup>I</sup></b> | <b>Placebo,<br/>N = 150<sup>I</sup></b> | <b>Overall,<br/>N = 301<sup>I</sup></b> |
|-------------------------------------------|-------------------------------------|-----------------------------------------|-----------------------------------------|
| Age                                       | 65 (9)                              | 64 (9)                                  | 64 (9)                                  |
| Male                                      | 120 (79%)                           | 118 (79%)                               | 238 (79%)                               |
| Hypertension                              | 97 (64%)                            | 92 (61%)                                | 189 (63%)                               |
| Diabetes                                  |                                     |                                         |                                         |
| Non-insulin dependent                     | 40 (26%)                            | 24 (16%)                                | 64 (21%)                                |
| Insulin-dependent                         | 9 (6.0%)                            | 11 (7.3%)                               | 20 (6.6%)                               |
| Hyperlipidaemia                           | 113 (75%)                           | 104 (69%)                               | 217 (72%)                               |
| <b>Smoking Status</b>                     |                                     |                                         |                                         |
| Never smoked                              | 65 (43%)                            | 50 (33%)                                | 115 (38%)                               |
| Ex-smoker                                 | 67 (44%)                            | 84 (56%)                                | 151 (50%)                               |
| Current smoker                            | 19 (13%)                            | 16 (11%)                                | 35 (12%)                                |
| <b>Left ventricular systolic function</b> |                                     |                                         |                                         |
| Normal                                    | 144 (95%)                           | 146 (97%)                               | 290 (96%)                               |
| Mild impairment                           | 6 (4.0%)                            | 3 (2.0%)                                | 9 (3.0%)                                |
| Moderate impairment                       | 1 (0.7%)                            | 1 (0.7%)                                | 2 (0.7%)                                |

| Canadian Cardiovascular Society Class       |             |             |             |
|---------------------------------------------|-------------|-------------|-------------|
| I                                           | 10 (6.6%)   | 1 (0.7%)    | 11 (3.7%)   |
| II                                          | 87 (58%)    | 87 (58%)    | 174 (58%)   |
| III                                         | 54 (36%)    | 62 (41%)    | 116 (39%)   |
| Angina duration (months)<br>Median (IQR)    | 8 (4 to 14) | 8 (5 to 14) | 8 (5 to 14) |
| <sup>1</sup> Mean (SD); n (%); Median (IQR) |             |             |             |

*Data are mean (SD) and n (%) unless otherwise stated. PCI = Percutaneous coronary intervention.*

Table 5.2: Antianginal prescribing

|                   | Antianginal units prescribed |             |
|-------------------|------------------------------|-------------|
|                   | PCI                          | Placebo     |
| Pre-enrolment     |                              |             |
| Mean              | 2.23                         | 2.31        |
| Median (range)    | 2 (0 to 8)                   | 2 (0 to 10) |
| Pre-randomisation |                              |             |
| Mean              | 0.47                         | 0.57        |
| Median (range)    | 0 (0 to 7)                   | 0 (0 to 9)  |
| Follow-up         |                              |             |
| Mean              | 0.46                         | 0.61        |
| Median (range)    | 0 (0 to 7)                   | 0 (0 to 7)  |

*Quantity of prescribed antianginal medication stratified by timepoint of the trial and randomisation group. Antianginal dosing is expressed in antianginal equivalent units for integration into the ORBITA Score primary endpoint. Dose conversion into standardised units for common antianginal medications is described in Table 3.4.*

Table 5.3: Blood results for randomised patients

|                            | PCI         | Placebo     |
|----------------------------|-------------|-------------|
| Haemoglobin (g/L)          | 143 (13)    | 142 (14)    |
| HbA1c (mmol/mol)           | 45 (12)     | 44 (11)     |
| Creatinine ( $\mu$ mol/L)  | 83 (21)     | 82 (25)     |
| Triglycerides (mmol/L)     | 1.45 (1.01) | 1.37 (0.80) |
| Total cholesterol (mmol/L) | 3.95 (1.42) | 3.81 (0.96) |
| HDL cholesterol (mmol/L)   | 1.19 (0.35) | 1.21 (0.40) |
| LDL cholesterol (mmol/L)   | 1.99 (0.98) | 2.02 (0.67) |

Data are presented as mean (SD).

Table 5.4: Procedural characteristics

|                                                     | PCI                 | Placebo             | Overall             |
|-----------------------------------------------------|---------------------|---------------------|---------------------|
| No. vessels                                         |                     |                     |                     |
| Single vessel disease                               | 122 (81%)           | 120 (82%)           | 242 (81%)           |
| Two vessel disease                                  | 25 (17%)            | 24 (16%)            | 49 (16%)            |
| Three vessel disease                                | 4 (2.6%)            | 3 (2.0%)            | 7 (2.3%)            |
| Vessels                                             |                     |                     |                     |
| Left anterior descending                            | 108 (56%)           | 100 (54%)           | 208 (55%)           |
| Circumflex                                          | 16 (8.3%)           | 17 (9.2%)           | 33 (8.8%)           |
| Right coronary artery                               | 42 (22%)            | 41 (22%)            | 83 (22%)            |
| Branch vessels                                      | 27 (14%)            | 26 (14%)            | 53 (14%)            |
| Serial Stenoses                                     | 29 (19%)            | 20 (14%)            | 49 (16%)            |
| Quantitative coronary angiography diameter stenosis |                     |                     |                     |
| Mean (SD)                                           | 60.5 (18.2)         | 62.0 (17.1)         | 61.2 (17.7)         |
| Median (IQR)                                        | 59.8 (48.5 to 74.5) | 62.8 (50.4 to 74.2) | 61.0 (49.1 to 74.4) |
| Quantitative coronary angiography area stenosis     |                     |                     |                     |

|                                      |                     |                     |                     |
|--------------------------------------|---------------------|---------------------|---------------------|
| Mean (SD)                            | 80.3 (15.3)         | 81.7 (14.7)         | 81.0 (15.0)         |
| Median (IQR)                         | 83.0 (73.4 to 91.9) | 85.1 (74.8 to 92.7) | 84.1 (73.5 to 92.1) |
| FFR                                  |                     |                     |                     |
| Mean (SD)                            | 0.60 (0.17)         | 0.62 (0.16)         | 0.61 (0.16)         |
| Median (IQR)                         | 0.61 (0.47 to 0.74) | 0.65 (0.51 to 0.75) | 0.63 (0.49 to 0.75) |
| iFR*                                 |                     |                     |                     |
| Mean (SD)                            | 0.68 (0.22)         | 0.71 (0.23)         | 0.70 (0.22)         |
| Median (IQR)                         | 0.76 (0.50 to 0.86) | 0.81 (0.58 to 0.89) | 0.78 (0.55 to 0.87) |
| Interventions                        |                     |                     |                     |
| No. stents implanted                 | 2                   | -                   | -                   |
| Median (IQR)                         | (1 to 2)            | -                   | -                   |
| Total length of stent implanted (mm) | 42                  | -                   | -                   |
| Median (IQR)                         | (23 to 64)          | -                   | -                   |
| Stent diameter (mm)                  | 3.0 (2.5 to 3.5)    | -                   | -                   |
| Median (IQR)                         |                     |                     |                     |
| Post-dilation (n=284)                | 242 (86%)           | -                   | -                   |

| Drug eluting stent type |                     |   |   |
|-------------------------|---------------------|---|---|
| Everolimus-eluting      | 171 (60%)           | - | - |
| Zotarolimus-eluting     | 83 (29%)            | - | - |
| Others                  | 29 (10%)            |   |   |
| Post-PCI FFR            |                     |   |   |
| Mean (SD)               | 0.89 (0.07)         | - | - |
| Median (IQR)            | 0.89 (0.85 to 0.93) | - | - |
| Post-PCI iFR*           |                     |   |   |
| Mean (SD)               | 0.94 (0.05)         | - | - |
| Median (IQR)            | 0.93 (0.91 to 0.97) | - | - |

*Data are mean (SD) and n (%) unless otherwise stated. PCI = Percutaneous coronary intervention. FFR = Fractional Flow Reserve. iFR = instantaneous wave-Free Ratio. \*Where iFR was not available, an alternative non-hyperaemic pressure ratio was utilised.*

Table 5.5: Primary and secondary endpoints of ORBITA-2

| Primary Endpoint                                                  |                                                                                     |                  |                                            |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|--------------------------------------------|
|                                                                   | Odds ratio of transitioning to a better clinical state each day with PCI vs placebo |                  | Probability of benefit with PCI vs placebo |
| ORBITA Score<br>Follow-up (Day 84)<br>Follow-up (Day 2)           | OR 1.88, 95% CrI 1.57 to 2.27<br>OR 1.54, 95% CrI 1.32 to 1.81                      |                  | >99.9%<br>>99.9%                           |
| Components of primary endpoint                                    |                                                                                     |                  |                                            |
| Angina episodes<br>Follow-up (Day 84)<br>Follow-up (Day 2)        | OR 1.93, 95% CrI 1.58 to 2.33<br>OR 1.51, 95% CrI 1.29 to 1.78                      |                  | >99.9%<br>>99.9%                           |
| Antianginal medication<br>Follow-up (Day 84)<br>Follow-up (Day 2) | OR 1.09, 95% CrI 0.46 to 2.62<br>OR 1.43, 95% CrI 0.72 to 2.94                      |                  | 57.5%<br>84.0%                             |
| Secondary Endpoints                                               |                                                                                     |                  |                                            |
|                                                                   | PCI                                                                                 | Placebo          |                                            |
| Treadmill exercise time                                           |                                                                                     |                  |                                            |
| n                                                                 | 123                                                                                 | 112              |                                            |
| Baseline median (s)                                               | 619                                                                                 |                  |                                            |
| Follow-up (s)                                                     | 694 (658 to 729)                                                                    | 642 (603 to 680) |                                            |
| Increment (s)                                                     | 76 (39 to 111)                                                                      | 23 (-16 to 62)   |                                            |
| Benefit of PCI over placebo (s)                                   | 52 (12 to 92)                                                                       |                  | 99.5%                                      |
| Canadian Cardiovascular Society class                             |                                                                                     |                  |                                            |
| n                                                                 | 147                                                                                 | 146              |                                            |
| Baseline median                                                   | 2                                                                                   |                  |                                            |

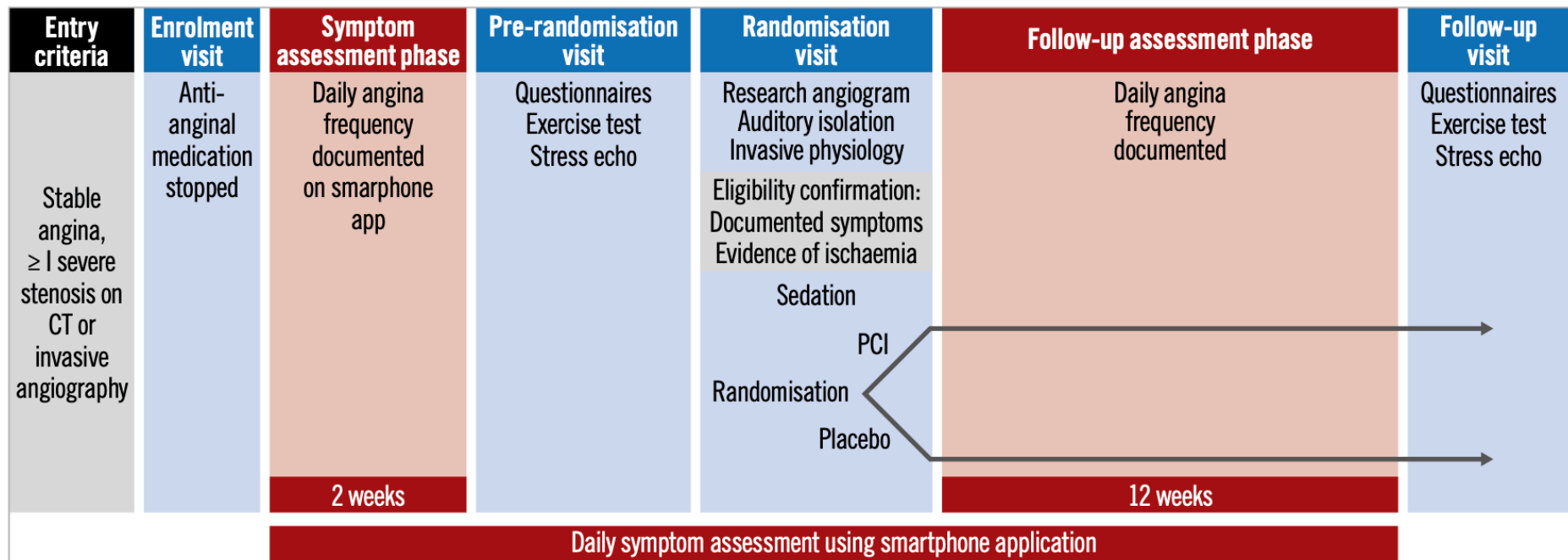
|                             |                        |                        |        |
|-----------------------------|------------------------|------------------------|--------|
| Follow-up                   | 0·94 (0·77 to 1·11)    | 1·65 (1·47 to 1·85)    |        |
| Increment                   | -1·06 (-1·23 to -0·89) | -0·34 (-0·53 to -0·15) |        |
| Benefit of PCI over placebo | -0·72 (-0·95 to -0·49) |                        | >99·9% |
| SAQ angina frequency        |                        |                        |        |
| n                           | 146                    | 145                    |        |
| Baseline median             | 60·0                   |                        |        |
| Follow-up                   | 79·6 (75·5 to 83·6)    | 65·1 (60·3 to 69·8)    |        |
| Increment                   | 19·6 (15·5 to 23·6)    | 5·1 (0·3 to 9·8)       |        |
| Benefit of PCI over placebo | 14·6 (9·5 to 19·5)     |                        | >99·9% |
| SAQ physical limitation     |                        |                        |        |
| n                           | 139                    | 144                    |        |
| Baseline median             | 66·7                   |                        |        |
| Follow-up                   | 82·7 (79·1 to 86·1)    | 73·7 (70·0 to 77·5)    |        |
| Increment                   | 16·0 (12·4 to 19·5)    | 7·1 (3·3 to 10·9)      |        |
| Benefit of PCI over placebo | 8·9 (5·0 to 12·8)      |                        | >99·9% |
| SAQ angina stability        |                        |                        |        |
| n                           | 145                    | 145                    |        |
| Baseline median             | 50·0                   |                        |        |
| Follow-up                   | 61·4 (56·9 to 65·9)    | 55·4 (50·7 to 60·4)    |        |
| Increment                   | 11·4 (6·9 to 15·9)     | 5·4 (0·7 to 10·4)      |        |

|                             |                        |                          |        |
|-----------------------------|------------------------|--------------------------|--------|
| Benefit of PCI over placebo | 6.0 (0.4 to 11.7)      |                          | 98.0%  |
| SAQ quality of life         |                        |                          |        |
| n                           | 145                    | 145                      |        |
| Baseline median             | 41.7                   |                          |        |
| Follow-up                   | 61.9 (57.6 to 66.2)    | 51.9 (47.6 to 56.2)      |        |
| Increment                   | 20.2 (15.9 to 24.5)    | 10.3 (6.0 to 14.6)       |        |
| Benefit of PCI over placebo | 10.0 (5.2 to 14.9)     |                          | >99.9% |
| EQ-5D descriptive system    |                        |                          |        |
| n                           | 145                    | 144                      |        |
| Baseline median             | 0.75                   |                          |        |
| Follow-up                   | 0.80<br>(0.77 to 0.83) | 0.73<br>(0.70 to 0.76)   |        |
| Increment                   | 0.05<br>(0.03 to 0.08) | -0.02<br>(-0.05 to 0.01) |        |
| Benefit of PCI over placebo | 0.07<br>(0.04 to 0.11) |                          | >99.9% |
| EQ-VAS                      |                        |                          |        |
| n                           | 146                    | 143                      |        |
| Baseline median             | 70.0                   |                          |        |
| Follow-up                   | 72.8 (69.8 to 75.8)    | 66.7 (63.2 to 70.1)      |        |
| Increment                   | 2.8 (-0.2 to 5.8)      | -3.3 (-6.8 to 0.1)       |        |
| Benefit of PCI over placebo | 6.1 (2.3 to 9.7)       |                          | >99.9% |

| Stress echocardiography score |                           |                         |        |
|-------------------------------|---------------------------|-------------------------|--------|
|                               | PCI                       | Placebo                 |        |
| n                             | 119                       | 111                     |        |
| Baseline mean                 | 1.81                      |                         |        |
| Follow-up                     | 0.96<br>(0.72 to 1.21)    | 1.84<br>(1.46 to 2.28)  |        |
| Increment                     | -0.86<br>(-1.09 to -0.61) | 0.03<br>(-0.35 to 0.46) |        |
| Benefit of PCI over placebo   | -0.88<br>(-1.25 to -0.52) |                         | >99.9% |

*PCI = Percutaneous coronary intervention, SAQ = Seattle Angina Questionnaire. For the primary endpoint, results are reported for both the start of the follow-up period (Day 2), and the end (Day 84). Treadmill exercise time and stress echocardiography score are presented for the patients who had both pre-randomisation and follow-up scores.*

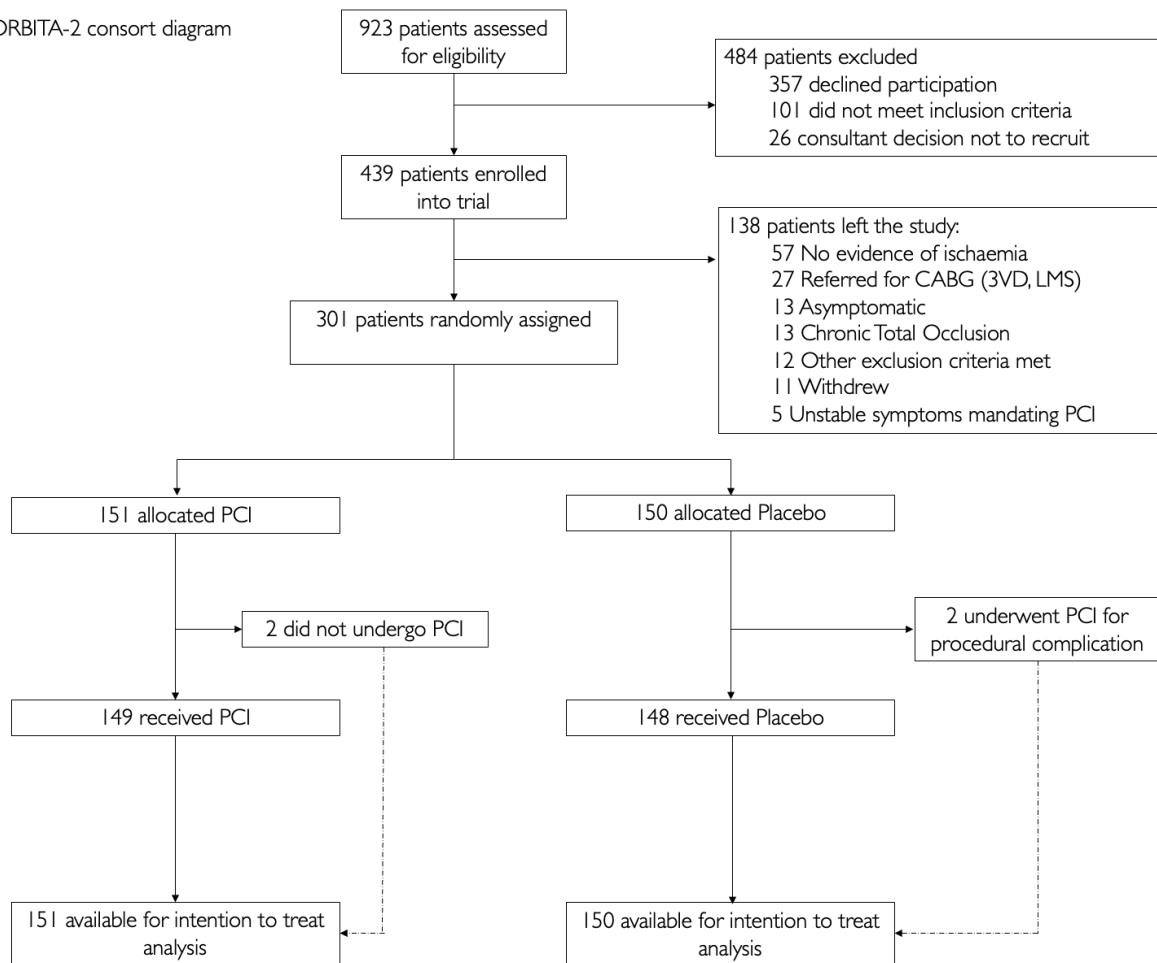
Figure 5.1: ORBITA-2 study design



CT: computed tomography; PCI percutaneous coronary intervention

Figure 5.2: ORBITA-2 Consort diagram

ORBITA-2 consort diagram



PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; 3VD = 3 vessel disease; LMS = left main stem disease

Figure 5.3: Angiographic images of the first 12 randomised stenoses

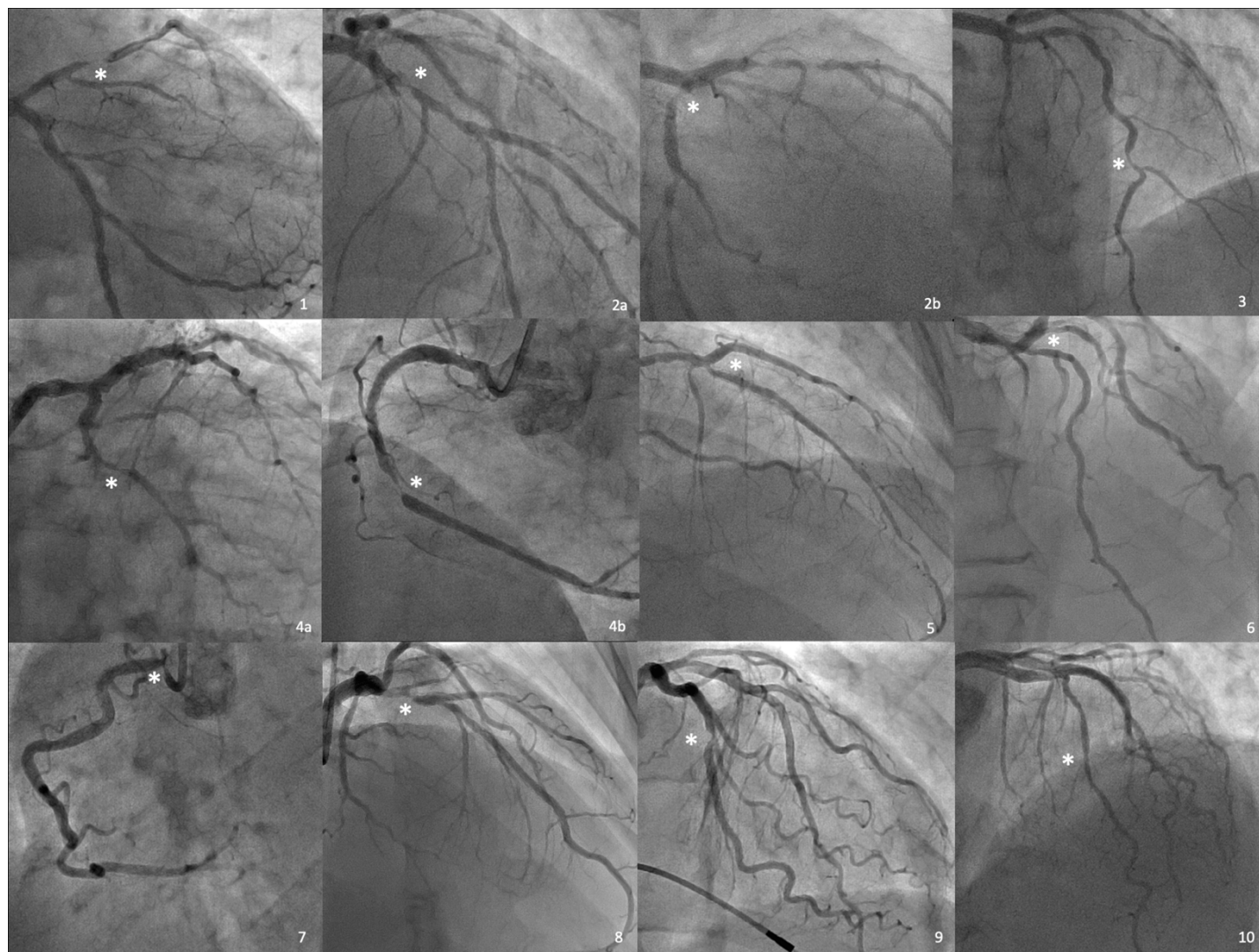
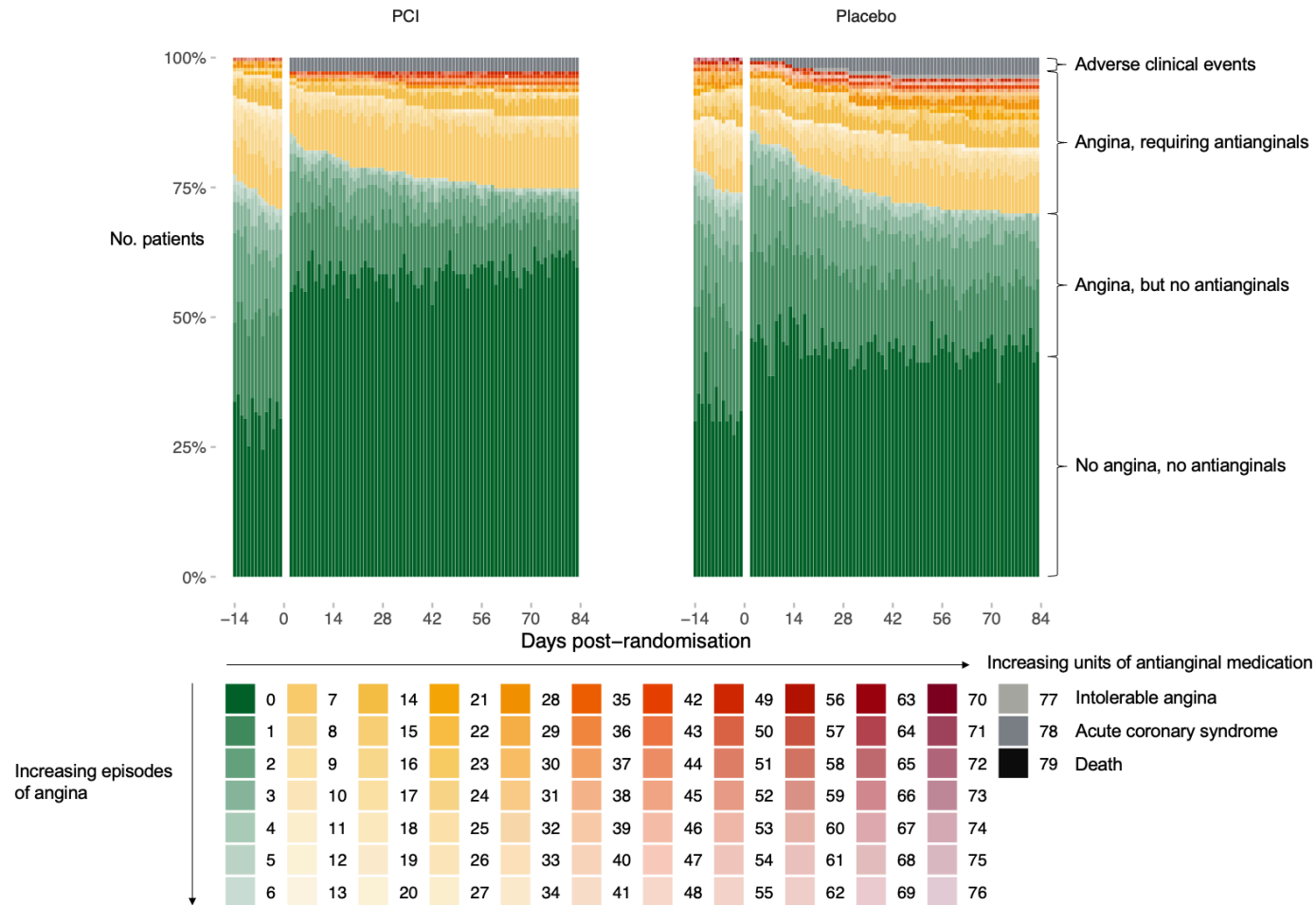
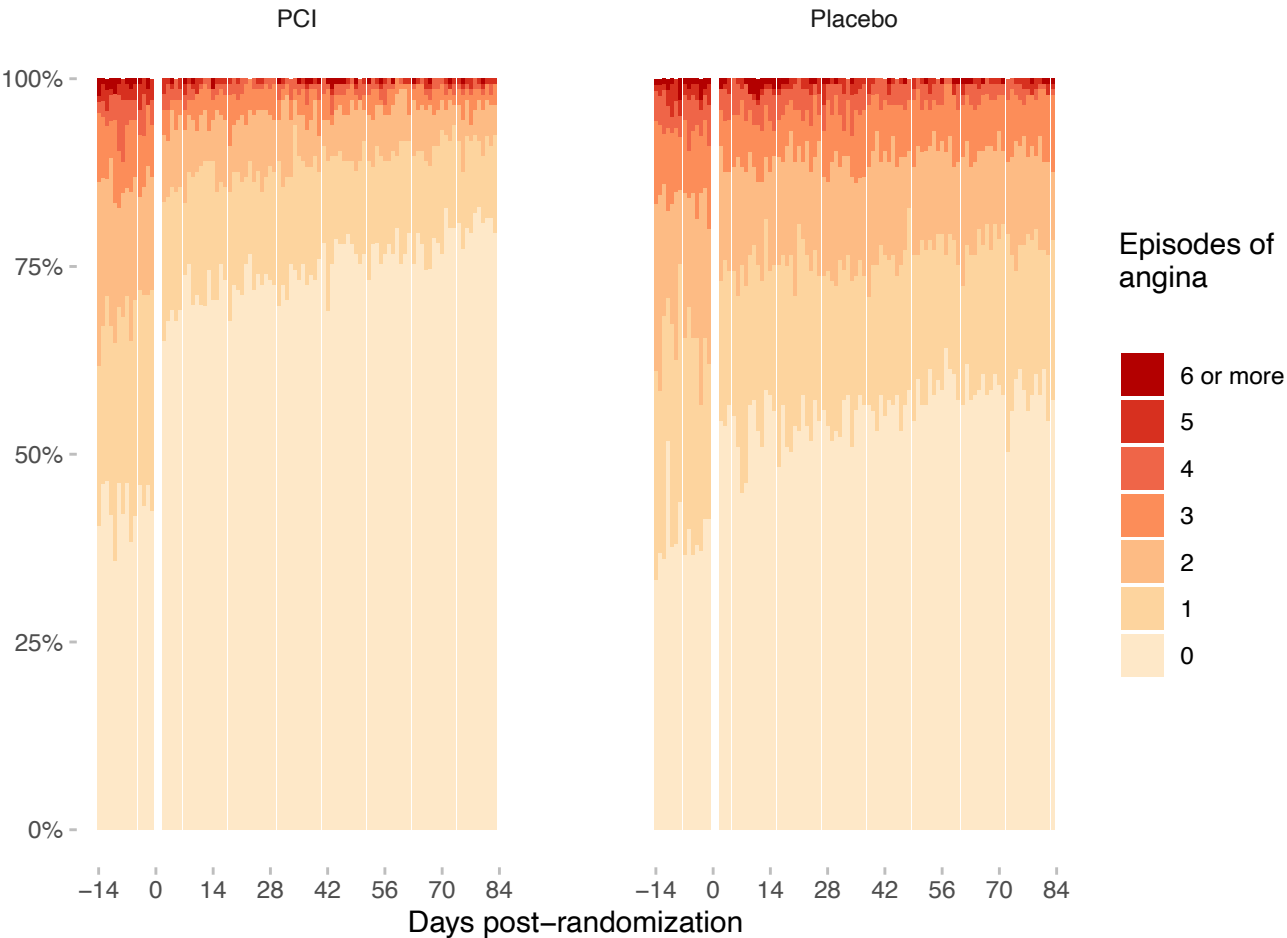


