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

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Abstract

Percutaneous coronary intervention (PCI) is widely believed to reduce angina in stable coronary artery disease but this has never been tested in a blinded randomised controlled trial. Such a study design exposed another highly credible therapy, renal denervation for hypertension, to be far less efficacious than unblinded evidence suggested.

The results of Simplicity HTN3 study highlighted the placebo effects of interventional procedures, and there is increasing recognition for the need for placebo-controlled studies to investigate the effects of interventional therapies. The evidence for PCI in stable coronary artery disease in the reduction of myocardial infarction and mortality remains uncertain. The remit of coronary intervention in this setting may primarily be to offer symptom relief and improvement in quality of life. However, the clinical effects of PCI for these goals will be contributed to by both a true physical and a placebo component. The magnitude of the placebo-controlled effect of PCI on symptoms and exercise capacity has never been tested before.

In order to scientifically address this question a double blind trial of coronary angioplasty versus a placebo procedure in patients with stable coronary artery disease was required. I designed, conducted and led the first placebo-controlled trial of PCI in stable coronary artery disease. In this thesis I will present the primary and secondary outcomes from the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial. I will also present the results of subsequent analyses stratifying the results of ORBITA by pre-randomisation invasive physiology using fractional flow reserve and instantaneous wave-free ratio and by pre-randomisation dobutamine stress echocardiography score. The results of this trial may have far-reaching consequences for the management of stable angina.

Declaration of Originality

For this thesis I designed and conducted the ORBITA trial. I formulated the research questions and hypotheses and wrote the trial protocol. I then applied for ethical and R&D approval, coordinated the site-specific assessments and contracting for each site. I attended the ethics meeting and made all ethical amendments. I designed the online case report form, the dobutamine stress echocardiography reporting tool and wrote all standardised operating protocols. I registered the trial with clinicaltrials.org and made all amendments to the online form. I applied for Clinical Research Network approval and filed all recruitment updates.

I coordinated and led the trial throughout. I recruited all of the patients enrolled in the trial and conducted the medical optimisation for all patients. At Imperial College London and Essex CTC I conducted the enrollment visit and tests for all patients. I was the unblinded interventional cardiologist recording all invasive physiology measurements at every research angiogram at each of the 5 sites. At these procedures I led the research case, randomised every patient and ensured that blinding was maintained. The follow-up assessment was conducted by a blinded researcher and physiologist. After this assessment I performed unblinding of all patients.

I presented all adverse events at the Data Safety Monitoring Board meetings. I presented all clinical trial updates at the Trial Steering Committee meetings. An independent statistician performed the primary analysis. For all secondary analyses I performed the statistical analysis with another statistician. I then synthesised all of the data and was the lead author for all subsequent papers and publications to date. I have presented all late breaking clinical trial presentations at scientific congresses and was the first author on the primary and secondary manuscripts published in The Lancet and Circulation respectively.

I hereby declare that the work presented in this thesis is my own and all else is referenced appropriately.

Rasha Kadem Al-Lamee

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Dedication

I dedicate this thesis to the most important people in my life.

My husband, Pete, who has never stopped being my greatest fan and who has supported me throughout my career. You have helped me to reach my greatest potential and have never wavered in your love and encouragement.

My wonderful son, Laith, who was with me in the catheter laboratory even before he was born and has grown up watching his mother hard at work. Even though I haven't been there at the school gates as much as I might have liked, you always made me feel that you are proud of me. More importantly, I grow prouder of you every single day as you grow up to be an amazing young boy.

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List of Abbreviations

PCI = Percutaneous coronary intervention

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

CAD = Coronary artery disease

ACS = Acute coronary syndrome

MI = Myocardial infarction

CABG = Coronary artery bypass graft surgery

COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation

ISCHEMIA = International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

OMT = Optimum medical therapy

FAME 2 = Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2

ECG = Electrocardiograph

CPET= Cardiopulmonary exercise testing

DSE = Dobutamine stress echocardiography

FFR = Fractional flow reserve

iFR = Instantaneous wave-free ratio

CCS = Canadian Cardiovascular Society class

DSMB = Data safety monitoring board

QCA = Quantitative coronary angiography

OD = once daily

BD = twice daily

ACEI = Angiotensin converting enzyme inhibitor

ARB = Aldosterone receptor blocker

CI = Confidence intervals

SD = Standard deviation

IQR = Interquartile range

IV = Intravenous

MARISA = Monotherapy Assessment of Ranolazine In Stable Angina

BMI = Body mass index

LV = Left ventricle

BP = Blood pressure

LAD = Left anterior descending

RCA = Right coronary artery

Cx = Circumflex

OM1 = First obtuse marginal

D1 = First Diagonal

IM = Intermediate

HDL = High-density lipoprotein

LDL = Low-density lipoprotein

ACME = Angioplasty Compared to MEdicine

RITA-2 = Randomised Intervention Treatment of Angina 2

MASS-II = Medicine, Angioplasty, or Surgery Study II

ETT = Exercise tolerance test

MIBI = Nuclear medicine myocardial perfusion scan

MRI = Magnetic resonance imaging

CCS = Canadian Cardiovascular Society

1 Introduction

1.1 Stable coronary artery disease

Coronary artery disease (CAD) is a leading cause of mortality in the UK, accounting for 82,000 deaths each year. In the UK, 2.7 million people have CAD and 2 million people are affected by symptoms of angina.[1] The annual mortality rate in patients with stable CAD is 1.5% per year and rises to 3% per annum in the presence of significant levels of myocardial ischaemia.[2,3] Stable angina remains the commonest clinical symptom of CAD worldwide.[4] It is associated with significant morbidity in terms of primary care consultations and hospital admissions with a significant impact on the quality of life of patients with CAD and significant costs for the healthcare system.[5]

1.2 Percutaneous coronary intervention in stable coronary artery disease

While definitive evidence-based data have shown that percutaneous coronary intervention (PCI) in the setting of acute coronary syndrome (ACS) reduces death and subsequent myocardial infarction (MI)[6], the evidence for the best treatment in stable CAD is less clear.

At the outset PCI was developed to improve quality of life and symptoms of CAD. However, in recent years this indication has seemingly been forgotten as multiple studies have compared the mortality and MI rates with PCI when compared against either coronary artery bypass graft surgery (CABG) or medical therapy. The focus shifted from symptomatic relief to considering PCI to be efficacious in preventing the sequela of CAD in terms of MI, left ventricular dysfunction and death. Whilst this focus on outcomes was important, by neglecting to explore the original reasons for the development of PCI, *namely angina relief*, the negative results of large randomised outcome trials[7] led to the use of PCI for this condition being questioned.[8] The lack of evidence that PCI improved long terms outcomes and led to the pendulum swinging away from PCI as the primary treatment for stable angina with the guidelines recommending risk factor modification and anti-anginal therapy as first line treatment for this condition.[9] Whilst this may be appropriate from the evidence base, it ignores the fact that millions of patients continue to live daily with the

symptoms of stable angina, for many reasons including poor medication compliance and drug side effects.[10] For these patients angina relief is the primary remit of PCI and requires further study for this endpoint.

1.3 Percutaneous coronary intervention for prevention of mortality and myocardial infarction

A number of randomised studies were developed to compare clinical outcomes following PCI versus medical therapy with conflicting results.[11-14] The results led to disheartened interventional Cardiologists when they did not come out in favour of PCI.[11,12,15,16] Low event rates with good medical therapy meant that initial trials focusing on death or MI showed no reduction in events in the PCI arm,[11,12,16,17] although subsequent trials,[18] sub-analysis[19] and meta-analyses focusing on patients with objective evidence of myocardial ischaemia have given conflicting results[15,20]. It took a published network meta-analysis of over 93 thousand patients to suggest survival benefit following PCI with new generation drug eluting stents by a chain of indirect comparisons.[21]

In retrospect it is perhaps unsurprising that PCI did lead to MI reduction or survival benefit in previous trials given that the event rate in stable CAD is relatively low with combined cardiac mortality and MI rates of up to 2.3% annually in observational studies[4] and 1.9% in randomised controlled trials;[22,23] therefore even the largest study the Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation (COURAGE) of 2287 patients was underpowered to detect a modest but clinically important difference in event rates.[11] Whilst the large network meta-analysis suggested PCI may be superior to medical therapy alone[21] the answer to this question must ideally be answered by a much large randomised controlled trial.

The need for such as study formed the basis for the design of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, which has enrolled over 5179 patients worldwide (NCT01471522). However, even this study may be inadequately powered. Indeed, the initial sample size calculation for ISCHEMIA stated that 8000 patients was necessary to answer the question but due to recruitment pressures the recruitment goal was

changed over time with enrollment completed at 5179 patients. Furthermore, using conservative estimates of an event rate of 2% mortality annually and for a risk reduction of 10% following PCI, a randomised controlled trial would actually need to enroll over 150,000 patients to be sufficiently powered to assess a difference in mortality between PCI and medical therapy.

1.4 Percutaneous coronary intervention for symptomatic relief

Angina has a significant impact on quality of life[24,25] and costs to society.[26] The main reason to perform PCI in stable angina is to offer symptom reduction and improvement in quality of life to our patients. Previous unblinded trials have reported angina relief in patients receiving PCI.[12-14,25] These outcomes are important to patients regardless of the long-term impact on MI or death. Even if current evidence suggests clinical equipoise for MI and mortality between PCI and medical therapy,[27] if PCI could be shown to offer clear objective gains in the improvement in symptoms and quality of life many patients may still opt for PCI instead of long term anti-anginal therapy.

1.5 Is medical therapy truly a viable alternative?

While guidelines recommend optimisation of medical therapy as the first line in the treatment of stable CAD,[21,27-29] this may not always be practical for patients and physicians. It is well recognised that adherence to medical therapy is an issue in all medical conditions. It is particularly evident in chronic conditions, such as diabetics in which up to 50% of patients demonstrate poor adherence rates.[30] Even in randomised controlled trials average adherence rates range from 43 to 78%.[31] Compliance rates in stable CAD have not been studied, however less than half the patients in COURAGE met the pre-specified risk factor treatment goals of the trial.[32] Even post lung and heart transplantation drug non-adherence rates range from 1 to 43%.[33] If these poor compliance rates are seen in the context of meticulously conducted clinical research with the full armamentarium of research resources, what is the best we can expect in the real world?

Whilst it is correct that guidelines for the treatment of stable angina state that medical therapy must be first line, this data is based on the current evidence base showing clinical equipoise for hard endpoints between PCI and medical therapy. Given all we know about drug compliance and tolerability should PCI be the primary therapy we offer our patients for angina relief? Many patients may still prefer to choose an upfront procedure with low potential risk to avoid long term anti-anginal therapy with its associated side effects.

1.6 Why was a placebo-controlled trial needed?

Prior to adoption of any diagnostic or therapeutic procedure it is essential to ensure that we are delivering best practice for our patients. To this end there are many questions that need to be answered. Firstly, what is the potential benefit from the procedure? Secondly, what are potential risks of the procedure? Thirdly, is it universally effective or does it only work for selected patients based on certain criteria? And finally, what is the best way to evaluate the therapy?

Unblinded randomised trials have shown significant angina relief and quality of life improvement from PCI.[16,18,21,25,34] However, symptomatic responses are (necessarily) subjective and contain both the true physical effect and the placebo effect.[35] Moreover, in an open trial, if patients randomised to no PCI have an expectation that PCI is advantageous, this may colour their reporting (and the physicians' interpretation) of symptoms, artifactually increasing the rate of unplanned revascularisation in the control arm. [18,36]

Placebo effects are known to be larger for invasive than non-invasive treatments.[37] Interventional cardiologists and patients with stable angina have a pre-conception that PCI offers symptomatic relief.[38] [39] Additionally, cardiologists often present a decisive approach to diagnosis and treatment which can lead to a greater placebo effect.[40] In the absence of blinding, the effect size of PCI on symptomatic endpoints may be overestimated due to the addition of the placebo effect to the true physiological effect of intervention.[41] Since in all previous trials, both investigators and patients were

aware of the treatment allocation,[11,18] the contribution of placebo effect has never been quantified.

Cardiologists are resistant to conducting a placebo-controlled trial of angina relief from PCI for two main reasons. The first is the widespread perception that PCI unquestionably improves angina.[42] Though this is only based on unblinded clinical experience. The second reason is that they have a perception that it would be unethical to expose patients to an invasive placebo procedure. However, a systematic review of placebo-controlled surgical trials has shown no evidence of harm to placebo groups.[43]

When offering an invasive intervention such as PCI to a relatively low risk population group for whom therapy is aimed at delivering symptom relief, functional improvement, reduction in drug use and improved quality of life, knowledge of the true physical effect of the therapy is essential. A risk to benefit analysis must be made, particularly as an alternative in the form of medical therapy exists. In order to make an accurate assessment, the placebo-resistant efficacy of PCI is required. Moreover while PCI is an extremely safe procedure, it is not without risk with complication rates in the current era of 1 to 2%.[44] Additionally PCI in stable angina is not universally effective with refractory angina in 5 to 15% of patients with stable CAD.[45,46] Furthermore the effect size is variable and a continuum with attenuation in the incremental benefit of angina relief is seen over time.[34]

All previous stable angina trials have been open label, and skeptics have rightly pointed to the substantial risk of bias to overstate effects.[47] Leaders in medical and interventional Cardiology provided timely and well-argued call for trials designed to eliminate this bias by using a placebo procedure for the control when assessing medical devices and in particular assessing the benefits of PCI to angina relief in the treatment of stable CAD.[48,49]

The need for placebo-control was most recently illustrated by the Symplicity HTN3 study which tested the effects of renal denervation therapy against placebo.[50] The existence of a control arm and the presence of blinding, led to the blinded effect size

being much smaller than with previous unblinded trials that were prone to inadvertent bias.[51-53]

Within cardiology, previous blinded trials of left internal mammary ligation and laser myocardial revascularisation led to both procedures both abandoned as therapies for stable angina when placebo-controlled trials showed lack of efficacy[54,55] (Table 1.1). In non-cardiac specialties, other therapies such as knee arthroscopy for osteoarthritis[56] and vertebroplasty for painful osteoporotic vertebral fractures[57] were found to have no significant benefit compared to a placebo procedure. Placebo-controlled trials of surgery have often provided insightful data for therapies that were considered clinically effective. Despite this knowledge they remain an exception for interventional procedures when compared to drug trials where they are the gold standard.

Both Redberg[48] and King et al[49] described issues associated with non-placebo controlled trials, which are magnified when assessing more subjective clinical endpoints. Therefore, with the controversy over the potential inappropriate use of PCI for stable CAD, and the well-documented tendency of open-label studies to overstate effect sizes, a placebo-controlled PCI study was necessary and indeed had started enrollment prior to these well-timed editorials.

Cardiologists in clinical practice need clear, bias-resistant data on the true (beyond-placebo) efficacy of PCI in relieving angina, and whether there are patients who benefit more than others. To correctly answer the question of whether PCI improves the symptoms and functional capacity of patients with stable angina over and above optimum medical therapy (OMT), a double-blinded comparison with a placebo-control arm and both patients and investigators having no knowledge of the treatment arm allocation was absolutely paramount.

The ORBITA trial is the first blinded comparison of PCI versus placebo treatment on a background of OMT. It is therefore a unique trial designed to address one of the most important unanswered questions in clinical medicine, “What is the placebo-

controlled efficacy of PCI for symptom and functional capacity improvement in stable CAD?"

1.7 "Placebo" or "sham"?

For pharmacotherapy we have long recognised that therapies that have subjective goals such as symptom relief can only be validly evaluated against placebo. Why is that we do not apply the same gold standard to the assessment of interventional procedures?

Sham-control is often used to describe the control arm of a placebo-controlled trial of an interventional therapy. However, the definition of sham is "bogus or false" leading to our community's reservation in applying its use as the control arm of interventional studies. In order to apply the rigorous blinded methodology of drug trials to studies of interventional procedures, the terminology should be necessarily aligned and therefore we should refer to placebo-controlled rather than sham-controlled trials of intervention.

When the blinded Simplicity-3 HTN study showed a very small effect size for renal denervation, it was a painful reminder that even the consensus of hundreds of experts, based on dozens of well powered but unblinded trials, can be completely incorrect. It could be asked, "Who had the sham? The denervation arm or the control arm?"

1.8 Ischaemic burden and clinical outcomes

Scientifically it seems logical that the level of ischaemic burden may be associated with clinical outcomes. However, the data on this subject remains unclear. Earlier studies showed that in order to obtain a survival benefit of revascularisation over and above medical therapy, greater than 10% of the myocardium needed to be ischemic.[2] However, this was based on observational data assessing difference in outcomes at a range of levels of ischaemia assessed by myocardial perfusion imaging with patients allocated to 2 groups depending on whether or not intervention was performed. As the data were not randomised, it was confounded by the fact that the risk profile of the

patients in the medical therapy group may have been significantly greater than those in the early revascularisation group. Additionally, we do not know if those patients in the medical therapy group were suitable for intervention or if the reason they received medical therapy because revascularization was not an option. Indeed, the medical therapy arm consisted of 9956 patients while the revascularisation group was only made up of 671 patients suggesting significant selection bias that may have affected the results.

The first nuclear sub-study of the COURAGE trial is often misquoted as showing that survival improvement following PCI was greatest in those patients with the greatest ischemic burden at baseline and the most significant reduction in ischemia following PCI.[19] However, this is not the correct interpretation of these data. Firstly, it was a small post-hoc study which included only those patients from COURAGE who had 2 consecutive myocardial perfusion scans before randomisation and at 6 to 18 months follow-up. Secondly, while data showed greater ischaemia reduction in the PCI group compared to the control group (33% vs. 19%, p=0.0004), there was still a level of ischaemia reduction in the control group. Thirdly, although patients with ischaemia had lower unadjusted risk of myocardial infarction or death, the difference for both endpoints became non-significant once it was adjusted for risk.

The second nuclear sub-study of COURAGE had clearer conclusions.[19] 1381 patients who had baseline stress myocardial perfusion imaging prior to randomisation were included. Mild ischemia was defined as <3 ischaemic segments and moderate to severe ischaemia defined at ≥3 ischaemic segments. At baseline the proportion of patients with moderate to severe ischaemia was similar between PCI and medical therapy arms (p=0.36). There was no difference at follow-up for the primary endpoint of death or MI or in the number of patients with moderate to severe ischaemia. Therefore, the level of ischaemia did not predict long term outcomes in this analysis.

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial is also often quoted as showing long term benefits from PCI in patients with evidence of ischaemia on invasive physiology defined as FFR≤0.80.[14] The primary endpoint of FAME 2 was a composite of urgent revascularisation, MI

and death. The trial was halted early as the data safety monitoring board felt there was an imbalance of urgent revascularisation events in the control group. Unfortunately, over 50% of these events were caused by presentation with chest pain in the absence of cardiac enzyme rise or electrocardiograph (ECG) changes, therefore an increase in the number of chest pain events as a result of the unblinded knowledge that a physiological significant lesion had been left untreated in the control arm cannot be excluded. It is likely that lack of blinding may have caused some of these unplanned revascularisation events. In the 2-year follow-up analysis of FAME-2 the statistical methodology was changed to add in a landmark analysis in which events in the first 7 days post-procedure were excluded.[18] This resulted in lower rates of death or MI in the PCI group than the medical therapy group but, as a secondary analysis using statistical methods that were not pre-specified, there are limitations in drawing conclusions from this analysis.

Therefore, while it theoretically seems likely that those patients with the highest ischemic burden at baseline will have the greatest improvement in symptoms, MI and death rates following PCI, the data on this subject is not without limitations and requires further study.

1.9 Addressing the need for sham control

The ORBITA trial aimed to address the lack of blinding and placebo control in clinical trials comparing PCI to medical therapy. ORBITA is the first double blind randomised controlled trial of PCI versus placebo in the treatment of stable angina (NCT02062593).[58]

The study was designed around the fundamental principle of blinding, with both investigators and participants unaware of treatment arm allocation and to this end the control arm included a placebo angioplasty procedure. In designing the trial we also aimed to avoid the pitfalls of previous trials in which the results may have been affected by under-representation of higher risk coronary lesions,[11] incomplete revascularisation in multi-vessel disease,[59] low levels of attainment of medical therapy targets,[32] subjective assessment of functional capacity solely using qualitative

questionnaire data[25] and outdated PCI techniques.[11,12,17] To this end the trial period was relatively short at 12 weeks to encourage the recruitment of severe lesions. The enrollment criteria were restricted to single vessel coronary artery disease to ensure complete revascularisation. The protocol included an intensive medical optimisation phase to meet guideline standards. An objective primary endpoint was selected to be a change in treadmill exercise time with secondary endpoints including patient-reported and physician-assessed symptoms and quality of life. Drug eluting stents were mandated for PCI with blinded invasive physiology measured post-procedure.

Table 1.1: Summary of placebo-controlled trials of intervention in stable angina

Study	Treatment	Control	Sample size	Exercise time endpoints	Difference between active and placebo arms
Cobb et al, NEJM 1959[54]	Internal mammary ligation n=8	Placebo procedure n=9	17	Pre-post-difference in exercise time on treadmill	+1.0min v. +0.3 min, i.e. numerical difference between arms of **0.7min ≈42s**
Stone et al, JACC 2002[60]	Transmyocardial laser revascularisation in non-recanalisable chronic total occlusions n= 71	Placebo procedure in non-recanalisable chronic total occlusions n=70	141	Pre-post-difference in exercise time on treadmill	+64s v. +52s (p=0.73), i.e. numerical difference between arms of **7s**
Salem et al, AJC 2004[61]	Percutaneous myocardial laser revascularisation n=40	Placebo procedure n=42	82	Final exercise time on treadmill	620s v. 604s (p>0.1), i.e. numerical difference between arms of **16s**
Leon et al, JACC 2005[55]	Laser myocardial revascularisation: High dose n=98 Low dose n=98	Placebo procedure n=102	298	Final exercise time on treadmill	431.2s (high dose) v. 425.7s (low dose) v. 395.3s (placebo) (p=0.334), i.e. numerical difference between high dose and placebo of **35.9s**
Verheye et al, NEJM 2015[62]	Coronary sinus reducing device n=52	Placebo procedure n=52	104	Pre-post-difference in exercise time on treadmill	+59s v. +4s (p=0.07), i.e. numerical difference between high dose and placebo of **54s**

1.10 Aims of this thesis

Despite four decades of PCI for stable CAD with a primary indication of symptomatic relief, the efficacy of PCI had never been tested in a placebo-controlled trial. The clinical benefit we see from PCI in this condition will contain a contribution of both a true physical effect and a placebo component. The magnitude of the former has never been quantified in a blinded trial.

In this thesis I report the efficacy of PCI on exercise capacity, symptomatic relief and changes in the functional assessment of ischaemia from the placebo-controlled ORBITA trial.

I use the results of ORBITA to help to address unanswered questions regarding PCI for the treatment of stable CAD. This thesis will focus on three main questions. Firstly, does PCI produce an improvement in functional capacity in patients taking optimum medical therapy? Secondly, can invasive physiology at baseline predict the change in functional capacity gained from PCI? Thirdly, can non-invasive ischaemic assessment using stress echocardiography at baseline predict changes following placebo-controlled PCI?

Most importantly, this data will provide a framework for other interventional studies testing the efficacy of therapy using placebo-control as is the gold standard for drug trials.

1.11 Principal research questions

1. What is the incremental effect of PCI over placebo procedure on the objective exercise capacity of patients with stable angina on OMT?

2. What is the relationship between the degree of incremental improvement in objective exercise capacity from PCI and non-invasive and invasive physiological measures of myocardial ischaemia?

3. Which non-invasive and invasive measures of ischaemia can be used to predict incremental changes in objective exercise capacity from PCI versus placebo?

1.12 Rationale for ORBITA

All previous studies comparing PCI to OMT in the treatment of stable angina have been unblinded with no placebo arm for comparison. Under such conditions the effects of potential investigator and participant bias cannot be excluded. The ORBITA trial was designed to assess the degree of functional improvement with PCI when compared to the effects of a placebo procedure.

There are no blinded data on changes in symptoms and functional capacity following PCI when compared to OMT. Functional capacity greatly affects quality of life and therefore a study to assess the efficacy of PCI for this primary outcome could have significant implications for treatment in stable CAD.

1.13 Study hypotheses

1.13.1 Hypothesis 1:

Under bias-resistant blinded measurement conditions, PCI increases objective exercise capacity more than placebo procedure, with both groups receiving OMT.

1.13.2 Hypothesis 2:

The stenting-induced increment in exercise capacity is related to the severity of ischaemia assessed at pre-randomisation using:

(1) Invasive physiological measures
(2) Dobutamine stress echocardiography

(The stenting-induced increment is defined the increment seen in the PCI group minus the increment seen in the placebo group.)

2 Materials and Methods

2.1 Design

ORBITA was a UK-based, multi-centre, prospective, randomised trial comparing the efficacy of PCI versus placebo in patients with single vessel coronary disease on a background of OMT. An overview of the study design is seen in Figure 2.1.

2.2 Setting

Patients were recruited a five study sites in the UK: Imperial College Healthcare NHS Trust, Basildon and Thurrock University Hospitals NHS Trust, Royal Bournemouth and Christchurch Hospitals NHS Trust, East Sussex Healthcare NHS Trust and Royal Devon and Exeter University Hospitals NHS trust.

2.3 Population

Patients eligible for the trial were aged ≥18 years with symptoms of angina or equivalent symptoms and at least one angiographically significant lesion ≥70% in a single vessel that was suitable for PCI with drug eluting stents (Table 2.1). These patients were clinically eligible for PCI.

Exclusion criteria included angiographic stenosis ≥50% in non-target vessel, acute coronary syndrome, previous coronary artery bypass graft surgery, left main stem disease, severe valvular disease, severe left ventricular dysfunction, contra-indications to drug eluting stents, chronic total occlusion, life expectancy <2 years, age <18 years or >85 years and inability to consent (Table 2.2).

The London Central Research Ethics Committee (reference 12/LO/1340) approved the study. All patients were screened following diagnostic angiography. Following informed and written consent they were enrolled into the study. The details of those patients who provide consent but later withdrew from the study prior to randomisation were recorded.

2.4 Study interventions

2.4.1 Enrollment

At enrollment patients completed the validated Seattle Angina Questionnaire[63], Rose angina questionnaire[64], International Physical Activity Questionnaire[65] and EuroQOL EQ-5D-5L questionnaire[66]. Patients had baseline ECG and pulse, blood pressure, height and weight measurements recorded. They also had physician assessment of their angina severity using Canadian Cardiovascular Society class (CCS).

2.4.2 Medical therapy optimisation phase

Patients then entered into the medical therapy optimisation phase of the protocol in which they had telephone review 2 to 3 times per week by a physician. During these consultations, symptom burden, blood pressure and pulse measurements were assessed. Blood pressure and pulse recordings were made by patients at home using the Omron M6 monitor (Omron, Kyoto, Japan) with the focus to introduce and up-titrate secondary prevention and anti-anginal medications (Table 2.3).

2.4.3 Pre-randomisation assessment

After six weeks of medication up-titration, patients attended Imperial College London for pre-randomisation assessment of symptoms, quality of life, exercise capacity and non-invasive assessment of ischaemia. At this stage they had all angina and quality of life questionnaires repeated and had blood investigations for brain natriuretic peptide and high-sensitivity troponin pre-exercise. They then went onto have cardiopulmonary exercise testing (CPET) using a smoothed modified Bruce protocol on full medical therapy including rate-controlling agents. Three hours post-exercise brain natriuretic peptide and high-sensitivity troponin were repeated. After this assessment patients went onto have dobutamine stress echocardiography (DSE). Dual antiplatelet therapy was started at this stage where not already prescribed.

2.4.4 Cardiopulmonary exercise testing

To provide a full spread of values rather than preferential clustering at three minute stages, a smoothed Bruce treadmill protocol[67] was used. This provided broad equivalence to a standard modified Bruce protocol but with the steps broken down into 15-second increments.

2.4.5 Dobutamine stress echocardiography

An online tool was used for DSE reporting (Figure 2.2). The 17-segment left ventricle segmentation model was used to score regional wall motion. Wall motion was scored at rest, peak stress and recovery during a dobutamine infusion and was quantified as 1-normal, 2-hypokinetic, 3-akinetic, 4-dyskinetic, 5-aneurysmal. To quantify the wall motion index the sum of the wall motion scores of the individual myocardial segments was divided by the number of segments (n=17) to provide a wall motion index score.

2.5 Randomisation

2.5.1 Coronary angiography +/- angioplasty procedure

Coronary angiography was performed via radial or femoral arterial approach. An additional femoral venous line was inserted for administration of intravenous adenosine for measurement of fractional flow reserve (FFR). To ensure blinding of treatment arm allocation, patients wore over-the-ear headphones and listened to music throughout the procedure. Invasive physiological assessment of the target vessel was performed as has been previously described using FFR[68] and instantaneous wave-free ratio (iFR)[69]. Invasive physiological assessment was performed with the clinical operator blinded to the results, as follows. The clinical operator, in all cases a consultant interventional cardiologist experienced in physiology measures, positioned the pressure wire radiographically but was not able to see the physiology display. A separate research interventional cardiologist observed the physiology display to confirm signal quality and document the values digitally but did not convey the physiology values to the clinical operator.

The reason to keep the clinical operator blinded to the physiology measures was to enable patients with a range of values to be randomised in a single trial, with all decision making and outcome assessment identical regardless of physiological value. This distinguishes ORBITA from previous evaluations of physiology in which patients above FFR 0.75 were evaluated in one unblinded trial with one protocol for outcome assessment,[70] and those with FFR 0.80 or below were assessed in another unblinded trial with a different protocol for outcome assessment.[18]

After administration of intracoronary nitrate and normalisation of the pressure wire, FFR and iFR were measured using standard techniques with the wire placed at least 3 vessel diameters distal to the most distal stenosis. Three consecutive iFR measurements were made. Intravenous (IV) adenosine was then administered (140mcg/kg/min) via a femoral venous line or antecubital fossa vein and FFR was measured. Drift check was recorded.

The operator then waited for 10 minutes. Intracoronary nitrate was re-administered, the wire was re-normalised and re-advanced into the same distal position using cine images from the first physiological assessment as a guide. A second set of 3 iFR measurements were taken. Intravenous adenosine was then re-administered and repeat FFR measurement made. Drift check was once again performed.

If at any stage there was significant wire drift (PdPa ratio outside the range 1.00±0.02), the wire was re-normalised and iFR and FFR measurements were repeated with final drift check.

In ORBITA, the research iFR value was defined as the average of all 6 iFR readings. The research FFR value was defined as the average of both FFR readings.

The invasive physiological results were not used to guide treatment. Following physiological assessment, incremental doses of opiates and benzodiazepines were administered until a deep level of conscious sedation was achieved to ensure the patient was unaware of the treatment allocation arm. Randomisation was then performed using the SRUB online randomisation tool with 1:1 randomisation to PCI versus placebo.

Where randomisation was to PCI; PCI was performed at the operator's discretion but guided by angiography. Intravascular imaging and optical coherence tomography were used at the operator's discretion. Operators were mandated to aim for complete angiographic revascularisation of the vessel. Drug-eluting stent implantation was mandated, and post-dilatation was recommended to achieve optimum angiographic

and intravascular imaging results. Following PCI, FFR and iFR measurements were repeated. Again, the operator was blinded to the results. It was mandated that all staff from the catheterisation laboratory were not involved in any aspect of patient care during the trial follow-up period. Following the procedure all patients, whether PCI or placebo, were treated as per standard PCI protocols and were discharged on dual antiplatelet therapy.

2.6 Follow-up assessment

During the blinded follow-up period all patients had long-term activity tracking using a wearable activity monitor (ActiGraph, ActiGraph LLC). After a follow-up period of 6 weeks, patients re-attended for repeat of all pre-randomisation tests.

After the follow-up assessment, study participation was complete. Both patients and physicians were unblinded to the treatment arm allocation. Patients in the placebo arm had the opportunity to choose to undergo PCI, after consultation with their physician.

2.7 Blinding procedures and blinding index

Before randomisation (and therefore before the procedure) patients were counselled that they might experience pain and shortness of breath. Sensory isolation was provided as follows:

a) Before the procedure began, the patient received headphones playing music that ensured auditory isolation and prevented hearing of communication between staff, even before sedation.
b) Sedation was achieved, after invasive physiological assessment, by administration of incremental doses of intravenous opiate and intravenous benzodiazepine such that the patient was unresponsive to verbal or tactile stimulus, but that airway, ventilation and cardiovascular function were maintained. Physiological support with oxygenation and intravenous fluids was administered as necessary. Randomisation was performed only after sedation was achieved.
c) Patients did not receive any useful cues from the duration of the procedure because the additional physiological tests at baseline made the procedure much

longer than a diagnostic angiogram. Moreover, patients randomised to placebo were kept in the catheter laboratory for a minimum of 15 minutes post-randomisation. Finally, the benzodiazepine caused patients to have no recollection of the proceedings.

d) 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 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 for the period of handover.

e) The ward staff managed all patients as if they had had PCI, in terms of post-procedural monitoring and care. The catheter laboratory staff involved in the procedure had no contact with the patient after handover.

f) 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 +/- angioplasty, 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 six weeks. This standardised letter was approved by the local ethics committee and was given to all patients and their general practitioners on discharge.

g) 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. The blinded fellow performed all the communication with the patient after discharge and performed all the follow-up tests. At the six-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.

h) 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 follow-up but at that time they had the benefit of knowing the symptomatic responses 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 grade 1-5 with 5 being most sure.[71]

i) All patients were discharged home with dual antiplatelet therapy.

2.8 Study protocol cross over

Patients were not eligible for randomisation if:

a. They had progression of coronary artery disease.

Patients would cross over from placebo to PCI arm in the following circumstances:

a. They had intractable angina necessitating PCI.
b. They developed ACS.

2.9 Study endpoints

2.9.1 Primary endpoint

Change in exercise time on treadmill

2.9.2 Secondary endpoints

1. Change in peak VO_2

2. Change in time to 1mm ST depression
3. Angina severity as measured by CCS class
4. Angina score a measured by Seattle Angina Questionnaire score
5. Quality of life as measured by EQ-5D-5L questionnaire
6. Duke treadmill score
7. DSE wall motion index

2.10 Sample size calculation

Hypothesis 1 was to be tested by comparing the increment in exercise duration (from pre to post) between the groups. This was to be done by an unpaired t-test. A sample size of 100 patients per arm had just over 80% power to detect a difference in increment in exercise duration between the 2 study arms of 30s, at the 5% significance level. This assumed a between patient standard deviation of change in exercise time of 75s.

To allow for a one third dropout rate in the six-week period of medical optimisation between enrollment and randomisation we therefore initially planned to enroll 300 patients.

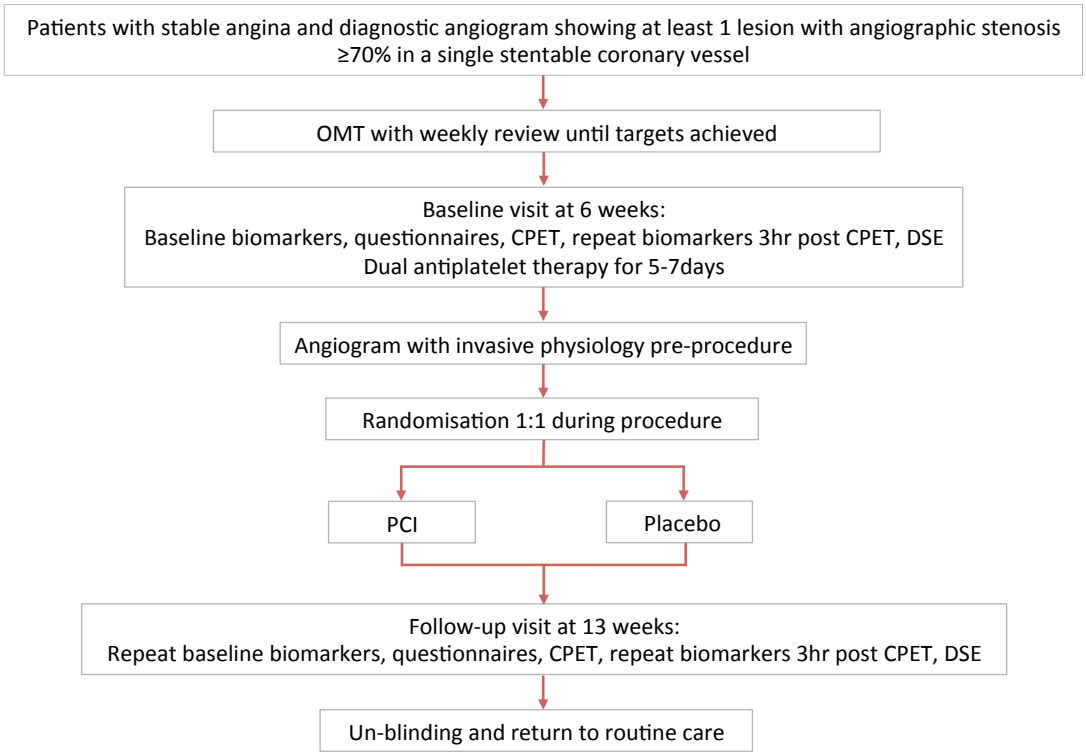
2.11 Reporting procedures

An online case report form was used throughout the study. This was secure, and compatible with current guidelines to ensure security of patient data. All documentation was collected electronically using the OpenClinica database (Figure 2.3). Clinical, and physiological records were saved to DVD and then to a central server in accordance with Good Clinical Practice guidelines.

2.12 Data Safety Monitoring Board

As this was a short study of symptom relief by a current standard therapy that had been shown not to affect survival,[11] our internal risk analysis judged that it was unlikely that there would be sufficient events during study participation for it to be

appropriate to stop the trial. An independent data safety monitoring board (DSMB) reviewed the trial events at six-month intervals and had the authority to stop the trial if, against expectations, event rates were high and unbalanced. The DSMB reviewed all clinical events and adjudicated and classify the events accordingly.



OMT= Optimum medical therapy, CPET= Cardiopulmonary exercise test, DSE= Dobutamine stress echocardiography, PCI= Percutaneous coronary intervention

Figure 2.1: ORBITA Study flow diagram

Table 2.1: ORBITA Inclusion criteria

Inclusion criteria
Patients with stable angina or equivalent symptoms, who have had diagnostic angiography showing at least 1 lesion with angiographic stenosis ≥70% in a single vessel that is suitable for PCI.

Table 2.2: ORBITA Exclusion criteria

Exclusion criteria
Acute coronary syndrome within the last 6 months
Previous coronary artery bypass graft surgery
Left main stem disease
Contraindications to PCI or drug-eluting stent implantation
Heavily calcified or tortuous vessels precluding pressure wire insertion
Known severe valvular disease
Known severe left ventricular systolic impairment
Chronic total occlusion in target vessel
Life expectancy <2yr
Pregnancy
Age <18yr or >85yr
Angiographic stenosis ≥ 50% in non-target vessel
Inability to consent

PCI= Percutaneous coronary intervention

Table 2.3: ORBITA Medical therapy protocol

Risk factor modification	Dose
Aspirin	75mg OD
Atorvastatin	≥ 40mg OD
Clopidogrel (or equivalent antiplatelet therapy)	75mg OD
Perindopril (if known hypertension) (or equivalent ACEI or ARB)	≥ 4mg OD
Anti-anginal therapy At least 2 anti-anginals from the following:	Dose
Bisoprolol (or equivalent β-blocker)	≥ 5mg OD
Amlodipine (or equivalent Ca-channel antagonist)	≥ 5mg OD
Isosorbide mononitrate slow-release (or equivalent long acting oral nitrate)	25mg OD
Nicorandil	10mg BD
Ivabradine	7.5mg BD
Ranolazine	500mg BD

OD= once daily, BD= twice daily, ACEI= Angiotensin converting enzyme inhibitor, ARB= Aldosterone receptor blocker

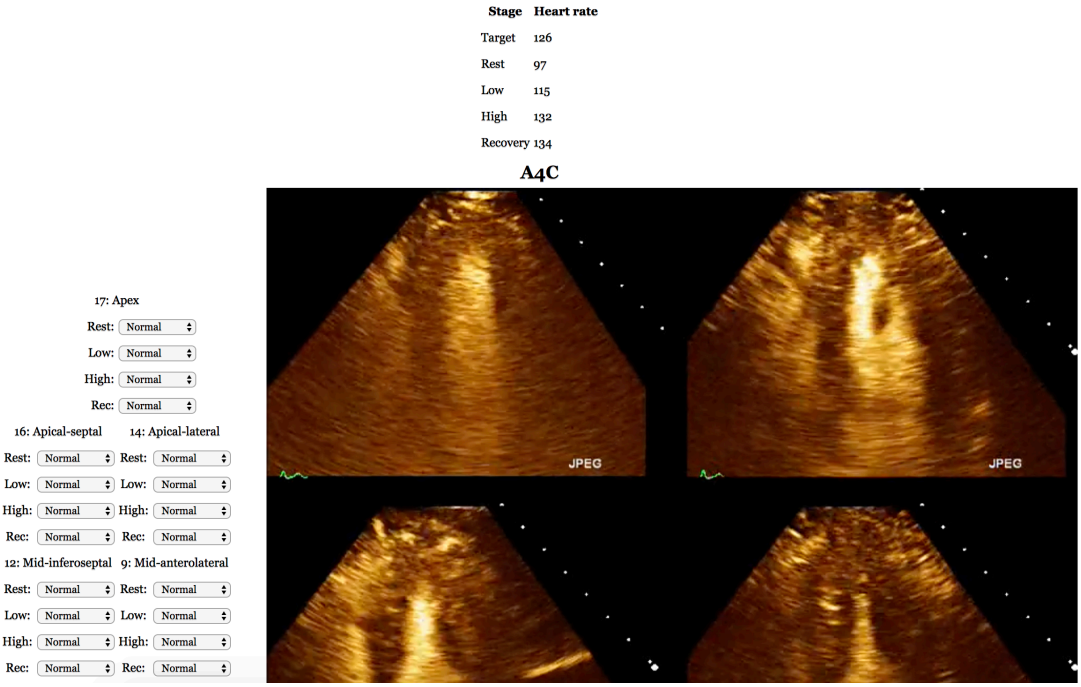


Figure 2.2: Example of ORBITA online dobutamine stress echocardiography reporting tool