Figure 5.4: Primary outcome of ORBITA Score



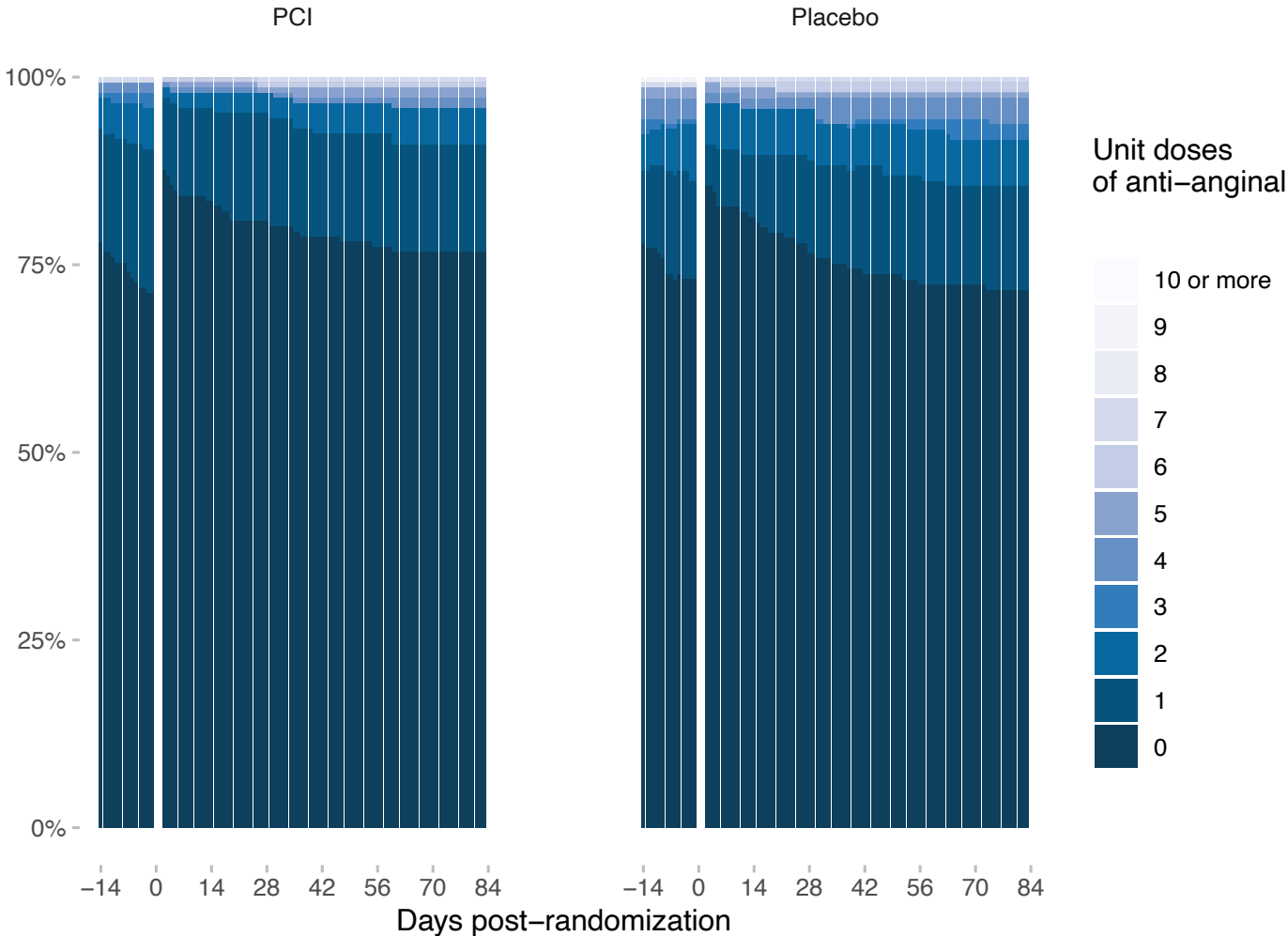
Individual patient data composition of the primary endpoint (ORBITA Score) stratified by treatment allocation. The method for derivation of the score is depicted below and the overall calculated score is shown next to the coloured box.

Figure 5.5: Angina Episodes



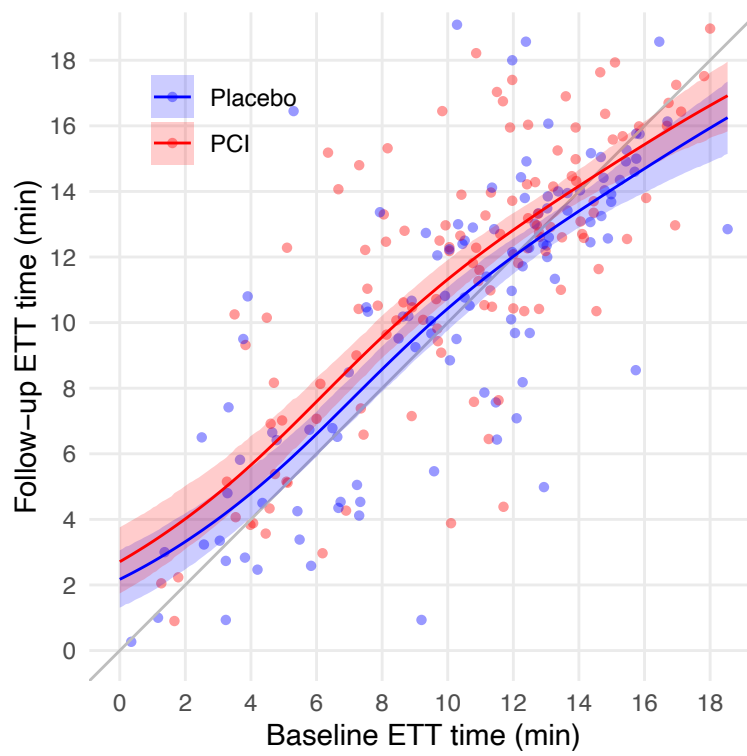
Individual patient data of daily angina episodes irrespective of the units of antianginal medication prescribed in each treatment arm.

Figure 5.6: Antianginal use



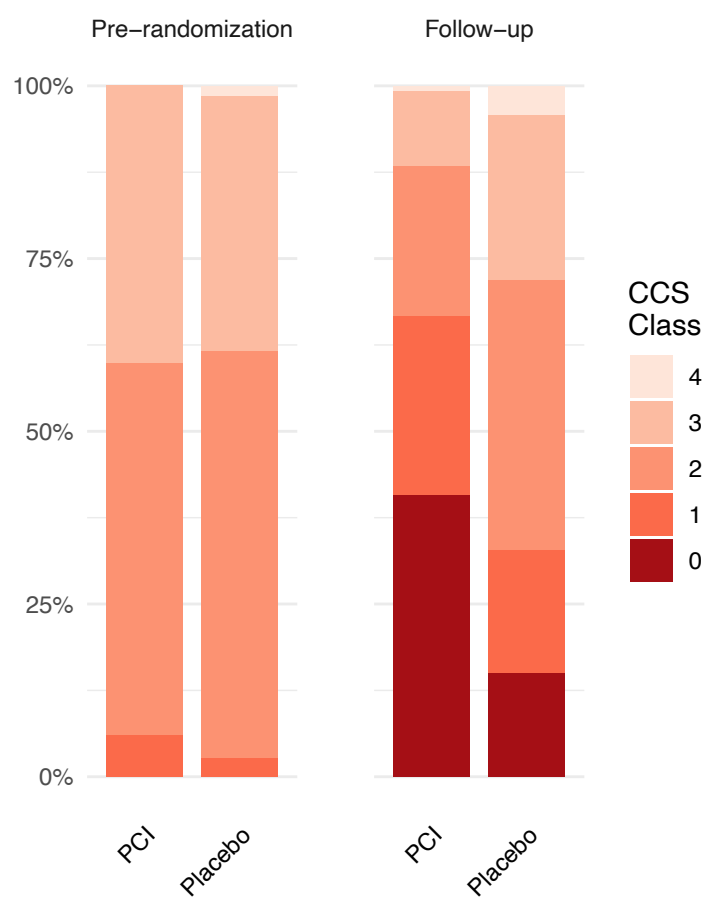
Number of units of antianginal medication prescribed for each patient on each day of the trial by treatment arm.

Figure 5.7: Treadmill exercise time



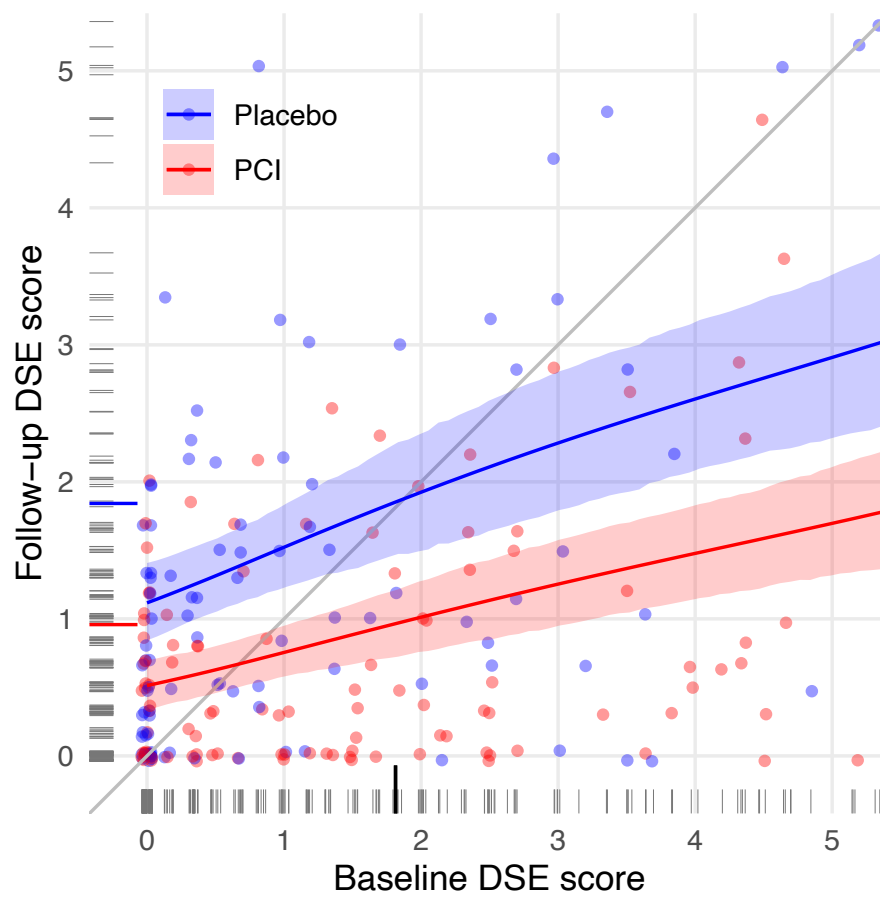
Treadmill exercise at follow-up stratified by baseline performance. ETT = exercise treadmill time.

Figure 5.8: Canadian Cardiovascular Society class



Distribution of CCS class according to treatment group at pre-randomisation and follow-up. CCS = Canadian Cardiovascular Society class.

Figure 5.9: Dobutamine stress echocardiography score



Stress echocardiography score at follow-up stratified by baseline score. DSE = Dobutamine stress echocardiography

## 6 Systematic Trial of Angina Assessment prior to Revascularisation: An n-of-1 placebo-controlled study in stable coronary artery disease (ORBITA-STAR)

Parts of this chapter have been published as:

### **N-of-1 Trial of Angina Verification Before Percutaneous Coronary Intervention.**

**Rajkumar CA**, Foley MJ, Ahmed-Jushuf F, Simader FA, Mohsin M, Ganesanathan S, Nowbar AN, Chotai S, Sen S, Petraco R, Nijjer SS, Sehmi J, Ruparelia N, Dzung JN, Kabir A, Tang K, Gamma R, Davies JR, Kotecha T, Cole GD, Howard JP, Keeble TR, Clesham G, O'Kane PD, Harrell FE Jr, Francis DP, Shun-Shin MJ, Al-Lamee RK.

J Am Coll Cardiol. 2024 Jul 2;84(1):1-12.

PMID: 38752902

## **6.1 Abstract**

### **6.1.1 Background**

In stable coronary artery disease, 30-60% of patients continue to experience symptoms despite successful revascularisation. The reasons for this are multifactorial, however, perhaps not all symptoms reported by a patient with myocardial ischaemia and a severe coronary stenosis are, in fact, angina. This study tested whether independent symptom verification using a placebo-controlled ischaemic stimulus could distinguish which patients achieved symptom relief from percutaneous coronary intervention (PCI).

### **6.1.2 Methods**

ORBITA-STAR was a multicentre, n-of-1, placebo-controlled study in patients with single-vessel coronary artery disease who were undergoing PCI for stable chest pain. Participants underwent four, 60-second episodes of low-pressure balloon occlusion across their coronary stenosis to induce ischaemia. These episodes were paired with four episodes of placebo occlusion in a randomised order. Patients reported the similarity of the induced symptom in comparison to their usual symptom on a visual analogue scale. The similarity score ranged from -10 (placebo occlusion replicated their symptom more than balloon occlusion) to +10 (balloon occlusion exactly replicated their symptom, and placebo occlusion did not). The primary endpoint was the ability of the mean similarity score to predict symptom relief following PCI.

### **6.1.3 Results**

Fifty-one patients completed the study protocol. The mean age was 62.9 (8.6) years, and 78% were male. In the target vessels, the median fractional flow reserve (FFR) was 0.68 (0.57 to 0.79),

instantaneous wave-free ratio (iFR) 0.80 (0.48 to 0.89) and coronary flow reserve (CFR) 1.42 (1.08 to 1.85). Following PCI, the median FFR, iFR and CFR improved to 0.92 (0.90 to 0.96), 0.96 (0.93 to 0.99) and 2.34 (1.68 to 2.72), respectively.

Thirty-nine (76%) patients had a similarity score greater than 0, indicating greater symptom similarity with balloon occlusion than placebo occlusion. Across the cohort, the median placebo-controlled similarity score was 3 (0.875 to 5.25).

The placebo-controlled similarity score was a strong predictor of symptom relief following PCI: a patient at the upper quartile with a similarity score of 5.25 was significantly more likely to have reduced symptom frequency at the end of follow up (OR 8.01 (2.39 to 15.86)) than a patient at the lower quartile with a similarity score of 0.875 (OR 1.31 (0.71 to 1.99)),  $\text{Pr}(\text{difference}) > 99.9\%$ .

#### **6.1.4 Conclusions**

The placebo-controlled similarity score was a strong predictor of symptom relief following PCI. Independent symptom verification may improve our ability to target revascularisation procedures towards those patients most able to benefit.

## 6.2 Introduction

The principal role for percutaneous coronary intervention (PCI) in stable coronary artery disease is to relieve angina<sup>2,7,32</sup>. The *Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina-2* (ORBITA-2) Trial confirmed that PCI is an effective antianginal treatment beyond placebo<sup>86</sup>. However, despite successful PCI, with near complete resolution of ischaemia, 59% of patients had residual symptoms in this blinded trial. Even in unblinded datasets, with therapeutic effect sizes that are enhanced by the larger and unquantified placebo component, 30% of patients continue to report symptoms following PCI<sup>83</sup>. The reason for this is unclear.

One reason for uncertainty is that focus is more often placed upon treatment than on evaluating the symptoms themselves. If a patient has a severe stenosis amenable to PCI, relatively little attention is routinely given to differentiating symptoms as typical, atypical, or even breathlessness that is considered “angina equivalent”.

Second, although PCI can only relieve angina that is truly caused by a coronary stenosis, there is currently no evidence-based method to map a symptom to a stenosis. Without this, we cannot accurately predict symptom improvement from PCI.

During PCI, balloon inflation that occludes a coronary artery can produce ischaemia-related ECG changes and trigger symptoms. When these symptoms mimic the patient’s presenting complaint, this is often taken as confirmation that the presentation was angina, and the PCI is likely to be effective. However, there has been no systematic description of the nature of these symptoms and no comparison of how, in an individual patient, they relate to the symptom being treated. If they are a close match, PCI may be more likely to relieve the patient’s complaint.

The Systematic Trial of Angina Assessment prior to Revascularisation (ORBITA-STAR) study used a placebo-controlled invasive experiment to determine whether symptoms induced in the catheter laboratory predict symptom improvement with PCI, as a potential basis for future personalised angina therapy.

## 6.3 Methods

### 6.3.1 Study design and participants

ORBITA-STAR was a multicentre *n-of-1* placebo-controlled study performed at 5 sites in the United Kingdom. A list of trial centres is provided in the supplementary appendix. The study was approved by the London Central Research Ethics Committee (Ref: 19/LO/1194). All participants provided written informed consent prior to enrolment.

Patients aged 18-85 years were eligible for inclusion if they met the following criteria: angina or angina equivalent symptoms, referred for PCI, with at least one  $\geq 70\%$  stenosis in a single coronary artery on invasive coronary angiography or coronary computed tomography angiography (CCTA).

Exclusion criteria were age younger than 18 or older than 85 years, recent acute coronary syndrome, multivessel coronary artery disease, previous coronary artery bypass graft surgery, significant left main stem coronary disease, chronic total occlusion in the target vessel, contraindication to percutaneous coronary intervention or drug-eluting stent implantation, contraindication to antiplatelet therapy, contraindication to adenosine infusion, severe valvular disease, severe LV systolic impairment, severe respiratory disease, life expectancy less than 2 years, pregnancy or unable to consent.

Patients enrolled into the study following a CCTA were withdrawn if they were subsequently identified to have unsuitable anatomy, not meeting inclusion criteria, at invasive angiography.

The study consisted of two symptomatic assessment phases: 2 weeks pre-PCI and 12 weeks post-PCI. These symptom assessment phases were separated by the invasive research procedure which comprised a placebo-controlled invasive protocol and clinically indicated PCI (Figure 6.1).

### 6.3.2 Study Protocol

Following enrolment, all antianginal medications were suspended. Exemptions applied if antianginal medications were required for other clinical indications such as beta-blockers for rate control in atrial fibrillation, left ventricular impairment or post-myocardial infarction. In patients with hypertension, antianginal medication was replaced with anti-hypertensive agents with no antianginal properties and home blood pressure monitors were provided for remote monitoring.

Symptoms at baseline were assessed using Canadian Cardiovascular Society (CCS) class. The Seattle Angina Questionnaire (SAQ) and 5-level version of the EuroQol 5 dimensions (EQ-5D-5L) questionnaire were performed.

After enrolment, patients entered a 2-week pre-PCI symptom assessment phase, during which time participants used a dedicated smartphone application to report daily angina frequency (Figure 6.2)<sup>59,60</sup>. Daily reporting of symptoms was employed to create datasets with high temporal definition and a low probability of recall bias. Patient-reported angina frequency was instantaneously transmitted to the research team and the data stored in a secure server.

Prior to PCI, patients underwent a treadmill exercise test using the modified Bruce protocol and dobutamine stress echocardiography (DSE).

### 6.3.3 Invasive Protocol

All patients were pre-treated with dual antiplatelet therapy prior to the invasive research procedure. Coronary angiography was performed via the radial or femoral approach.

Pre-PCI coronary physiological assessments were performed using a Doppler and pressure sensor tipped wire ('Combwire', Volcano Corp, San Diego, California). The combowire was normalised and then advanced distal to the target stenosis. Physiological assessments including instantaneous wave-free ratio (iFR), fractional flow reserve (FFR) and coronary flow reserve (CFR) were performed. An intravenous infusion of adenosine of 140mcg/kg/min was used for measurement of hyperaemic indices. Following resolution of hyperaemia, a coronary angioplasty wire was placed beyond the stenosis alongside the Combwire.

#### 6.3.3.1 *Placebo-controlled symptom assessment*

The placebo-controlled invasive protocol consisted of 4 pairs of episodes to establish the degree of similarity between a patient's experimentally induced symptom of ischaemia and their day-to-day symptom (Figure 6.3). Each pair of episodes consisted of a balloon occlusion episode and a placebo inflation episode in a randomised order. Each of these 8 episodes lasted a minimum of 60 seconds. Patients were informed when each episode started and finished but were not informed of the nature of the episode: balloon occlusion or placebo inflation. Surgical screening was used to ensure that patients were unable to visualise the operator and the catheter laboratory screens.

**(a) Balloon occlusion:** A semi-compliant angioplasty balloon sized with 1:1 balloon: artery ratio, based on angiographic assessment, was positioned within the stenosis. It was inflated to the lowest pressure which occluded flow to the distal vessel (typically 1-3 atm). Vessel

occlusion was confirmed with loss of the Combwire Doppler flow trace, and angiographic contrast injection. After 60 seconds, the balloon was deflated and withdrawn into the guiding catheter.

**(b) Placebo inflation:** The deflated angioplasty balloon remained inside the guiding catheter.

To maintain blinding, the operator inflated and deflated a second “decoy” balloon positioned outside of the patient’s body to recreate the sound of real balloon occlusion episodes.

Symptom assessment following each episode was identical regardless of whether the episode was real or placebo. Patients reported their symptoms immediately on termination of each episode in a structured format with two values:

- **Intensity Score (0-10):** The intensity of the symptom at its most severe, where 0 = no perceived sensation, 10 = worst imaginable pain.
- **Similarity Score (0-10):** The similarity between the character of the provoked sensation to the patient’s day-to-day symptom, where 0 = no similarity, 10 = identical to day-to-day symptom.

After each episode, balloon occlusion or placebo inflation, a minimum of 30 seconds recovery time was mandated before the next episode began. If symptoms or ECG abnormalities persisted, the recovery time was extended until the symptoms completely resolved, plus an additional 30 seconds to prevent symptom crossover between episodes. The Doppler flow trace from the

Combwire was used to confirm that hyperaemia, induced by balloon occlusion episodes had resolved before the next episode was commenced.

An adaptive design was utilised to maximise the probability of symptom provocation in each patient: If a patient reported a zero-intensity score (no perceived sensation) to balloon occlusion of 60 seconds, the following pairs of episodes were extended sequentially by 30 seconds. This was continued up to a maximum episode duration of 2.5 minutes. Conversely, if a patient experienced symptoms with 60 second episodes, no prolongation of subsequent episodes was required.

Patients were blinded to the results of their similarity score calculation until the end of follow up.

#### *6.3.3.2 Percutaneous coronary intervention of target lesion*

Following the placebo-controlled symptom assessment, all patients had clinically indicated PCI of the target lesion with implantation of drug eluting stents. Use of drug coated balloons was permitted when clinically indicated. Use of intravascular imaging and post-dilation of stents was encouraged. Post-PCI invasive coronary physiology was repeated with iFR, FFR and CFR measurements.