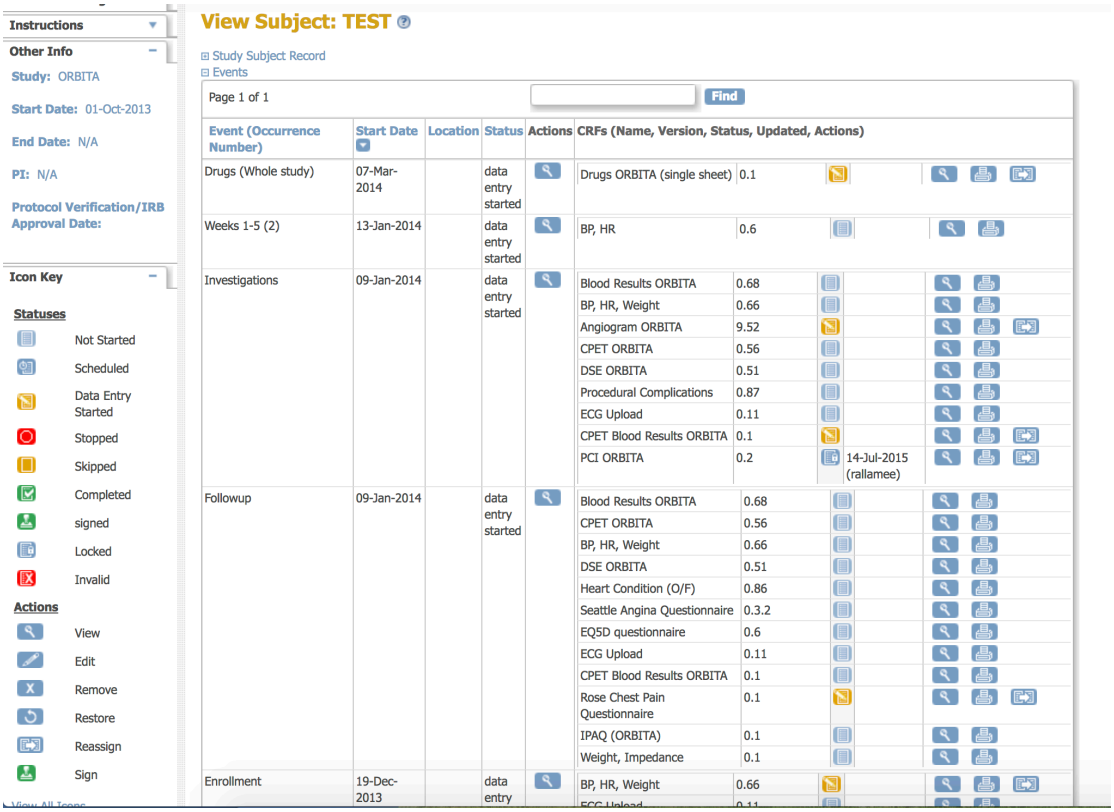


Figure 2.3: Example of ORBITA OpenClinica case report form

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

3.1 Abstract

3.1.1 Background

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

3.1.2 Methods

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

3.1.3 Findings

ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase, 200 patients were randomised between January 2014 to August 2017, 105 to PCI and 95 to placebo. Lesions had mean area stenosis 84.4% (SD 10.2), FFR 0.69 (SD 0.16) and iFR 0.76 (SD 0.22). There was no significant difference in the primary endpoint of exercise time increment between arms (PCI minus placebo 16.6 seconds, 95% CI -8.9 to 42.0, p=0.200). There was no mortality. Significant adverse events included 4 wire complications in the placebo group requiring PCI and 5 major bleeding events (2 PCI, 3 placebo).

3.1.4 Interpretation

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

3.2 Research in context

3.2.1 Evidence before this study

Over 500,000 PCIs are carried out annually worldwide for relief of angina but no placebo-controlled trial has been performed. Unblinded PCI is reported to increase exercise time by 96 seconds more than medical therapy. Single anti-anginal agents typically increase exercise time by over 45 seconds compared with placebo. ORBITA was designed conservatively, to detect an effect size of 30 seconds.

3.2.2 Added value of this study

ORBITA evaluated the efficacy of PCI beyond placebo to improve exercise capacity in patients with severe coronary disease on guideline-directed optimum medical therapy. The coronary stenoses were severe (average area reduction 84.4%) and had large haemodynamic effects (average FFR 0.69 and iFR 0.76). Despite PCI markedly improving haemodynamic and imaging indices, there was no significant difference between PCI and placebo in exercise time increment.

3.2.3 Implications of all the available evidence

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

3.3 Introduction

PCI was originally introduced to treat stable angina.[72] Over 500,000 PCI procedures are carried out annually worldwide for stable angina. The COURAGE trial showed no difference in myocardial infarction and mortality rates between PCI and control.[11] Meta-analyses have shown similar results.[15]

Angina relief remains the primary reason to conduct PCI in stable CAD.[36] Guidelines recommend anti-anginal medication as first line, with PCI reserved for those patients who remain symptomatic.[73]

Many patients remain symptomatic despite medical therapy.[25] Unblinded randomised trials have shown significant angina relief and quality of life improvement from PCI.[34] However, symptomatic responses are subjective and include both a true therapeutic effect and a placebo effect.[35] Moreover, in an open trial, if patients randomised to no PCI have an expectation that PCI is advantageous, this may colour their reporting (and their physician's interpretation) of symptoms, artifactually increasing the rate of unplanned revascularisation in the control arm.[14,36]

Placebo effects are known to be larger for invasive than non-invasive treatments.[37] Interventional cardiologists and patients with stable angina have a pre-conception that PCI offers symptomatic relief.[39] Additionally, cardiologists present a decisive approach to diagnosis and treatment which can lead to a greater placebo effect.[40] In the absence of blinding, the effect size of PCI on symptomatic endpoints may be overestimated because of the addition of the placebo effect to the true physiological effect of intervention.[41] In all previous trials, both investigators and patients were aware of the treatment allocation.[11,14] Therefore, before ORBITA, PCI had never been tested against placebo in a blinded randomised controlled trial.

Cardiologists have hitherto been resistant to conducting a placebo-controlled trial of angina relief from PCI for two main reasons. The first is the widespread perception that PCI unquestionably improves angina;[42] a perception based on unblinded clinical experience. The second reason is that it might be unethical to expose patients to an invasive placebo procedure. However, a systematic review of placebo-controlled surgical trials shows no evidence of harm to placebo groups.[43]

When offering an invasive intervention for symptomatic relief, it is essential to know the true efficacy of the intervention, particularly when the patient could choose to continue conservative treatment instead. Moreover, although PCI has become progressively safer, there remains a complication rate of 1 to 2%.[44]

Placebo-controlled randomised controlled trials show that single anti-anginal therapies provide 48 to 55 second improvements in exercise time.[74,75] ORBITA was designed to assess the effect of PCI against placebo on exercise time in patients with stable ischaemic symptoms. It was conservatively designed to be able to detect an effect size of 30 seconds.

3.4 Methods

3.4.1 Study design and participants

ORBITA was a multi-centre, randomised trial performed at five study sites in the UK: Imperial College Healthcare NHS Trust, Basildon and Thurrock University Hospitals NHS Trust, Royal Bournemouth and Christchurch Hospitals NHS Trust, East Sussex Healthcare NHS Trust and Royal Devon and Exeter NHS Trust. The London Central Research Ethics Committee (reference 13/LO/1340) approved the study and written consent was obtained from all patients prior to enrollment. The Trial Steering Committee provided overall supervision of the trial with an independent chairperson leading the committee. Independent data monitoring was conducted. The independent Data Safety Monitoring Board adjudicated all study adverse events and had the authority to terminate the trial if necessary. The trial was registered with ClinicalTrials.gov identifier: NCT02062593. The protocol summary is published at http://www.thelancet.com/protocol-reviews/14PRT-06897.[58]

Patients eligible for the trial were aged 18-85 years with angina or equivalent symptoms and at least one angiographically significant lesion ≥70% in a single vessel that was clinically appropriate for PCI. Exclusion criteria were angiographic stenosis ≥50% in a non-target vessel, acute coronary syndrome, previous coronary artery bypass graft surgery, left main stem coronary disease, contra-indications to drug-eluting stents, chronic total coronary occlusion, severe valvular disease, severe left ventricular systolic impairment, moderate-severe pulmonary hypertension, life expectancy <2 years, and inability to consent.

Eligible patients were approached after diagnostic angiography. They were enrolled after giving written informed consent.

After enrollment, the study consisted of two consecutive phases (Figure 3.1). The first was the six-week medical optimisation phase focusing on the initiation and up-titration of guideline directed anti-anginal therapy. Patients then had baseline pre-randomisation assessment, followed by the randomised blinded procedure.

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

3.4.2 Enrollment

At enrollment patients completed the Seattle Angina Questionnaire[76] and EQ-5D-5L questionnaire.[77] Patients had baseline ECG, pulse, blood pressure measurements, and height and weight recorded measurements for calculation of body mass index.

3.4.3 Medical therapy optimisation phase

After enrollment, patients spent the initial six weeks in the medical therapy optimisation phase of the protocol in which they had telephone consultations with a consultant cardiologist one to three times per week, supported by home measurements of pulse and blood pressure using equipment provided by the investigators (Omron M6 monitor, Omron Ltd, UK). Medications were introduced and up-titrated according to the trial protocol. The up-titration focused on anti-anginal therapy, aiming for at least two anti-anginal therapies per patient. Medication side effects were recorded, and patients had direct access at any time to the consultant cardiologist to make dose adjustments.

3.4.4 Pre-randomisation assessment

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

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

3.4.5 Invasive assessment and randomised blinded procedure

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

3.4.6 Invasive assessment

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

3.4.7 Randomisation

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

3.4.8 PCI

In the PCI arm, the clinical operator used drug-eluting stents to treat all lesions that were deemed angiographically significant, with a mandate to achieve angiographic

complete revascularisation. Stent optimisation with post-dilatation was recommended. Intravascular ultrasound or optical coherence tomography were used as necessary. After PCI, iFR and FFR were repeated. The clinical operator remained blinded to both pre-PCI and post-PCI values.

3.4.9 Placebo procedure

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

3.4.10 Blinding procedures and blinding index

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

3.4.11 Follow up investigations

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

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

3.4.12 Cardiopulmonary exercise testing

All cardiopulmonary exercise test investigations were performed using the QUARK CPET breath-by-breath metabolic measurement system (COSMED, Rome, Italy). A blinded physician and a blinded physiologist performed all tests. The test was continued until the development of limiting symptoms (angina, dyspnoea or fatigue), heart rhythm or blood pressure abnormalities or marked ST-segment deviation ($\geq$0.20mV associated with typical angina or in the first stage of exercise). The CPET endpoints were double reported by two physicians blinded to treatment allocation and

order. The Duke treadmill score was calculated using methods as previously described.[71]

3.4.13 Dobutamine stress echocardiography

Rest and stress cardiac regional wall motion was assessed using DSE. Investigations were performed by a blinded physician and blinded echo-sonographer. The 17-wall segment model was used for reporting. DSEs were double reported using an online DSE reporting tool by two imaging cardiology consultants who were blinded to treatment allocation and order. Wall motion was scored at rest, during peak and at recovery using a quantitative score (normal scored as 1, hypokinetic scored as 2, akinetic scored as 3, dyskinetic scored as 4, and aneurysmal scored as 5). Rest and stress wall motion score indices were then calculated using the 17-segment model, with scores averaged between the reporters.

3.4.14 Quantitative coronary angiography

Intracoronary nitrate was administered to achieve vasodilatation prior to performing any fluoroscopic run. Fluoroscopic images from two angles at least 30 degrees apart were acquired prior to physiological assessment. QCA measurements were made offline using the McKesson Cardiology^{TM} 14.0 QCA software system. QCA was double reported by two interventional cardiologists, blinded to treatment allocation, with scores averaged between the reporters.

3.4.15 Outcomes

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

3.4.16 Statistical analysis

The primary endpoint of ORBITA was the difference between PCI and placebo arms in the change in treadmill exercise time. Recent single anti-anginal agents have been

found to increase treadmill exercise time beyond placebo by over 45 seconds.[74,75] We designed ORBITA conservatively, to detect an effect size of invasive PCI smaller than a single anti-anginal agent: 30 seconds. We calculated that from the point of randomisation, a sample size of 100 patients per arm had >80% power to detect a between-arm difference in increment in exercise duration of 30 seconds, at the 5% significance level, using the 2-sample t-test of the difference between arms. This calculation assumed a between-patient standard deviation of change in exercise time of 75 seconds. There has been no previous trial of placebo-controlled trial of PCI. We therefore initially allowed for a one third dropout rate in the six-week period of medical optimisation between enrollment and randomisation and therefore planned to enroll 300 patients. In fact, the dropout rate was much lower, and therefore only 230 patients had to be enrolled to randomise 200 participants.

The continuous endpoints were analysed using the 2-sample t-test of the difference between arms and reported as the difference in mean change between study arms with 95% confidence intervals (CI) and p-values. Analyses calculated the difference as PCI minus placebo. Changes within study arms between pre-randomisation and follow-up were described using a paired approach as the mean and 95% confidence interval of the change. The comparison between arms for time to 1mm ST depression was made by a test of proportions between those showing an improvement versus those showing deterioration. Improvement was defined as a lengthening of time to ST depression, or having 1mm ST depression at pre-randomisation but not at follow-up. Deterioration was defined as shortening of the time to 1mm ST depression, or having ST depression at follow-up but not at pre-randomisation.

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

The Seattle Angina Questionnaire scales were derived from the patients' answers according to the published guidelines.[76] For the EQ-5D-5L, the overall health state value was calculated based on the five individual EQ-5D-5L questions using the value set for England.[77]

Blinding indices in the two study arms, for both the patients and the blinded medical team, were calculated using the method by Bang et al.[71] The recommended threshold of 20% to interpret the success or failure of blinding was applied.

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

3.5 Results

Between December 2013 and July 2017, 368 patients with angina and single vessel coronary disease were assessed for eligibility (Figure 3.2). Of these, 230 were enrolled and entered the medical therapy optimisation phase. Details of patients who were enrolled but later withdrew are given in Figure 3.2. Four patients in the placebo group were withdrawn from the trial (acute coronary syndrome, severe drug reaction, hospitalisation for pulmonary oedema, unexplained leg pain, as listed above) and therefore did not undergo follow-up exercise testing. One patient in the placebo group declined to perform the follow-up exercise test because of residual pain following peri-procedural haematoma. One patient in the PCI group was found to be in atrial flutter at the follow-up visit and therefore it was decided (blinded) that exercise test data would not be valid for the trial.

3.5.1 Patient characteristics

Two hundred patients (Table 3.1) were randomised to receive either PCI or placebo procedure between January 2014 and August 2017. There were no significant differences in the baseline demographics of the two groups. Almost all (97.5%) were in CCS class II or III at enrollment

Medical therapy in the two periods: enrollment to pre-randomisation and pre-randomisation and follow-up are shown in Table 3.2. By randomisation 98%, 98% and 94% patients were taking aspirin, a second anti-platelet and a statin respectively in the PCI arm, and 98%, 99% and 96% in the placebo arm. By the time of randomisation 78% of patients were taking beta-blockers, and 91% were taking calcium channel antagonists in the whole group. The mean (SD) number of anti-anginal medications at enrollment, pre-randomisation, and follow-up was 0.90 (0.8), 2.8 (1.2), 2.9 (1.1) in the PCI arm and 1.0 (0.9), 3.1 (0.9), 2.9 (1.1) in the placebo arm (p=0.357, 0.097, 0.891 respectively).

Both blood pressure and heart rate fell between enrollment and pre-randomisation measurement, and subsequently rose at the follow-up measurement. There were no differences between the trial arms in the values or their changes between time-points (Table 3.3).

Fasting lipids, which were measured at the pre-randomisation time-point, showed mean total cholesterol level of 3.4mmol/L (SD 1.0) in the PCI arm and 3.3mmol/L (SD 0.9) in the placebo arm and low-density lipoprotein of 1.8mmol/L (SD 0.7) in the PCI arm and 1.8mmol/L (SD 0.8) in the placebo arm (Table 3.4).

Details of anti-anginal therapy by CCS grade are shown at enrollment in Table 3.5 and at pre-randomisation in Table 3.6. As the number of anti-anginal therapies increased, the proportion of patients with CCS 0 and I increased.

3.5.2 Procedural characteristics

Procedural characteristics are shown in Table 3.7. The majority of lesions were in the left anterior descending artery (69.0%). The coronary stenoses were angiographically and haemodynamically severe. Images of the coronary lesions of the first 12 patients randomised are shown in Figure 3.3, and of all 200 randomised patients are shown in Figure 9.3 in the Appendix. Across all patients, the mean area stenosis by QCA was 84.4% (SD 10.2), the mean FFR was 0.69 (SD 0.16) and the mean iFR was 0.76 (SD 0.22). Fifty-seven patients (28.5%) had FFR>0.80 and 64 (32%) had iFR>0.89. Lesion location and lesion distribution by QCA are shown in Table 3.8 and Table 3.9.

All PCI was performed using drug-eluting stents. The median length of stent implanted was 24mm (IQR 18-33). Post-dilatation with a new balloon was performed in 75% of stents. After PCI, the mean FFR improved to 0.90 (SD 0.06) and iFR to 0.95 (SD 0.04).

3.5.3 Primary and secondary endpoints

Complete pre-randomisation and follow-up data for exercise time was available in 104 patients in the PCI arm and 90 patients the placebo arm and is shown in Table 3.10 (dataset for all randomised patients including those without paired tests is shown in Table 3.11).

For the primary endpoint, there was no significant difference between arms in the increment in exercise time (PCI minus placebo, 16.6 seconds, 95% CI -8.9 to 42.0, p=0.200). The exercise time increments in the individual arms were 28.4 seconds (95% CI 11.6 to 45.1) in the PCI arm and 11.8 seconds (95% CI -7.8 to 31.3) in the placebo arm.

Secondary endpoint analysis showed no significant difference between the arms in the change in the time to 1mm ST depression (p=0.164) or change in peak oxygen uptake (-12.9ml/min, 95% CI -90.2 to 64.3, p=0.741).

CCS angina grade was assessed at all three time-points in all patients (Table 3.12, Table 3.13 and Figure 3.4). There was no significant difference between the arms in the proportion of patients that improved by one CCS class or by two or more CCS classes (p=0.916).

Symptoms were assessed by the Seattle Angina and EQ-5D-5L questionnaires (Table 3.10). During the randomised blinded period there was no significant difference between arms in the change (from pre-randomisation to follow-up) in Seattle Angina Questionnaire physical limitation score (2.4, 95% CI -3.5 to 8.3, p=0.420) and the Seattle Angina Questionnaire angina frequency score (3.5, 95% CI -2.6 to 9.6,

p=0.260). There was also no significant difference between the arms in the change in EQ-5D-5L (0.00, 95% CI -0.04 to 0.04, p=0.994)

The change in Duke treadmill score (Table 3) was not significantly different between arms (1.12, 95% CI -0.23 to 2.47, p=0.104).

The DSE peak stress wall motion score index (Table 3.10) improved more with PCI than placebo (-0.07, 95% CI -0.11 to -0.04, p<0.0001).

3.5.4 Efficacy of blinding on patients

Efficacy of blinding was assessed on discharge from the randomisation procedure with an a-priori threshold of 20% to interpret the success or failure of blinding.[78] The blinding index is 0 for perfect blinding and 1 for completely ineffective blinding (allocation arm guessed correctly by all). The results are summarised in Table 3.14. Patients were also asked to guess their treatment allocation at the end of follow-up.

3.5.5 Efficacy of blinding on medical staff

Staff were asked to guess the allocation at the same two time-points. At the follow-up time-point this was before the staff had spoken to patient about symptoms.

3.5.6 Primary assessment of blinding: discharge from procedure

At this time-point the patient had experienced the procedure but did not yet have experience of any change in symptoms. This is therefore the recommended time-point for the primary assessment of the efficacy of blinding.[71]

The primary assessment of blinding was prior to discharge from the randomisation procedure (Table 3.14). The blinding index was perfect (all responded “don’t know”) in the placebo arm and near perfect in the PCI arm (2/105 guessed, both correctly, blinding index 0.02, 95% CI -0.003 to 0.04).

After the patients completed the six-week follow-up period, 80/105 PCI patients felt able to guess their treatment allocation, 50 correctly and 30 incorrectly (blinding

index 0.19, 95% CI 0.05 to 0.33). In the placebo arm 69/91 felt able to guess, 34 correctly and 35 incorrectly (blinding index -0.01, 95% CI -0.16 to 0.14).

The medical team also demonstrated successful blinding, with blinding index of -0.01 (95% CI -0.03 to 0.01) for the PCI arm and 0.01 (95% CI -0.01 to 0.03) for the placebo arm.