#### **6.3.4 Post PCI symptom assessment**

Following PCI, patients entered the post-PCI symptom assessment phase. During this period, patients continued to report daily angina frequency using the dedicated ORBITA-STAR smartphone application.

Follow-up assessments were completed for 12 weeks following PCI. All follow-up assessments were completed by a physician blinded to the results of the placebo-controlled invasive protocol. CCS class assessment, symptom and quality of life assessment, treadmill exercise testing and DSE were repeated.

### **6.3.5 Outcomes**

The pre-specified primary endpoint was the ability of the placebo-controlled similarity score to predict reduction in angina frequency with PCI in an individual patient at 30-day follow up.

Secondary outcomes included the ability of the placebo-controlled similarity score to predict change in treadmill exercise time, CCS class, physical limitation, angina stability and angina frequency as assessed by the SAQ, quality of life as assessed by the EQ-5D-5L and stress wall motion index score at 12 weeks.

Dobutamine stress echo stress wall motion index score was double-reported by three imaging consultants (JS, GDC, DPF) blinded to treatment allocation and timepoint using an online reporting tool and previously reported methodology<sup>57</sup>.

### **6.3.6 Statistical analysis**

The primary endpoint was the ability of the similarity score to predict the change in the app-derived daily number of episodes of angina. This was derived by constructing a Bayesian Markov longitudinal model which maximises power by utilising the daily episodes of angina. The model includes the previous day's number of episodes (i.e. a first order Markov model), the mean daily number of episodes of angina occurring during the 14 days prior to PCI, study day number, and similarity score.

The study day number was allowed to interact with the similarity score to allow for variation in effect over time. Effects were allowed to be non-linear with restricted cubic splines (three knots) and partial proportional odds with constraints. The model provides the daily odds ratio of improving or reducing the number of episodes of angina ( $OR > 1$ ), at specified covariate values. For the primary endpoint, we derived the probability that a patient with a similarity score at the 75<sup>th</sup> centile would have a better response than a patient at the 25<sup>th</sup> centile. We also present the magnitude of effect and the associated credible intervals constructed from the highest posterior density interval.

Secondary endpoints were assessed at baseline and at follow up. For both continuous and ordinal outcome variables, a Bayesian ordinal proportional odds model was used. The follow up value was conditioned on the baseline value and the similarity score. Non-linearity was allowed in both these variables with use of a restricted cubic spline with 3 knots. No interactions were specified. This model produces an odds ratio which was transformed to the original scale using a weighted mean of the possible response levels with weights equal to the cell probabilities from the proportional odds model. Again, we calculate the probability that a patient with a similarity score at the 75<sup>th</sup> centile is more likely to improve than a patient at the 25<sup>th</sup> centile. We also present the magnitude of the effect and the associated credible intervals. Priors have been published elsewhere<sup>95</sup>.

All analyses were conducted using the statistical environment R. Using the package “rsmb” for Bayesian modelling<sup>87</sup>.

This study was registered with clinical trials.gov (NCT04280575).

## **6.4 Results**

### **6.4.1 Patients**

Between 9<sup>th</sup> December 2019 and 1<sup>st</sup> May 2023, 51 patients completed the full trial protocol. The consort diagram is available in Figure 6.4.

Baseline characteristics are described in Table 6.1. Most patients (88%) were in CCS class II or III. The median number of antianginal agents at enrolment and before protocolised cessation was 1 (mean 1.2). This equated to 1 (mean 1.5) standardised antianginal units.

### **6.4.2 Procedures**

Procedural characteristics are reported in Table 6.2. Most patients (72.5%) had disease of the left anterior descending artery. Stenoses were anatomically and physiologically severe. The median diameter stenosis by quantitative coronary angiography was 68.7% (60.0 to 76.4%). The pre-PCI iFR, FFR and CFR values were 0.80 (0.48 to 0.89), 0.68 (0.57 to 0.79) and 1.42 (1.08 to 1.85), respectively.

The median number of stents implanted was 1, stent length 24.5mm (18-33mm) and stent diameter 3.0mm (2.75 to 3.5mm). Intravascular imaging was performed in 26/51 (51%). Across the cohort, the median post-PCI iFR, FFR and CFR had improved to 0.96 (0.93 to 0.99), 0.92 (0.90 to 0.96) and 2.34 (1.68 to 2.72), respectively.

### **6.4.3 Primary endpoint**

The primary endpoint was the ability of the placebo-controlled similarity score to predict reduction in angina frequency with PCI (Table 6.3).

The similarity score can range from -10 (a participant who reported that placebo inflation replicated their symptoms more than balloon occlusion) to +10 (a participant who reported that balloon occlusion perfectly replicated their symptom, and placebo inflation did not). In ORBITA-STAR, the observed patient similarity scores ranged from -9 to +10, the median value was 3 (0.875 to 5.25). Thirty-nine (76%) patients had a mean similarity score greater than 0.

There was strong evidence that the placebo-controlled similarity score predicted angina relief after PCI,  $\text{Pr}(\text{difference}) > 99.9\%$ , (relative explained variance = 9% (5-16%)). At follow-up, angina frequency was more likely to be lower in a patient in the upper quartile, with a similarity score of 5.25, (OR 8.01 (2.39 to 15.86)) than a patient in the lower quartile with a similarity score of 0.875 (OR 1.31 (0.71 to 1.99)) (Figure 6.5).

Figure 6.6 shows the impact of the whole range of similarity scores on the treatment effect at day 30.

#### **6.4.4 Secondary Endpoints**

The ability of the placebo-controlled similarity score to predict change in secondary endpoints is reported in Table 6.3.

#### **6.4.5 Adverse Events**

One patient with a background of atrial fibrillation sustained a peri-procedural myocardial infarction due to embolic occlusion of a non-target vessel which occurred on the day after the

interventional research procedure. This vessel was successfully treated with PCI. There were no other peri-procedural infarcts or unplanned revascularisation procedures. There were no strokes, spontaneous myocardial infarctions, or deaths.

## **6.5 Discussion**

### **6.5.1 Summary of results**

In this *n-of-1* study of patients with single vessel stable coronary artery disease undergoing PCI for symptom relief, placebo-controlled symptom verification with balloon occlusion was a strong predictor of symptomatic benefit at follow-up. Our findings indicate that when day-to-day symptoms are replicated by balloon occlusion, there is a high likelihood of achieving freedom from angina with PCI. In contrast, residual symptoms are more likely to persist post-PCI in patients who report that the sensation during balloon occlusion differs from their day-to-day symptom.

### **6.5.2 Results in the wider context of “residual angina”**

Symptoms often persist after PCI both in clinical trials and real-world clinical settings. While the aetiology of these symptoms remains uncertain, the hypothesised causes include residual ischaemia originating from the epicardial coronary arteries, microvascular angina, or non-cardiac symptoms<sup>96</sup>.

In the first ORBITA Trial, 61% of patients randomised to PCI continued to report symptoms during follow-up despite concurrent use of high dose antianginal medications<sup>50</sup>. In ORBITA-2, on little or no antianginal medications, 59% of patients reported persistent symptoms after PCI<sup>86</sup>. In both trials, PCI was successful with near complete eradication of ischaemia on dobutamine stress echocardiography, suggesting the cause was not residual epicardial disease. Moreover, by design, the two trials covered the extremes of antianginal medication intensity from zero antianginals in ORBITA-2 to maximal antianginal therapy in the first ORBITA trial, and yet a virtually identical proportion of patients remained symptomatic. This suggests that neither epicardial nor microvascular disease was responsible.

The first descriptions of stable coronary artery disease focussed on a diagnosis based on symptom characteristics. Heberden first described angina as “*a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes*”<sup>33</sup>. For many decades, Diamond and Forrester’s classification of the typical features of angina has been taught<sup>38</sup>. Over time, tests to detect the presence of anatomic disease and myocardial ischaemia, have become increasingly sensitive for the diagnosis of CAD, but at a cost of ever worsening specificity for stable angina<sup>97</sup>. These tests have also introduced the concept of cardiovascular “risk”. Once the diagnosis of CAD has been made, it is all too easy to connect symptoms to a severe stenosis and ischaemia, even when there are no typical cardiac features. To compound the problem, the act of treating a stenosis reinforces the label of “angina”, even for symptoms which persist after the stenosis has been eradicated.

### **6.5.3 Precision patient selection for revascularisation**

ORBITA-STAR provides data to inform precision medicine in the field of stable angina. It stratified patients along a continuum, from patients with precise replication of their day-to-day symptom with balloon occlusion, through to patients who reported that the sensation during balloon occlusion was very different to their usual symptom. The higher frequency of residual symptoms with PCI in the latter group supports the hypothesis that many of the symptoms commonly labelled residual “angina” are unlikely to have a coronary cause.

In clinical trials, calculating a mean treatment effect across participants can lead to misleading results. The reality is a continuum of response within a range of individuals. For symptomatic treatments, the extent of benefit depends not only on the efficacy of a treatment in eliminating the underlying pathology, but also on the fidelity of the relationship between the symptoms we measure and the pathology we treat. ORBITA-STAR has shown that for PCI, super responders

can be identified as those who have a demonstrable and reproducible link between symptoms and stenosis. In the context of treating stable angina, most research focuses on optimising the technical results of PCI. However, our findings suggest that to maximise symptom relief, more could be gained by focusing instead on identifying the symptoms that we can genuinely address with existing treatments. Perhaps, we have been too focussed on the challenge of treatment when the problem always lay upstream in the diagnosis.

In this trial, an experimental model of ischaemia was developed using repeated episodes of low-pressure balloon inflation across a coronary stenosis. All patients subsequently underwent PCI. Angioplasty balloon inflation, even at low pressure could, in theory, cause damage to the endothelium, and at present, the absence of studies examining the safety of this technique will prevent its use as a stand-alone diagnostic test for angina. However, this proof-of-concept study has revealed that placebo-controlled verification of symptoms accurately distinguishes responders from non-responders. The next step is to determine the optimum method of symptom induction, which permits deferral of PCI when symptoms are non-reproducible.

#### **6.5.4 Study Limitations**

Although we blinded patients to the nature of each episode, real or placebo inflation, and the calculated similarity scores, all patients were aware that they would receive PCI at the end of the procedure. Therefore, all symptom data collected during the follow up period was unblinded and subject to the placebo effect of PCI. The ability of the similarity score to predict symptom relief is therefore made even more remarkable by the fact that all patients will have benefitted from the placebo effect, which may have attenuated the true physical differences between participants.

Persistence of symptoms from one experimental episode to another could have affected the results. We attempted to mitigate for this by use of a combowire which allowed us to delay the initiation of the next episode until hemodynamic conditions, including any reactive hyperaemia and symptoms, had resolved. Nevertheless, it is possible that some persistence occurred.

Some secondary outcome measures including the Seattle Angina Questionnaire and physician assessed CCS class focus only on symptoms deemed classical of angina. When symptoms do not align with these definitions, we do not know how a change in symptom frequency is reflected in these questionnaires. It was therefore interesting to see that the stratification between patients was most pronounced using the primary endpoint of the smartphone application, in which the patient defined their own symptom, rather than being asked to interpret their symptoms according to fixed descriptors.

As the first-of-its-kind, we conducted this study in patients with single vessel disease to simplify the experimental design, and to allow precise symptom-to-stenosis mapping. We do not know how the results would translate to patients with multivessel ischaemia. Our assessment of the microcirculation was limited to measurement of CFR; we did not perform more advanced assessments. However, all participants were recruited to the trial with a severe epicardial stenosis to which symptoms had been attributed, and in whom microvascular assessments are poorly validated<sup>98</sup>. Our relatively small sample size is likely to be underpowered for some secondary endpoints. Finally, antianginal medications were suspended during the trial protocol to amplify the unattenuated observable effect of PCI. ORBITA-2 has shown that PCI is effective as a standalone antianginal procedure<sup>86</sup>. However, our results may have been different if antianginal medications had continued.

## 6.6 Conclusion

In this study of symptomatic patients referred for PCI of a single vessel coronary stenosis, placebo-controlled symptom verification using an ischaemic stimulus of balloon occlusion was a strong predictor of symptom relief with PCI. Symptom-based personalisation of therapy for stable CAD may offer the potential to maximise the therapeutic benefits of PCI by identifying those most able to benefit, and reduce the clinical risk associated with futile revascularisation in those who will not.

Table 6.1: Baseline characteristics in ORBITA-STAR

| Characteristic                     | n (%)      |
|------------------------------------|------------|
| Age (years)                        | 62.9 (8.6) |
| Male                               | 40 (78.0)  |
| Diabetes                           | 14 (27.5)  |
| Hypertension                       | 31 (60.8)  |
| Hyperlipidaemia                    | 33 (64.7)  |
| Smoking history                    | 24 (47.0)  |
| Previous PCI                       | 5 (9.8)    |
| Angina duration (weeks)            | 43 (26-78) |
| Left ventricular systolic function |            |
| Normal                             | 48 (94.1)  |
| Mildly impaired                    | 2 (3.9)    |
| Moderately impaired                | 1 (2.0)    |
| CCS class                          |            |
| I                                  | 6 (11.8)   |
| II                                 | 34 (66.7)  |
| III                                | 11 (21.6)  |

Data are mean (SD) and n (%) unless otherwise stated. PCI = percutaneous coronary intervention, CCS = Canadian Cardiovascular Society.

Table 6.2: Procedural characteristics

| Target vessel                           | n (%)                         |
|-----------------------------------------|-------------------------------|
| Left anterior descending (proximal)     | 37 (72.5)<br>19 (37.3)        |
| Right coronary artery                   | 6 (11.8)                      |
| Circumflex                              | 5 (9.8)                       |
| First diagonal                          | 2 (3.9)                       |
| Obtuse marginal                         | 1 (2.0)                       |
| Diameter stenosis by QCA - median (IQR) | 68.7% (60.0 to 76.4%)         |
| FFR                                     |                               |
| Mean (s.d)                              | 0.66 (0.15)<br>n=50           |
| Median (IQR)                            | 0.68 (0.57 to 0.79)<br>n=50   |
| iFR                                     |                               |
| Mean (s.d)                              | 0.70 (0.24)                   |
| Median (IQR)                            | 0.80 (0.48 to 0.89)           |
| CFR                                     |                               |
| Mean (s.d)                              | 1.56 (0.65)<br>(n=42)         |
| Median (IQR)                            | 1.42 (1.08 to 1.85)<br>(n=42) |
| Treatment modalities                    |                               |
| Everolimus drug eluting stent           | 48 (68.6)                     |
| Zotarolimus drug eluting stent          | 19 (27.1)                     |
| Drug eluting balloon                    | 3 (4.3)                       |

| Procedural characteristics          |                             |
|-------------------------------------|-----------------------------|
| Stent length (mm)<br>Median (IQR)   | 24.5 (18 to 33)             |
| Stent diameter (mm)<br>Median (IQR) | 3.0 (2.75 to 3.5)           |
| Post-dilation                       | 57 (85.1%)<br>n=67          |
| Intravascular imaging               | 26 (51%)                    |
| FFR post PCI                        |                             |
| Mean (s.d)                          | 0.93 (0.06)<br>n=50         |
| Median (IQR)                        | 0.92 (0.90 to 0.96)<br>n=50 |
| iFR post PCI                        |                             |
| Mean (s.d)                          | 0.96 (0.04)                 |
| Median (IQR)                        | 0.96 (0.93 to 0.99)         |
| CFR post PCI                        |                             |
| Mean (s.d)                          | 2.36 (0.97)<br>n=42         |
| Median (IQR)                        | 2.34 (1.68 to 2.72)<br>n=42 |

*Data are mean (SD) and n (%) unless otherwise stated. PCI = Percutaneous coronary intervention. FFR = fractional flow reserve. iFR = instantaneous wave-Free Ratio. CFR = coronary flow reserve.*

Table 6.3: Primary and secondary endpoints

|                                                |                                                  |                                                  |                                                                                 |
|------------------------------------------------|--------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------|
|                                                | Similarity score at the 25 <sup>th</sup> centile | Similarity score at the 75 <sup>th</sup> centile | Probability of greater benefit in a patient with a higher similarity score (Pr) |
| Similarity score                               | 0.875                                            | 5.25                                             |                                                                                 |
| Primary Endpoint: Angina frequency at 4 weeks* |                                                  |                                                  |                                                                                 |
| Odds of improvement                            | 1.31<br>(0.71 to 1.99)                           | 8.01<br>(2.39 to 15.86)                          |                                                                                 |
| Odds ratio                                     | 5.67<br>(2.24 to 14.70)                          |                                                  | >99.9%                                                                          |
| Exercise time (s)                              |                                                  |                                                  |                                                                                 |
| Baseline                                       | 790                                              |                                                  |                                                                                 |
| Follow up                                      | 843<br>(767 to 922)                              | 905<br>(853 to 954)                              |                                                                                 |
| Difference                                     | 62<br>(-27 to 149)                               |                                                  |                                                                                 |
| SAQ angina frequency                           |                                                  |                                                  |                                                                                 |
| Baseline                                       | 60                                               |                                                  |                                                                                 |

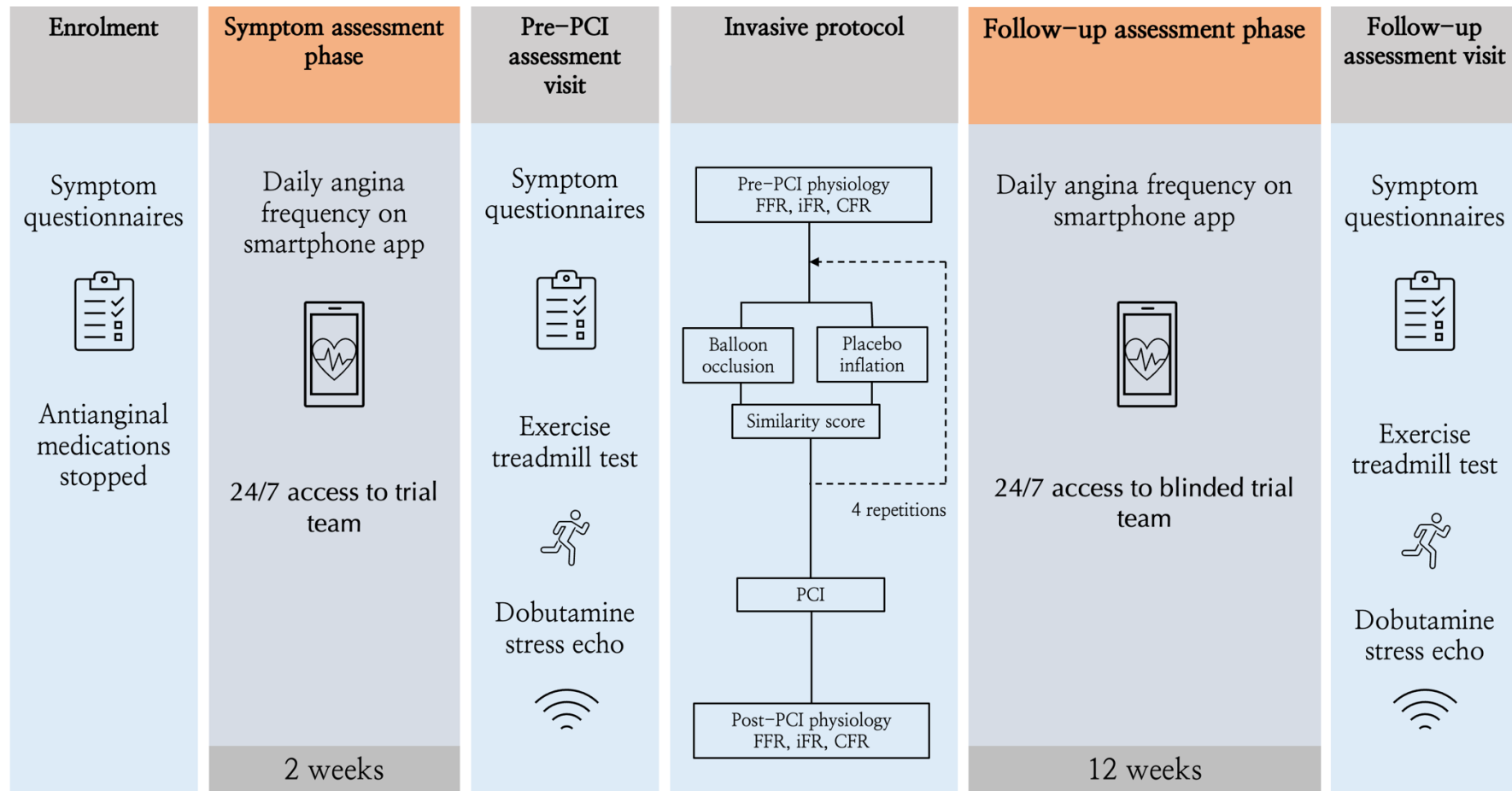
|                            |                        |                        |       |
|----------------------------|------------------------|------------------------|-------|
| Follow up                  | 83.4<br>(73.1 to 92.9) | 91.0<br>(84.1 to 97.3) |       |
| Difference                 | 7.7<br>(-1.5 to 17.3)  |                        | 96.2% |
| SAQ physical limitation    |                        |                        |       |
| Baseline                   | 72                     |                        |       |
| Follow up                  | 82.0<br>(71.3 to 91.8) | 90.9<br>(83.7 to 97.3) |       |
| Difference                 | 8.9<br>(0.0 to 18.7)   |                        | 98.1% |
| SAQ quality of life        |                        |                        |       |
| Baseline                   | 50                     |                        |       |
| Follow up                  | 69.7<br>(58.9 to 79.8) | 82.4<br>(74.4 to 89.5) |       |
| Difference                 | 12.7<br>(3.5 to 22.0)  |                        | 99.8% |
| SAQ treatment satisfaction |                        |                        |       |
| Baseline                   | 100                    |                        |       |

|            |                         |                        |       |
|------------|-------------------------|------------------------|-------|
| Follow up  | 97.0<br>(93.7 to 99.6)  | 99.6<br>(98.4 to 100)  |       |
| Difference | 2.5<br>(0.2 to 5.5)     |                        | 99.8% |
| EQ-5D      |                         |                        |       |
| Baseline   | 0.78                    |                        |       |
| Follow up  | 0.84<br>(0.79 to 0.89)  | 0.87<br>(0.83 to 0.92) |       |
| Difference | 0.03<br>(-0.01 to 0.08) |                        | 92.7% |
| EQ-VAS     |                         |                        |       |
| Baseline   | 75                      |                        |       |
| Follow up  | 77.2<br>(70.9 to 82.9)  | 79.9<br>(74.6 to 84.9) |       |
| Difference | 2.7<br>(-2.8 to 8.2)    |                        | 83.9% |
| CCS Class  |                         |                        |       |
| Baseline   | 2                       |                        |       |

|                                     |                           |                        |       |
|-------------------------------------|---------------------------|------------------------|-------|
| Follow up                           | 0.68<br>(0.40 to 0.99)    | 0.56<br>(0.30 to 0.83) |       |
| Difference                          | -0.12<br>(-0.44 to 0.21)  |                        | 23.5% |
| Peak stress wall motion index score |                           |                        |       |
| Baseline                            | 1.75                      |                        |       |
| Follow up                           | 0.75<br>(0.28 to 1.30)    | 0.72<br>(0.29 to 1.19) |       |
| Difference                          | -0.04<br>(-0.54 to -0.46) |                        | 44.5% |

*\*Patient reported angina frequency from the smartphone app. PCI = percutaneous coronary intervention, SAQ = Seattle Angina Questionnaire, EQ-5D = EuroQOL 5 dimensions, and EQ-VAS denotes EuroQOL visual analogue scale. CCS = Canadian Cardiovascular Society.*

Figure 6.1: ORBITA-STAR Trial design



PCI = percutaneous coronary intervention, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, CFR = coronary flow reserve

Figure 6.2: Screenshots of the ORBITA-STAR smartphone application

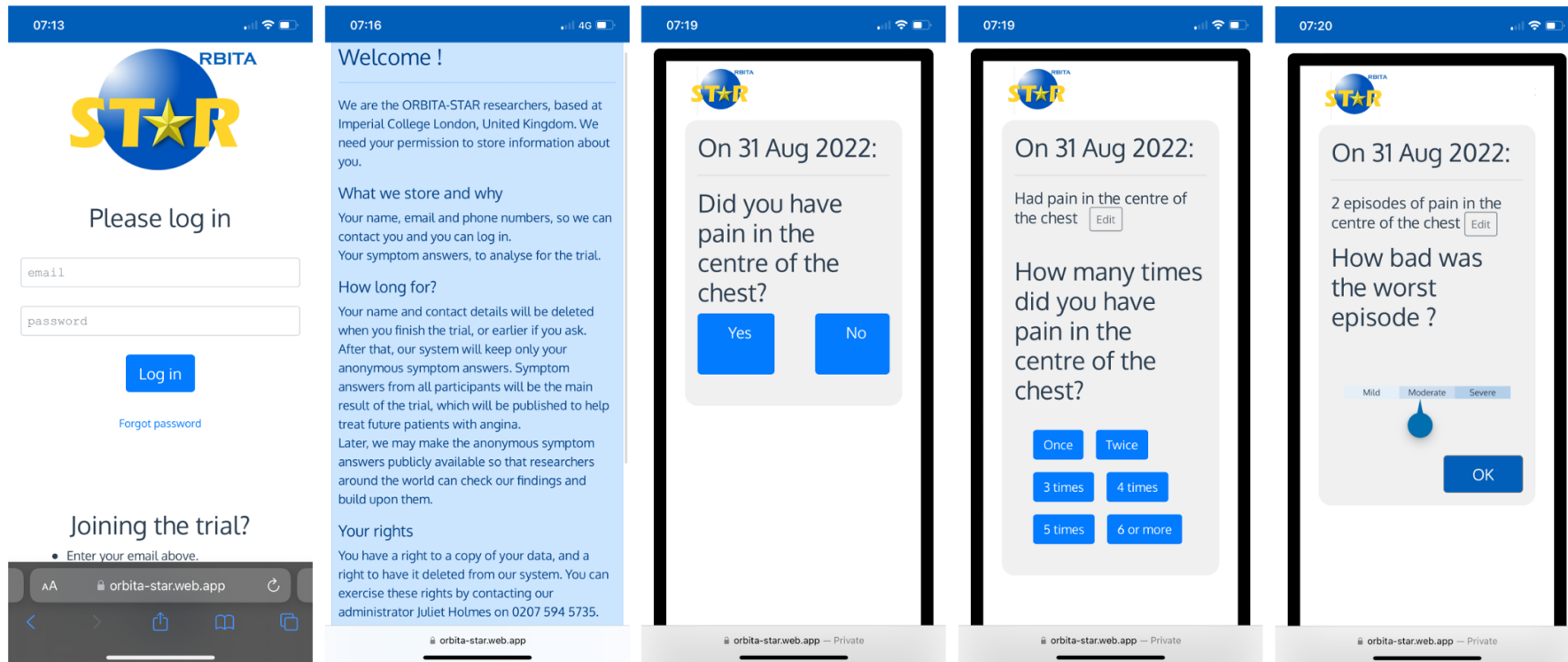


Figure 6.3: Placebo-controlled symptom assessment

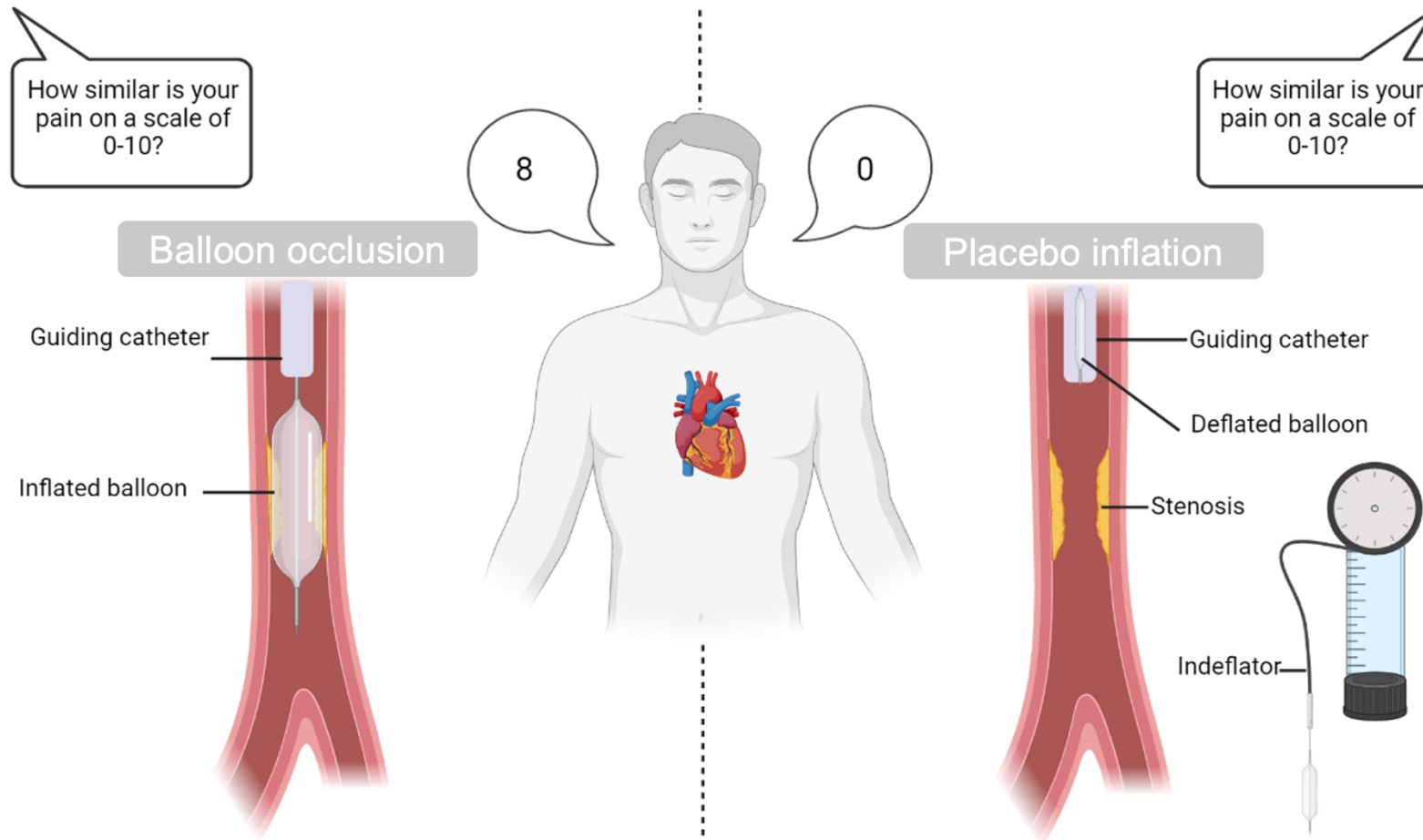
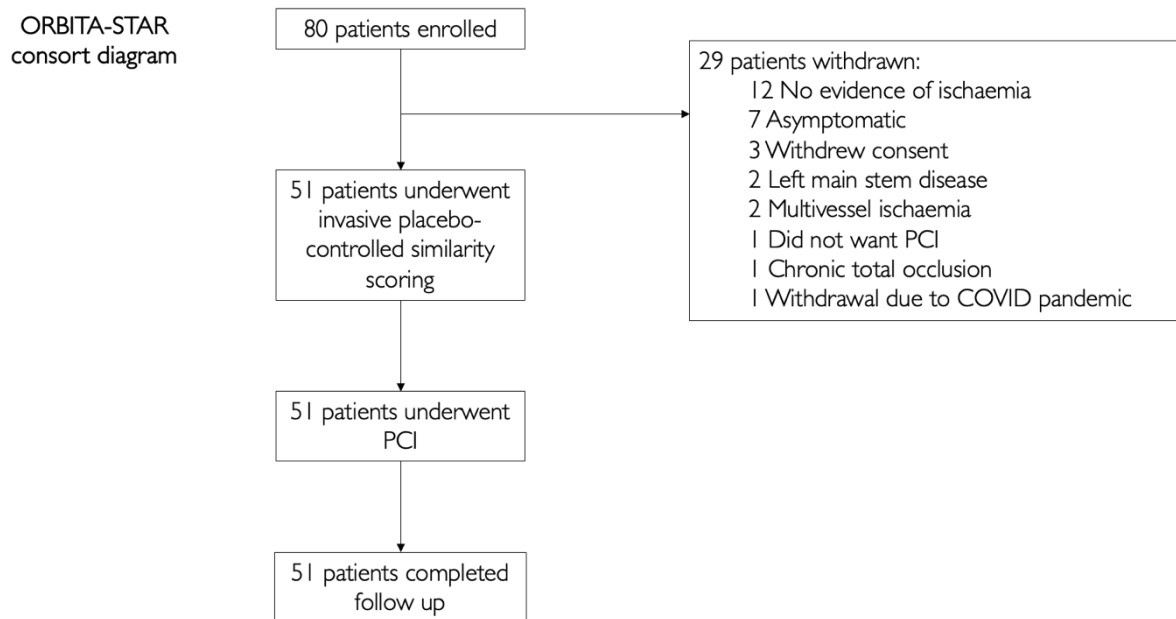
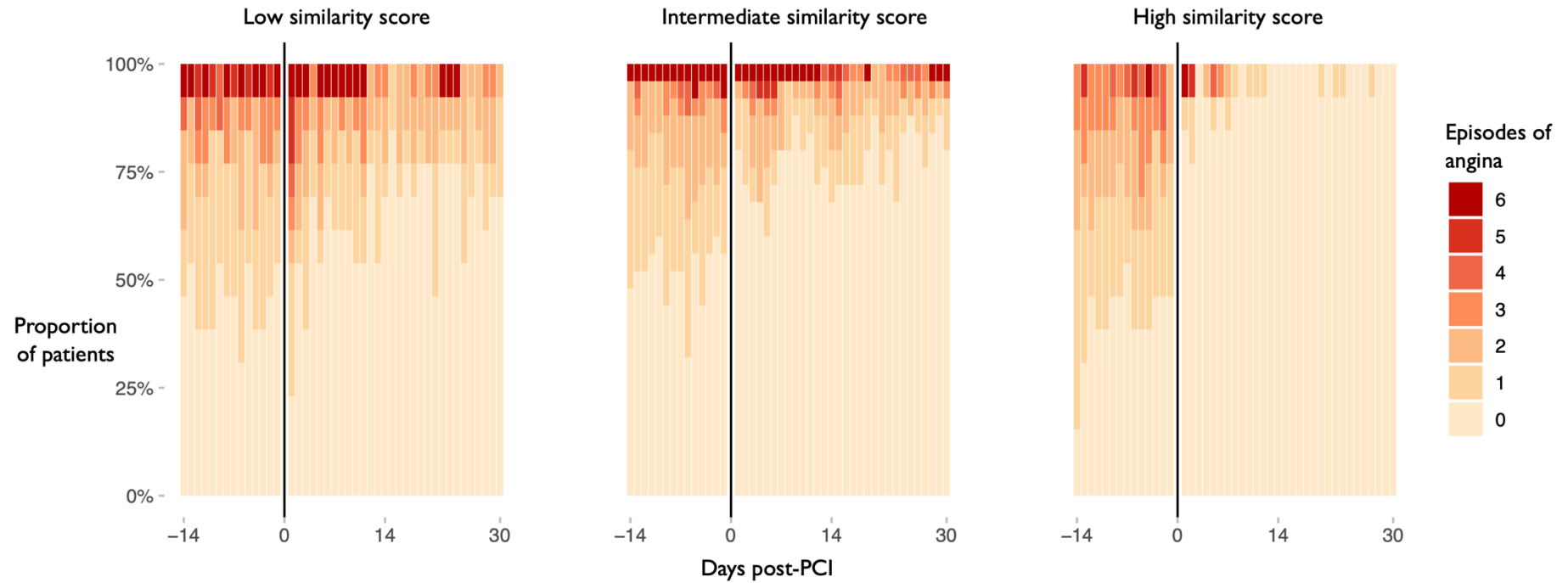


Figure 6.4: Consort Diagram



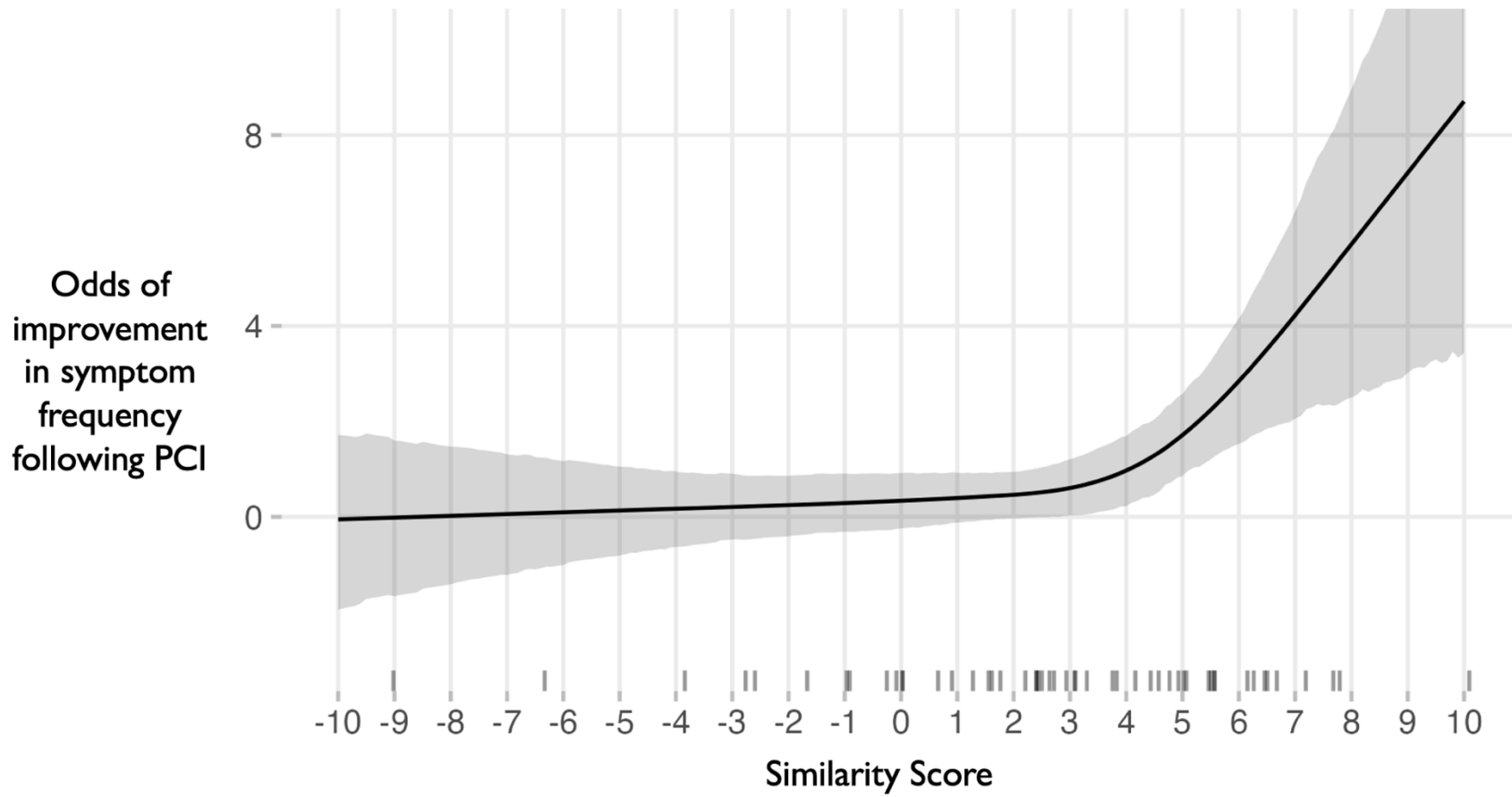
*Each withdrawn participant was allocated a singular reason for exclusion.*

Figure 6.5: Primary Endpoint - Similarity score as a predictor of symptom reduction following PCI.



Daily individual patient data of symptom frequency pre-and post-PCI stratified by low (bottom quartile), intermediate ( $Q1$  to  $Q3$ ) and high (upper quartile) similarity score. Darker colours indicate increased symptom frequency. PCI = percutaneous coronary intervention.

Figure 6.6: Odds of symptomatic improvement following PCI according to similarity score.



*PCI = percutaneous coronary intervention.*

## 7 The role of the collateral circulation in stable coronary artery disease: an invasive placebo-controlled study.

### 7.1 Abstract

#### 7.1.1 Background

Little correlation exists between severity of ischaemia and severity of angina in patients with stable coronary artery disease (CAD). The reasons for this are not understood. We performed an invasive, placebo-controlled, *n-of-1* study to investigate the relationship between the collateral circulation, ischaemia, and symptoms in patients with stable CAD. Additionally, we investigated whether progressive collateral recruitment is a mechanism for ischaemic preconditioning.

#### 7.1.2 Methods:

51 patients with severe single-vessel CAD and symptoms of angina were recruited. Participants suspended any antianginal medications and then documented their symptoms of angina daily using a dedicated smartphone application for 14 days. Participants then attended for the invasive protocol, which incorporated pressure wire studies and coronary flow reserve (CFR) assessment. Each patient then underwent four, 60-second episodes of low-pressure balloon occlusion across their coronary stenosis. Each episode was paired with an audio-visually identical placebo episode in a randomised order. Patients were blinded to the nature of the episode, real or placebo. After each episode, they scored the intensity of pain on a ten-point scale. Collateral flow index (CFI) was calculated from simultaneous measures of aortic, right atrial, and distal coronary wedge pressure.

### 7.1.3 Results:

The mean ( $\pm$ SD) age was  $63 \pm 9$  years, and 78% were male. The median (IQR) instantaneous wave-free ratio (iFR) was 0.80 (0.48 to 0.89), the median fractional flow reserve (FFR) was 0.68 (0.57 to 0.79), the median CFR was 1.42 (1.08 to 1.85).

There was little correlation between day-to-day angina frequency and severity of ischaemia as assessed by iFR (Somer's D 0.052 [-0.11 to, 0.11],  $\text{Pr} \geq 0 = 83.8\%$ ) or FFR (Somer's D 0.122 [0.054 to 0.158],  $\text{Pr} \geq 0 = 97.0\%$ ).

However, physiological stenosis severity was strongly associated with greater collateral circulation; lower, more ischaemic iFR and FFR values were associated with significantly greater CFI: Somer's D 0.314 [0.237 to 0.335],  $\text{Pr} \geq 0 = 99.9\%$  and 0.299 [0.160 to 0.358],  $\text{Pr} \geq 0 = 99.9\%$ , respectively.

In assessing the functional relevance of collateral flow, greater collateralisation, indicated by higher CFI, was strongly associated with reduced placebo-controlled pain intensity scores (Somer's D 0.341 [0.338 to 0.384],  $\text{Pr} \geq 0 = 99.9\%$ ).

Finally, when assessing for ischaemic preconditioning, we did not observe any significant change in pain intensity scores or CFI with sequential balloon occlusion episodes within individual patients.

### 7.1.4 Conclusion:

The coronary collateral circulation develops in response to ischaemia in patients with stable CAD. The collateral circulation attenuates the severity of ischaemic chest pain and may be responsible

for the non-linear relationship between stenosis, ischaemia, and angina. However, acute ischaemic pre-conditioning was not observed.

## 7.2 Introduction

Angina resulting from obstructive disease in the epicardial coronary arteries appears to be a straightforward mechanistic construct. Restricted augmentation of blood flow through a stenosis during stress results in ischaemia, a supply-demand imbalance of oxygen delivery which is manifested symptomatically as angina. Intuitively, one would expect that the most severe stenoses, with the greatest burden of ischaemia, would cause the most severe symptoms, and therefore derive the most benefit from revascularisation. Accordingly, treatment decisions, including revascularisation frequently rely on anatomic or physiological measures of stenosis severity<sup>1,99</sup>. However, contrary to expectations, little correlation exists between the severity of a stenosis, and the severity of symptoms<sup>100,101</sup>. Despite the significance of this observation for the treatment of hundreds of thousands of patients per year, the reasons for this disconnect are not well understood.

One possible explanation may lie in the coronary collateral circulation, which provides an alternative source of blood flow to myocardium affected by ischaemia through neo-angiogenesis. Anastomoses between the left and right coronary arteries were first described in autopsy samples by Richard Lower in 1669<sup>102</sup>. Whilst the connection to anatomy was not made at the time, in his first description of angina pectoris, William Heberden remarked upon a patient who was cured of his angina by setting himself the task of sawing wood for half an hour per day<sup>3</sup>. This phenomenon, in which angina appeared to attenuate with repeated effort, was later encouraged by physicians who instructed patients to “walk through the pain”.

In some clinical settings, the collateral circulation is recognised to have clear functional relevance. In the presence of a chronic total occlusion, a mature collateral circulation develops over time and

is able to maintain viability of the subtended myocardium<sup>103</sup>. Similarly, in the setting of acute myocardial infarction, the presence of angiographic collaterals has been shown to limit infarct size and is associated with improved clinical outcomes<sup>104</sup>. However, little is known regarding the extent or functional relevance of the collateral circulation in modulating symptoms of chronic stable angina.

We performed an invasive, placebo-controlled, *n-of-1* study to answer three hypotheses: Firstly, in patients with stable CAD, does more severe ischaemia, result in more severe day-to-day angina? Second, in patients with stable angina, does the collateral circulation develop in response to ischaemia? Finally, does the collateral circulation have functional relevance in attenuating the severity of ischaemic chest pain?

We also investigated whether progressive collateral recruitment was a mechanism for ischaemic preconditioning.

## **7.3 Methods**

### **7.3.1 Study design and participants**

This is an analysis from the multicentre, n-of-1, placebo-controlled Systematic Trial of Angina Assessment prior to Revascularisation (ORBITA-STAR) trial (Chapter 6). This study was approved by the London Central Research Ethics Committee (Ref: 19/LO/1194). All participants provided written informed consent.

This study recruited patients with symptoms of angina or angina equivalent symptoms, with severe single vessel coronary artery disease ( $\geq 70\%$ ) on invasive coronary angiography or computed tomography coronary angiography (CTCA), who were referred for revascularisation. A full list of inclusion and exclusion criteria are listed in Table 7.1 and Table 7.2.

Patients enrolled into the study through the CTCA pathway were subsequently withdrawn if they were found to have unsuitable anatomy, not meeting inclusion criteria at subsequent invasive angiography.

### **7.3.2 Study Protocol**

The features of the ORBITA-STAR design relevant to this sub-study are shown in Figure 7.1.

At enrolment, participants suspended all antianginal medications. Exemptions were permitted for patients who required a beta-blocker for rate control in atrial fibrillation or for a prognostic indication in left ventricular impairment or post myocardial infarction. If patients had a diagnosis of hypertension, any antianginal medications with antihypertensive properties were replaced with

antihypertensives with no antianginal properties. Hypertensive patients were provided with home blood pressure monitors, and remote monitoring was performed by the trial team.

#### *7.3.2.1 Symptom assessment*

Symptom severity at baseline was documented using physician assessed Canadian Cardiovascular Society (CCS) class. Patients also completed the Seattle Angina Questionnaire (SAQ) and the 5-level version of the EuroQol 5 dimensions questionnaire.

Following enrolment, patients entered a 2-week pre-PCI symptom assessment phase. During this period, they reported their angina frequency daily using a dedicated smartphone application (Figure 6.2). Daily reports were transmitted instantly to the trial team and all data were stored in an approved server. Patients had 24/7 access to the trial team during this period and could restart antianginal medications in collaboration with the trial team if these were required.

Before the invasive protocol, patients attended for the pre-PCI assessment visit. This included repeat symptom questionnaires, exercise treadmill testing using the modified Bruce protocol and dobutamine stress echocardiography.

#### *7.3.2.2 Invasive protocol*

Patients were administered dual antiplatelet therapy prior to the invasive protocol. Coronary angiography was performed from the radial or femoral approach. Central venous access was obtained through the femoral or brachial vein.

The invasive protocol consisted of 4 stages:

## **1. Pre-PCI coronary physiology**

A Doppler and pressure sensor tipped wire ('Combwire', Volcano Corp, San Diego, California) was used for all physiological assessments. Intracoronary nitres were administered, prior to equalisation of the Combwire. The wire was then positioned distal to the coronary stenosis. Baseline instantaneous wave-free ratio (iFR), fractional flow reserve (FFR) and coronary flow reserve (CFR) were measured. For hyperaemic indices, an intravenous infusion of adenosine at 140mcg/kg/min was administered.

## **2. Collateral flow index and pain intensity assessment during placebo-controlled balloon occlusion**

The invasive protocol was designed to permit simultaneous assessments of the patient's collateral circulation and their symptomatic response to ischaemia.

A pigtail catheter was placed through the venous sheath and positioned in the right atrium for central venous pressure monitoring. An angioplasty wire was placed alongside the Combwire distal to the stenosis. The placebo-controlled balloon occlusion protocol consisted of 4 pairs of episodes. Patients were informed when each episode started and finished. Within each pair, there was one 60 second episode of low-pressure balloon occlusion across the patient's stenosis designed to provoke ischaemia, and one 60-second placebo inflation episode in which ischaemia was not induced. These real and placebo episodes were performed in a randomised order (resulting in a total of eight, 60-second episodes). Patients were blinded to the nature of each episode, real balloon occlusion or placebo inflation, with use of surgical drapes to ensure that the patient was not able

to visualise the operator or the catheter laboratory screens. A diagram of the experimental model is shown in Figure 7.2.

(a) Balloon occlusion

A semi compliant angioplasty balloon, sized from angiographic appearances in a 1:1 balloon: artery ratio, was placed within the coronary stenosis. At the start of the episode, it was inflated to the lowest pressure which occluded flow to the distal vessel (typically 1-3 atmospheres). An injection of contrast confirmed that the balloon was occlusive and this was confirmed with loss of the distal Doppler flow trace from the Combwire. After 60 seconds, the balloon was deflated and withdrawn from the stenosis into the guiding catheter.

(b) Placebo inflation

The deflated angioplasty balloon remained within the guiding catheter. To preserve blinding, the operator used a decoy balloon outside the patient's body, inflating it and deflating it at the start and end of the episode, respectively, to recreate the sound of the real balloon occlusion episode.

### **Pain intensity scoring**

Immediately following termination of each episode, patients reported the intensity of the pain experienced on an ordinal scale from 0 (no perceived sensation) to 10 (worst pain imaginable) (Figure 7.3). Ascertainment of the pain intensity score was carried out in an identical manner regardless of whether the episode was real or placebo.

Following each episode, balloon occlusion or placebo inflation, a recovery period with a minimum duration of 30 seconds was mandatory before the next episode could begin. If symptoms or ECG abnormalities persisted, the recovery time was extended until they had resolved, plus an additional

30 seconds to avoid crossover to the next episode. The Combowire Doppler flow trace distal to the stenosis was used to confirm that hyperaemia, induced by balloon occlusion, had resolved and that coronary flow had returned to baseline before the next episode began.

### **Calculation of the collateral flow index (CFI)**

During each balloon occlusion episode, pressure-derived CFI was calculated according to published methods<sup>105,106</sup>. CFI was calculated from haemodynamic data in the final 10 seconds of each 60-second balloon occlusion episode. This required simultaneous measurements of aortic pressure (Pa), distal coronary wedge pressure ( $P_{occl}$ ) measured from the combowire positioned distal to the occluding balloon, and finally the central venous pressure (CVP), measured from the pigtail catheter in right atrium (Figure 7.2). Example pressure waveforms are shown in Figure 7.4.

CFI was calculated using the following formula:

$$CFI = \frac{P(occl) - CVP}{Pa - CVP}$$

*Where CFI = Collateral flow index,  $P(occl)$  = distal coronary wedge pressure during balloon occlusion,  $Pa$  = aortic pressure and  $CVP$  = central venous pressure. CFI ranges from 0 – 1 (no units), where higher values indicate greater collateral flow.*

### **3. Percutaneous coronary intervention of target lesion**

Following the placebo-controlled balloon occlusion protocol, all participants underwent PCI of the target lesion with implantation of drug eluting stents. Use of drug coated balloons was permitted when clinically indicated. Post-dilation of stents and use of intracoronary imaging was recommended.

#### **4. Post PCI-coronary physiology**

Following PCI, intracoronary nitrates were administered and the Combowire was used to re-assess post-PCI iFR, FFR and CFR.

##### **7.3.3 Outcomes**

The placebo-controlled intensity score was calculated on an individual basis as the mean of the pain intensity during balloon occlusion episodes controlled for the mean pain intensity during the placebo inflation episodes.

The collateral flow index was calculated using the formula described above<sup>105,106</sup>.

Dobutamine stress echo stress wall motion index score was double-reported by three imaging consultants (JS, GDC, DPF) using an online reporting tool and previously reported methodology<sup>57</sup>. Reporters were blinded to patient's coronary anatomy and placebo-controlled pain intensity scores.

##### **7.3.4 Statistical analysis**

The associations between the physiological parameters (iFR and FFR) and dobutamine stress echo wall motion score with symptom parameters were assessed using a Bayesian ordinal proportional odds model.

Non-linearity in the predictor was allowed with use of a restricted cubic spline with 3 knots. This model produces an odds ratio which was transformed to the original scale using a weighted mean of the possible response levels with weights equal to the cell probabilities from the proportional

odds model. The strength of association was measured using the ordinal correlation coefficient Somer's D and presented with associated confidence intervals and the probability the association was greater than chance.

To assess the impact of repeated balloon inflations (i.e. testing for evidence of preconditioning), the inflation number (random intercept) clustered under the study ID was used as the predictor in a Bayesian ordinal proportional odds model. The probability the inflation number coefficient is greater than 1 is presented along with the model predicted means on the first and last balloon inflation.

All analyses were conducted using the statistical environment R using the package “rsmb” for Bayesian modelling<sup>87</sup>.

This study is registered with clinical trials.gov (NCT04280575).

## 7.4 Results

### 7.4.1 Patients

Fifty-one patients completed the study protocol from 9<sup>th</sup> December 2019 to 1<sup>st</sup> May 2023. Participants were recruited from 5 trial centres. The consort diagram is shown in Figure 6.4.

Baseline characteristics are presented in Table 7.3. The majority (78%) of participants were male, 28% were diabetic and 10% had undergone previous PCI. The median duration of angina at enrolment was 43 (26-78) weeks. Most patients (88%) had symptoms consistent with CCS class II or III angina.