3.5.7 Supplementary assessment of blinding: follow-up time-point

At this time-point patients had experience of any change in symptoms, which could therefore have influenced their guess.

The blinding index for patients in the PCI arm was 0.19 (95% CI 0.05 to 0.33) and in the placebo arm was -0.01 (95% CI -0.16 to 0.14).

The medical team completed their blinding questionnaire immediately before speaking to the patient at the follow-up visit. Blinding was perfect for both study arms, as the team answered, “don’t know” for study arm allocation in all cases.

3.5.8 Serious adverse events

All adverse events were reviewed by the independent DSMB. Peri-procedural and other serious adverse events are described in Table 3.15 and Table 3.16. There was no mortality. There were three peri-procedural major bleeding events (2 PCI, 1 placebo). In four patients in the placebo arm, PCI was required for a pressure-wire related complication. During the follow-up phase 1 patient (placebo arm) developed ACS and 2 patients (placebo arm) had major bleeding on dual anti-platelet therapy.

Major bleeding events consisted of a neck haematoma secondary to radial angioplasty, and two groin haematomas secondary to a femoral puncture for angiography each requiring 2 units of blood transfusion.

One patient remained in hospital overnight for acute confusion following the deep sedation with complete resolution of symptoms over 6 hours.

Four patients who were randomised to placebo required treatment with PCI due to intra-procedural coronary dissection caused by the pressure wire used for physiological assessment. Similar events may have occurred in the PCI arm but would not have been documented as an adverse event because the patient was already randomised to PCI.

In one patient the pressure wire snapped as it was pulled out of a severe calcified lesion and required retrieval with a snare.

One patient was kept in hospital post-procedure for IV diuresis following fluid overload caused by IV fluid administration before and during the procedure.

One patient who had been randomised to placebo developed ACS during the blinded period and was therefore unblinded and treated with urgent PCI.

One patient was hospitalised for investigation of atypical chest pain with negative cardiac enzymes and no ischaemic changes on ECG.

One patient was hospitalised for right heart failure due to chronic obstructive pulmonary disease.

One patient was hospitalised for bilateral leg pain with no neurological or musculoskeletal cause found.

One patient was hospitalised for pulmonary oedema that was attributed by the admitted clinicians as due to mitral regurgitation.

One patient had a severe drug reaction with angio-oedema secondary to angiotensin converting enzyme inhibitor requiring intubation and ventilation.

Two major bleeds occurred; in both cases investigations revealed erosive gastritis. The bleeding was attributed to the dual antiplatelet therapy.

3.6 Discussion

3.6.1 Main findings of ORBITA

In ORBITA, the first blinded, placebo-controlled trial of PCI for stable angina, PCI did not improve exercise time beyond placebo. This was despite the patients having ischaemic symptoms, severe coronary stenosis both anatomically (84.4% area reduction) and haemodynamically (on-treatment FFR 0.69 and iFR 0.76), and incontrovertible objective relief of anatomical stenosis, invasive pressure, and non-invasive perfusion indices (FFR $p<0.0001$, iFR $p<0.0001$, stress wall motion score index $p<0.0001$). There was also no improvement beyond placebo in the other exercise and patient-centred endpoints including CCS class and the metrics of the Seattle angina and EQ-5D-5L questionnaires.

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

3.6.2 The necessity for placebo-controlled trials of intervention therapy

The necessity for placebo-controlled trials has been rediscovered several times in cardiology, typically to considerable surprise.[47] Often a therapy is thought to be so beneficial that a placebo-controlled trial is considered unnecessary and perhaps unethical, sometimes even attracting droll analogies to testing the need for a parachute.

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

3.6.3 The link between coronary stenosis and angina

ORBITA has implications for our clinical understanding. The concept of a simple linear link between a tight stenosis and angina is attractive to patients, easily explained by physicians, and biologically plausible. Moreover, since relieving the anatomical and haemodynamic features of stenosis by unblinded PCI is followed by

the patient reporting angina relief, it is understandable that this link becomes generally accepted.

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

3.6.4 Clinical application of the results

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

3.6.5 Specific features of the ORBITA trial

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

The trial was designed to achieve good quality background anti-anginal therapy as is recommended.[27,28] To minimise the period of deferral of PCI, which may have been a barrier to participation, the medical optimisation phase, was designed to be more intensive than routine clinical practice. Patients were up-titrated to an average of three anti-anginal agents during the initial six weeks before randomisation. Achieving this required one to three consultations per week with a consultant cardiologist. The longest half-life of the drugs introduced was 40 hours for amlodipine. Because this was second line it was never added in the final two weeks and therefore no patient had pharmacokinetically insufficient time. The changes in heart rate and blood pressure confirm physiological effects. Thirty-nine out of 230 enrolled patients had

become free of angina (CCS 0) at the pre-randomisation time-point with anti-anginal therapy. This may have been due to the anti-anginal therapy or self-restriction of physical activity. Seventeen patients exited the trial at this time but 22 went forward for randomisation. The other 178 randomised patients (89%) had angina despite anti-anginal therapy. Of the randomised patients, the majority were taking at least two anti-anginal drugs.[27,28]

The ORBITA patients had ischaemia as evidenced by anginal symptoms, severe coronary disease, with haemodynamic severity similar to unblinded trials of PCI. In ORBITA the mean FFR was 0.69, comparable to 0.71 in FAME and 0.68 in FAME-2.[14,79] The 2017 guidelines state that PCI is appropriate for this cohort of patients with single vessel coronary disease and angina on at least two anti-anginals, with no requirement for any further tests.[80] Angiographic images of all 200 patients are shown in Figure 9.3 in the Appendix for comparison with other trials.

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

ORBITA was designed to detect a clinically relevant effect size. Contemporary placebo-controlled trials of single agent anti-anginal therapies have reported effect sizes of 48 to 55 seconds.[74,75] ORBITA was designed to be able to detect an effect size of 30 seconds (55% to 63% of a single anti-anginal agent), which is a relatively conservative goal for an invasive therapy that has a small but non-negligible risk. In practice the variability in exercise time increments was slightly larger than predicted and therefore the trial could in retrospect be considered to be powered for a 34 second

effect. ORBITA is comparable in size to the 191 patient Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial of single agent anti-anginal therapy.[75]

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

3.6.6 Study limitations

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

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

This trial set an objective and continuous variable as the primary endpoint: difference in exercise time increment between PCI and placebo. There are many other possible symptom-based variables, but exercise time has proved to be a discriminating test for many anti-anginal therapies and is the recommended for this by both the U.S. Food and Drug Administration authority and the European Medicines Agency.

The follow-up time was only six weeks, so that patients and physicians would not be deterred by the prospect of remaining indefinitely without the option of PCI. However the anatomic and haemodynamic effects of stenting on the coronaries are immediate, and symptomatic and exercise test improvements from unblinded PCI is well documented at 30 days,[25] 37 days[81] and 6 weeks.[82] As a result of the limited duration of ORBITA, it cannot address long-term myocardial infarction and mortality endpoints. Other trials such ISCHEMIA (NCT01471522) will do this.

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

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

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

3.7 Conclusions

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

Table 3.1: ORBITA Baseline characteristics

	PCI (n=105)	Placebo (n=95)	All (n=200)
Age (years)	65.9 (9.5)	66.1 (8.4)	66.0 (9.0)
Male	74 (70.5%)	72 (75.8%)	146 (73.0%)
BMI	28.0 (4.7)	29.5 (5.1)	28.7 (5.0)
Diabetes	15 (14.3%)	21 (22.1%)	36 (18.0%)
Hypertension	72 (68.6%)	66 (69.5%)	138 (69.0%)
Hyperlipidaemia	81 (77.1%)	62 (65.3%)	143 (71.5%)
Current smoker	11 (10.5%)	15 (15.8%)	26 (13.0%)
Previous MI	5 (4.8%)	7 (7.4%)	12 (6.0%)
Previous PCI	10 (9.5%)	15 (15.8%)	25 (12.5%)
LV systolic function			
Normal	98 (93.3%)	85 (89.5%)	183 (91.5%)
Mild impairment	3 (2.9%)	7 (7.4%)	10 (5.0%)
Moderate impairment	4 (3.8%)	3 (3.2%)	7 (3.5%)
CCS class			
I	2 (1.9%)	3 (3.2%)	5 (2.5%)
II	64 (61.0%)	54 (56.8%)	118 (59.0%)
III	39 (37.1%)	38 (40.0%)	77 (38.5%)
Angina duration (months)	9.5 (15.7)	8.4 (7.5)	9.0 (12.5)

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

Table 3.2: ORBITA Medical therapy optimisation

Medication	Time-interval	PCI	Placebo	p-value
Aspirin	Enrollment to randomisation	103/105 (98%)	93/95 (98%)	0.919
	Randomisation to follow-up	104/105 (99%)	88/91 (97%)	0.247
Clopidogrel or other antiplatelet	Enrollment to randomisation	103/105 (98%)	94/95 (99%)	0.621
	Randomisation to follow-up	105/105 (100%)	89/91 (98%)	0.127
Atorvastatin or other statin	Enrollment to randomisation	99/105 (94%)	91/95 (96%)	0.626
	Randomisation to follow-up	102/105 (97%)	87/91 (96%)	0.563
Perindopril or other ACEI or ARB	Enrollment to randomisation	84/105 (80%)	74/95 (78%)	0.715
	Randomisation to follow-up	85/105 (81%)	72/91 (79%)	0.749
Bisoprolol or other β blocker	Enrollment to randomisation	82/105 (78%)	74/95 (78%)	0.973
	Randomisation to follow-up	85/105 (81%)	69/91 (76%)	0.383
Amlodipine or other Ca channel blocker	Enrollment to randomisation	95/105 (90%)	87/95 (92%)	0.786
	Randomisation to follow-up	96/105 (91%)	81/91 (89%)	0.568
Long acting nitrate	Enrollment to randomisation	67/105 (64%)	64/95 (67%)	0.597
	Randomisation to follow-up	69/105 (66%)	60/91 (66%)	0.974
Nicorandil	Enrollment to randomisation	47/105 (45%)	58/95 (61%)	0.021
	Randomisation to follow-up	50/105 (48%)	54/91 (59%)	0.101
Ranolazine	Enrollment to randomisation	7/105 (7%)	13/95 (14%)	0.099
	Randomisation to follow-up	7/105 (7%)	13/91 (14%)	0.079

PCI=percutaneous coronary intervention. ACEI= angiotensin converting enzyme inhibitor. ARB=angiotensin II receptor blocker. Frequencies shown are the number of patients taking the drug at the end of the time-interval. P values are for the comparison between arms of patients who started or continued to take the drug in the time interval.

Table 3.3: ORBITA Blood pressure and heart rate at enrollment, pre-randomisation and follow-up

	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart rate (bpm)	
	PCI	Placebo	PCI	Placebo	PCI	Placebo
Enrollment	136.5 (16.9) n=105	137.9 (18.6) n=95	76.6 (11.6) n=105	76.2 (9.6) n=95	65.3 (13.0) n=105	66.2 (11.3) n=95
Pre-randomisation	125.3 (16.9) n=104	126.0 (17.0) n=95	70.4 (11.1) n=104	70.4 (11.0) n=95	60.5 (11.1) n=104	61.9 (9.2) n=95
Follow-up	130.5 (17.5) n=105	133.4 (20.0) n=91	70.8 (11.8) n=105	74.0 (12.7) n=91	62.7 (11.1) n=105	66.2 (13.5) n=91
Δ (Enrollment to pre-randomisation)	-11.5 (18.0) (p<0.001)	-11.9 (21.1) (p<0.001)	-6.3 (10.8) (p<0.001)	-5.8 (12.5) (p<0.001)	-4.7 (11.3) (p<0.001)	-4.3 (12.3) (p<0.001)
Difference in Δ between groups (Enrollment to pre-randomisation)	0.4 (95% CI -5.1 to 5.9) (p=0.88)		-0.6 (95% CI -3.8 to 2.7) (p=0.74)		-0.4 (95% CI -3.7 to 2.9) (p=0.81)	
Δ (Pre-randomisation to follow-up)	5.3 (18.0) (p=0.004)	7.3 (18.6) (p=0.004)	0.5 (12.0) (p=0.65)	3.3 (12.5) (p=0.01)	2.1 (10.4) (p=0.04)	4.2 (12.8) (p=0.002)
Difference in Δ between groups (Pre-randomisation to follow-up)	-2.0 (95% CI -7.2 to 3.2) (p=0.44)		-2.7 (95% CI -6.2 to 0.8) (p=0.12)		-2.1 (95% CI -5.4 to 1.2) (p=0.20)	

Data are mean (SD). PCI=percutaneous coronary intervention. BP= blood pressure.

Table 3.4: ORBITA Blood investigations at pre-randomisation

	PCI	Placebo
Haemoglobin (g/dL)	12.6 (1.5)	12.7 (1.3)
HbA1C (mmol/mol)	42.1 (12.5)	43.3 (11.3)
Creatinine (μmol/L)	81.3 (18.4)	90.8 (62.5)
Triglycerides (mmol/L)	0.8 (0.4)	0.8 (0.5)
Cholesterol (mmol/L)	3.4 (1.0)	3.3 (0.9)
HDL cholesterol (mmol/L)	1.1 (0.4)	1.2 (0.4)
LDL cholesterol (mmol/L)	1.8 (0.7)	1.8 (0.8)

Data are mean (SD). PCI=percutaneous coronary intervention.
HDL=high-density lipoprotein. LDL=low-density lipoprotein.

Table 3.5: ORBITA Anti-anginal therapy by Canadian Cardiovascular Society class at enrollment

		Number of anti-anginal medications							
CCS Class		0		1		2		≥3	
		PCI	Placebo	PCI	Placebo	PCI	Placebo	PCI	Placebo
	0	0	0	0	0	0	0	0	0
	I	2 (100%)	3 (100%)	0	0	0	0	0	0
	II	23 (36%)	18 (33%)	31 (48%)	26 (48%)	10 (16%)	9 (17%)	0	1 (2%)
	III	7 (18%)	9 (24%)	22 (56%)	11 (29%)	9 (23%)	14 (37%)	1 (3%)	4 (10%)
	IV	0	0	0	0	0	0	0	0

CCS= Canadian Cardiovascular Society. PCI=percutaneous coronary intervention.

Table 3.6: ORBITA Anti-anginal therapy by Canadian Cardiovascular Society class at pre-randomisation

		Number of anti-anginal medications							
CCS Class		0		1		2		≥3	
		PCI	Placebo	PCI	Placebo	PCI	Placebo	PCI	Placebo
	0	0	0	0	0	4 (44%)	2 (23%)	5 (56%)	10 (77%)
	I	0	0	2 (13%)	0	3 (20%)	4 (40%)	10 (67%)	6 (60%)
	II	0	0	7 (13%)	1 (2%)	16 (29%)	11 (27%)	33 (58%)	29 (71%)
	III	2 (8%)	0	4 (16%)	1 (3%)	3 (12%)	4 (13%)	16 (64%)	26 (84%)
	IV	0	0	0	0	0	0	0	0

CCS= Canadian Cardiovascular Society. PCI=percutaneous coronary intervention.

Table 3.7: ORBITA Procedural characteristics

	PCI (n=105)	Placebo (n=95)	p value	All (n=200)
Procedural time (min)	90 (27)	61 (17)	<0.0001	76 (27)
Vessel name			0.509	
LAD	72 (68.6%)	66 (69.5%)		138 (69.0%)
RCA	17 (16.2%)	15 (15.8%)		32 (16.0%)
Cx	9 (8.6%)	10 (10.5%)		19 (9.5%)
OM1	4 (3.8%)	0 (0%)		4 (2.0%)
D1	2 (1.9%)	2 (2.1%)		4 (2.0%)
IM	1 (1.0%)	2 (2.1%)		3 (1.5%)
Serial lesions	17 (16.2%)	12 (12.6%)	0.475	29 (14.5%)
Area stenosis by QCA (%)	84.6 (10.2)	84.2 (10.3)	0.781	84.4 (10.2)
Median (IQR)	86.0 (77.5-92.7)	84.9 (77.1-93.0)		85.7 (77.4-93.0)
FFR	0.69 (0.16)	0.69 (0.16)	0.778	0.69 (0.16)
Median (IQR)	0.72 (0.57-0.82)	0.73 (0.59-0.80)		0.72 (0.57- 0.81)
iFR	0.76 (0.22)	0.76 (0.21)	0.751	0.76 (0.22)
Median (IQR)	0.85 (0.68-0.92)	0.85 (0.68-0.89)		0.85 (0.68-0.90)
Drug-eluting stent type				
Everolimus-eluting	83			
Zotarolimus-eluting	52			
Biolimus-eluting	3			
Stent length (mm) Median (IQR)	24 (18-33)			
Stent diameter (mm)	3.1 (0.5)			
Post-dilatation performed	103 (75%)			
FFR post-PCI	0.90 (0.06)			
Median (IQR)	0.90 (0.87 - 0.94)			
iFR post-PCI	0.95 (0.04)			
Median (IQR)	0.94 (0.92-0.97)			

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

Table 3.8: ORBITA Location of lesions within coronary vessels

Lesion location	PCI (n=105)	Placebo (n=95)	p value
LAD	72 (68.6%)	66 (69.5%)	
Ostial	4	1	0.135
Proximal	42	29	
Mid	34	39	
Distal	4	8	
Cx	9 (8.6%)	10 (10.5%)	0.125
Ostial	0	0	
Proximal	3	2	
Mid	4	8	
Distal	5	1	
RCA	17 (16.2)	15 (15.8)	0.091
Ostial	2	2	
Proximal	9	1	
Mid	6	9	
Distal	5	5	

LAD= Left anterior descending artery, Cx= Circumflex, RCA= Right coronary artery

Table 3.9: ORBITA Distribution of lesion severity as assessed by quantitative coronary angiography

Area stenosis by QCA (%)	PCI (n=105)	Placebo (n=95)	p value
<50%	1 (1.0%)	0	0.486
50-70%	6 (5.7%)	10 (10.5%)	
>70%	98 (93.3%)	85 (89.5%)	

QCA= Quantitative coronary angiography

Table 3.10: ORBITA Primary and secondary endpoints

Total exercise time		
Exercise time (seconds)	PCI (n=104)	Placebo (n=90)
Pre-randomisation	528.0 (178.7)	490.0 (195.0)
Follow-up	556.3 (178.7)	501.8 (190.9)
Δ (Pre-randomisation to follow-up)	28.4 (95% CI 11.6 to 45.1)	11.8 (95% CI -7.8 to 31.3)
Difference in Δ between arms	16.6 (95% CI -8.9 to 42.0) (p=0.200)	
Time to 1mm ST depression		
Time to 1mm ST depression (seconds)	PCI	Placebo
Pre-randomisation	n=27 479.7 (141.4)	n=18 471.1 (128.7)
Follow-up	n=23 472.7 (129.1)	n=21 470.1 (176.0)
p value between arms	p=0.164	
Peak oxygen uptake		
Peak oxygen uptake (ml/min)	PCI (n=99)	Placebo (n=89)
Pre-randomisation	1715.0 (638.1)	1707.4 (567.0)
Follow-up	1713.0 (583.7)	1718.3 (550.4)
Δ (Pre-randomisation to follow-up)	-2.0 (95% CI -54.1 to 50.1)	10.9 (95% CI -47.2 to 69.0)
Difference in Δ between arms	-12.9 (95% CI -90.2 to 64.3) (p=0.741)	
Physical limitation		
SAQ-Physical limitation	PCI (n=100)	Placebo (n=88)
Pre-randomisation	71.3 (22.5)	69.1 (24.7)
Follow-up	78.6 (24.0)	74.1 (24.7)
Δ (Pre-randomisation to follow-up)	7.4 (19.7) (95% CI 3.5 to 11.3)	5.0 (21.2) (95% CI 0.5 to 9.5)
Difference in Δ between arms	2.4 (95% CI -3.5 to 8.3) p=0.420	
Angina frequency		
SAQ-Angina frequency	PCI (n=103)	Placebo (n=90)
Pre-randomisation	63.2 (20.4)	60.0 (25.1)
Follow-up	74.4 (21.4)	67.7 (22.1)
Δ (Pre-randomisation to follow-up)	11.2 (20.3) (95% CI 7.2 to 15.1)	7.7 (22.7) (95% CI 2.9 to 12.4)
Difference in Δ between arms	3.5 (95% CI -2.6 to 9.6) p=0.260	
Angina stability		
SAQ-Angina stability	PCI (n=102)	Placebo (n=89)
Pre-randomisation	64.7 (25.5)	68.5 (24.3)
Follow-up	60.5 (23.7)	63.5 (25.6)
Δ (Pre-randomisation to follow-up)	-4.2 (33.4) (95% CI -10.7 to 2.4)	-5.1 (31.6) (95% CI -11.7 to 1.6)
Difference in Δ between arms	0.9 (95% CI -8.4 to 10.2) p=0.851	
Quality of life		
EQ-5D-5L QOL	PCI (n=103)	Placebo (n=89)
Pre-randomisation	0.80 (0.21)	0.79 (0.22)
Follow-up	0.83 (0.21)	0.82 (0.20)
Δ (Pre-randomisation to follow-up)	0.03 (0.14) (95% CI 0.00 to 0.06)	0.03 (0.17) (95% CI 0.00 to 0.07)
Difference in Δ between arms	0.00 (95% CI -0.04 to 0.04)	

	p=0.994	
Peak stress wall motion index score		
Peak stress wall motion index score	PCI (n=91)	Placebo (n=70)
Pre-randomisation	1.08 (0.12)	1.07 (0.11)
Follow-up	1.02 (0.05)	1.09 (0.14)
Δ (Pre-randomisation to follow-up)	-0.05 (0.12) (95% CI -0.08 to -0.03)	0.02 (0.10) (95% CI -0.01 to 0.04)
Difference in Δ between arms	-0.07 (95% CI -0.11 to -0.04) (p<0.0001)	
Duke treadmill score		
Duke treadmill score	PCI (n=104)	Placebo (n=90)
Pre-randomisation	4.24 (4.82)	4.18 (4.65)
Follow-up	5.46 (4.79)	4.28 (4.98)
Δ (Pre-randomisation to follow-up)	1.22 (4.36) (95% CI 0.37 to 2.07)	0.10 (5.20) (95% CI -0.99 to 1.19)
Difference in Δ between arms	1.12 (95% CI -0.23 to 2.47) (p=0.104)	

Data are mean (SD) unless otherwise specified. PCI=percutaneous coronary intervention. Total exercise time was available for 104 patients in the PCI arm and 90 patients in the placebo arm. Time to 1mm ST depression was compared between the arms as the proportion of patients whose time to ST depression improved versus deteriorated, in the patients who had 1mm ST depression on at least one time-point (32 in the PCI arm and 25 in the placebo arm). Valid metabolic gas exchange data were available for 99 patients in the PCI arm and 89 patients in the placebo arm. SAQ=Seattle angina questionnaire. QOL=quality of life**.** Peak stress wall motion index score and Duke treadmill score data are shown for the patients who had both pre-randomisation and follow-up tests.