Anatomic and physiological characteristics of the target lesions are provided in Table 7.4. The target lesion was located in the left anterior descending artery in 72.5% of participants. The median diameter stenosis by quantitative coronary angiography was 68.7% (60.0 to 76.4%). The median pre-PCI iFR, FFR and CFR values were 0.80 (0.48 to 0.89), 0.68 (0.57 to 0.79) and 1.42 (1.08 to 1.85), respectively.

### 7.4.2 Association between day-to-day angina severity and burden of ischaemia

Angina frequency for each patient in the 2-weeks prior to PCI was calculated from daily symptom reports from the smartphone app. There was little correlation between day-to-day angina frequency and severity of ischaemia as assessed by iFR (Somer's D 0.052 [-0.11 to, 0.11],  $\text{Pr} \geq 0 = 83.8\%$ ) or FFR (Somer's D 0.122 [0.054 to 0.158],  $\text{Pr} \geq 0 = 97.0\%$ ).

Individual patient data is presented in Figure 7.5.

Similarly, there was little relationship between iFR and pre-PCI SAQ angina frequency (Somer's D 0.16 [-0.002 to 0.216],  $\text{Pr} \geq 0 = 95.5\%$ ). A stronger correlation was observed between FFR and pre-PCI SAQ angina frequency (Somer's D 0.265 [0.199 to 0.297],  $\text{Pr} \geq 0 = 99.0\%$ ).

There was a weak association between ischaemia as assessed by stress echo wall motion index score and daily angina frequency (Somer's D 0.163 [0.046 to 0.233],  $\text{Pr} \geq 0 = 97.0\%$ ), and no significant association between stress echo wall motion index score and SAQ angina frequency (Somer's D 0.113 [-0.058, 0.218],  $\text{Pr} \geq 0 = 87.3\%$ ).

#### **7.4.3 Association between ischaemia and the collateral circulation in patients with stable angina.**

The extent of the collateral circulation in each patient was estimated using the mean collateral flow index (CFI) in the final 10 seconds of each of four balloon occlusion episodes. Physiological stenosis severity was significantly associated with CFI. Lower, more ischaemic, iFR values were strongly associated with higher CFI (Somer's D 0.314 [0.237 to 0.335],  $\text{Pr} \geq 0 = 99.9\%$ ) (Figure 7.6). Similarly, lower, more ischaemic FFR values were strongly associated with higher CFI (Somer's D 0.299 [0.160 to 0.358],  $\text{Pr} \geq 0 = 99.9\%$ . (Figure 7.7).

A greater burden of ischaemia as assessed with dobutamine stress echo wall motion index score was significantly associated with greater CFI (Somer's D 0.300 [0.211 to 0.343],  $\text{Pr} \geq 0 = 99.9\%$ ).

#### **7.4.4 Association between collateral flow index and pain intensity scores.**

The placebo-controlled pain intensity score was calculated for each pair of episodes by subtracting the pain intensity score during placebo inflation from the pain intensity score during balloon occlusion. The mean result of 4 pairs of episodes was carried forward as the individual participant's

placebo-controlled pain intensity score. The observed placebo-controlled pain intensity scores ranged from 0.0 (participant with no perceived difference in pain intensity between real and placebo episodes) to 8.5 (the participant with maximal difference in pain intensity between real and placebo episodes).

Greater collateral flow index (higher CFI) was strongly associated with reduced placebo-controlled pain intensity score (Somer's D 0.341 [0.338 to 0.384],  $\text{Pr} \geq 0 = 99.9\%$ ) (Figure 7.8).

#### **7.4.5 Change in pain intensity scores with sequential balloon occlusion episodes.**

To assess for the presence of progressive collateral recruitment as a mechanism for ischaemic preconditioning, we tested whether CFI increased from the first to the fourth balloon inflation. We found no progressive increase in CFI across the cohort: model predicted mean CFI for 1<sup>st</sup> inflation 0.19 (0.16 to 0.22), 4<sup>th</sup> inflation 0.18 (0.16 to 0.21),  $\text{Pr} > 0 = 96.8\%$ .

Concordantly, there was no significant reduction in the pain intensity score between the 1<sup>st</sup> balloon inflation and the 4<sup>th</sup> balloon inflation (model predicted mean pain intensity score for 1<sup>st</sup> inflation 4.6 (3.6 to 5.7), 4<sup>th</sup> inflation 5.1, (3.9 to 6.2),  $\text{Pr} \geq 0 = 16.0\%$ ).

## 7.5 Discussion

In this study of patients with single-vessel coronary artery disease and stable chest pain, we found little relationship between severity of ischaemia as assessed by invasive coronary physiology and daily burden of patient reported symptoms. However, stenoses with more severe flow limitation were associated with greater collateral flow, suggesting that the development of collateralising vessels may be an adaptive response to ischaemia. We evaluated the functional significance of this collateral flow using a placebo-controlled pain intensity score, finding a significant inverse relationship with the Collateral Flow Index (CFI); higher collateral flow reduced the severity of ischemic chest pain. Finally, we found no evidence of acute ischaemic pre-conditioning within the confines of this study.

### 7.5.1 Collateralisation as an adaptive response to ischaemia

Previous studies have identified severity of coronary artery disease as the principal determinant of collateralisation, whilst other factors such as age, left ventricular hypertrophy and the presence of systemic factors such as anaemia have also been associated<sup>107–109</sup>. In patients with non-occlusive CAD, increasing percentage diameter stenosis has been shown to predict CFI<sup>110</sup>, while stenosis severity, duration of angina and proximal lesion location have also been identified as independent predictors of recruitable collaterals on contralateral artery injection<sup>111</sup>. The unifying association which connects each of these predictive factors is their mechanistic link to myocardial ischaemia.

The presence of a trans-stenotic pressure gradient is known to be a principal stimulus for arteriogenesis<sup>112</sup>. Pre-clinical studies have shown that increased haemodynamic shear stress caused by larger pressure gradients between the unobstructed donor and stenosed recipient vessel promote changes in gene expression which upregulate angiogenic growth factors such as basic fibroblast growth factor and transforming growth factor- $\beta$ <sup>113,114</sup>.

Whilst previous studies have investigated the relationship between *anatomic* measures of stenosis severity and collateral function, this is the first study which has assessed the association between *haemodynamic* pressure gradients and CFI. It could be argued that parameters such as FFR and iFR are a priori dependent on the variable under assessment, CFI. Since increases in collateral flow will naturally increase the pressure in the vessel distal to the coronary stenosis, affecting the FFR or iFR value. For this reason, these parameters are not truly independent of each other from first principals, and a linear relationship would not be expected. Nevertheless, we found a significant relationship with both FFR and iFR, whereby more severe flow limitation in the stenosed vessel, was clearly associated with greater CFI. The fact that this relationship can still be identified from a relatively limited number of patients, when collateral flow would naturally attenuate the severity of physiological pressure gradients, suggests that whilst the collateral circulation is clearly a dynamic response to ischaemia, it is not capable of normalising pressure gradients, and the substrate for ischaemia is not fully reversed.

### **7.5.2 Impact of collateral flow index on pain intensity during ischaemia**

As the heart's adaptive response to ischaemia, a functional manifestation of collateralisation, should, in theory, be a reduction in ischaemic chest pain through improved perfusion of ischaemic myocardium. The presence or absence of chest pain during coronary balloon occlusion was originally used as one of the simplest, and perhaps most crude assessments of coronary collateral function. Previous studies have found that angina was significantly more likely during 1 minute coronary balloon occlusion in patients with lower collateral flow indices<sup>115</sup>.

However, previous studies examining this phenomenon have suffered several limitations. Simplistic dichotomisation of angina as either present or absent is imprecise and restricts statistical

power, since pain, like all biological variables, is a continuum rather than a dichotomy. Secondly, the assessment of chest pain during cardiac catheterisation requires placebo-control, since patients undergoing cardiac catheterisation may experience symptoms from a number of aspects of the procedure, over and above the specific manifestations of ischaemia. Finally, blinding is particularly important as the negative expectation of symptoms when patients are informed that blood flow is being restricted to the heart will naturally lead to the perception of pain in some patients, as an example of the nocebo effect.

Our study overcame these limitations by, for the first time, using a placebo-inflation stimulus. This blinded the patient to the nature of the episode; to remove the power of anticipation from their reported symptoms and served as a control for other sensations the patient may experience during cardiac catheterisation. We also employed an ordinal scale for pain intensity assessment during real and placebo balloon inflation episodes, giving maximal statistical power.

With this design, we found that patients with greater collateralisation had significantly attenuated placebo-controlled pain intensity scores, confirming the hypothesis that the collateral circulation has functional relevance in reducing the symptoms of ischaemia.

Severity of ischaemic chest pain is likely to be dependent on several factors. Aside from the role of collateralisation, as proven in this study, the intensity of ischaemic chest pain may also vary depending on the duration of ischaemia, volume of myocardium at risk, viability of the myocardium, autonomic nerve dysfunction and the individual pain threshold and psychological characteristics of the patient. When these factors are taken into consideration, it is perhaps less surprising that a predictable relationship between ischaemia and angina does not exist, and that

the expectation of angina relief from revascularisation is less reliable than has previously been understood.

### **7.5.3 Adaptation to ischaemia: Collateralisation or ischaemic preconditioning**

Ischaemic preconditioning describes myocardial adaptation in response to repeated short durations of ischaemia and reperfusion. The phenomenon was originally described in dogs who exhibited smaller infarct sizes when they had undergone preconditioning with four preceding 5-minute coronary occlusions<sup>116</sup>. In the original study, there was no difference in collateral flow between pre-conditioned and non-preconditioned dogs, but separately, the quantity of collateral blood flow did predict the infarct size in the control arm. Subsequently, in the human model, myocardial adaptation to repeated episodes of ischaemia has been attributed to both progressive collateral recruitment and separately to preconditioning, a biochemically driven phenomenon distinct from the process of collateralisation<sup>117,118</sup>.

Whilst previous studies have documented a progressive rise in CFI with repeated episodes of balloon occlusion, this was not observed in our cohort<sup>117</sup>. Similarly, we observed no attenuation of pain intensity score on repeated balloon occlusion episodes, in contrast to other observers<sup>117</sup>. From our study, it is therefore not possible to draw conclusions regarding the mechanism of myocardial adaption to ischaemia, as no adaptation was observed. There are several possible explanations for our divergent results from previous studies. Firstly, we routinely made use of 60-second balloon occlusion episodes to induce ischaemia. This duration is shorter than the 2 or 3-minute balloon occlusion episodes performed in other studies<sup>117,118</sup>. Secondly, we deliberately enrolled patients with a broad spectrum of stenosis severity and burden of ischaemia. These different substrates may respond differently to sequential balloon occlusion. Finally, unlike

previous unblinded studies, our protocol incorporated placebo-control. In unblinded studies, a reduction in pain with subsequent episodes may be expected as the patient becomes psychologically conditioned to the sensation to be expected. Our findings are more robust to this phenomenon as we incorporated placebo-control episodes in a randomised order.

#### **7.5.4 Limitations**

Our assessment of the collateral circulation was based upon the continuous quantifiable haemodynamic metric of collateral flow index. We did not use the angiography derived Rentrop collateral grading system as this is an ordinal classification which would reduce statistical power<sup>119</sup>. Use of the CFI is also subject to less inter-observer variability as it does not require interpretation of angiographic images. Finally, as patients were deliberately recruited into this trial with a range of stenosis severities, many had no visible collateralisation. Use of the more sensitive CFI allowed quantification of the lower collateral pressures typical of this population.

This study only included patients with single vessel coronary artery disease. This retained simplicity of the experimental design and allowed for precise assessment of how unobstructed donor arteries contribute to collateralisation of a diseased vessel. Our conclusions are therefore limited to a single vessel disease population, rather than a multivessel disease cohort in which the observed associations are likely to be more complex.

We placed a combowire in the distal vessel during the balloon occlusion protocol to ensure that resting flow conditions had returned to baseline, with resolution of reactive hyperaemia, before then next episode began. This was to prevent any haemodynamic cross over between balloon occlusion episodes. We also required resolution of any pain following a balloon occlusion episode

before continuation of the experimental protocol was allowed. Despite these efforts, cross over of symptom or haemodynamic disturbance from one episode to another remains possible.

## **7.6 Conclusion**

Development of a collateral circulation is an adaptive response to ischaemia in patients with severe single vessel stable coronary artery disease. This collateralisation has functional relevance in attenuating the severity of ischaemic chest pain and may be partly responsible for the non-linear relationship between stenosis severity and symptom burden.

*Table 7.1: Inclusion Criteria*

| Inclusion Criteria                                                                      |
|-----------------------------------------------------------------------------------------|
| Angina or angina equivalent symptoms                                                    |
| $\geq 70\%$ stenosis of a single coronary artery on invasive coronary angiogram or CTCA |
| Referred for PCI                                                                        |

*PCI = Percutaneous coronary intervention. CTCA: Computed tomography coronary angiography*

*Table 7.2: Exclusion Criteria*

| Exclusion Criteria                                                                        |
|-------------------------------------------------------------------------------------------|
| Age younger than 18 years or older than 85 years                                          |
| Recent acute coronary syndrome (< 6 months)                                               |
| Multivessel coronary artery disease                                                       |
| Previous coronary artery bypass graft                                                     |
| Significant left main stem coronary disease                                               |
| Chronic total occlusion in the target vessel                                              |
| Contraindication to percutaneous coronary intervention or drug-eluting stent implantation |
| Contraindication to antiplatelet therapy                                                  |
| Contraindication to adenosine infusion                                                    |
| Severe valvular disease                                                                   |
| Severe left ventricular systolic impairment                                               |
| Severe respiratory disease                                                                |
| Life expectancy less than 2 years, pregnancy, unable to consent                           |

Table 7.3: Baseline characteristics

| Characteristic                     | n (%)      |
|------------------------------------|------------|
| Age (years)                        | 62.9 (8.6) |
| Male                               | 40 (78.0)  |
| Diabetes                           | 14 (27.5)  |
| Hypertension                       | 31 (60.8)  |
| Hyperlipidaemia                    | 33 (64.7)  |
| Smoking history                    | 24 (47.0)  |
| Previous PCI                       | 5 (9.8)    |
| Angina duration (weeks)            | 43 (26-78) |
| Left ventricular systolic function |            |
| Normal                             | 48 (94.1)  |
| Mildly impaired                    | 2 (3.9)    |
| Moderately impaired                | 1 (2.0)    |
| CCS class                          |            |
| I                                  | 6 (11.8)   |
| II                                 | 34 (66.7)  |
| III                                | 11 (21.6)  |

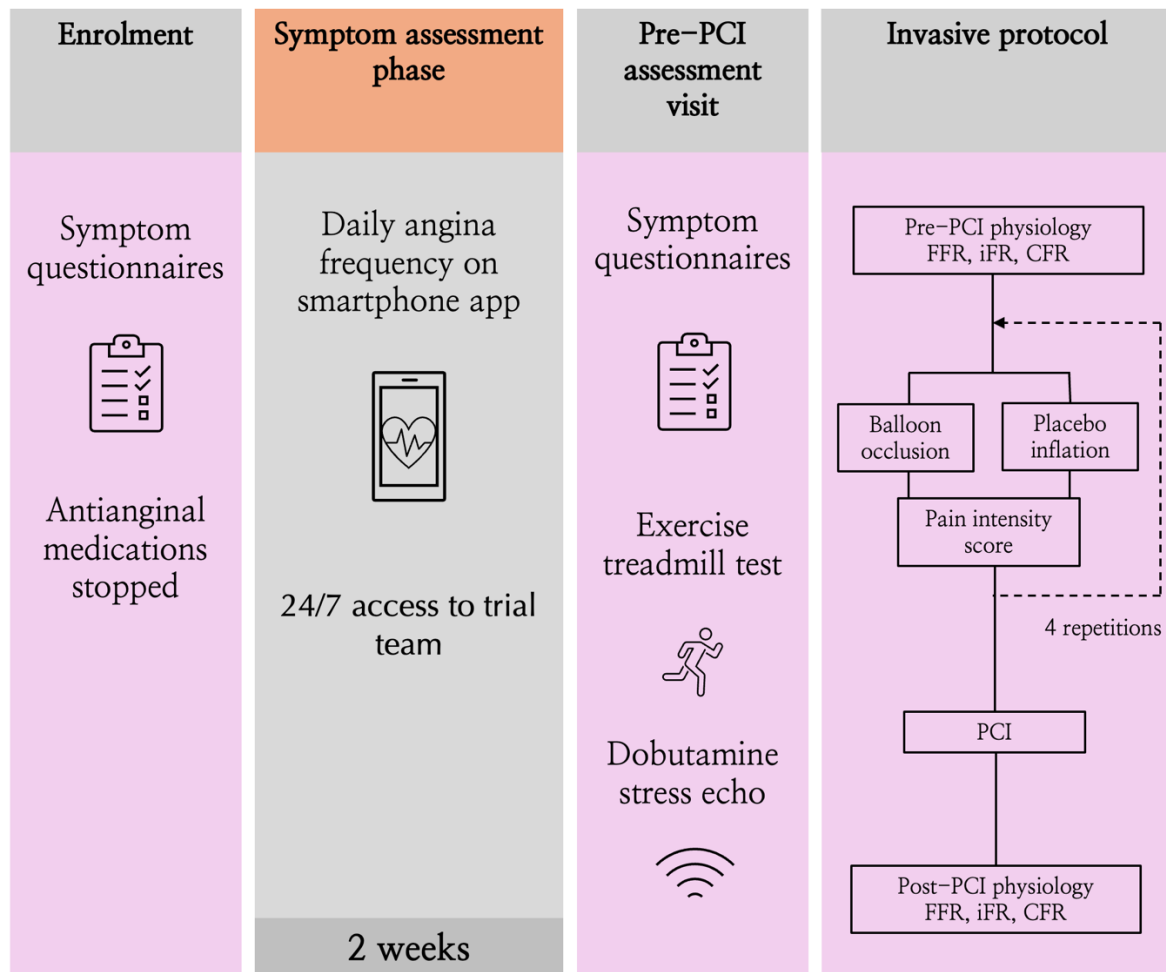
Data are mean (SD) and n (%) unless otherwise stated. PCI = percutaneous coronary intervention, CCS = Canadian Cardiovascular Society.

Table 7.4: Stenosis characteristics

| Target vessel                           | n (%)                         |
|-----------------------------------------|-------------------------------|
| Left anterior descending (proximal)     | 37 (72.5)<br>19 (37.3)        |
| Right coronary artery                   | 6 (11.8)                      |
| Circumflex                              | 5 (9.8)                       |
| First diagonal                          | 2 (3.9)                       |
| Obtuse marginal                         | 1 (2.0)                       |
| Diameter stenosis by QCA - median (IQR) | 68.7% (60.0 to 76.4%)         |
| FFR                                     |                               |
| Mean (s.d)                              | 0.66 (0.15)<br>n=50           |
| Median (IQR)                            | 0.68 (0.57 to 0.79)<br>n=50   |
| iFR                                     |                               |
| Mean (s.d)                              | 0.70 (0.24)                   |
| Median (IQR)                            | 0.80 (0.48 to 0.89)           |
| CFR                                     |                               |
| Mean (s.d)                              | 1.56 (0.65)<br>(n=42)         |
| Median (IQR)                            | 1.42 (1.08 to 1.85)<br>(n=42) |

Data are mean (SD) and n (%) unless otherwise stated. QCA = Quantitative coronary angiography. FFR = fractional flow reserve. iFR = instantaneous wave-Free Ratio. CFR = coronary flow reserve.

Figure 7.1: Study design.



PCI = percutaneous coronary intervention, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, CFR = coronary flow reserve

Figure 7.2: Experimental model for the invasive protocol.

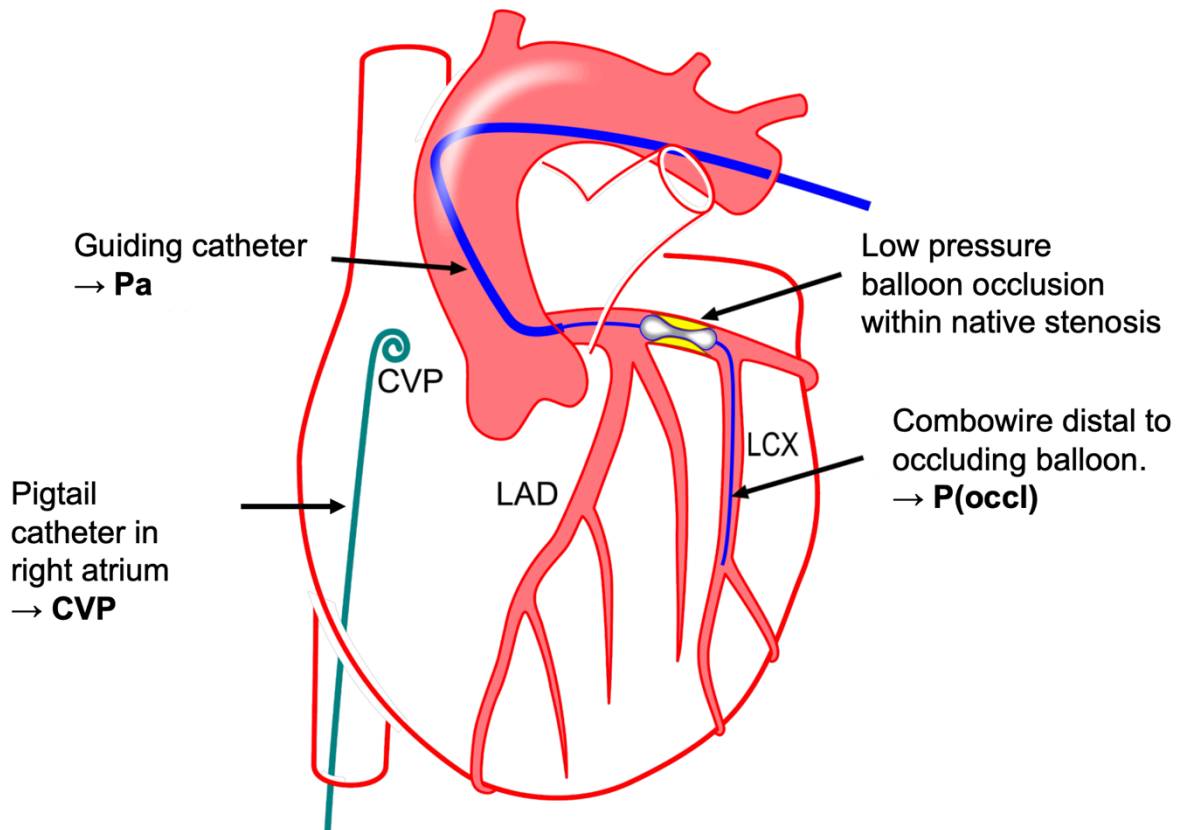


Figure 7.2 Experimental model for the placebo-controlled balloon occlusion protocol. A guiding catheter was placed into the coronary ostium. A pressure and Doppler sensor tipped Combowire was placed beyond the stenosis. A pigtail catheter was placed into the right atrium. Collateral flow index (CFI) was calculated during low pressure balloon occlusion episodes from simultaneous measures of aortic pressure ( $P_a$ ) from the guiding catheter, distal coronary wedge pressure  $P(occl)$  from the Combowire distal to the occluding balloon, and central venous pressure (CVP) from the pigtail catheter in the right atrium. Figure adapted from Traupe et al.<sup>103</sup>

Figure 7.3: Pain intensity scoring during placebo-controlled balloon occlusion protocol

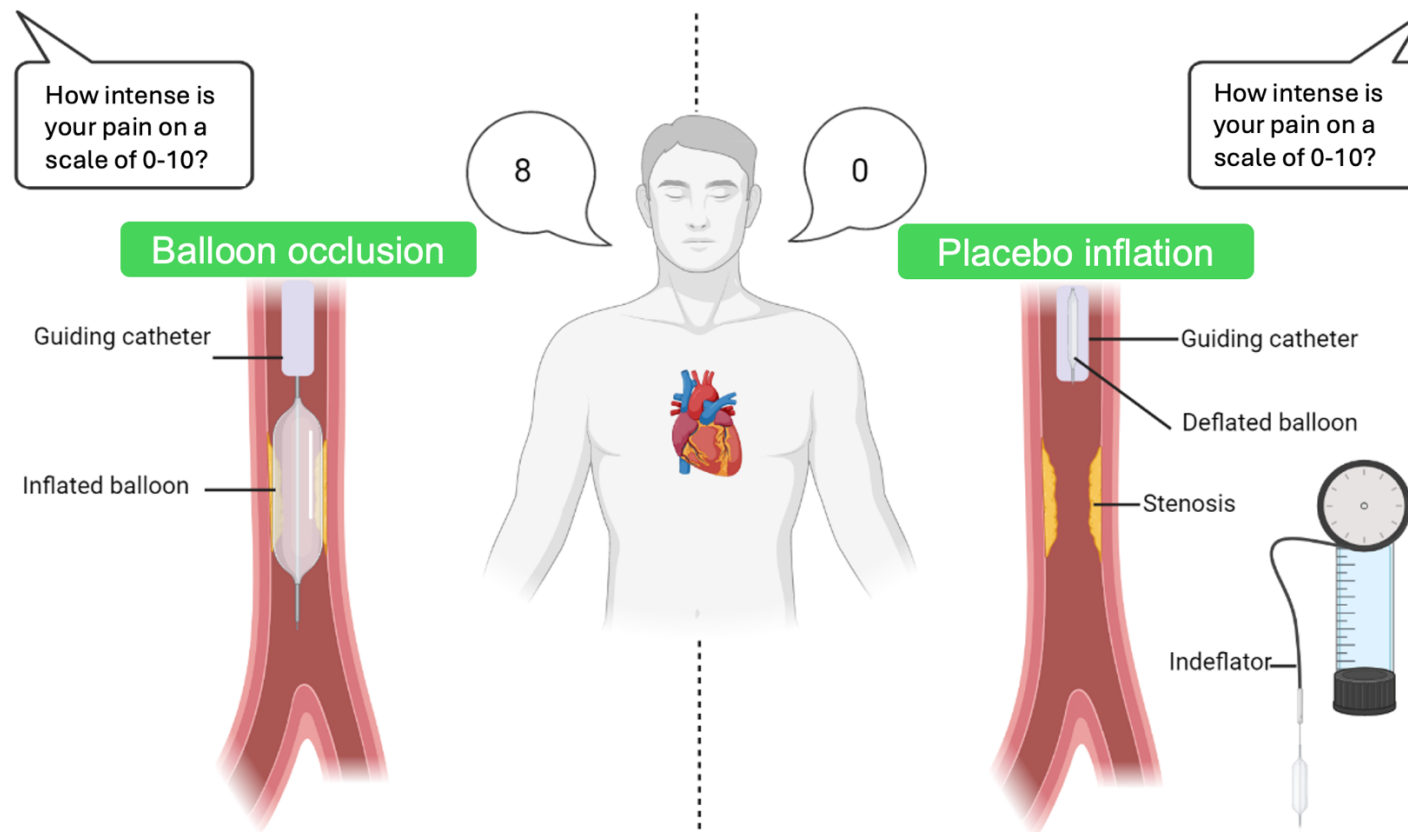


Figure 7.3. After each episode, balloon occlusion or placebo inflation, patients reported the intensity of any pain experienced on a 10-point ordinal scale where 0 = no perceived sensation and 10 = worst imaginable pain.

Figure 7.4: Example pressure waveforms for the derivation of collateral flow index (CFI)

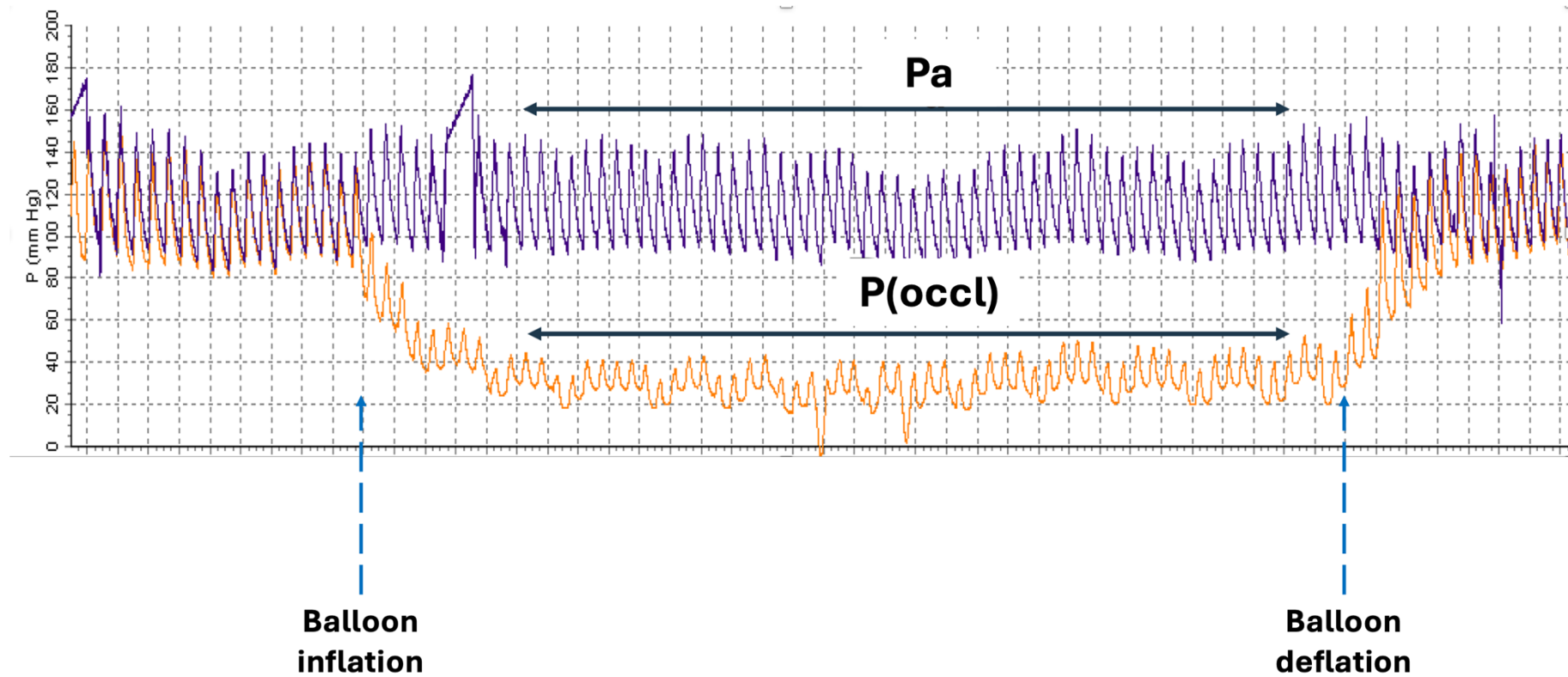


Figure 7.4: Example pressure waveforms displaying simultaneous aortic pressure ( $P_a$ ) and distal coronary wedge pressure ( $P(occl)$ ) during a 60 second balloon occlusion episode. The distal coronary pressure (green line) can be seen to fall to a steady pulsatile nadir as the occluding balloon is inflated ( $P(occl)$ ). This pressure is a surrogate of collateral blood flow. As the occluding balloon is deflated, the distal coronary pressure returns to baseline.

Figure 7.5: Association between daily angina frequency and physiological stenosis severity

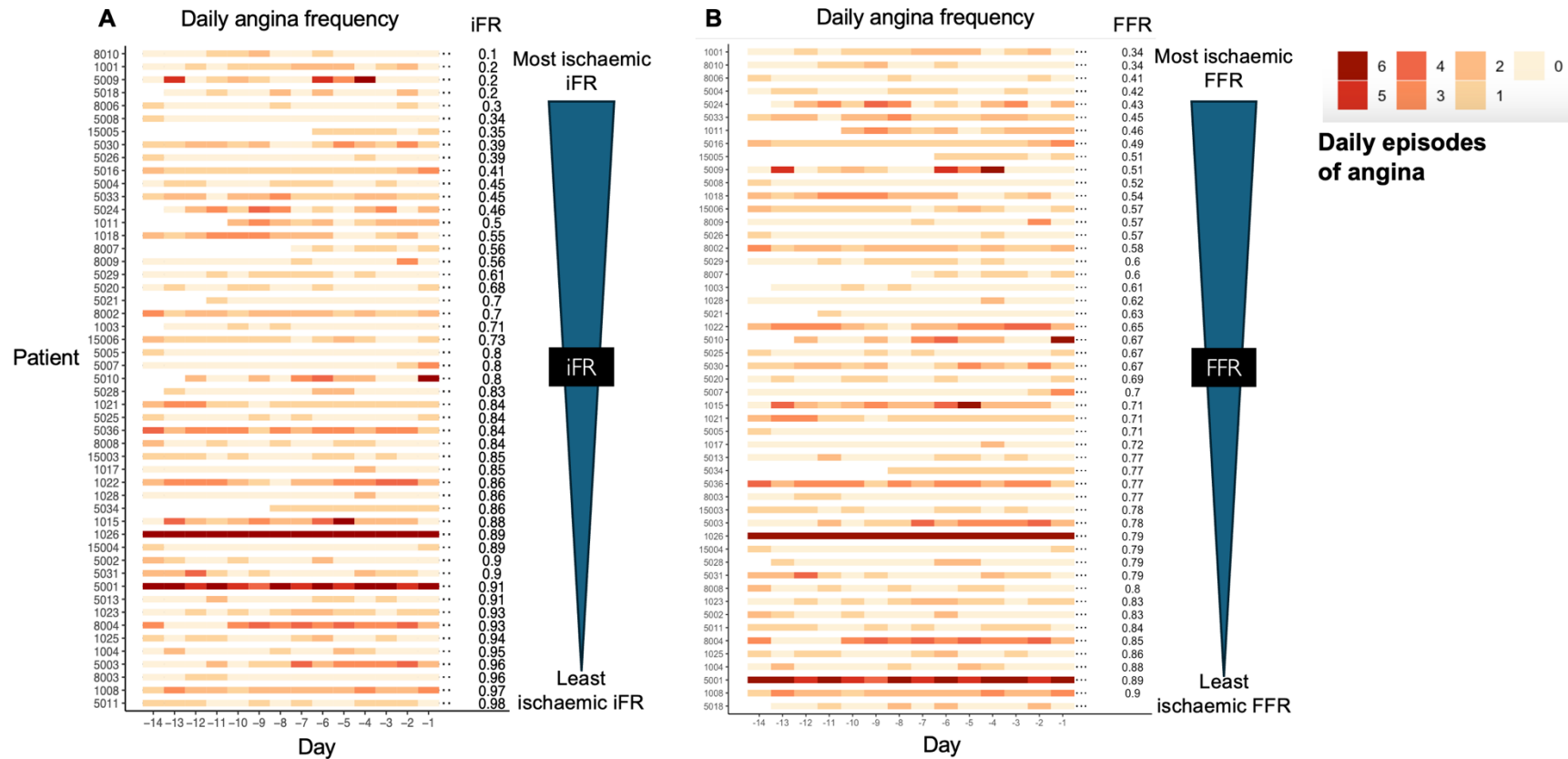


Figure 7.5: Association between daily angina frequency reported via the smartphone app and physiological stenosis severity as assessed by (A) iFR and (B) FFR. In each panel, each patient is depicted by an individual row. Each coloured panel is an individual day, where darker colours indicate greater angina frequency. The patients have been sorted with the most ischaemic (lowest iFR and FFR) stenoses towards the top, and the least ischaemic (highest iFR and FFR) stenoses towards the bottom. There was little detectable relationship between physiological stenosis severity and daily angina frequency.

Figure 7.6: Association between iFR and collateral flow index (CFI)

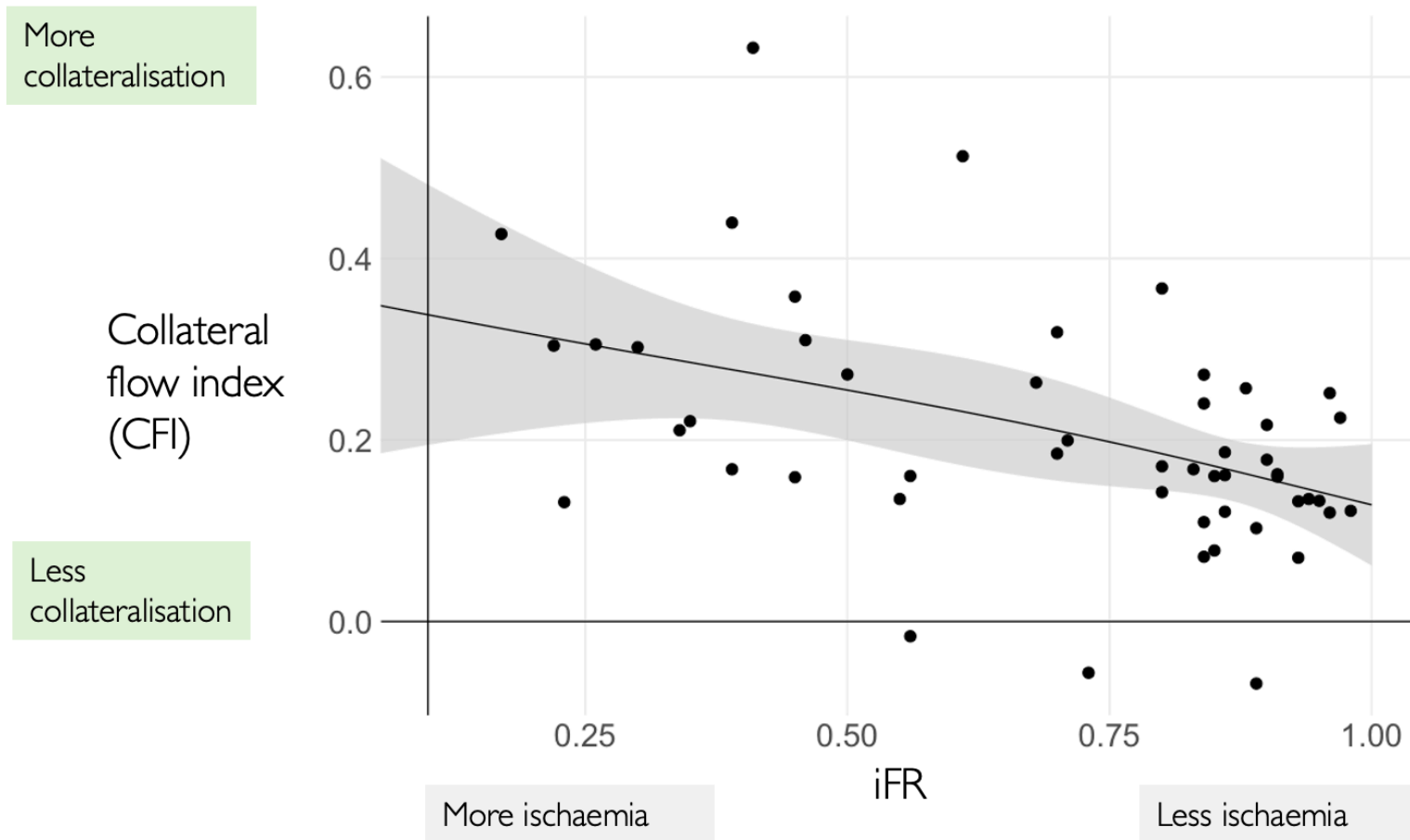


Figure 7.6: A greater burden of ischaemia, as assessed by iFR (x-axis), was significantly associated with greater collateral blood flow ( $P \geq 0 = 99.9\%$ ). iFR = instantaneous wave-free ratio, CFI = Collateral flow index.

Figure 7.7: Association between FFR and collateral flow index (CFI)

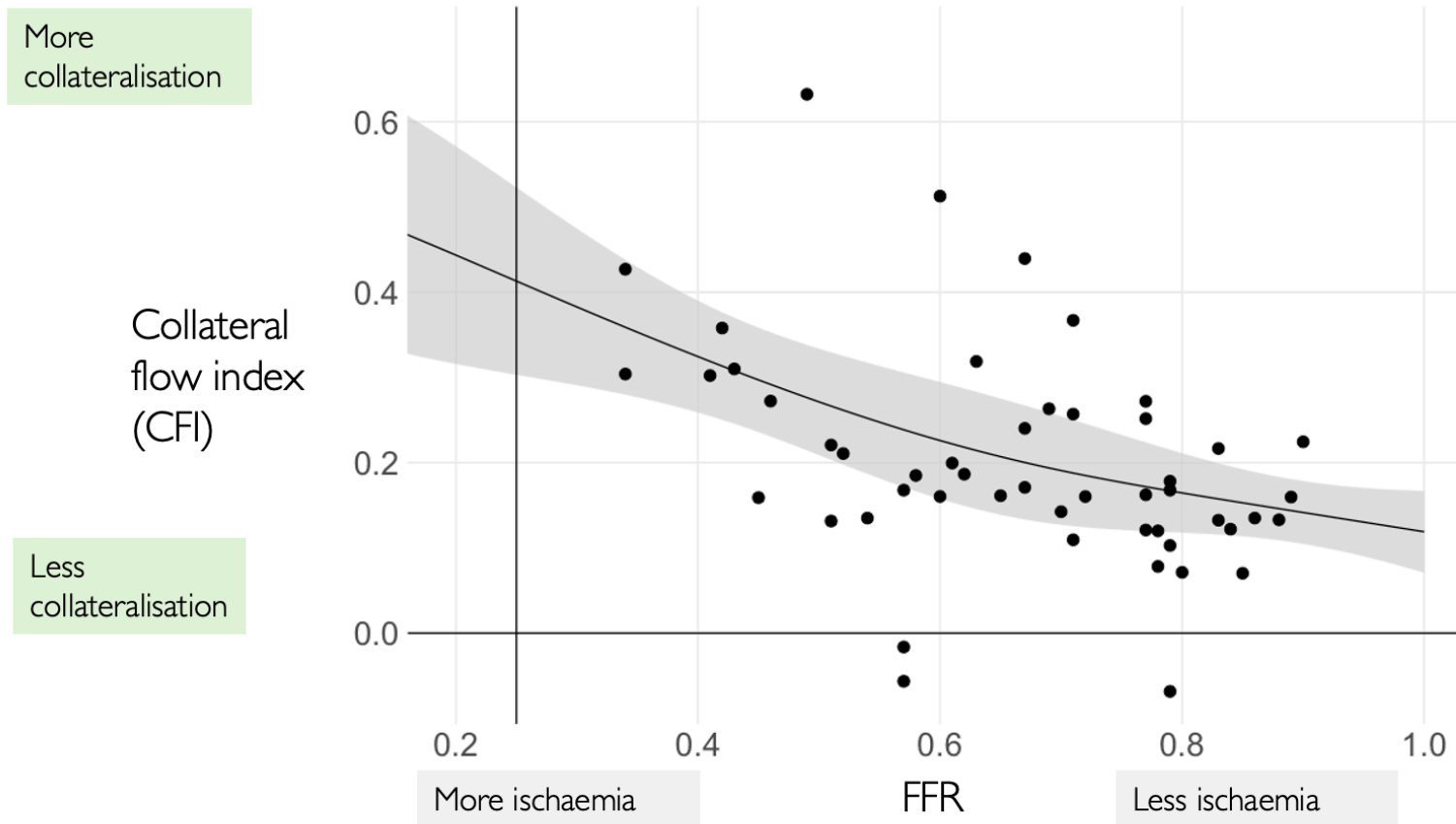


Figure 7.8: Association between collateral flow index and the placebo-controlled pain intensity score

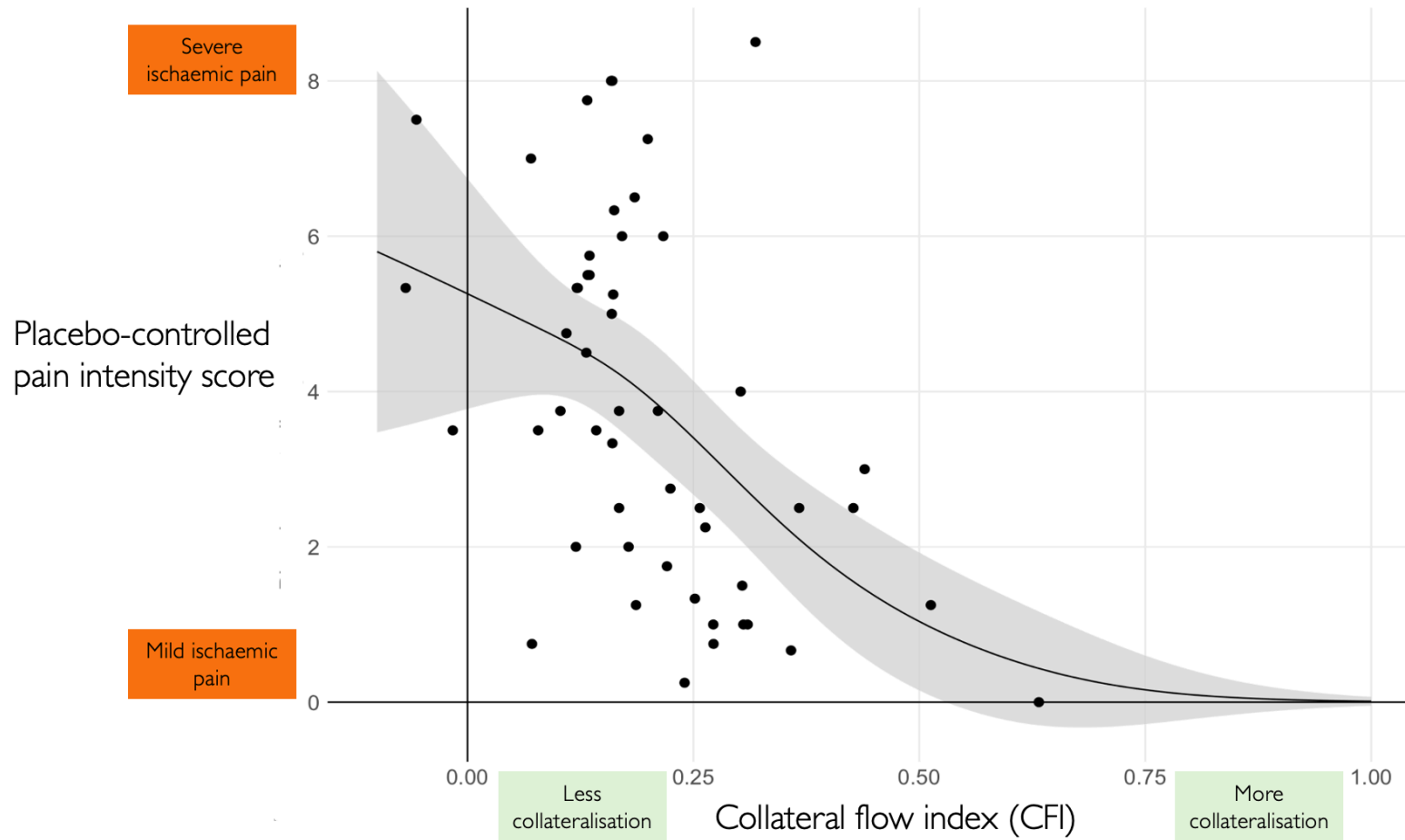


Figure 7.8: Greater collateralisation, as indicated by higher CFI, was associated with a significantly attenuated (milder) placebo-controlled pain intensity score ( $Pr \geq 0 = 99.9\%$ ). Participants with less collateral blood flow were more likely to have severe pain with balloon occlusion, that was not replicated by placebo inflation. CFI = collateral flow index.

## 8 Synthesis

### 8.1 Summary

In this thesis I explored the symptom of angina and its relationship to epicardial coronary artery disease. I was able to show that percutaneous coronary intervention of severe epicardial stenoses relieves the symptom of angina, improves exercise tolerance and quality of life. Despite many decades of use, and wide acceptance of this therapy, PCI had not previously been proven to be effective against placebo-control. In ORBITA-2, the benefit of PCI became apparent in the absence of antianginal medications. This highlights that the symptomatic benefit of PCI is attenuated by background antianginal medication.

Despite excellent reduction of ischaemia in patients randomised to PCI in ORBITA-2, 59% of patients continued to report symptoms. I performed ORBITA-STAR to investigate which symptoms were cured by PCI and which symptoms would persist despite successful revascularisation. ORBITA-STAR showed that when an individual's day-to-day symptom can be reproduced with experimentally induced ischaemia, that symptom can be reliably eradicated with PCI. However, if the symptom provoked by ischaemia differs from a patient's usual pain, that pain is likely to persist, even with effective revascularisation. Whilst these conclusions may seem intuitive, an experiment of this kind was necessary to highlight the simple reality that PCI can only be a therapy for symptoms truly caused by the epicardial stenosis. PCI is not a treatment for all symptoms, even in patients with severe epicardial stenoses.

Finally, the coronary collateral sub study of ORBITA-STAR investigated the relationship between pain intensity and burden of ischaemia. Despite guidelines advocating ischaemia testing as the gatekeeper for revascularisation procedures, patients with the most ischaemia are often not

the most symptomatic, and severity of ischaemia correlates poorly with the symptomatic result from PCI. This study found that the coronary collateral circulation develops as an adaptive response to ischaemia and actively attenuates the severity of ischaemic chest pain. This likely explains the non-linear relationship between ischaemia and angina which is encountered in research studies and clinical practice alike.

## **8.2 The ORBITA Trials: Implications for clinical guidelines**

### **8.2.1 Two Trials with two separate questions**

The gold standard for licensing of new drugs designed to treat symptoms are placebo-controlled trials demonstrating benefit. Unfortunately, for procedures designed to treat symptoms, no such standard is applied. The first ORBITA trial was designed to mirror clinical guidelines<sup>50</sup>. For the first time, it tested the symptomatic benefits of PCI for stable angina against a placebo-procedure. But importantly, it did so in a guideline directed manner: namely on a background of maximally tolerated antianginal medical therapy. It found that in this setting, PCI offered no additional anginal relief compared to placebo. Disbelief in the result was perhaps fuelled, in part, by the fact that this previously untested paradigm had already been entrenched in guidelines and clinical practice for decades.

ORBITA left cardiologists with a question: is PCI simply ineffective as an antianginal treatment, or does guideline directed antianginal medication attenuate the additional effects of PCI? Regardless of which hypothesis was correct, what ORBITA did establish was that the clinical guidelines were no longer backed up by the evidence.

The challenge for the next trial, ORBITA-2, was to determine the unattenuated effect of PCI, without background antianginal medications which may have diminished its effect compared to placebo. More simply, ORBITA-2 tested our fundamental understanding of PCI as a treatment for angina.

To answer this pivotal question required a departure from clinical guidelines. Following enrolment, antianginal medications were stopped, and risk reduction medications were optimised before patients were randomised to PCI or placebo. Whilst antianginal medication cessation was controversial, stopping this non-prognostic therapy was a necessary step to answer the clinical question.

ORBITA-2 revealed the unattenuated effect of PCI. Compared to placebo, PCI had a clear antianginal effect which was visible on the first day following randomisation, and was sustained throughout follow up. PCI offered a 59.5 second larger improvement in treadmill exercise time than the placebo procedure, contrasting with 16.6 seconds in the first ORBITA trial. PCI was also associated with improvements in every domain of the Seattle Angina Questionnaire and quality of life benefits. While these results provide the first placebo-controlled validation of PCI for stable angina, an understandable next question might be, how will these results impact the clinical guidelines? To answer this, we must consider the results of both trials together.

### **8.2.2 Antianginal medication and antianginal procedures: Synergistic or saturating effects?**

Ischaemic symptom reduction is the therapeutic target of both antianginal medications and PCI. A common misconception is that the ORBITA trials compared these two therapies. However, in each trial, the antianginal medication was the same in both randomisation arms. The ORBITA trial assessed the *additive* effect of PCI on a background of antianginal medications. The ORBITA-2 trial assessed the *isolated* effect of PCI without antianginal medications. These were strategy trials, which revealed the effect of PCI in two different circumstances.

In both trials, regardless of the level of background antianginal medications, PCI successfully resolved ischaemia but did not eradicate symptoms in the majority. It would be easy to attribute symptom persistence to a deficiency of antianginal medications, or coexistent microvascular disease. We might therefore believe that these patients required a combination of PCI *with* antianginal medication to achieve freedom from angina. However, since the proportion of patients with residual symptoms, regardless of the level of antianginals, was nearly identical in both trials, these hypotheses are incorrect. Intensification of antianginal therapy did not intensify angina relief.

The success of any symptomatic treatment depends on two factors. Firstly, the ability of the treatment to target pathology, and secondly, the strength of the causal link between the pathology and the symptoms. Patients with stable CAD present with symptoms along a continuum of “typicality”, from those which meet all of Diamond and Forrester’s original description<sup>38</sup>, through to patients with “angina-equivalent” symptoms, for whom antianginal treatments are still offered in the hope that these symptoms are caused by the stenosis. Even within an individual patient, symptom reporting can be variable with only a proportion being attributable to the stenosis. Since cardiologists have no means of objectively testing the

proportion of symptoms that are causally linked to a coronary stenosis, we rely on the crude measure of overall undifferentiated symptom burden in real world practice and in clinical trials.

Whilst PCI and antianginal medications target the symptoms of ischaemia in different ways, the amount of ischaemia reduction that is possible in any given patient is finite and may be saturated by effective use of either therapy alone. Beyond this, any additional therapy is no longer synergistic. ORBITA-STAR has shown us that refractory symptoms are likely to lie on a different causal pathway and require a different approach.

The combined results of ORBITA and ORBITA-2 tell us that both antianginal medications and PCI are powerful therapies for stable angina. In fact, so potent, that the first therapy appears to saturate all the potential therapeutic window of the second. These findings also underscore why performing unblinded trials of symptomatic therapies is not only uninformative, but actively misleading. Since the placebo effect does not differentiate between ischaemic and non-ischaemic symptoms, unblinded trials may show a false cumulative benefit when PCI is added to maximal antianginals, with no saturation of effect.

### **8.2.3 Guidelines for stable angina: the case for change**

In their current form, clinical guidelines advocating initiation and uptitration of antianginal medications to their highest tolerated dose will eliminate ischaemic symptoms in those patients with ischaemia. Persistent symptoms, despite maximal antianginal therapy, are likely to have a non-ischaemic cause. We might have believed that this population reflects patients with more severe symptoms, requiring more intensive therapy. Perhaps we need to acknowledge that the failure to treat symptoms may not be due to a failure of therapy but is more likely to be a failure of diagnosis.

Indeed, the first ORBITA trial tested the ability of PCI to improve symptoms once optimum antianginal medications had failed and showed little additive effect. Therefore, guidelines which were designed to encourage judicious use of PCI, after antianginal medications, were inadvertently selecting the patients with the least to gain.