Table 3.11: ORBITA Cardiopulmonary exercise test data for complete unpaired data-set

Total exercise time		
Exercise time (seconds)	PCI	Placebo
Pre-randomisation	526.9 (178.2) n=105	482.3 (194.3) n=95
Follow-up	556.3 (178.7) n=104	501.8 (190.9) n=90
Time to 1mm ST depression		
Time to 1mm ST depression (seconds)	PCI	Placebo
Pre-randomisation	479.7 (141.4) n=27	471.1 (128.7) n=18
Follow-up	472.7 (129.1) n=23	470.1 (176.0) n=21
Peak oxygen uptake		
Peak oxygen uptake (ml/min)	PCI	Placebo (n=89)
Pre-randomisation	1727.6 (649.9) n=102	1687.5 (567.3) n=93
Follow-up	1716.7 (578.6) n=101	1718.3 (550.4) n=89

Data are mean (SD) unless otherwise specified. PCI=percutaneous coronary intervention.

Table 3.12: ORBITA Canadian Cardiovascular Society class at pre-randomisation and follow-up

	Pre-randomisation			Follow-up		
CCS Class	PCI (n=105)	Placebo (n=95)	p value	PCI (n=105)	Placebo (n=91)	p value
0	9 (9%)	13 (14%)	0.241	41 (39%)	26 (29%)	0.107
I	15 (14%)	10 (11%)		14 (13%)	18 (20%)	
II	56 (53%)	41 (43%)		37 (35%)	31 (34%)	
III	25 (24%)	31 (33%)		13 (12%)	15 (16%)	
IV	0 (0%)	0 (0%)		0 (0%)	1 (1%)	

PCI=percutaneous coronary intervention. CCS=Canadian Cardiovascular Society

Table 3.13: ORBITA Changes in Canadian Cardiovascular Society class

	From enrollment to pre-randomisation			From pre-randomisation to follow-up		
Change in CCS	PCI (n=105)	Placebo (n=95)	p value	PCI (n=105)	Placebo (n=91)	p value
No change or deterioration	63 (60%)	59 (62%)	0.916	51 (49%)	50 (55%)	0.633
1 class improvement	27 (26%)	22 (23%)		27 (26%)	22 (24%)	
≥2 class improvement	15 (14%)	14 (15%)		27 (26%)	19 (21%)	

PCI=percutaneous coronary intervention. CCS=Canadian Cardiovascular Society

Table 3.14: ORBITA Assessment of blinding index

	PCI	Placebo	Don't know	Total	Blinding index (95% CI)
Patients post randomisation					
PCI	2	0	103	105	0.02 (-0.003 to 0.04)
Placebo	0	0	95	95	0 (. to .)
Total	2	0	198	200	
Patients at follow-up					
PCI	50	30	25	105	0.19 (0.05 to 0.33)
Placebo	35	34	22	91	-0.01 (-0.16 to 0.14)
Total	85	64	47	196	
Team post randomisation					
PCI	0	1	104	105	-0.01 (-0.03 to 0.01)
Placebo	0	1	94	95	0.01 (-0.01 to 0.03)
Total	0	2	198	200	
Team at follow-up					
PCI	0	0	105	105	0 (. to .)
Placebo	0	0	91	91	0 (. to .)
Total	0	0	196	196	

Table 3.15: ORBITA Peri-procedural serious adverse events

Serious adverse event	PCI N=105	Placebo N=95	All patients N=200
Major bleeding	2	1	3
Acute confusion	1	0	1
Converted to PCI for procedural complication	Not counted (PCI already intended)	4	4
Wire snapped requiring snare retrieval	1	0	1
Pulmonary oedema	0	1	1

Table 3.16: ORBITA Other serious adverse events

Serious adverse event	PCI N=105	Placebo N=95	All patients N=200
Acute coronary syndrome	0	1	1
Hospitalisation for atypical chest pain	0	1	1
Hospitalisation for right heart failure	0	1	1
Hospitalisation for leg pain	0	1	1
Hospitalisation for pulmonary oedema	0	1	1
Severe drug reaction	0	1	1
Major bleeding on dual antiplatelet therapy	0	2	2

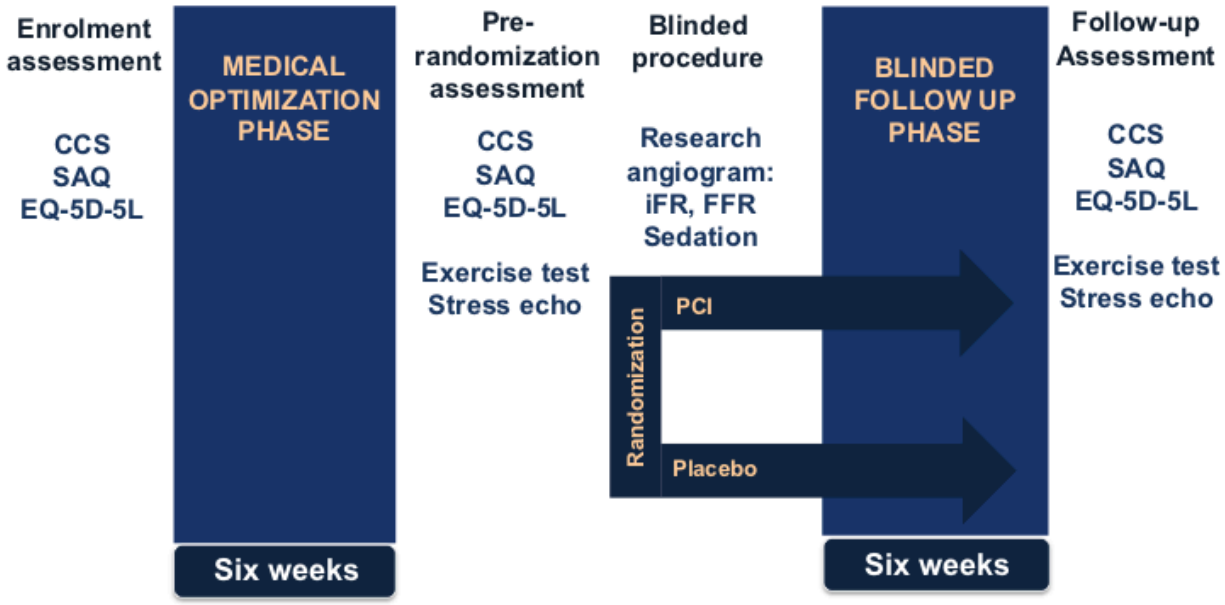


Figure 3.1: ORBITA Study overview diagram

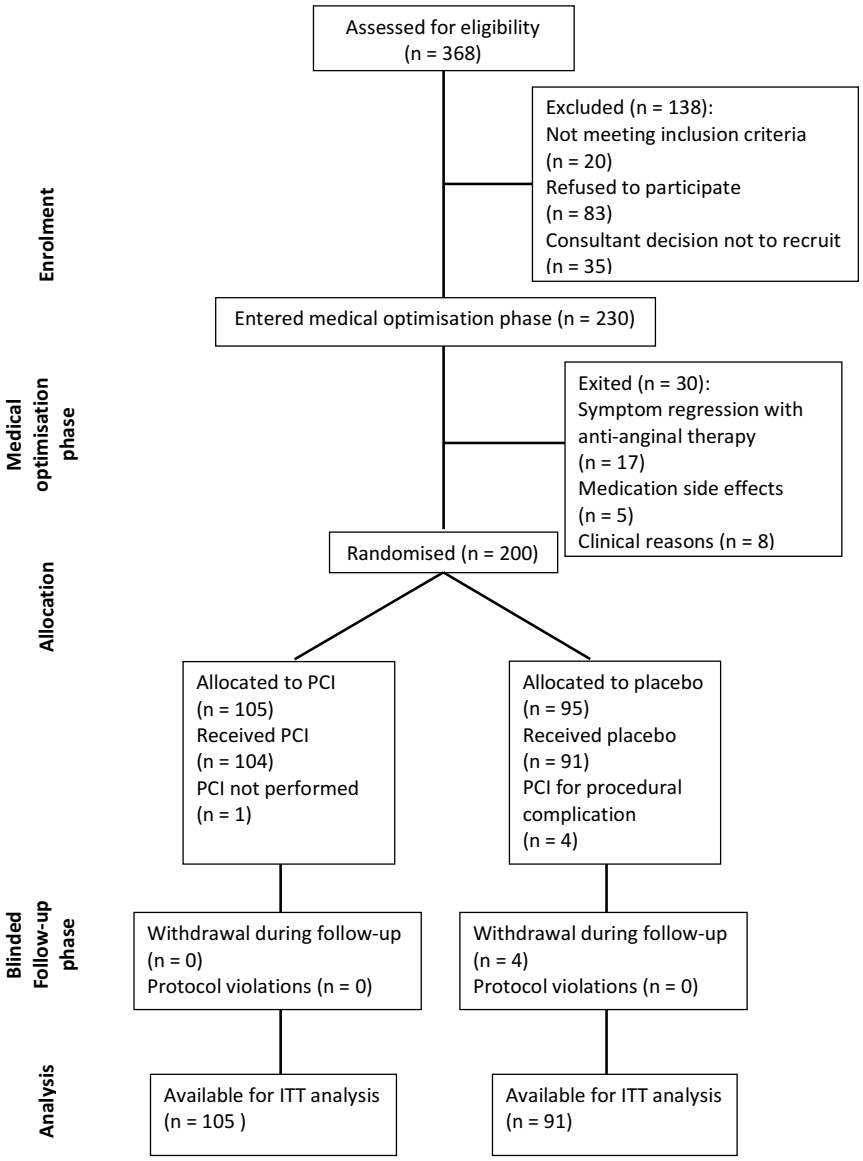


Figure 3.2: ORBITA Consort diagram

CCS = Canadian Cardiovascular Society angina severity grading
BP = Blood pressure
HR = Heart rate
CPET = Cardiopulmonary exercise testing
DSE = Dobutamine stress echocardiography

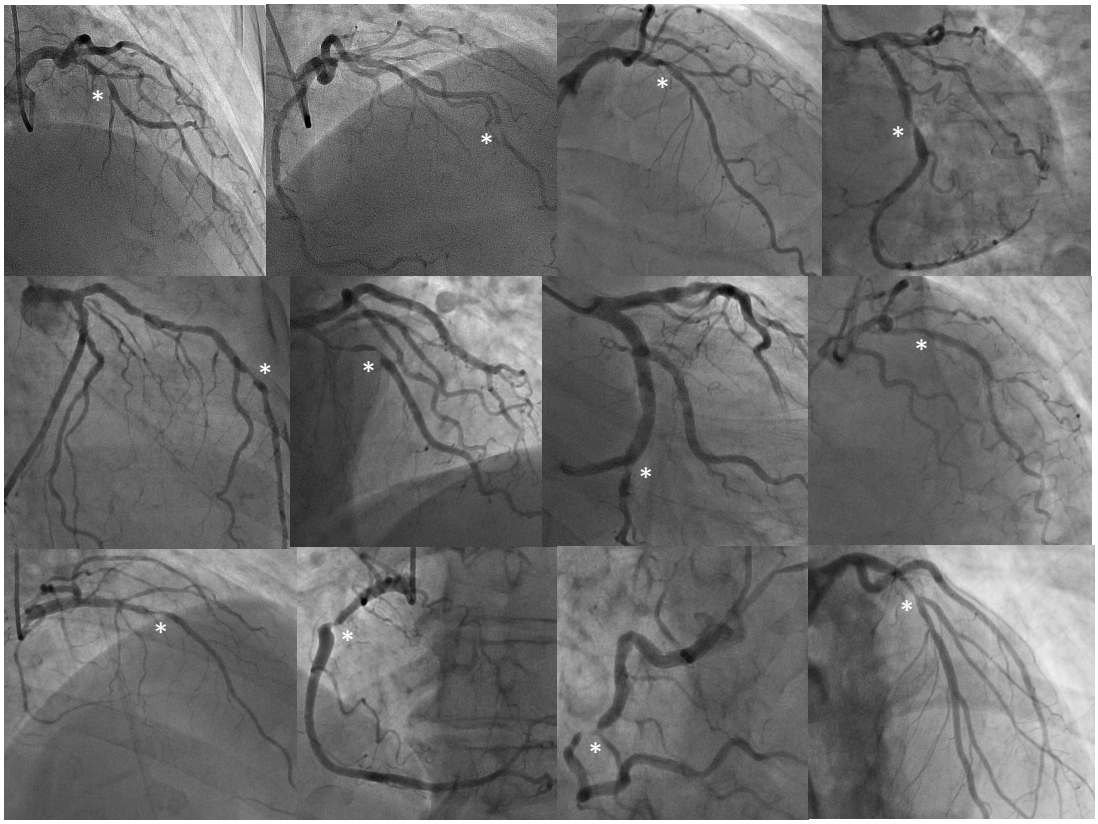


Figure 3.3: ORBITA Coronary angiograms of the first 12 consecutively randomised patients

The target vessel is marked with an asterisk.

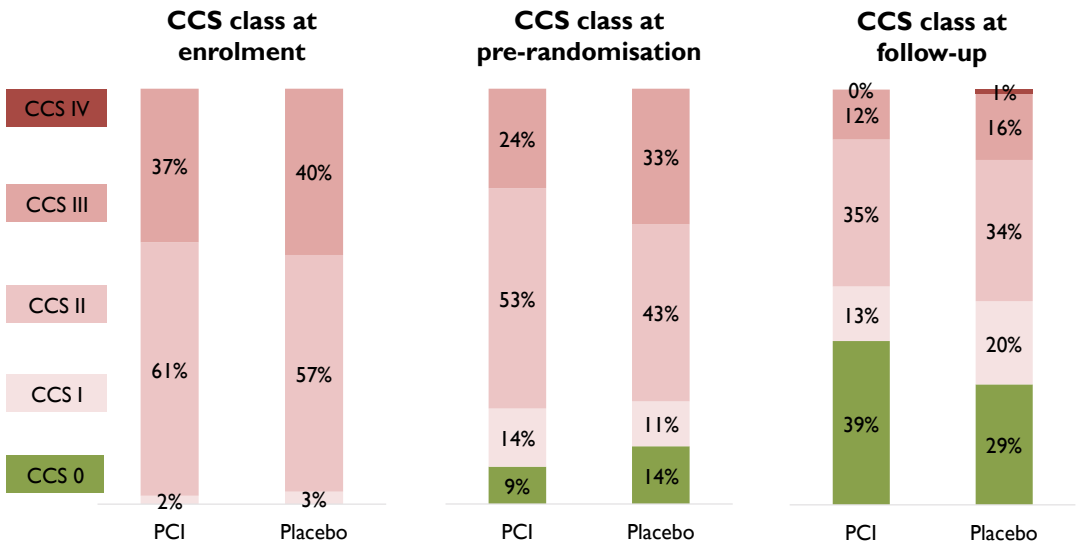


Figure 3.4: ORBITA Canadian Cardiovascular Society class at enrollment, pre-randomisation and follow-up

4 Effects of fractional flow reserve and instantaneous wave-free ratio on the placebo-controlled response to percutaneous coronary intervention in stable coronary artery disease: the physiology-stratified analysis of ORBITA

4.1 Abstract

4.1.1 Background

There are no data on how FFR and iFR affect the degree of placebo-controlled efficacy of PCI in stable CAD.

4.1.2 Methods

We report the effect of pre-randomisation invasive physiology within ORBITA, a randomised placebo-controlled trial which enrolled patients with stable angina and angiographically severe single vessel coronary disease eligible for PCI on clinical criteria. Patients underwent a pre-randomisation research assessment of FFR and iFR. The operator was blinded to these values. Assessment of response variables, stress echo wall motion abnormality, patient-reported symptom frequency, physician-assessed angina severity, and treadmill exercise time were performed before randomisation and at blinded follow-up. Effects were calculated by analysis of covariance. The ability of FFR and iFR to predict placebo-controlled changes in response variables was tested using regression modelling.

4.1.3 Results

Invasive physiology data were available in 196 patients (103 PCI and 93 placebo). At enrollment the majority of patients had CCS class II or III symptoms (191/196, 97.4%) and patient-reported daily or weekly angina episodes (130/191, 71.1%). Mean FFR and iFR were 0.69±0.16 and 0.76±0.22 respectively. 97% of patients had one or more positive ischaemia tests.

PCI improved stress echo score more than placebo (1.07 segment units, 95% CI 0.70 to 1.44, $p<0.000001$). The placebo-controlled effect of PCI on the stress echo score increased progressively with decreasing FFR ($p_{interaction}<0.00000001$) and with decreasing iFR ($p_{interaction}<0.00000001$). PCI did not improve angina frequency score more than placebo (OR 1.64, 95% CI 0.96 to 2.80; $p=0.072$) with no detectable evidence of interaction between either FFR ($p_{interaction}=0.849$) or iFR ($p_{interaction}=0.783$). PCI was more likely to result in patient-reported freedom from angina than placebo

(OR 2.47; 95% CI 1.30 to 4.72; p=0.006) but neither FFR nor iFR modified this effect ($p_{interaction}$=0.693 and $p_{interaction}$=0.761 respectively).

The estimated effect of PCI on baseline-adjusted total exercise time between the two arms was 20.7s (95% CI -4.0 to 45.5; p = 0.100) with no interaction of FFR and iFR ($p_{interaction}$=0.318 and $p_{interaction}$=0.523 respectively).

4.1.4 Conclusions

In patients with stable angina and severe coronary stenosis, stress echo score was more sensitive than patient-reported angina frequency or change in treadmill exercise time at detecting the effect of PCI. The lower the FFR or iFR, the greater the magnitude of stress echocardiographic improvement caused by PCI.

4.2 Clinical perspective

4.2.1 What is new?

1) This report of ORBITA stratified by invasive physiology provides the first placebo-controlled evidence of the effect of FFR and iFR on the size of benefits attributable to PCI.
2) The degree of invasive ischaemia did not predict the degree of patient-reported or physician-assessed symptoms or treadmill exercise time.
3) PCI improved stress echo score more clearly than symptoms or exercise time, and the degree of improvement was markedly predicted by pre-randomisation FFR and iFR.

4.2.2 What are the clinical implications?

1) Under blinded conditions, technically successful PCI, with large improvements in invasive physiology and stress echo score, is difficult to detect by patients or physicians.
2) The contrast between this finding and unblinded clinical experience of large benefit from PCI suggests that knowledge that the lesion has been eliminated may make an important contribution to symptoms and exercise time.
3) The efficacy of PCI on objective stress echocardiography ischaemia is progressively larger with lower FFR or iFR values before PCI.

4.3 Introduction

PCI for stable CAD is widely accepted to alleviate angina based on unblinded clinical experience and unblinded randomised controlled trials.[13,17,18,25,83,84] However, in the first blinded trial, ORBITA, the placebo-controlled effect of PCI on the pre-specified primary endpoint of exercise time at 6 weeks, by pre-specified statistical methods,[58] unexpectedly[13] did not meet the criteria for statistical significance (point estimate 16.6s, 95% CI -8.9 to 42.0).[85]

ORBITA used conventional, clinical criteria for eligibility for PCI, including symptoms and angiographic assessment. All patients were treated with guideline-directed medical therapy with an average of 3 anti-anginal agents. In ORBITA, 94% of patients had one or more positive ischaemia tests. The unexpected result of the blinded trial suggested that the commonly observed link between unblinded PCI of severe anatomic stenosis and improvement in symptoms and exercise capacity may be mediated by more complex pathways than a simple progression from anatomy to physiology to patient-perceived benefit.

ORBITA showed that stress echocardiography was a more sensitive marker of physiological efficacy of PCI (point estimate -0.07 wall motion score index units, 95% CI -0.11 to -0.04) than treadmill exercise time or patient-reported or physician-assessed symptoms.

In principle, the sequence of steps by which PCI relieves angina is simple. The angiographic stenosis is relieved, which improves coronary haemodynamics, and improves perfusion that is detectable as improvement of wall motion by stress echocardiography. This would then improve patient-reported symptoms. These in turn may be detected by the physician and may impact exercise time.

Routine unblinded clinical practice breaks this mechanistic sequence because the physician appropriately provides reassurance to the patient that the lesion has been

eliminated. The impact of this is difficult to recognise unless PCI is tested under blinded conditions.

A key aim of ORBITA was to document the impact of FFR and iFR on the placebo-controlled response to PCI. To do this, the main enrollment criterion was that the patient was clinically appropriate for PCI. After the decision had been made on conventional clinical criteria, research FFR and iFR measurements were made. This report, the physiology-stratified analysis of ORBITA, describes how FFR and iFR determine the placebo-controlled effect of PCI on stress echo score, patient-reported and physician-assessed symptoms, quality of life, and treadmill exercise time.

4.4 Methods

4.4.1 Study design

The design of the ORBITA trial has been previously described.[85] In summary, patients with stable angina and angiographically severe single vessel coronary disease were enrolled at 5 UK sites. At enrollment patients had assessment of symptoms by CCS angina class and completed questionnaires on angina and quality of life. The trial consisted of 2 consecutive phases: (1) six-week medical optimisation phase of antianginal medication uptitration, ending with pre-randomisation assessment and the blinded angiography procedure, and (2) six-week blinded follow-up phase ending with the follow-up assessment. The study was approved by a national ethics committee and all patients provided written consent.

The pre-randomisation assessment included: (1) physician-assessed grading of angina severity (CCS class), (2) patient-reported symptoms using Seattle Angina Questionnaire,[63] (3) quality of life using EQ-5D-5L questionnaire, (4) cardiopulmonary exercise testing using the smoothed modified Bruce protocol[67] which incorporates an initial 3 minutes of low level exercise that is not present in the standard Bruce protocol, and (5) dobutamine stress echocardiography.

4.4.2 Invasive physiological assessment

Patients then attended for the invasive procedure, which included research invasive pressure measurements and then randomisation. Patients wore over-the-ear headphones playing music for auditory isolation. Coronary angiography was performed via the radial or femoral approach.

Invasive physiological assessment was performed with the clinical operator blinded to the results, as follows. The clinical operator, in all cases a consultant interventional cardiologist experienced in physiology measures, positioned the pressure wire radiographically but was not able to see the physiology display. A separate research interventional cardiologist was observing the physiology display to confirm signal quality and document the values digitally but did not convey the physiology values to the clinical operator.

The reason to keep the clinical operator blinded to the physiology measures was to enable patients with a clinically representative range of values to be randomised in a single trial, with all decision making and outcome assessment identical regardless of physiological value. This distinguishes ORBITA from previous evaluations of physiology in which patients in different FFR ranges were randomised with different protocols for outcome assessment.[18,70]

After administration of intracoronary nitrate and normalisation of the pressure wire, FFR and iFR were measured using standard techniques with the wire placed at least 3 vessel diameters distal to the most distal stenosis. IV adenosine was then administered (140mcg/kg/min) via a femoral venous line or antecubital fossa vein and FFR was measured. Drift check was recorded.

The operator then waited for 10 minutes. Intracoronary nitrate was re-administered, the wire was re-normalised and re-advanced into the same distal position using cine images from the first physiological assessment as a guide. iFR and FFR measurements were repeated. Drift check was once again performed.

If at any stage there was significant wire drift (Pd/Pa ratio outside the range 1.00 ± 0.02), the wire was re-normalised and iFR and FFR measurements were repeated with final drift check.

The mean values of FFR and of iFR were used for analysis.

4.4.3 Blinding and randomisation

After physiological assessment, patients received incremental doses of intravenous benzodiazepine and opiate until a deep level of conscious sedation was achieved. Once this was confirmed, they were then randomised to receive PCI or placebo procedure.

If randomised to placebo no further invasive measurements were made and the patient remained in the catheter laboratory for a minimum of 15 minutes.

If randomised to PCI, this was performed using angiographic guidance with drug eluting stents implanted and complete angiographic revascularisation mandated. Post-dilatation was recommended, and intravascular ultrasound or optical coherence tomography were used at the operator's discretion.

After PCI, iFR and FFR were re-measured, and again the clinical operator was blinded to the results.

The patient and all subsequent medical caregivers were blinded to the treatment allocation using methods described previously.[85]

4.4.4 Study endpoints and follow-up

At the end of the blinded follow-up period patients re-attended to have repeat assessment of questionnaires, cardiopulmonary exercise testing and stress echocardiography. They were then unblinded and returned to routine clinical care pathways. Patients in the placebo arm were able to receive PCI if they wished.

Dobutamine stress echocardiography

Rest and stress cardiac regional wall motion was assessed using dobutamine stress echocardiography. The test was performed by a physician and sonographer. The patient, physician and sonographer were all blinded to allocation arm.

Analysis was also performed blinded to treatment allocation and phase (pre-randomisation or follow up), using an online reporting tool. In the original ORBITA publication, analysis had been performed by 2 imaging consultants.

For the present physiology-stratified analysis of ORBITA, each scan received 12 opinions. Each scan was examined twice by 6 imaging consultants who were blinded to treatment allocation, time-point of the scan, their colleagues' opinions, and (on the second viewing) their own first opinion.

In this physiology-stratified analysis of ORBITA, for ease of reader interpretation, stress echo results are presented in a manner that represents the number of hypokinetic segments (with akinetic segments scoring double, and dyskinetic scoring triple, and aneurysmal segments scoring quadruple). In detail, the left ventricle was divided into the standard 17 segments. Wall motion was scored as follows: normal = 0, hypokinetic = 1, akinetic = 2, dyskinetic = 3 or aneurysmal = 4. These individual wall abnormality scores at peak stress were summed, giving a total that could range from 0 (for normal) to theoretically 3×17. Both opinions from all 6 consultants were then averaged. This stress echo score can be broadly converted to classical wall motion score index as follows: wall motion score index = 1+(stress echo score)/17.

Cardiopulmonary exercise testing

All cardiopulmonary exercise tests investigations were performed using the QUARK CPET breath-by-breath metabolic measurement system (COSMED, Rome, Italy). Cardiopulmonary exercise testing was performed using the smoothed modified Bruce protocol and endpoints reported as previously described.[85]

4.4.5 Statistical analysis

For physiology-stratified analysis of ORBITA the data available consisted of all patients with at least one form of invasive physiological assessment at pre-randomisation. Summary statistics were presented as appropriate for baseline characteristics.

The main ORBITA report applied unpaired t-tests of change scores for continuous variables because that was the pre-specified method of analysis.[58] However, regression models (a generalised form of analysis of covariance) provide increased statistical power, and allow the interaction between FFR and iFR and benefit to be tested, and so these are used for this physiology-stratified analysis of ORBITA.[86]

The Seattle Angina Questionnaire scales for angina frequency, physical limitation and angina stability scores were derived from the patient's answers in accordance with published guidelines.[76]

For each endpoint, a model was fitted. For the continuous endpoints of EQ-5D-5L, Seattle Angina Questionnaire physical limitation score, total exercise time and stress echo score linear models were used. For the ordinal variables of Seattle Angina Questionnaire angina frequency and angina stability and CCS class a proportional odds ordinal logistic model was used.

To aid interpretation we also report frequency of angina from the Seattle Angina Questionnaire. Angina was defined as chest pain, chest tightness or anginal attacks.[63] For these categorical data, to enhance instant interpretability,[63] we have presented the data in its original ordinal categories (daily, weekly, monthly or absence of patient-reported angina episodes) and used a proportional odds logistic regression model for frequency of angina and freedom from angina.

For both continuous and categorical outcome variables we modelled the follow-up value conditioned on the pre-randomisation value transformed by a restricted cubic spline with three parameters, and randomisation arm. A model was then fitted for each outcome variable with pre-randomisation FFR or iFR interacting with the randomisation arm with a restricted cubic spline with three parameters, i.e. the shape

of effect was allowed to vary over treatments.[86] Graphs of the endpoints against FFR and iFR, and the contrast between the arms was generated adjusting for the median value of the pre-randomisation value.

All analyses were performed using the open-source statistical environment "R",[87] with the package "rms" for regression modelling,[88] and "ggplot2" for graphs.[89]

4.5 Results

ORBITA enrolled 230 patients. After the medical optimisation phase 200 patients were randomised to PCI (n=105) versus placebo (n=95). Four patients in the ORBITA dataset did not have physiological assessment because in 3 patients the lesion could not be crossed with the pressure wire, and in 1 patient crossing of the lesion with the pressure wire caused intimal disruption requiring immediate PCI. Therefore, 196 randomised patients had invasive physiological assessment and were available for the physiology-stratified analysis of ORBITA (103 in PCI arm and 93 in placebo arm). Within this dataset there were 2 patients in whom we were unable to elicit a hyperemic response with intravenous or intracoronary adenosine, and therefore only iFR data were obtained.

4.5.1 Patient demographics

Patient demographics are shown in Table 4.1. The majority of patients (98.1% in PCI arm and 96.8% in placebo arm) had physician-assessed CCS class II or III angina severity at enrollment. The majority of patients reported by questionnaire that they had daily or weekly episodes of angina (69.3% in PCI arm, 66.7% in placebo arm) at enrollment (Table 4.2 and Table 4.3).

4.5.2 Medical therapy

At pre-randomisation, the majority of patients were taking more than 2 antianginal medications (85.4% in PCI vs. 90.3% in placebo, Table 4.4). 97.1% of patients in the PCI arm and 96.8% in the placebo arm were taking dual antiplatelet therapy. Three patients in the PCI arm and 3 patients in the placebo arm were only on a single antiplatelet agent because of aspirin intolerance.

4.5.3 Procedural demographics

Procedural demographics are shown in Table 4.5. The majority of patients (69.9%) had lesions in the left anterior descending artery, these lesions were in the ostium or proximal segment of the left anterior descending artery in 55.5% and mid left anterior descending artery in 51.8%.

The FFR and iFR distributions are shown in Figure 4.1 and Figure 4.2 respectively. The mean FFR was 0.69 (SD 0.16): 145/194 (74.7%) had FFR≤0.80, mean 0.62 (SD 0.13); the remainder had mean FFR 0.87 (SD 0.04). The mean iFR was 0.76 (SD 0.22): 136/196 (69.4%) had iFR≤0.89, with mean 0.69 (SD 0.21); the remainder had mean iFR 0.94 (SD 0.03).

Overall 191 patients (97%) had 1 or more positive ischemia tests by time of randomisation; these consisted of a pre-enrollment clinical test, research stress echo, FFR≤0.80 or iFR≤0.89. The angiographic images of the remaining 5 patients are shown in Figure 4.3.

All patients in the PCI arm had drug eluting stents implanted. Post-dilatation was performed with a non-compliant balloon in 86 (83.5%) of these stents. Mean post-PCI FFR was 0.90 (SD 0.06) and post-PCI iFR 0.95 (SD 0.04). Six (6.3%) patients had FFR≤0.80 post procedure: their mean FFR was 0.76 (SD 0.06). Five (4.9%) patients had iFR≤0.89 post procedure: their mean iFR was 0.86 (SD 0.04).

4.5.4 Study endpoints

Dobutamine stress echocardiography

The stress echo dataset consists of 159 patients (90 PCI, 69 placebo), each with pre-randomisation and follow-up scans, with each scan having reported twice by 6 imaging consultants, and each with pre-randomisation FFR and iFR values. Overall, PCI improved the stress echo score when compared to placebo (difference 1.07 segment units, 95% CI 0.70 to 1.44; $p<0.000001$, Table 4.6).

There was an interaction between FFR and the stress echo improvement from PCI over placebo ($p_{interaction}<0.00000001$), with a progressively larger improvement at lower pre-randomisation FFR values. Figure 4.4 shows this relationship, modelled with a spline; with the confidence interval shaded in.

Similarly, there was an interaction between iFR and the stress echo improvement ($p_{interaction}<0.00000001$, Figure 4.5), with a progressively larger improvement at lower pre-randomisation iFR values.

Patient-reported symptoms and quality of life

Paired patient-reported data at pre-randomisation and follow-up from the Seattle Angina Questionnaire was available in 192 patients (103 in the PCI arm and 89 in the placebo arm).

There was little evidence that PCI improved Seattle Angina Questionnaire angina frequency score more than placebo (OR 1.64, 95% CI 0.96 to 2.80; p=0.072, Table 4.6). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}=0.848$) or iFR ($p_{interaction}=0.783$) and the effect of PCI on angina frequency score (Figure 4.6 and Figure 4.7).

PCI was more likely to result in patient-reported freedom from angina than placebo (OR 2.47; 95% CI 1.30 to 4.72; p = 0.006, Figure 4.8; Table 4.6). There was no detectable evidence of interaction between either FFR or iFR and the effect of PCI on the likelihood of patient-reported freedom from angina ($p_{interaction}=0.693$; Figure 4.9 and $p_{interaction}=0.761$; Figure 4.10).

PCI did not improve Seattle Angina Questionnaire physical limitation score more than placebo: point estimate 2.59 units (95% CI -2.93 to 8.10; p = 0.356, Table 4.6). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}=0.806$) or iFR ($p_{interaction}=0.616$) and the effect of PCI on physical limitation score (Figure 4.11 and Figure 4.12).

PCI did not improve Seattle Angina Questionnaire angina stability score more than placebo (OR 1.30; 95% CI 0.74 to 2.27; p = 0.357, Table 4.6). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.568) or iFR ($p_{interaction}$=0.930) and the effect of PCI on angina stability score (Figure 4.13 and Figure 4.14).

Paired EQ-5D-5L data was available for 189 patients (102 in the PCI arm and 87 in the placebo arm).

PCI did not improve EQ-5D-5L quality of life score more than placebo: point estimate 0.001 (95% CI -0.039 to 0.042; p=0.951, Table 4.6). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.730) or iFR ($p_{interaction}$=0.933) and the effect of PCI on EQ-5D-5L quality of life score (Figure 4.15 and Figure 4.16).

Physician-assessed symptoms

Paired CCS data were available for 192 patients in the physiology-stratified analysis of the ORBITA dataset (103 in PCI arm and 89 in placebo arm). At enrollment there were no patients with CCS 0, at pre-randomisation 8.74% patients in the PCI arm and 14.0% patients in placebo arm were classified as CCS 0, by follow-up 39.8% of patients in the PCI arm and 28.0% of patients in placebo arm were classified as CCS 0 (Table 4.7). PCI did not improve CCS class more than placebo (OR 0.73, 95% CI 0.43 to 1.25; p=0.254, Table 4.6). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.877) or iFR ($p_{interaction}$=0.841) and the effect of PCI on change in CCS class (Figure 4.17 and Figure 4.18).

Exercise time

Paired exercise time data were available for 190 patients in the physiology-stratified analysis of the ORBITA dataset (102 in PCI arm and 88 in placebo arm). The estimated effect of PCI over placebo on exercise time using regression modelling was 20.7 seconds (95% CI -4.0 to 45.5; p=0.100, Table 4.6). For this relatively small effect, there was no detectable evidence of interaction between either FFR

($p_{interaction}$=0.318) or iFR ($p_{interaction}$=0.523) and the effect of PCI on exercise time increment (Figure 4.19 and Figure 4.20).

4.6 Discussion

4.6.1 Main findings of the physiology-stratified analysis of ORBITA

This physiology-stratified analysis of ORBITA provides placebo-controlled data on the relationship between baseline invasive physiology and the efficacy of PCI in stable coronary artery disease. Along a notional mechanistic pathway from severe angiographic stenosis to symptom relief, there was a progressively smaller effect of PCI, and smaller impact of FFR and iFR on this effect.

The initial anatomical and haemodynamic effects of PCI were large. Next in the pathway, the stress echo score was very clearly improved by PCI versus placebo. The more severe the FFR and iFR, the larger the PCI effect on stress echo score.

The next detectable point in the pathway is patient-reported change in symptoms, of which the most binary is absence versus presence of symptoms: on this endpoint of patient-reported freedom from angina, PCI was more effective than placebo. The other downstream endpoints of Seattle Angina Questionnaire angina frequency score, physical limitation score, angina stability score and EQ-5D-5L quality of life score did not show an effect of PCI beyond placebo. Nor could physician-assessment (CCS) of patient symptoms or treadmill exercise time detect the effect of PCI beyond placebo.

For all the endpoints in which PCI did not show a detectable effect there was no evidence of interaction between either FFR or iFR and the effect of PCI. While freedom from angina showed a detectable effect of PCI above placebo, it too showed no interaction between FFR or iFR and the effect of PCI. This means that there is no sign of the unexpected primary result of ORBITA[85] being the consequence of inclusion of some patients with FFR>0.80.

4.6.2 The effect of blinding

Two themes emerge. First, in routine clinical practice PCI of straightforward single vessel coronary disease often gives good angina relief that may make the ORBITA results difficult to accept. The Angioplasty Compared to Medicine (ACME) trial, which resembles ORBITA in many aspects except that patients were informed that the lesion had been fixed, showed a 96 second benefit of balloon angioplasty mirroring day-to-day practice which is similarly unblinded.[13] A possible explanation for the difference in findings is that the ACME trial and routine practice are unblinded while the ORBITA trial was blinded. This would imply that the dominant component of the day-to-day experience of symptomatically effective PCI is not mediated in the manner we commonly assume, but by the power of the physician-patient interaction.

The second theme arising from ORBITA is that of the mechanistic sequence of events. This physiology-stratified analysis reveals the close tie between invasive haemodynamics and myocardial functional response to stenting. PCI in ORBITA was successful not only anatomically and haemodynamically but also in allowing cardiac function under stress to normalise. The progressive impact of FFR and iFR supports this being a mechanistic sequence.

What remains puzzling is why this did not translate as well as hoped into relief of patient symptoms under blinded conditions. An effect was just detectable, in only one marker, freedom from angina directly reported by the patient. There was no sign of an impact of FFR or iFR. The other downstream endpoints including physician interpretation of symptom severity and treadmill exercise time, showed neither a significant effect of PCI nor an impact of FFR or iFR on the PCI effect.

4.6.3 Statistical methodology for endpoint analysis

ORBITA was analysed as pre-specified,[58] with unpaired t-test of change scores. An alternative statistical approach, applied in this stratified analysis of ORBITA, is regression modelling, which offers advantages including the ability to adjust appropriately for baseline values and to measure the interaction between FFR and iFR on the effect size. The pre-specified primary endpoint was change in the objective and continuous variable of exercise time, as was used in previous unblinded testing of PCI[13] and is commonly done for anti-anginal medications.[74,75] The increment of

exercise time with PCI over placebo, regardless of method of analysis, was smaller than might have been expected based on previous unblinded evidence.[13] The cause of the difference between ORBITA and ACME appears to be the imposition of blinding and not the sample size, pre-randomisation treadmill exercise time or statistical methods.

4.6.4 Mechanistic pathway from angiographic stenosis to exercise time improvement

Exercise treadmill time has a long track record of detecting the effect of anti-anginal medication against placebo. However, on reflection, there is no reason to suppose that PCI works through the same mechanistic steps as drugs. At the simplest level, PCI opens the stenosis and anti-anginals do not. This may explain why treadmill exercise time under placebo-controlled conditions responds differently to PCI than to anti-anginal medications.

Ultimately the patient-centred symptomatic aim is to reduce episodes of angina and ideally render patients free from angina. Under blinded conditions more patients directly reported freedom from angina with PCI than with placebo. It is possible that this endpoint detected an effect of PCI because it is easier to be sure that one is free of angina than to reliably distinguish different levels of pain.[90]

Physician-assessed was less sensitive than patient-reported symptom status, which may be for several reasons. First, the questionnaires are closer to the direct patient experience, unfiltered by physician interpretation.[91] Second, completion of a questionnaire may be less likely than a verbal conversation to be influenced by the relationship between the patient and the staff member. Third, the questionnaires specifically assess frequency of patient-reported angina rather than the level of activity considered to trigger angina. However, once all of these patient-reported and physician reported endpoints, including patient-reported freedom from angina, were stratified by pre-randomisation physiology, there was no interaction between either FFR or iFR and the endpoints by randomisation arm.

The physiology-stratified analysis of ORBITA provides the first placebo-controlled evidence of the efficacy of PCI on stress echo score and shows that the degree of benefit is greatest in those patients with the highest degree of ischaemia measured by invasive physiology. It additionally provides data that patients in the PCI arm were more likely to report freedom from angina at follow-up compared to placebo but that this effect was not predicted by pre-randomisation FFR and iFR values.