#### **8.2.4 Should PCI be offered as a first line treatment for stable angina?**

PCI is different from antianginal medications in many ways. PCI is associated with upfront risk, and an upfront cost to health service providers. PCI, and more broadly, revascularisation, has anatomic and technical considerations which medications do not, and for some individuals, complete revascularisation will not be possible. Although thought of by many patients as a more definitive treatment than tablets, PCI has long term considerations of antiplatelet therapy and possible late complications such as stent thrombosis and restenosis. With this in mind, should PCI be considered as an option for first line therapy?

All decisions in healthcare are questions of risk versus benefit. With new data, patients should now be made aware that upfront PCI, without antianginal medication, offers an immediate, meaningful, and lasting antianginal relief, albeit with non-negligible risk, cost, and long-term considerations.

But perhaps the most compelling argument for a change in clinical guidelines is that when procedures do carry a degree of risk, they should be performed when they are able to offer their greatest benefit. For PCI, this greatest benefit is seen at the beginning of the treatment algorithm, before antianginal therapy has eliminated the majority, if not all the ischaemic

symptoms. To reserve PCI until after antianginal medicine optimisation, is to offer patients all the risk, with little reward.

In the absence of a head-to-head comparison between PCI and antianginal medication monotherapy strategies, we are left balancing the merits and risks of two pathways. ORBITA shows us that one effective approach begins and ends with antianginal and risk reduction medication. ORBITA-2 has given us an alternative which consists of PCI and risk reduction medication alone. Both approaches are valid, and guidelines should now give patients and physicians the choice.

## 9 References

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## 10 Appendix

### 10.1 Publications arising from this thesis

#### [A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina \(ORBITA-2\).](#)

**Rajkumar CA**, Foley MJ, Ahmed-Jushuf F, Nowbar AN, Simader FA, Davies JR, O'Kane PD, Haworth P, Routledge H, Kotecha T, Gamma R, Clesham G, Williams R, Din J, Nijjer SS, Curzen N, Ruparelia N, Sinha M, Dungu JN, Ganesanathan S, Khamis R, Mughal L, Kinnaird T, Petraco R, Spratt JC, Sen S, Sehmi J, Collier DJ, Sohaib A, Keeble TR, Cole GD, Howard JP, Francis DP, Shun-Shin MJ, Al-Lamee RK; ORBITA-2 Investigators. *N Engl J Med.* 2023 Dec 21;389(25):2319-2330.

PMID: 38015442

#### [N-of-1 Trial of Angina Verification Before Percutaneous Coronary Intervention.](#)

**Rajkumar CA**, Foley MJ, Ahmed-Jushuf F, Simader FA, Mohsin M, Ganesanathan S, Nowbar AN, Chotai S, Sen S, Petraco R, Nijjer SS, Sehmi J, Ruparelia N, Dungu JN, Kabir A, Tang K, Gamma R, Davies JR, Kotecha T, Cole GD, Howard JP, Keeble TR, Clesham G, O'Kane PD, Harrell FE Jr, Francis DP, Shun-Shin MJ, Al-Lamee RK.

*J Am Coll Cardiol.* 2024 May 8: S0735-1097(24)06824-4.

PMID: 38752902

#### [Placebo Control and Blinding in Randomized Trials of Procedural Interventions: A Systematic Review and Meta-Regression.](#)

**Rajkumar CA**, Thomas KE, Foley M, Ganesanathan S, Evans H, Simader F, Syam S, Nour D, Beattie C, Khan C, Reddy RK, Ahmed-Jushuf F, Francis DP, Shun-Shin M, Al-Lamee RK.

*JAMA Surg.* 2024 Apr 17: e240718.

PMID: 38630462

### 10.2 Other first author publications during PhD Studies

#### [Association Between High-Sensitivity Cardiac Troponin, Myocardial Ischemia, and Revascularization in Stable Coronary Artery Disease.](#)

**Rajkumar CA**, Wereski R, Parsonage W, Cullen L, Khamis R, Foley M, Harrell FE Jr, Shun-Shin MJ, Mills NL, Al-Lamee RK.

*J Am Coll Cardiol.* 2022 May 31;79(21):2185-2187.

PMID: 35618353.

**Typical angina and coronary artery disease: is the common ground smaller than we think?**

**Rajkumar C**, Simader F, Al-Lamee RK.

**Heart.** 2023 Sep 13;109(19):1422-1423.

PMID: 37290899

**Mechanical thrombectomy with retrievable stents and aspiration catheters for acute ischaemic stroke: a meta-analysis of randomised controlled trials.**

**Rajkumar CA**, Ganesanathan S, Ahmad Y, Seligman H, Thornton GD, Foley M, Nowbar AN, Howard JP, Francis DP, Keeble TR, Grunwald IQ, Al-Lamee RK, Malik I, Shun-Shin MJ.

**EuroIntervention.** 2022 Apr 1;17(17): e1425-e1434.

PMID: 34503942

**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, Ganesanathan S, Amarín 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, Ruparel N, Malik IS, Nijjer S, Sen S, Francis DP, Al-Lamee R.

**Circ Cardiovasc Interv.** 2021 Aug;14(8): e009891.

PMID: 34340523

**The Goldilocks Guide to Getting Medical Therapy 'Just Right': Insights from the ISCHEMIA Trial.**

**Rajkumar CA**, Foley M, Al-Lamee R.

**Circ Cardiovasc Qual Outcomes.** 2019 Nov;12(11): e006265.

PMID: 31718295

**Facilitating right-sided axillary artery access for transcatheter aortic valve replacement using the Edwards Sapien 3 and ultra valves: Technical considerations.**

**Rajkumar CA**, Cook C, Shalhoub J, Chukwuemeka A, Jaffer U, Hadjiloizou N, Sen S, Ruparel N, Mikhail G, Malik IS.

**Catheter Cardiovasc Interv.** 2020 Dec;96(7): E747-E754.

PMID: 31631520

**Upcoding of Clinical Information to Meet Appropriate Use Criteria for Percutaneous Coronary Intervention.**

**Rajkumar CA**, Suh WM, Francis DP.

**Circ Cardiovasc Qual Outcomes.** 2019 Mar;12(3): e005025.

PMID: 30871374

### 10.3 Co-authored publications during PhD Studies

#### Symptoms as a Predictor of the Placebo-Controlled Efficacy of PCI in Stable Coronary Artery Disease.

Simader FA, **Rajkumar CA**, Foley MJ, Ahmed-Jushuf F, Chotai S, Bual N, Khokhar A, Gohar A, Lampadakis I, Ganesanathan S, Pathimagaraj RH, Nowbar A, Davies JR, Keeble TR, O'Kane PD, Haworth P, Routledge H, Kotecha T, Spratt JC, Williams R, Nijjer SS, Sen S, Curzen N, Sinha M, Howard JP, Cole G, Harrell FE Jr, Francis DP, Shun-Shin MJ, Al-Lamee RK; ORBITA-2 Investigators.

**J Am Coll Cardiol.** 2024 May 10; **S0735-1097(24)06948-1**.

PMID: 38759906

#### Physiological Assessment with iFR prior to FFR Measurement in Left Main Disease.

Warisawa T, Cook CM, Ahmad Y, Howard JP, Seligman H, **Rajkumar C**, Toya T, Doi S, Nakajima A, Nakayama M, Vera-Urquiza R, Yuasa S, Sato T, Kikuta Y, Kawase Y, Nishina H, Al-Lamee R, Sen S, Lerman A, Matsuo H, Akashi YJ, Escaned J, Davies JE.

**Cardiovasc Interv Ther.** 2024 Apr 20.

PMID: 38642290

#### Coronary sinus reducer for the treatment of refractory angina (ORBITA-COSMIC): a randomised, placebo-controlled trial.

Foley MJ, **Rajkumar CA**, Ahmed-Jushuf F, Simader FA, Chotai S, Pathimagaraj RH, Mohsin M, Salih A, Wang D, Dixit P, Davies JR, Keeble TR, Cosgrove C, Spratt JC, O'Kane PD, De Silva R, Hill JM, Nijjer SS, Sen S, Petraco R, Mikhail GW, Khamis R, Kotecha T, Harrell FE, Kellman P, Francis DP, Howard JP, Cole GD, Shun-Shin MJ, Al-Lamee RK.

**Lancet.** 2024 Apr 20; **403(10436):1543-1553**.

PMID: 38604209

#### A Placebo-Controlled Trial of PCI for Stable Angina. Reply.

Al-Lamee RK, **Rajkumar CA**.

**N Engl J Med.** 2024 Mar 21; **390(12):1151-1152**.

PMID: 38507763

#### Why Does a Cardiologist Believe in a Therapy? The Role of Intuitiveness and Understanding the Mechanism.

Foley MJ, **Rajkumar CA**, Ahmed-Jushuf F, Nowbar AN, Simader F, Bello O, Al-Lamee R.

**Circ Cardiovasc Qual Outcomes.** 2024 Mar; **17(3): e010664**.

PMID: 38362766

#### A double-blind, randomised, placebo-controlled trial of the coronary sinus Reducer in refractory angina: design and rationale of the ORBITA-COSMIC trial.

Foley MJ, **Rajkumar CA**, Ahmed-Jushuf F, Simader F, Pathimagaraj RH, Nijjer S, Sen S, Petraco R, Clesham G, Johnson T, Harrell FE Jr, Kellman P, Francis D, Shun-Shin M, Howard J, Cole GD, Al-Lamee R.

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**EuroIntervention. 2024 Feb 5;20(3): e216-e223.**

PMID: 38214677

**Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications.**

Kandzari DE, Townsend RR, Kario K, Mahfoud F, Weber MA, Schmieder RE, Pocock S, Tsioufis K, Konstantinidis D, Choi J, East C, Lauder L, Cohen DL, Kobayashi T, Schmid A, Lee DP, Ma A, Weil J, Agdirlioglu T, Schlaich MP, Shetty S, Devireddy CM, Lea J, Aoki J, Sharp ASP, Anderson R, Fahy M, DeBruin V, Brar S, Böhm M; SPYRAL HTN-ON MED Investigators.

**J Am Coll Cardiol. 2023 Nov 7;82(19):1809-1823. doi: 10.1016/j.jacc.2023.08.045.**

PMID: 37914510

**The ability of contemporary cardiologists to judge the ischemic impact of a coronary lesion visually.**

Foley M, **Rajkumar CA**, Ahmed-Jushuf F, Nour D, Fung CH, Seligman H, Pathimagaraj RH, Petraco R, Sen S, Nijjer S, Howard JP, Ahmad Y, Allahwala U, Bhindi R, Chamie D, Doi S, Kuwata S, Kaihara T, Koga M, Ishibashi Y, Higuma T, Tanabe Y, Nakayama M, Kawase Y, Watanabe A, Funayama N, Horinaka R, Hijikata N, Takahashi T, Matsuo H, Hansen PS, Manica A, Weaver J, Alzuhairi K, Yong TH, Warisawa T, Francis DP, Shun-Shin MJ, Al-Lamee RK.

**Cardiovasc Revasc Med. 2024 Feb; 59:60-66.**

PMID: 37612169

**Development of artificial intelligence tools for invasive Doppler-based coronary microvascular assessment.**

Seligman H, Patel SB, Alloula A, Howard JP, Cook CM, Ahmad Y, de Waard GA, Pinto ME, van de Hoef TP, Rahman H, Kelshiker MA, **Rajkumar CA**, Foley M, Nowbar AN, Mehta S, Toulemonde M, Tang MX, Al-Lamee R, Sen S, Cole G, Nijjer S, Escaned J, Van Royen N, Francis DP, Shun-Shin MJ, Petraco R.

**Eur Heart J Digit Health. 2023 May 3;4(4):291-301.**

PMID: 37538145

**Deferred Versus Performed Revascularization for Left Main Coronary Disease with Hemodynamic Significance.**

Warisawa T, Cook CM, Ahmad Y, Howard JP, Seligman H, **Rajkumar C**, Toya T, Doi S, Nakajima A, Nakayama M, Vera-Urquiza R, Yuasa S, Sato T, Kikuta Y, Kawase Y, Nishina H, Al-Lamee R, Sen S, Lerman A, Matsuo H, Akashi YJ, Escaned J, Davies JE.

**Circ Cardiovasc Interv. 2023 Jun;16(6): e012700.**

PMID: 37339234

**Physiology-guided PCI versus CABG for left main coronary artery disease: insights from the DEFINE-LM registry.**

Warisawa T, Cook CM, Kawase Y, Howard JP, Ahmad Y, Seligman H, **Rajkumar C**, Toya T, Doi S, Nakajima A, Tanigaki T, Omori H, Nakayama M, Vera-Urquiza R, Yuasa S, Sato T, Kikuta Y, Nishina H, Al-Lamee R, Sen S, Lerman A, Akashi YJ, Escaned J, Matsuo H, Davies JE.

**Cardiovasc Interv Ther.** 2023 Jul;38(3):287-298.

PMID: 37017899

**Daily angina documentation versus subsequent recall: development of a symptom smartphone app.**

Nowbar AN, Howard JP, Shun-Shin MJ, **Rajkumar C**, Foley M, Basu A, Goel A, Patel S, Adnan A, Beattie CJ, Keeble TR, Sohaib A, Collier D, McVeigh P, Harrell FE Jr, Francis DP, Al-Lamee RK.

**Eur Heart J Digit Health.** 2022 Apr 11;3(2):276-283.

PMID: 36713021

**Remote digital smart device follow-up in prospective clinical trials: early insights from ORBITA-2, ORBITA-COSMIC, and ORBITA-STAR.**

Ganesanathan S, **Rajkumar CA**, Foley M, Francis D, Al-Lamee R.

**Eur Heart J Suppl.** 2022 Nov 11;24(Suppl H):H32-H42.

PMID: 36382002

**Revascularization in stable coronary artery disease.**

Al-Lamee RK, Foley M, **Rajkumar CA**, Francis DP.

**BMJ.** 2022 Jun 13;377: e067085.

PMID: 35697356

**Effect of coronary tortuosity on invasive physiology.**

Maznyczka A, **Rajkumar C**, Hobson A, Haworth PA.

**BMJ Case Rep.** 2022 Jun 10;15(6): e249095.

PMID: 35688575

**Cardiopulmonary exercise testing and efficacy of percutaneous coronary intervention: a substudy of the ORBITA trial.**

Ganesanathan S, **Rajkumar CA**, Foley M, Thompson D, Nowbar AN, Seligman H, Petraco R, Sen S, Nijjer S, Thom SA, Wensel R, Davies J, Francis D, Shun-Shin M, Howard J, Al-Lamee R.

**Eur Heart J.** 2022 Sep 1;43(33):3132-3145.

PMID: 35639660

**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, Ahmed-Jushuf F, Howard JP, Seligman H, Petraco R, Sen S, Nijjer SS, Shun-Shin MJ, Keeble TR, Sohaib A, Collier D, McVeigh P, Harrell FE, Francis DP, Al-Lamee RK.

**EuroIntervention.** 2022 Apr 22;17(18):1490-1497.

PMID: 35156616

**Recruitment for placebo-controlled trials of interventional procedures: a patient-centred approach.**

Al-Lamee RK, Foley M, **Rajkumar C**, Nowbar AN.  
**EuroIntervention. 2021 Dec 17;17(12): e963-e965.**  
PMID: 34916182

**Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis.**

Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN, **Rajkumar CA**, Shun-Shin MJ, Ahmad Y, Sen S, Al-Lamee R, Petraco R; Coronary Flow Outcomes Reviewing Committee.  
**Eur Heart J. 2022 Apr 19;43(16):1582-1593.**  
PMID: 34849697

**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 RK.  
**Front Cardiovasc Med. 2021 Oct 11; 8:757030.**  
PMID: 34708098

**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 21;78(12):1210-1222.**  
PMID: 34531021

**Phasic flow patterns of right versus left coronary arteries in patients undergoing clinical physiological assessment.**

Seligman H, Nijjer SS, 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 C**, Nowbar A, 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 JE, Francis DP, Petraco R.  
**EuroIntervention. 2022 Feb 18;17(15):1260-1270.**  
PMID: 34338643

**Correlation of Intravascular Ultrasound and Instantaneous Wave-Free Ratio in Patients with Intermediate Left Main Coronary Artery Disease.**

El Hajj SC, Toya T, Warisawa T, Nan J, Lewis BR, Cook CM, **Rajkumar C**, Howard JP, Seligman H, Ahmad Y, Doi S, Nakajima A, Nakayama M, Goto S, Vera-Urquiza R, Sato T, Kikuta Y, Kawase Y, Nishina H, Nakamura S, Matsuo H, Escaned J, Akashi YJ, Davies JE, Lerman A.  
**Circ Cardiovasc Interv. 2021 Jun;14(6): e009830.**  
PMID: 34092096

**Optimising physiological endpoints of percutaneous coronary intervention.**

Al-Lamee R, **Rajkumar CA**, Ganesanathan S, Jeremias A.

**EuroIntervention.** 2021 Apr 2;16(18): e1470-e1483.

PMID: 33792544

**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.

PMID: 33762369

**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.

PMID: 33563623

**Achieving Optimal Medical Therapy: Insights from the ORBITA Trial.**

Foley M, **Rajkumar CA**, Shun-Shin M, Ganesanathan 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.

PMID: 33496201

**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.

PMID: 33196154

**Balloon-Assisted Tracking (BAT) of an Uncrossable Aortic Valve During Transcatheter Aortic Valve Implantation.**

Jabbour RJ, Cook C, Seligman H, **Rajkumar C**, Hadjiloizou N, Sen S, Ruparelia N, Ariff B, Mikhail GW, Malik IS.

**Cardiovasc Revasc Med.** 2020 Nov;21(11S):33-35.

PMID: 32487482

**Safety of Revascularization Deferral of Left Main Stenosis Based on Instantaneous Wave-Free Ratio Evaluation.**

Warisawa T, Cook CM, **Rajkumar C**, Howard JP, Seligman H, Ahmad Y, El Hajj S, Doi S, Nakajima A, Nakayama M, Goto S, Vera-Urquiza R, Sato T, Kikuta Y, Kawase Y, Nishina H, Petraco R, Al-Lamee R, Nijjer S, Sen S, Nakamura S, Lerman A, Matsuo H, Francis DP, Akashi YJ, Escaned J, Davies JE.

**JACC Cardiovasc Interv.** 2020 Jul 27;13(14):1655-1664.

PMID: 32417088

**Per-Vessel Level Analysis of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Discordance - Insights from the AJIP Registry.**

Warisawa T, Cook CM, Seligman H, Howard JP, Ahmad Y, **Rajkumar C**, Doi S, Nakayama M, Tanigaki T, Omori H, Nakajima A, Yamanaka F, Goto S, Yakuta Y, Karube K, Uetani T, Kikuta Y, Shiono Y, Kawase Y, Nishina H, Nakamura S, Escaned J, Akashi YJ, Matsuo H, Davies JE.

**Circ J.** 2020 May 25;84(6):1034-1038.

PMID: 32321880

**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.

PMID: 32063040

**Interference Between Pressure-Wire and Deployed Coronary Stents: Insights from a Bench Test.**

Warisawa T, Nour D, Seligman H, Doi S, Kuwata S, Howard JP, **Rajkumar C**, Cook CM, Nakayama Y, Kasahara M, Suzuki N, Matsuda H, Mizuno K, Akashi YJ.

**Cardiovasc Revasc Med.** 2020 Jun;21(6):765-770.

PMID: 31784356

**Determining the Predominant Lesion in Patients with Severe Aortic Stenosis and Coronary Stenoses: A Multicenter Study Using Intracoronary Pressure and Flow.**

Ahmad Y, Vendrik J, Eftekhari A, Howard JP, Cook C, **Rajkumar C**, Malik I, Mikhail G, Ruparelia N, Hadjiloizou N, Nijjer S, Al-Lamee R, Petraco R, Warisawa T, Wijntjens GWM, Koch KT, van de Hoef T, de Waard G, Echavarria-Pinto M, Frame A, Sutaria N, Kanaganayagam G, Ariff B, Anderson J, Chukwuemeka A, Fertleman M, Koul S, Iglesias JF, Francis D, Mayet J, Serruys P, Davies J, Escaned J, van Royen N, Götzberg M, Juhl Terkelsen C, Høj Christiansen E, Piek JJ, Baan J Jr, Sen S.

**Circ Cardiovasc Interv.** 2019 Dec;12(12): e008263.

PMID: 31752515

**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.**

PMID: 31707827

**Improving haemodynamic optimization of cardiac resynchronization therapy for heart failure.**

Sharp AJ, Sohaib SMA, Shun-Shin MJ, Pabari P, Willson K, **Rajkumar C**, Hughes AD, Kanagaratnam P, Mayet J, Whinnett ZI, Kyriacou AA, Francis DP.

**Physiol Meas. 2019 May 1;40(4):04NT01.**

PMID: 30933931

## 10.4 Abstracts presented at international conferences

**A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina (ORBITA-2).**

Late Breaking Clinical Trial

American Heart Association

Philadelphia, 2023

**N-of-1 Trial of Angina Verification Before Percutaneous Coronary Intervention.**

PCR's Got Talent Award

EuroPCR

Paris, 2024

**The role of the collateral circulation in stable coronary artery disease: a placebo-controlled study in patients with stable angina**

Transcatheter Therapeutics (TCT).

Boston, 2022

## Placebo-Controlled Efficacy of Percutaneous Coronary Intervention for Focal and Diffuse Patterns of Stable Coronary Artery Disease.

Transcatheter Therapeutics (TCT) 2020

Online

### 10.5 Invited conference presentations and lectures

#### *PCI should be offered first line for stable angina - debate*

British Cardiovascular Society (BCS) Conference, Manchester, June 2024

#### *Stable CAD – GDMT / Elective revascularisation (PCI vs CABG)*

Mayo Clinic / BCS Cardiology Review Course, March 2024, London

#### *Angio Review Session – Coronary perforation*

British Cardiovascular Intervention Society: Advanced Cardiovascular Intervention Annual Meeting 2024

#### *Future trials in coronary physiology and intracoronary imaging*

Transcatheter Therapeutics (TCT). San Francisco, CA. October 2023

#### *Stable CAD – GDMT / Elective revascularisation (PCI vs CABG)*

Mayo Clinic / BCS Cardiology Review Course, March 2023, London

#### *Invasive ischaemia testing: integrating anatomy, physiology and symptoms*

Royal Society of Medicine: Cardiac Imaging Training Day

27<sup>th</sup> July 2022. Royal Society of Medicine

#### *Upcoming clinical trials in stable CAD*

Transcatheter Therapeutics (TCT) Connect 2021. [Online]

#### *High-sensitivity cardiac troponin, myocardial ischemia and the effect of percutaneous coronary intervention in stable coronary artery disease: an analysis from the ORBITA trial*

National Heart and Lung Institute Away Day 2021

*Interventional Training is fit for purpose*

British Cardiovascular Intervention Society: Advanced Cardiovascular Intervention Annual Meeting 2021

*How to get a fellowship - The interview*

Royal Society of Medicine Research Training Day 2020

## **10.6 Prizes awarded**

**PCR's Got Talent Prize Winner 2024**

EuroPCR  
Paris, 2024

**Royal Society of Medicine Gold Medal President's Prize**

Royal Society of Medicine  
London, 2023

## 10.7 Press articles relating to the ORBITA-2 Trial

A selection of press articles discussing the results of the ORBITA-2 trial are presented below:

1. <https://www.tctmd.com/news/placebo-controlled-orbita-2-shows-pci-eases-symptoms-stable-angina>
2. <https://www.imperial.ac.uk/news/249437/heart-stents-offer-alternative-chest-pain/>
3. <https://www.medpagetoday.com/meetingcoverage/aha/107294>
4. <https://www.healio.com/news/cardiac-vascular-intervention/20231111/pci-improves-angina-symptoms-vs-sham-procedure-in-patients-with-stable-cad-orbita2>
5. <https://newsroom.heart.org/news/heart-stenting-relieved-chest-pain-and-improved-exercise-capacity>
6. <https://www.managedhealthcareexecutive.com/view/angioplasty-for-stable-angina-on-par-with-antianginal-medications-say-orbita-2-investigators-aha-scientific-sessions>
7. <https://docwirenews.com/post/orbita-2-study-heart-stenting-reduces-chest-pain-and-improves-exercise-capacity>
8. <https://www.medscape.com/s/viewarticle/998375?form=fpf>
9. <https://cardiovascularbusiness.com/topics/clinical/interventional-cardiology/pci-benefits-patients-stable-chest-pain>
10. <https://www.medscape.com/viewarticle/998123?form=fpf>
11. <https://www.tctmd.com/news/whats-going-be-hot-aha-2023>
12. <https://www.expresshealthcaremgmt.com/news2/stenting-can-improve-chest-pain-exercise-capacity-in-stable-angina/278419/#gsc.tab=0>
13. <https://www.expresshealthcaremgmt.com/news2/placebo-controlled-orbita-2-shows-pci-eases-symptoms-in-stable-angina-2/277436/#gsc.tab=0>
14. <https://www.expresshealthcaremgmt.com/news2/placebo-controlled-orbita-2-shows-pci-eases-symptoms-in-stable-angina/277435/#gsc.tab=0>
15. <https://www.expresshealthcaremgmt.com/news2/angioplasty-for-stable-angina-on-par-with-antianginal-medications-say-orbita-2-investigators/277497/#gsc.tab=0>
16. <https://vigourtimes.com/new-study-pci-found-to-alleviate-symptoms-of-stable-angina-in-placebo-controlled-orbita-2-trial/>
17. <https://oicadian.com/stenting-improves-chest-pain-and-exercise-capacity-in-stable-angina/>
18. <https://clinicaltrialresults.org/dr-christopher-rajkumar-dr-al-lamee-and-dr-c-michael-gibson-discuss-percutaneous-coronary-intervention-for-stable-angina-orbita-2-a-randomised-placebo-controlled-trial/>
19. <https://www.healio.com/news/cardiac-vascular-intervention/20231111/pci-improves-angina-symptoms-vs-sham-procedure-in-patients-with-stable-cad-orbita2>
20. <https://www.dailymail.co.uk/health/article-12737623/Jab-twice-year-send-high-blood-pressure-reverse-new-trial-finds-replacing-need-daily-pills.html>
21. <https://www.imperial.nhs.uk/about-us/news/stents-as-alternative-to-chest-pain-medication>
22. <https://www.nihr.ac.uk/news/new-hope-for-patients-with-angina-as-stents-proved-to-be-an-alternative-to-pain-medication/34956>
23. <https://www.tctmd.com/news/top-coronary-artery-disease-news-2023>
24. <https://www.tctmd.com/news/two-evidence-based-pathways-stable-angina-orbita-2-editorial>
25. <https://www.tctmd.com/videos/beyond-the-data-orbita2.6340948254112>

26. <https://www.tctmd.com/videos/tct-2023-day-3-wrapup.6339873295112>
27. <https://www.medscape.com/viewarticle/998213?form=fpf>

## 10.8 ORBITA-2 Patient consent form

**Imperial College  
London**

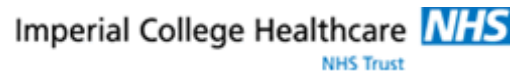
Imperial College Healthcare **NHS**  
NHS Trust

**International Centre of Circulatory Health  
NHLI, 2<sup>nd</sup> 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 1.11).                                                                                                                                                                                                                            | <input type="text"/>         |
| 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.                                                                                                                                         | <input type="text"/>         |
| 3. I have spoken to Dr.....                                                                                                                                                                                                                                                               | <input type="text"/>         |
| 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.                                                                                               | <input type="text"/>         |
| 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. | <input type="text"/>         |
| 6. I agree to take part in this research study.                                                                                                                                                                                                                                           | <input type="text"/>         |
| 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.                                                                                                          | <input type="text"/>         |
| Signature.....                                                                                                                                                                                                                                                                            | Date.....                    |
| Name (block capitals).....                                                                                                                                                                                                                                                                |                              |
| Signature of Study Investigator.....                                                                                                                                                                                                                                                      | Date.....                    |
| Name (block capitals).....                                                                                                                                                                                                                                                                |                              |

## 10.9 ORBITA-2 Patient information Sheet



International Centre of Circulatory Health  
NHLI, 2<sup>nd</sup> floor B Block  
Hammersmith Hospital  
London W12 0NN  
Tel No: 0207 594 5735

### 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.

#### **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 you on video 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), a magnetic scan of your heart (stress perfusion cardiac magnetic resonance scan) and an exercise test. These tests 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 3 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.

You then will receive sedation and music will be played to you through over the ear headphones. If the angiogram also shows that you have narrowing in one of the arteries supplying the left side of your heart (the left coronary artery system), we will determine how much the narrowing is directly affecting the blood supply to your heart cells when you exert yourself. To do this, we will place two tubes into a vein in your groin via a single needle puncture using ultrasound to guide the positioning of the needle; one tube will sit in a large vein in your heart (the coronary sinus) and the second tube will sit in one of the chambers of your heart (the right atrium). After sedation, we will speed up your heart rate (known as pacing) using the tube in the right heart chamber. We will then collect blood samples from the tube in your large heart vein to measure the levels of a series of markers of blood supply in your heart tissue. Some blood samples will also be stored for future analysis.

If you are suitable to continue in this study, you will randomly be assigned to have angioplasty (stent) or placebo. You will not be aware of what you have been assigned to. If you are allocated to placebo procedure, we will repeat the blood sampling procedure from your coronary sinus vein. After this, your catheter lab procedure will end.

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) and the blood sampling procedure from your coronary sinus vein. 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, magnetic heart scan, 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%.

During the coronary sinus blood sampling procedure, there is an increased risk of an irregular heartbeat. You may feel discomfort in your chest, some shortness of breath and dizziness as a result. There is a small added risk of blood clot forming in the heart vein, but this risk is reduced by giving blood thinning medication during the procedure. The overall complication rate is very low and is less than 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.

There are no short-term harmful effects from having a magnetic scan. If you have a cardiac pacemaker, metal fragments in your eye or previous brain surgery, your eligibility for this scan will be reviewed. Like dobutamine, there is a small risk that adenosine used to exercise the heart during the magnetic scan can make you feel flushed, headache, cause chest pain/tightness, shortness of breath or irregular heartbeats. There is also a small risk of severe allergic reaction (0.01% of cases) or side effects from the chemical we inject to obtain better views of the heart (known as the contrast agent). Mild side effects you may experience from the contrast agent include a metallic taste, itchy skin, pain in the injection site and feeling light-headed.

**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 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 and the British Heart Foundation.

**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 | [insert local site name]                      |
| Visit 2 | Imperial College Healthcare NHS Trust, London |
| Visit 3 | [insert local site name]                      |
| Visit 4 | 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 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**

**GP Information Sheet**

**Date:**

Dear Doctor,

**Re:**

Your above named patient has agreed to participate in the following research study:

**ORBITA-2: A placebo-controlled trial of percutaneous coronary intervention for the relief of stable angina**

Chief investigator: Dr Rasha Al-Lamee

**Background and Aims**

The first double-blinded randomised placebo-controlled trial of PCI in stable angina (ORBITA) was published in *The Lancet* in 2018. It showed that PCI was no more effective than a placebo procedure in improving treadmill exercise time or symptoms of angina.

The aim of this study (ORBITA-2) is to investigate whether treatment with PCI incrementally improves symptoms and exercise time of patients with stable angina when compared with a placebo procedure. It differs from ORBITA in that it will enrol patients with disease in one or more vessels (rather than just one), assess exercise capacity without anti-anginal medications which may obscure the picture (rather than on these medications) and maintain blinding for 12 weeks (rather than 6).

**What is involved for your patient**

Patients will attend Imperial College Healthcare NHS Trust for clinical assessment, blood test, dobutamine stress echocardiography, an exercise treadmill test and a clinical questionnaire set. Their antianginal medications will be stopped at the start of the trial. They will be provided with a smartphone application and begin daily scoring of symptoms using a visual analogue scale. The data will be monitored daily by the research team. If they have angina, antianginal medications will be initiated from a pre-specified panel. For patients with hypertension, blood pressure will be monitored daily using a home blood pressure machine supplied by the study team. Blood pressure readings will be recorded in the smartphone application and will be monitored by the research team. Medications will be restarted as required. If patients do not tolerate the medications due to side effects they will be adjusted or stopped as required. They will start taking 2 anti-platelet medications (aspirin and either clopidogrel, ticagrelor or prasugrel) unless already on them in which

case they should continue taking them. If they are at high risk of adverse gastrointestinal (GI) effects (based on previous GI ulceration, age, concomitant medications that increase risk) they will also be started on a proton pump inhibitor, lansoprazole, in accordance with NICE guidance on Gastro-oesophageal reflux disease and dyspepsia in adults (CG184). Aspirin will be continued lifelong. The second antiplatelet medication will be continued for 1 year after stent. If patients do not have a stent they will stop the second antiplatelet at the end of the follow-up period.

We will perform a coronary angiogram one week later with invasive assessment of coronary ischaemia using a pressure wire. Patients will then be randomised to receiving coronary angioplasty or a sham procedure. Patients and researchers will be blinded to the treatment strategy at this stage. The data collected will be stored on a computer and analysed later.

Patients will then return for a follow-up visit at Imperial College Healthcare NHS Trust 12 weeks after the procedure. At this stage we will repeat the blood test, dobutamine stress echocardiography, an exercise treadmill test and a clinical questionnaire set. Patients and clinicians will then be unblinded to the treatment strategy that patients had received and all patients in the placebo group will be given the option to receive coronary angioplasty.

All of the information that we take will be pseudonymised.

The patients have been given an information sheet explaining the study further.

### **Potential Benefits**

This study will not benefit your patient directly. We expect that the information that we gain from this study will however contribute to improvements in the management of patients with stable angina.

### **Potential Side effects**

At the coronary angiogram/angioplasty procedure the additional measurements that we will be making will slightly increase the radiation dose of the coronary angioplasty study that your patient will be having anyway. Also, those patients in the placebo arm of the study may have a third procedure with coronary angioplasty after unblinding which will be a small additional risk above standard care. Although all radiation exposure can increase the risk of harmful long-term effects, the total dose will still be significantly lower than a cardiac CT scan.

We will be passing a pressure measurement wire which can rarely lead to coronary artery dissection. However the procedure will be performed by experienced interventional cardiologists who are experienced in handling these wires will be performing the procedures. In the event of coronary artery dissection, patients will not undergo randomisation and we will go on to perform coronary angioplasty.

### **Adverse events and further information**

I would be grateful if you could report any adverse events to me on the address below.

No medications are specifically prohibited during the trial. Please contact us if you have any questions about the medications. Patients can also contact us if they have any questions.

Please do not hesitate to contact us for any further information on the following address:

Dr Rasha Al-Lamee and Dr Christopher Rajkumar

International Centre for Circulatory Health  
NHLI, 2<sup>nd</sup> Floor, B Block  
Hammersmith Hospital  
London  
W12 0NN

Telephone 0207 594 5735/ 07885 587409  
Email: [christopher.rajkumar@nhs.net](mailto:christopher.rajkumar@nhs.net)

#### **10.11 Medication prescribing standard operating procedure for ORBITA-2.**

This medication management SOP was developed in conjunction with the DSMB and has been previously published<sup>61</sup>.

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

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

###### *Dual antiplatelet therapy:*

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

###### *Gastrointestinal (GI) protection:*

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

###### *Lipid-lowering medication:*

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

## **2. Other concomitant risk factor modifying medication**

### *Antihypertensives:*

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

## **3. Antianginal medication**

Regular antianginal medications will be stopped on enrollment. All participants will be given glyceryl trinitrate spray to be used when necessary. The need for starting regular antianginals will be determined by participant preference and patient-reported symptoms.

An individualised protocol for potential introduction of antianginal medications will be prepared for each participant by the research team. This protocol will be based on the participant's medical history, heart rate, blood pressure and any medication intolerance. The preferred sequence will be as follows: Bisoprolol, nifedipine MR, isosorbide mononitrate MR, nicorandil, ranolazine.

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

## 10.12 ORBITA-STAR Patient Consent form

**Imperial College**  
London

Imperial College Healthcare **NHS**  
NHS Trust

**International Centre of Circulatory Health**  
**NHLI, 2<sup>nd</sup> floor B Block**  
**Hammersmith Hospital**  
**London W12 0NN**  
**Tel No: 0207 594 5735**

### CONSENT FORM

Is there a difference between clinical angina and experimentally inducible angina? A placebo-controlled experiment on symptoms in stable coronary artery disease

IRAS ID: 257148

Chief Investigator: Dr Rasha Al-Lamee

|                                                                                                                                                                                                                                                                                                                                                   | Please initial       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| 1. I confirm that I have read and understand the subject information sheet dated ..... version ..... for the above study and have had the opportunity to ask questions which have been answered fully.                                                                                                                                            | <input type="text"/> |
| 2. 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.                                                                                                                                                       | <input type="text"/> |
| 3. 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 where it is relevant to my taking part in this research. I give permission for these individuals to access my records. | <input type="text"/> |
| 4. I give permission for these individuals to access my records that are relevant to this research.                                                                                                                                                                                                                                               | <input type="text"/> |
| 5. I give permission for these individuals to access activity tracking data from an Apple Watch, where this has been provided                                                                                                                                                                                                                     | <input type="text"/> |
| 5. I give/do not give (delete as applicable) consent for information collected about me to be used to support other research in the future, including those outside of the EEA.                                                                                                                                                                   | <input type="text"/> |
| 6. I agree to take part in this research study.                                                                                                                                                                                                                                                                                                   | <input type="text"/> |
| 7. I understand that my GP will be 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.                                                                                                                                                         | <input type="text"/> |
| 8. I give/do not give (delete as applicable) consent to being contacted to potentially take part in other research studies.                                                                                                                                                                                                                       | <input type="text"/> |
| Signature.....                                                                                                                                                                                                                                                                                                                                    |                      |
| Name (block capitals) .....                                                                                                                                                                                                                                                                                                                       | Date.....            |
| Signature of Study Investigator.....                                                                                                                                                                                                                                                                                                              |                      |
| Name (block capitals) .....                                                                                                                                                                                                                                                                                                                       | Date.....            |

IRAS project ID: 257148

# Imperial College London

## Patient Information Sheet

### **Is there a difference between clinical angina and experimentally inducible angina? A placebo-controlled experiment on symptoms in stable coronary artery disease**

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?**

Patients often experience chest pain when blood supply to the heart is reduced due to a narrowing in a coronary artery supplying the heart muscle. We call this symptom 'angina'. We can treat angina with tablets; but sometimes this is not enough, and so doctors can open up the narrowing by inserting a metal stent into the artery (angioplasty).

Unfortunately, some patients still have pains even after this. This may be because the pain was not caused by the narrowing in the coronary artery but is due to another cause.

Cardiologists can test whether a narrowing is restricting blood flow but there is currently no test to say that a patient's pain is actually caused by the narrowing rather than something else. As a result, cardiologists cannot tell whether angioplasty will alleviate the pain or not. This is an important problem because some patients may have unnecessary angioplasty that does not make them feel any better as the procedure cannot be expected to relieve pain that was never caused by a narrowing.

The principal aim of this study is to test whether we can identify which patients have chest pain that is truly caused by a narrowed artery. We aim to do this by assessing your symptoms when a miniature balloon is inflated in the narrowed artery to restrict blood flow immediately before you undergo angioplasty. We will determine how similar this sensation is to your usual angina. If there is a close match, we would expect you to receive good symptomatic relief from angioplasty, but if the symptom elicited is very different, it may suggest that your pain is coming from elsewhere.

The data obtained from this study will support the award of a PhD for the clinical research fellow, Christopher Rajkumar.

#### **What are the findings and implications of previous trials?**

This study follows on from the ORBITA-1 study which was published by our research group in The Lancet. ORBITA-1 was the first trial to assess the difference in exercise time and symptoms with angioplasty compared a placebo procedure (a pretend procedure with all the

steps of angioplasty except the final step of opening up the artery with a stent). 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. Also, there was very little difference in symptom improvement in those patients who had angioplasty compared to those who had a placebo procedure.

One potential reason for this is that while many patients referred for angioplasty do indeed have symptoms, these symptoms are not in fact caused by the narrowed artery but are due to another cause which cannot be fixed by angioplasty.

**Why have I been chosen?**

You have been chosen because you have symptoms of angina, had an angiogram showing a narrowing in one 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. You will be provided with a smartphone application and begin daily scoring of symptoms using a visual analogue scale for 4 weeks. You will receive training on how to use the application. (If you have no symptoms during this 4 week period you will no longer be included in the trial and routine medical care will continue.)

We will offer you use of an Apple watch for the duration of the study, which you will return at the end of the study. This is so that we can collect data on your daily activity (step count, distance walked or run, and heart rate variability) before and after your angioplasty procedure. Your watch will be able to share your activity data with the study team. This data will be kept strictly confidential, stored securely, and the study team will not be able to see any other data about you other than the activity data described above. At enrolment, you will receive training on how to use the watch. If you prefer not to take part in the Apple watch activity tracking, you may still take part in all the other aspects of the study protocol.

If you are taking antianginal medications, these will be stopped when you start the trial. This is to assess your symptoms without medication. You will be asked to record your symptoms daily on the smartphone application which will be monitored daily by the research team. If you experience angina, and you find this intolerable, antianginal medication will be started by the research team.

Some antianginal medications also help to treat high blood pressure. Therefore, If you have high blood pressure you will be supplied with a home blood pressure monitor to ensure you blood pressure remains within safe limits when we stop any antianginal medications. We will ask you to record your blood pressure every day and we will monitor these readings with daily telephone calls. New medication will be started by the research team as required if your blood pressure is elevated. If the medications cause side effects they will be adjusted or stopped.

You will undergo the routine investigations required prior to angioplasty which include 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. Together these tests will take approximately 2 hours, and will be performed for all patients at Imperial College NHS Trust. If you are taking anti-anginal medications, you will need to stop them 72 hours before these tests. 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.

Four weeks after you were enrolled into the trial you will attend the catheter lab for your procedure. This will be performed at the hospital you were recruited from. We will enter the artery in your wrist or at the top of your leg with a needle. As per routine clinical practice, local anaesthetic will be used (by injection under the skin) to make the area numb. A small plastic tube called a cannula will also be inserted into a vein. Wires and a balloon will then be passed into the narrowed heart artery 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. The measurements will not prolong your recovery from the procedure.

Many patients only experience their symptom of angina when they perform exercise. For this reason, at times we may ask you to cycle on a specially designed supine bicycle whilst you are lying on the catheter laboratory table. Once you feel your sensation of angina, we will take some repeat measurements and then ask you to stop exercising and rest. If you are not able to cycle or would prefer not to, this part of the study will not be performed.

During a normal angioplasty, a miniature balloon will be inflated to expand the metal stent. This balloon inflation temporarily blocks blood flow and often causes pain. In this study we will conduct several such balloon inflations to intentionally restrict blood flow and ask you to describe the sensation in real time. We expect that if your angina was really caused by the narrowed artery, then blocking the artery should recreate your symptoms of angina. However, if the narrowed artery was not the cause of the symptoms, any symptoms you feel during the experiment would be different in nature. A unique feature of my experiment is that it will be blinded, which means sometimes we really will block the artery and other times it will only be pretend (placebo). The pain should come with the real episodes and not the pretend ones. Should you require any pain relief, this will be provided as per routine clinical practice.

After we have completed this experiment, you will have angioplasty with implantation of metal stents to treat the narrowing, just as you would have done if you had not taken part in the study.

You will then receive routine care on the cardiology ward, and have a blood test to measure cardiac troponin (a commonly measured enzyme released from the heart) three hours after the procedure is completed. The blood sample will be processed in the NHS laboratory, no further testing of this blood sample will be performed, and the sample will be destroyed in line with routine NHS practice. You will be discharged home later that day with medication.

We will then ask you to continue monitoring your symptoms via the smartphone app, and wearing the Apple watch every day for the next 6 months.

12 weeks into this period you will be invited to return to Imperial College NHS Trust 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. Once these tests are completed, the study is finished, and you will continue to have routine clinical care.

If you develop chest pain at rest at any time during the study, you should contact a member of the research team immediately (on phone number 07885587409, 24 hours a day, 7 days a week). If necessary, urgent angioplasty will be performed, and you may be withdrawn from 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 including 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. In order to administer the adenosine we will place a cannula in the arm which should not cause any discomfort.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause 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). The risk of coronary angioplasty is 1 in 100 (death, heart attack, stroke, renal impairment, need for emergency surgery). Using angioplasty balloons to restrict blood flow with inflation pressures (1-3atm) much lower than those used in standard angioplasty (15-20 atm), has been shown to be a safe and effective research technique with minimal procedural risk (Am J Cardiol. 2010;105:1716-22). Taking part in this study does not increase the risk above that of routine angioplasty. This risk is minimised as the procedure will be performed by an experienced senior consultant cardiologist.

We will place all wires and balloons under x-ray guidance; the mean effective x-ray dose from this procedure is equivalent to 13 years of natural background radiation and carries an additional lifetime cancer risk to a healthy individual of 0.1%.

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. There will be no delay in angioplasty as a result of taking part in this study.

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 artery is causing your chest pain.

**What if something goes wrong?**

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will 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 Chief Investigator (Dr Al-Lamee (Tel: 0207 594 5735). The normal National Health Service complaint mechanisms are also available to you. The Patient Advice and Liaison Service (PALS) is available at Hammersmith Hospital or by telephone: 020 3313 3322 or email: imperial.pals@nhs.net. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance 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 and by regulatory authorities, 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.

Individual data inputs into the smartphone symptom application are downloaded to our secure server based in Google Firebase which is ISO 27001:2013 compliant. Activity tracking data will be stored on the same server. Members of the research team will only have access to activity data on the apple watch. No personal data, or any other data, will be accessible to the research team at any point. This level of data security has been recommended by NHS digital National Guidance of 2018 and approved by Imperial College London Information Governance. This will be stored separately with encrypted back up to Imperial College's server.

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 will be stored for 10 years after the end of the study in accordance with the Data Protection Act 2018.

As part of this study you will be asked to complete a number of psychological questionnaires. Where your responses to these questionnaire raise concern regarding your mental health, we will discuss this with you and ask for your consent to inform your General Practitioner, or alternatively arrange referral to our trust's Mental Health team. The only circumstance in which we would break confidentiality would be if your mental health was deemed to pose a risk to yourself or others and you refused referral for specialist assessment. If this was the case, you would be informed prior to this break of confidentiality.

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and

will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you for 10 years after the study has finished in relation to data subject consent forms and primary research data. This information will be kept at your local NHS Trust. If you are recruited from Basildon and Thurrock University Hospitals NHS Foundation Trust, The Royal Free London NHS Foundation Trust, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust or Royal Berkshire NHS Foundation Trust some identifiable information will also be kept at Imperial College Healthcare NHS Trust.

Further information on Imperial College London's retention periods may be found at <https://www.imperial.ac.uk/media/imperial-college/administration-and-support-services/records-and-archives/public/RetentionSchedule.pdf>

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information from the Chief Investigator Dr. Al-Lamee (Tel: 0207 594 5735).

## **LEGAL BASIS**

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

## **INTERNATIONAL TRANSFERS**

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

## **CONTACT US**

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London's Data Protection Officer via email at [dpo@imperial.ac.uk](mailto:dpo@imperial.ac.uk), via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The

ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

**For Imperial College Healthcare NHS Trust Patients:**

- Imperial College Healthcare NHS Trust will collect information from you and your medical records for this research study in accordance with our instructions. Imperial College Healthcare NHS Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. Imperial College Healthcare NHS Trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

**For Basildon and Thurrock University Hospitals NHS Trust Patients:**

- Imperial College Healthcare NHS Trust and Basildon and Thurrock University Hospitals NHS Foundation Trust will collect information from you and your medical records for this research study in accordance with our instructions. Imperial College Healthcare NHS Trust and Basildon and Thurrock University Hospitals NHS Foundation Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. Imperial College Healthcare NHS Trust and Basildon and Thurrock University Hospitals NHS Foundation Trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

**For Royal Free London NHS Foundation Trust Patients:**

- Imperial College Healthcare NHS Trust and The Royal Free London NHS Foundation Trust will collect information from you and your medical records for this research study in accordance with our instructions. Imperial College Healthcare NHS Trust and Royal Free London NHS Foundation Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. Imperial College Healthcare NHS Trust and The Royal Free London NHS Foundation Trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

**For Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust Patients:**

- Imperial College Healthcare NHS Trust and The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust will collect information from you and your medical records for this research study in accordance with our instructions. Imperial College Healthcare NHS Trust and Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. Imperial College Healthcare NHS Trust and Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

**For Royal Berkshire NHS Foundation Trust Patients:**

- Imperial College Healthcare NHS Trust and Royal Berkshire NHS Foundation Trust will collect information from you and your medical records for this research study in

accordance with our instructions. Imperial College Healthcare NHS Trust and Royal Berkshire NHS Foundation Trust will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. Imperial College Healthcare NHS Trust and Royal Berkshire NHS Foundation Trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

Certain individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Imperial College London will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Study participants will be asked to allow anonymised data collected in this study to be used in future ethically approved research. This is optional. Participants will also be asked whether they consent to be contacted about participation in future research studies, and this is also optional.

**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 form the basis of a PhD research programme for Dr Christopher Rajkumar. 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 the Medical Research Council

**Who has reviewed the study?**

This study has been reviewed and given a favourable ethical opinion by the Local Research Ethics Committee.

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](mailto:christopher.rajkumar@nhs.net)

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

**GP Information Sheet**

**Date:**

Dear Doctor,

**Re:**

**Name:**

**DOB:**

**Address:**

Your above named patient has agreed to participate in the following research study:

**Is there a difference between clinical angina and experimentally inducible angina? A placebo-controlled experiment on symptoms in stable coronary artery disease**

Chief investigator: Dr Rasha Al-Lamee

**Background and Aims**

The first double-blinded randomised placebo-controlled trial of PCI in stable angina (ORBITA) was published in *The Lancet* in 2018. It showed that PCI was no more effective than a placebo procedure in improving treadmill exercise time or symptoms of angina.

One interpretation of this is that we cannot assume that all chest pain reported by a patient with a severe coronary stenosis and ischaemia is in fact angina. During angioplasty, we inflate a miniature balloon across a coronary stenosis; this impedes blood flow and often causes pain. In this study, we will assess the degree of match between a patient's day-to-day experience of angina, and the symptom elicited with balloon inflation across their stenosis. In order to assess this accurately, we will stop the patient's antianginal medications during this study.

We predict that if there is a close match, it would provide a strong reason to believe that the symptoms are indeed caused by the coronary stenosis and relief of the stenosis with stents would lead to improvement of the patient's symptoms. On the contrary, if there is little match, it may suggest that the symptoms were not caused by the stenosis to begin with.

**What is involved for your patient**

Patients will be enrolled after coronary angiography demonstrating severe single vessel coronary artery disease. During enrolment they will have a clinical assessment and complete a number of questionnaires. Their antianginal medications will be stopped at the start of the

study. They will be provided with a smartphone application and begin daily scoring of symptoms for 4 weeks. They will also be offered an Apple watch for daily activity tracking for the duration of the study.

The data will be monitored daily by the research team. If required, antianginal medications will be initiated from a pre-specified panel. For patients with hypertension, blood pressure will be monitored daily using a home blood pressure machine supplied by the study team. Blood pressure readings will be monitored by the research team. Medications will be restarted as required. If patients do not tolerate the medications due to side effects, they will be adjusted or stopped as required.

Patients will attend Imperial College NHS Trust for a resting ECG, exercise ECG and Dobutamine Stress Echocardiogram. They will then start taking 2 anti-platelet medications (aspirin and either clopidogrel, ticagrelor or prasugrel) unless already on them in which case they should continue taking them. If they are at high risk of adverse gastrointestinal (GI) effects (based on previous GI ulceration, age, concomitant medications that increase risk) they will also be started on a proton pump inhibitor, lansoprazole, in accordance with NICE guidance on Gastro-oesophageal reflux disease and dyspepsia in adults (CG184). Aspirin will be continued lifelong. The second antiplatelet medication will be continued for 1 year after stent.

Patients will undergo invasive assessment 1 week later at their recruiting (local) hospital. This is not a clinical trial, and there is no randomisation between treatment arms. All patients will receive clinically indicated percutaneous coronary intervention (PCI) including stent implantation at the end of the invasive protocol.

During the invasive assessment, the patient will undergo 5 pairs of episodes consisting of either real or placebo balloon inflation across their coronary stenosis. We will be assessing their symptoms during these episodes. Practically, they are likely to experience 5 short-lived episodes of chest pain and will be on the catheter laboratory table for 30 minutes of excess procedure time. Following completion of this invasive procedure, all patients will proceed immediately to clinically indicated PCI including stent implantation.

Patients will be discharged on the same day as their procedure and continue to document their symptoms using the smartphone app for a further 6 months. Patients will return for a follow-up visit at Imperial College NHS Trust 12 weeks into this period. At this stage we will repeat the dobutamine stress echocardiography, exercise ECG and clinical questionnaire set. Patients will then return to routine clinical care.

All of the information that we take will be pseudonymised.

The patients have been given an information sheet explaining the study further.

### **Potential Benefits**

This study will not benefit your patient directly. We expect that the information that we gain from this study will however contribute to improvements in the management of patients with stable angina.

### **Potential Side effects**

At the coronary angiogram/angioplasty procedure the additional measurements that we will be making will slightly increase the radiation dose of the coronary angioplasty study that your

patient will be having anyway. Although all radiation exposure can increase the risk of harmful long-term effects, the total dose will still be significantly lower than a cardiac CT scan.

We will be passing a pressure measurement wire which can rarely lead to coronary artery dissection. However the procedure will be performed by experienced interventional cardiologists who are experienced in handling these wires will be performing the procedures. In the event of coronary artery dissection, patients will exit the study and go on to receive coronary angioplasty.

**Adverse events and further information**

I would be grateful if you could report any adverse events to me on the address below.

No medications are specifically prohibited during the trial. Please contact us if you have any questions about the medications. Patients can also contact us if they have any questions.

Please do not hesitate to contact us for any further information on the following address:

Dr Rasha Al-Lamee and Dr Christopher Rajkumar  
International Centre for Circulatory Health  
NHLI, 2<sup>nd</sup> Floor, B Block  
Hammersmith Hospital  
London  
W12 0NN

Telephone 0207 594 5735 / 07885587409

Email [r.allamee13@imperial.ac.uk](mailto:r.allamee13@imperial.ac.uk), [christopher.rajkumar@nhs.net](mailto:christopher.rajkumar@nhs.net)