ORBITA and the physiology-stratified analysis of ORBITA remind us of the length and complexity of the biological pathway we are hoping to influence by PCI. Points further apart in the pathway may be progressively less closely tied. At the start of the pathway, performing PCI delivers an immediate dramatic improvement in angiographic appearance which is quickly confirmed by the improvement in haemodynamic measures. The magnitude of haemodynamic improvement is large enough for stress echocardiography to powerfully confirm that the intervention is allowing the myocardium to perform more normally under stress. Next comes the patient's self-report of frequency of angina. Finally, the most tenuous influence under placebo-controlled conditions is the physician interpretation of patient description of severity of angina. The exercise treadmill time may be even less tightly linked to this pathway, explaining its relative insensitivity when all the other points show a progressive influence albeit with progressively diminishing clarity of effect.

4.6.5 Study limitations

This physiology-stratified analysis of ORBITA is a sub-analysis describing the 196 patients for whom invasive physiology measurements were available, only 98% of the 200 randomised in ORBITA. Moreover, the effect size of PCI on treadmill exercise time fell far short of our expectations based on unblinded prior research and, therefore, this endpoint is not powered for probing the relationship between invasive physiology and placebo-controlled response to PCI.[13] Although it was the pre-specified primary endpoint, exercise time was one of the least influenced markers. It was therefore not surprising that there was no detectable interaction with FFR and iFR.

ORBITA intentionally included patients appropriate for clinical PCI across a range of FFR and iFR values, to allow the effect of FFR and iFR on exercise time, symptoms and stress echocardiography to be evaluated. While this spectrum may be considered a limitation of ORBITA,[92] we consider it essential to cover a range of FFR and iFR, in order to test the dependency of effect size on FFR and iFR. Notably 97% of patients had ischemia documented on one or more non-invasive or invasive tests at the time of randomisation.

In this physiology-stratified analysis of ORBITA symptoms were quantified both directly from written answers given by patients to standardised questionnaires, applying a proportional-odds model, and using the published Seattle Angina Questionnaire symptom scales. We present the data from the questionnaire-documented frequency of angina using readily-interpretable terminology which has the advantages being patient-centric and easy to interpret but may not necessarily be comparable with studies that have taken a different approach.

In the primary ORBITA report, stress echocardiography data was presented as pre-specified, in the form of wall motion score index. Normal was 1.0, a single segment of hypokinesia was scored as 1.0588 and 2 segments of hypokinesia were scored as 1.1176. Interpretation of such scores by non-imaging specialists can be difficult. To aid interpretation, in this report, we score normal as 0, 1 segment of hypokinesia as 1, 2 as 2 and so on. This is a simple linear transformation that has no effect on the statistics.

For the primary ORBITA report, each stress echocardiogram was only scored by 2 consultants blinded to treatment allocation and time-point. In this physiology-stratified analysis of ORBITA, each stress echocardiogram was scored by 6 consultants, twice each, blinded to treatment allocation and time-point. This is different from common clinical practice but maximises the statistical power of the analysis.

All patients were considered by the physician to have angina at enrollment (i.e. were CCS class 1 or above), but in the patient-reported question on frequency of angina

from the Seattle Angina Questionnaire, 14.1% of patients indicated no symptoms of angina in the immediately preceding four weeks. We cannot tell whether this was caused by pre-enrollment anti-anginal therapy, by self-limiting of day-to-day activities, or indeed the unique way the study was performed with close direct supervision by the research team. The proportions of patients in CCS 0 at enrollment were 0% in ORBITA, 9% in ACME, 11.2% in FAME-2 and 12.5% in COURAGE.[11,14]

We should not be surprised that 49.5% of patients in this physiology-stratified analysis of ORBITA continued to report episodes of angina after PCI. After blinded PCI, physician-assessed CCS II-III in the PCI arm was 47% in ORBITA.[85,93] After unblinded PCI, physician-assessed CCS II-III was 57.1% in the second Randomised Intervention Treatment of Angina (RITA-2) at 6 months,[83] 45.5% in Medicine, Angioplasty, or Surgery Study (MASS-II) at 1 year,[94] and 34% in COURAGE at 1 year.[25] This may be because a proportion of chest pain at presentation clinically or in clinical trials is not caused by the epicardial stenosis that is seen on angiography.

4.7 Conclusions

Stress echocardiography sensitively detected the resolution of the consequences of ischaemia. Stratification of the results of the ORBITA trial by pre-randomisation invasive physiology shows a progressively larger effect of PCI versus placebo on stress echo ischaemia with progressively more severe pre-randomisation FFR and iFR.

The severity of ischaemia as measured by invasive physiology did not influence the PCI effect on any of the other endpoints of patient-reported or physician-assessed symptoms and quality of life or treadmill exercise time.

The effect of PCI on endpoints, and the extent to which this effect depends on FFR and iFR, declines progressively along the pathway from resolution of angiographic stenosis, through haemodynamics and myocardial performance, through to patient experienced symptoms and their downstream consequences.

Table 4.1: ORBITA-PHYSIOLOGY Patient demographics at enrollment

	PCI (n=103) n (%)	Placebo (n=93) n (%)	Complete group (n=196) n (%)
Age (yrs)	65.7±9.5	66.1±8.3	65.9±9.0
Male	72 (69.9)	71 (76.3)	143 (73.0)
Hypertension	70 (68.0)	65 (69.9)	135 (68.9)
Hypercholesterolemia	79 (77.0)	61 (65.6)	140 (71.4)
Diabetes	15 (14.6)	21 (22.6)	36 (18.4)
Previous MI	4 (3.9)	7 (7.5)	11 (5.6)
Previous PCI	10 (9.7)	14 (14.1)	24 (12.2)
CCS class			
I	2 (1.9)	3 (3.2)	5 (2.5)
II	62 (60.2)	53 (57.0)	115 (58.7)
III	39 (37.9)	37 (39.8)	76 (38.8)
Angina duration (months) Mean (SD)	9.54±15.8	8.45±7.59	9.03±12.6
Positive functional test	55 (53.4)	42 (45.2)	97 (49.5)
ETT	26 (25.2)	17 (18.3)	43 (21.9)
MIBI	10 (9.7)	11 (11.8)	21 (10.7)
DSE	19 (18.4)	13 (14.0)	32 (16.3)
MRI perfusion	0 (0)	1 (1.1)	1 (0.5)

MI= Myocardial infarction
PCI= Percutaneous coronary intervention
CCS= Canadian Cardiovascular Society Angina class
SAQ= Seattle angina questionnaire
ETT= Exercise tolerance test
MIBI= Nuclear medicine myocardial perfusion scan
DSE= Dobutamine stress echocardiography
MRI= Magnetic resonance imaging

Table 4.2: ORBITA-PHYSIOLOGY Patient-reported frequency of angina

		PCI n (%)	Placebo N (%)
Enrollment		n=101	n=90
Frequency of angina	Daily angina	32 (31.7)	27 (30.0)
	Weekly angina	38 (37.6)	33 (36.7)
	Monthly angina	18 (17.8)	16 (17.8)
	Angina free	13 (12.9)	14 (15.6)
Pre-randomisation		n=102	n=92
Frequency of angina	Daily angina	20 (19.6)	21 (22.8)
	Weekly angina	39 (38.2)	35 (38.0)
	Monthly angina	28 (27.5)	18 (19.6)
	Angina free	15 (14.7)	18 (19.6)
Follow-up		n=101	n=89
Frequency of angina	Daily angina	9 (8.9)	12 (13.5)
	Weekly angina	26 (25.7)	31 (34.8)
	Monthly angina	16 (15.8)	18 (20.2)
	Angina free	50 (49.5)	28 (31.5)

Data are presented from patient-reported data on angina frequency from the Seattle Angina Questionnaire. Angina is categorised as "daily" if there are one or more episodes of angina per day. The remaining patients are categorised as "weekly" there are one or more episodes of angina per week. The remaining are categorised as "monthly" if there are one or more episodes of angina per week. Below one episode per month is categorised as "angina free".

Table 4.3: ORBITA-PHYSIOLOGY Patient-reported presence of angina

		PCI n (%)	Placebo n (%)
Enrollment		n=101	n=90
Presence of angina	Angina present	88 (87.1)	76 (84.4)
	Angina free	13 (12.9)	14 (15.6)
Pre-randomisation		n=102	n=92
Presence of angina	Angina present	87 (85.2)	74 (80.4)
	Angina free	15 (14.7)	18 (19.6)
Follow-up		n=101	n=89
Presence of angina	Angina present	51 (50.4)	61 (68.5)
	Angina free	50 (49.5)	28 (31.5)

Data are presented from patient-reported data on angina frequency from the Seattle Angina Questionnaire. More than one episode on angina per month is categorised as “angina present”. Below one episode per month is categorised as “angina free”.

Table 4.4: ORBITA-PHYSIOLOGY Medical therapy

	PCI (n=103) n (%)	Placebo (n=93) n (%)
Enrollment		
Dual antiplatelet therapy	33 (32.0)	26 (28.0)
Lipid lowering therapy	66 (64.08)	61 (65.6)
0 antianginal	32 (31.1)	28 (30.1)
1 antianginal	53 (51.5)	37 (39.8)
≥2 antianginal	18 (17.5)	28 (30.1)
Pre-randomisation		
Dual antiplatelet therapy	100 (97.1)	90 (96.8)
Lipid lowering therapy	98 (95.1)	89 (95.7)
0 antianginal	2 (1.9)	4 (4.3)
1 antianginal	13 (12.6)	5 (5.4)
≥2 antianginal	88 (85.4)	84 (90.3)
Follow-up		
Dual antiplatelet therapy	100 (97.1)	85 (91.4)
Lipid lowering therapy	101 (98.1)	85 (91.4)
0 antianginal	0 (0)	4 (4.3)
1 antianginal	14 (13.6)	5 (5.4)
≥2 antianginal	89 (86.4)	84 (90.3)

Table 4.5: ORBITA-PHYSIOLOGY Procedural demographics

	PCI (n=103) n (%)	Placebo (n=93) n (%)	Complete group (n=196) n (%)
Vessel			
Left anterior descending	72 (69.9)	65 (70.0)	137 (69.9)
Ostial/proximal	46 (44.7)	30 (32.3)	76 (38.8)
Mid	33 (32.0)	38 (40.9)	71 (36.2)
Distal	4 (3.9)	8 (8.6)	12 (6.1)
Right coronary	16 (15.5)	15 (16.1)	31 (15.8)
Circumflex	9 (8.7)	9 (9.7)	18 (9.1)
First obtuse marginal	3 (2.9)	-	3 (1.5)
First diagonal	2 (1.9)	2 (2.2)	4 (2.0)
Intermediate	1 (1.0)	2 (2.1)	3 (1.5)
Serial lesions	17 (16.5)	12 (12.9)	29 (1.5)
No. pts with diameter stenosis ≥50% by QCA	87 (84.4)	79 (85.0)	(84.7)
No. pts with area stenosis ≥70% by QCA	96 (93.2)	83 (89.2)	179 (91.3)
Diameter stenosis by QCA Mean (SD)	64.1±13.7	63.7 ±13.6	63.9±13.6
Area stenosis by QCA Mean (SD)	84.4±10.1	84.0±10.2	84.2±10.1
FFR Median (IQR)	0.69±0.16 0.72 (0.25)	0.69±0.16 0.73 (0.21) (n=91)	0.69±0.16 (n=194)
iFR Median (IQR)	0.76±0.22 0.85 (0.24)	0.76±0.21 0.85 (0.21)	0.76±0.22
No. pts with FFR ≤0.80	76 (73.8)	69 (75.8) (n=91)	145 (74.7) (n=194)
No. pts with iFR ≤0.89	68 (66.0)	68 (73.1)	136 (69.4)
Stent length (mm) Median (IQR)	28.4±14.8 24 (15)	-	-
Stent diameter (mm) Median (IQR)	3.07±0.46 3 (0.75)	-	-
FFR post PCI (n=101) Median (IQR)	0.90±0.06 0.9 (0.06)	-	-
iFR post PCI Median (IQR)	0.95±0.04 0.95 (0.05)	-	-
No. pts with post FFR>0.80	95 (94.1) (n=101)	-	-
No. pts with post iFR>0.89	98 (95.1) (n=103)	-	-

QCA= Quantitative coronary angiography
FFR= Fractional flow reserve
iFR= Instantaneous wave-free ratio

Table 4.6: ORBITA-PHYSIOLOGY Endpoint analysis

Endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)
Dobutamine wall motion score	1.07 (95% CI 0.70 to 1.44; $p < 0.000001$)
Total exercise time	20.7s (95% CI -4.0 to 45.5; $p = 0.100$)
SAQ physical limitation score	2.59 (95% CI -2.93 to 8.10; $p = 0.356$)
EQ-5D-5L	0.001 (95% CI -0.039 to 0.042; $p = 0.951$)
Endpoint	**Logistic (proportional odds) ordinal regression model estimate (PCI over placebo)**
CCS class	OR 0.73 (95% CI 0.43 to 1.25; $p = 0.254$)
SAQ angina frequency	OR 1.64 (95% CI 0.96 to 2.80; $p = 0.072$)
SAQ angina stability	OR 1.30 (95% CI 0.74 to 2.27; $p = 0.357$)
Patient-reported freedom from angina	OR 2.47 (95% CI 1.30 to 4.72; $p = 0.006$)

Table 4.7: ORBITA-PHYSIOLOGY Physician-assessed severity of angina

		PCI n (%)	Placebo N (%)
Enrollment	**Class**	n=103	n=93
CCS	0	0 (0)	0 (0)
	1	2 (1.94)	3 (3.23)
	2	62 (60.2)	53 (60.0)
	3	39 (37.9)	37 (39.8)
Pre-randomisation		n=103	n=93
CCS	0	9 (8.74)	13 (14.0)
	1	14 (13.6)	10 (10.8)
	2	55 (53.4)	40 (43.0)
	3	25 (24.3)	30 (67.7)
Follow-up		n=103	n=89
CCS	0	41 (39.8)	26 (28.0)
	1	14 (13.6)	18 (19.4)
	2	35 (34.0)	30 (32.3)
	3	13 (12.6)	14 (15.1)
	4	0 (0)	1 (1.08)

CCS= Canadian Cardiovascular Society angina class

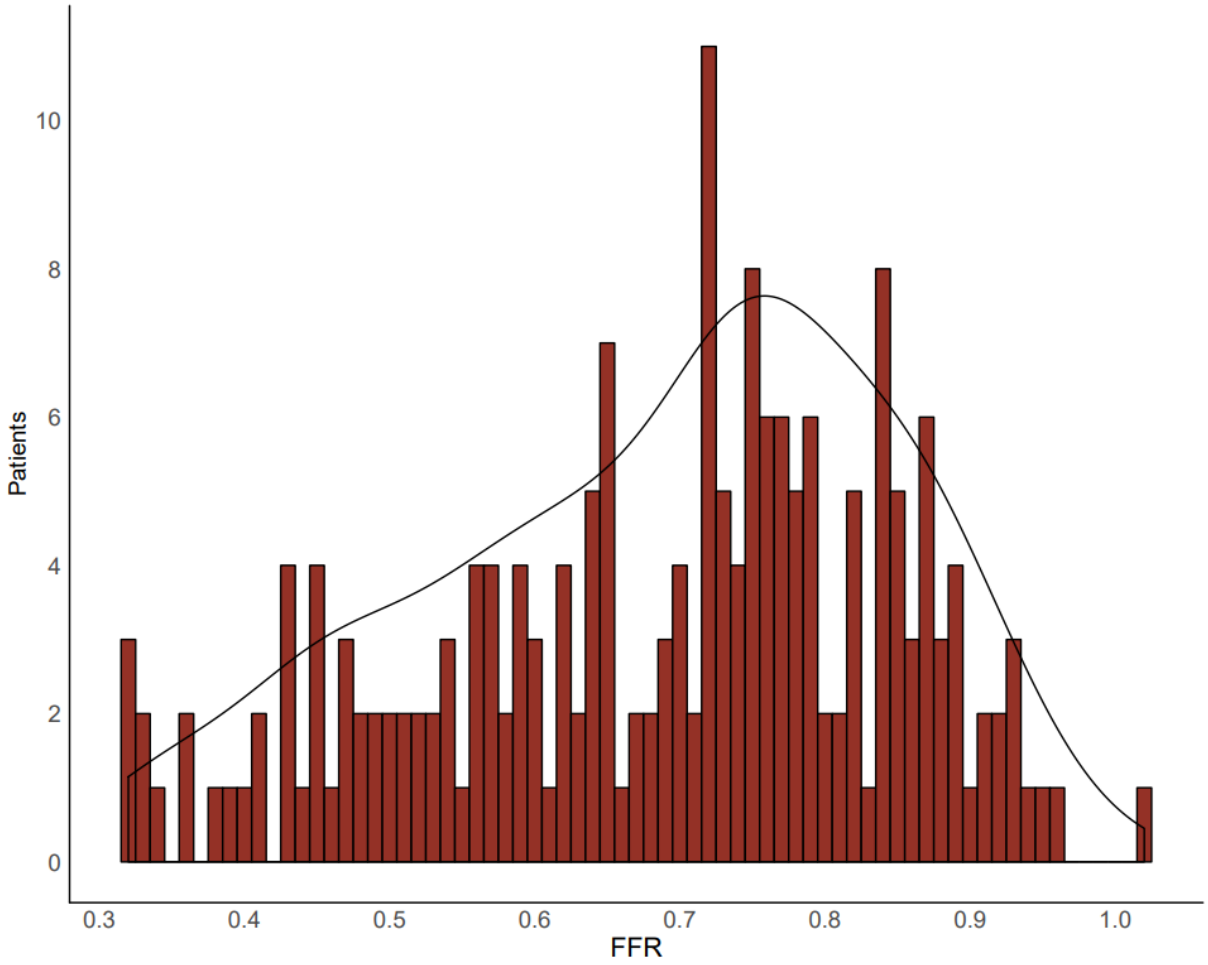


Figure 4.1: ORBITA-PHYSIOLOGY Distribution of FFR Values

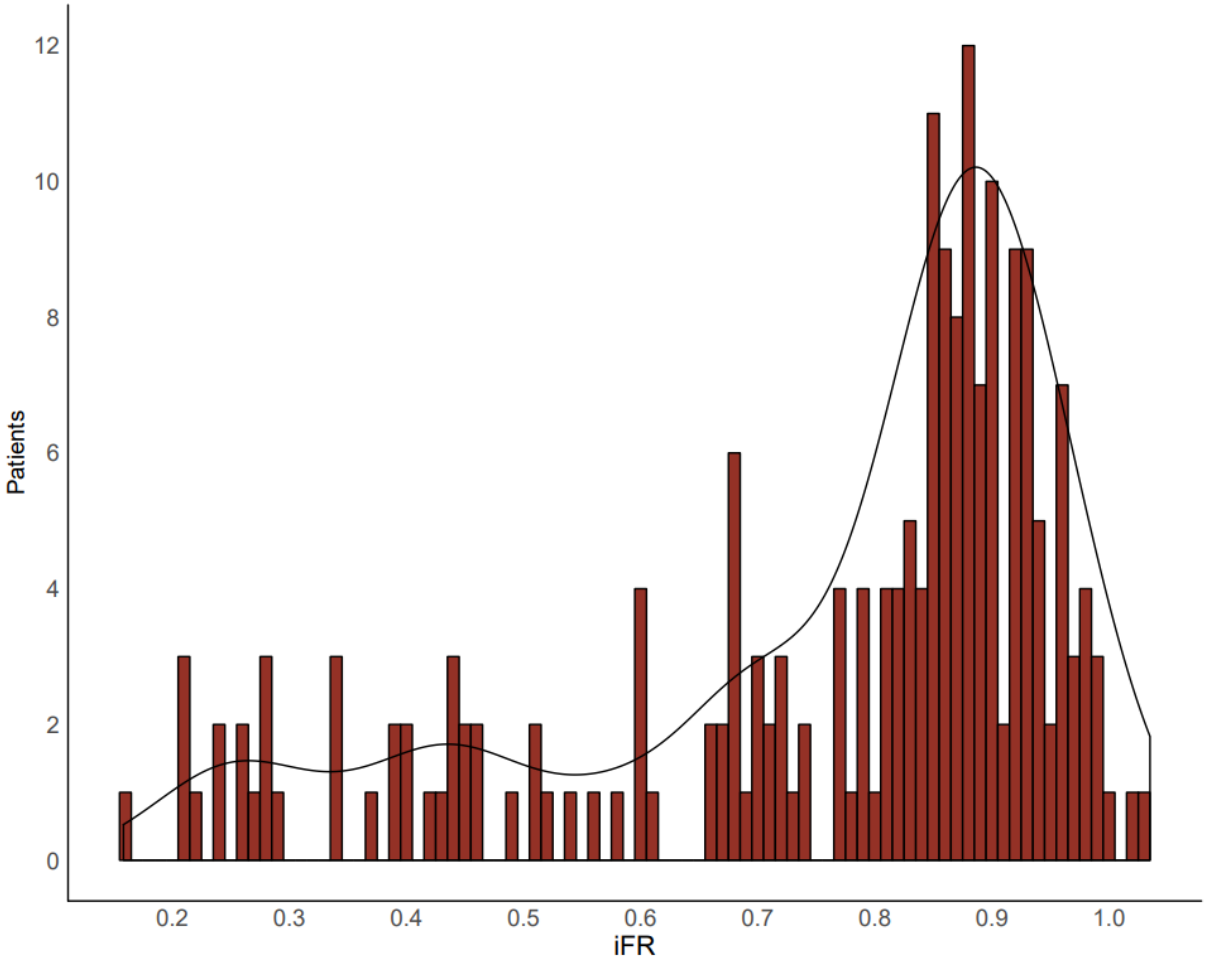


Figure 4.2: ORBITA-PHYSIOLOGY Distribution of iFR values

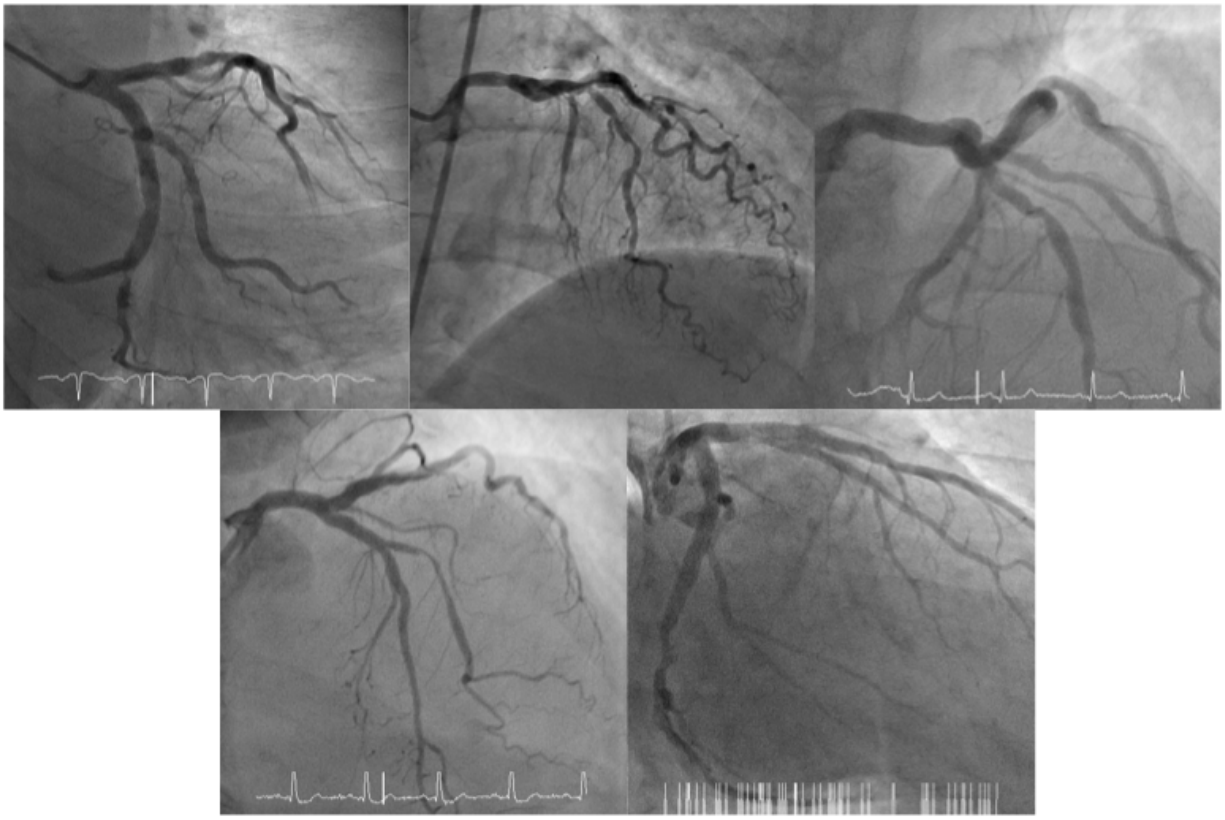


Figure 4.3: ORBITA-PHYSIOLOGY Angiographic images of patients with stable angina with no evidence of ischaemia on non-invasive or invasive functional test

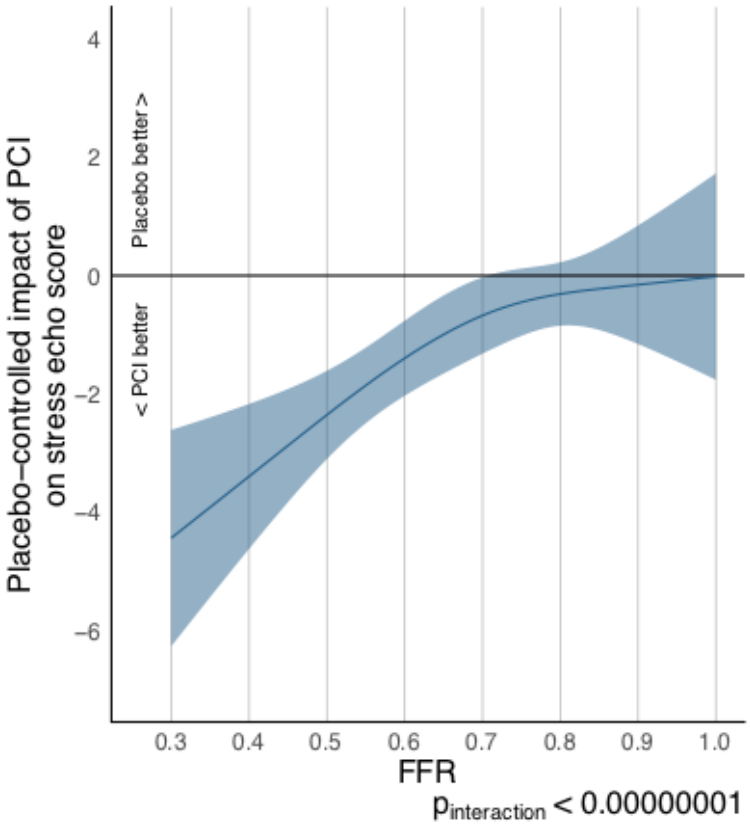


Figure 4.4: ORBITA-PHYSIOLOGY Relationship of treatment difference in stress echo score and pre-randomisation FFR by randomisation arm

At the right, with FFR≈1.0, the curve is ≈0, indicating that there is no difference between PCI and placebo. The shaded area represents the 95% CI for the estimate of this mean effect. At progressively lower FFR values, there is a progressively larger difference between PCI and placebo on the endpoint. This progressive tendency for larger effects on stress echo score with lower pre-randomisation FFR has $p_{interaction}<0.00000001$.

The stress echo score can be converted to classical Wall Motion Score Index as follows. Wall Motion Score Index = 1+(stress echo score)/17.

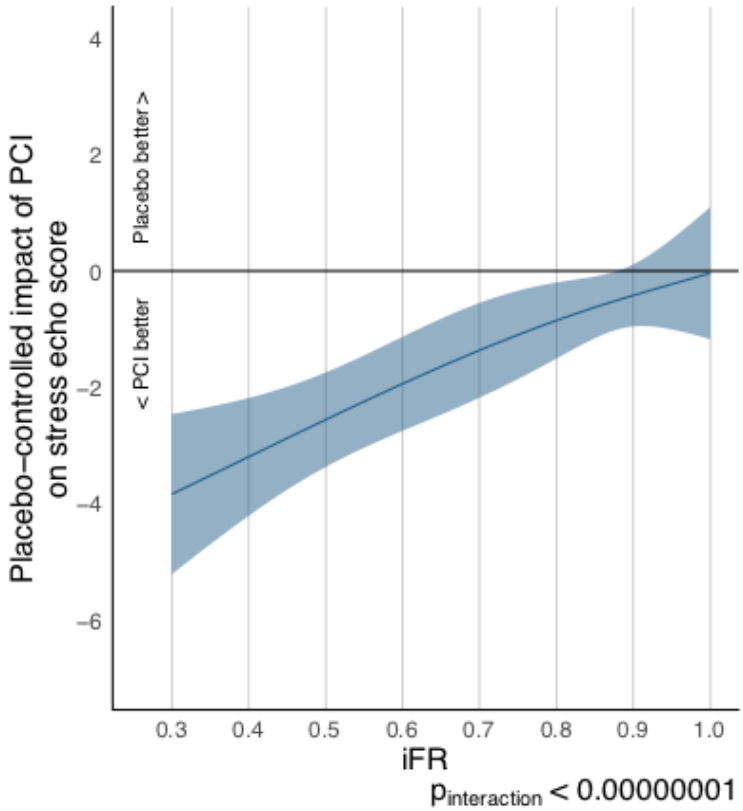


Figure 4.5: ORBITA-PHYSIOLOGY Relationship of treatment difference in peak stress echo score and pre-randomisation iFR by randomisation arm

At the right, with iFR≈1.0, the curve is ≈0, indicating that there is no difference between PCI and placebo. The shaded area represents the 95% CI for the estimate of this mean effect. At progressively lower iFR values, there is a progressively larger difference between PCI and placebo on the endpoint. This progressive tendency for larger effects on stress echo score with lower pre-randomisation iFR has $p_{interaction}<0.00000001$.

The stress echo score can be converted to classical Wall Motion Score Index as follows. Wall Motion Score Index = 1+(stress echo score)/17.

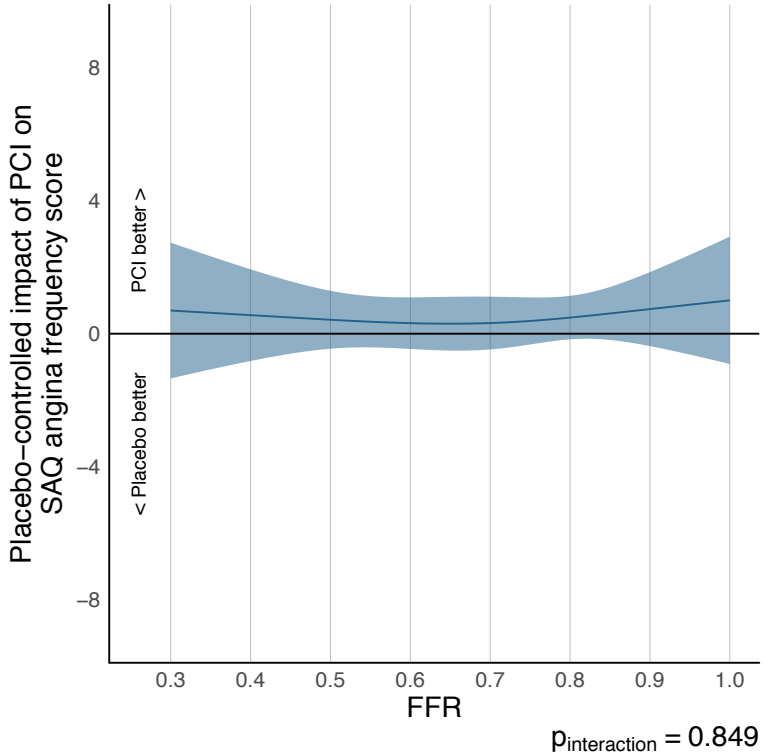


Figure 4.6: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

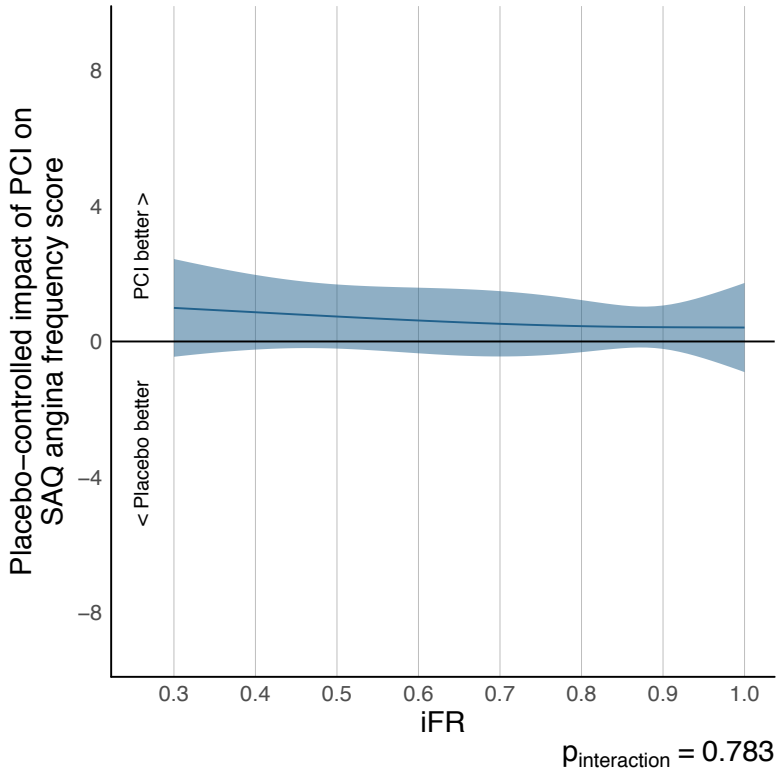
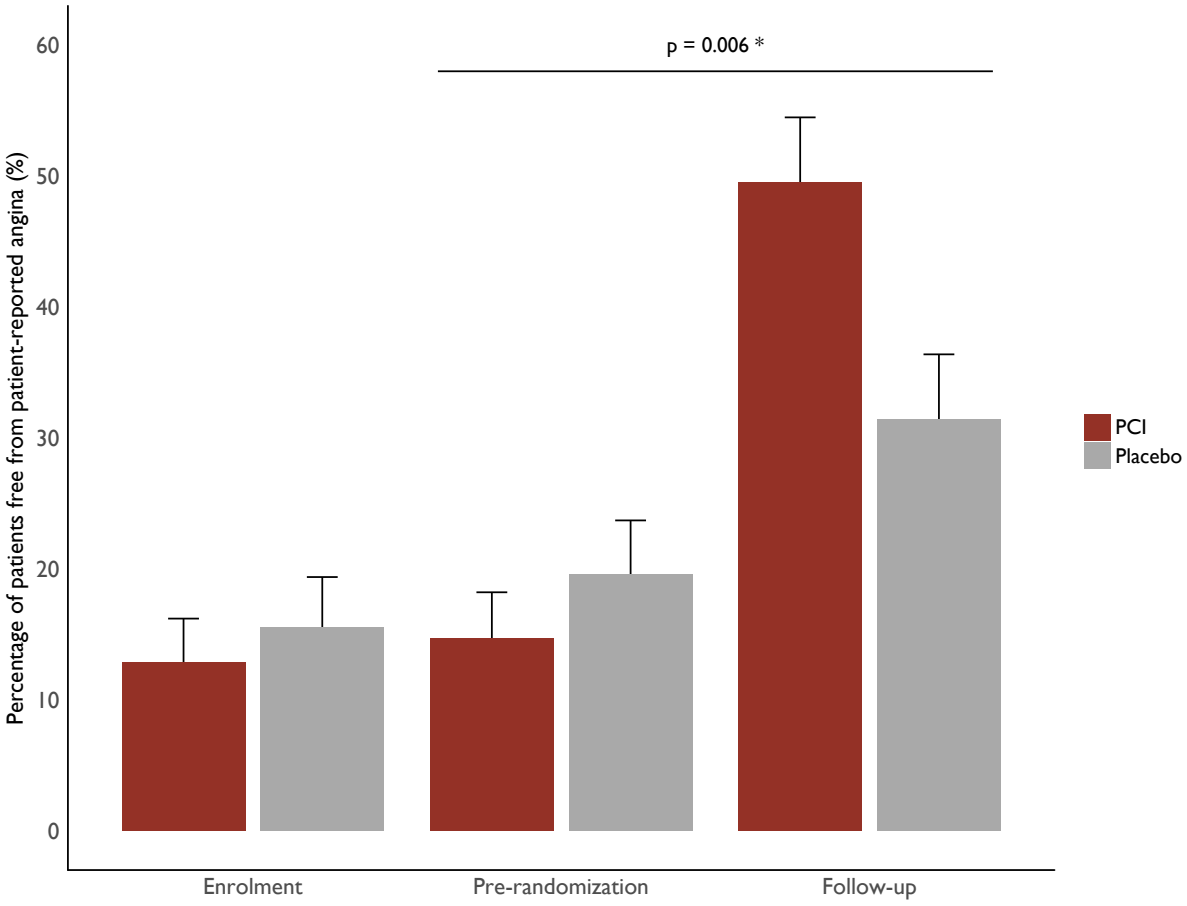


Figure 4.7: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.



* Proportional odds model of improvement between arms in freedom from patient-reported angina

Figure 4.8: ORBITA-PHYSIOLOGY Freedom from angina at enrollment, pre-randomisation and follow-up

Percentage of patients free of patient-reported angina at enrollment, pre-randomisation and follow-up per study arm based on patient-reported questionnaire data on frequency of angina. Proportional odds model for freedom from angina from pre-randomisation to follow-up

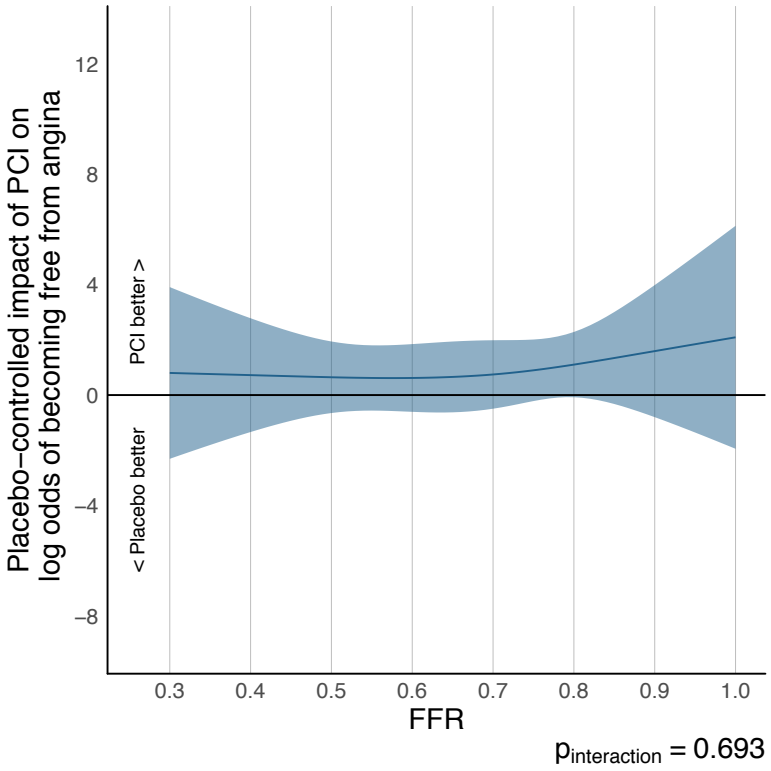


Figure 4.9: ORBITA-PHYSIOLOGY Relationship of treatment difference in patient-reported freedom from angina at follow-up to pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

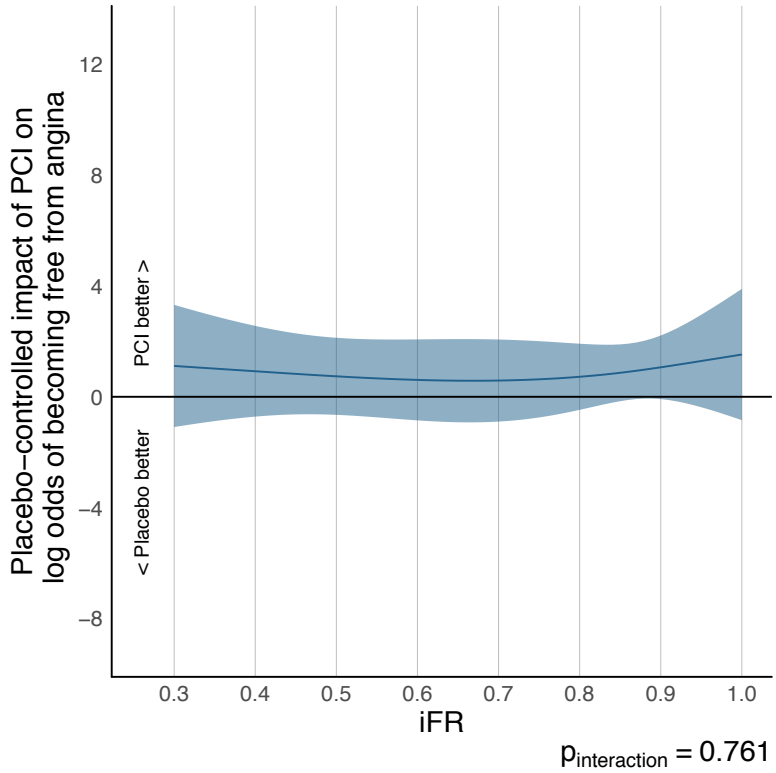


Figure 4.10: ORBITA-PHYSIOLOGY Relationship of treatment difference in patient-reported freedom from angina at follow-up to pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

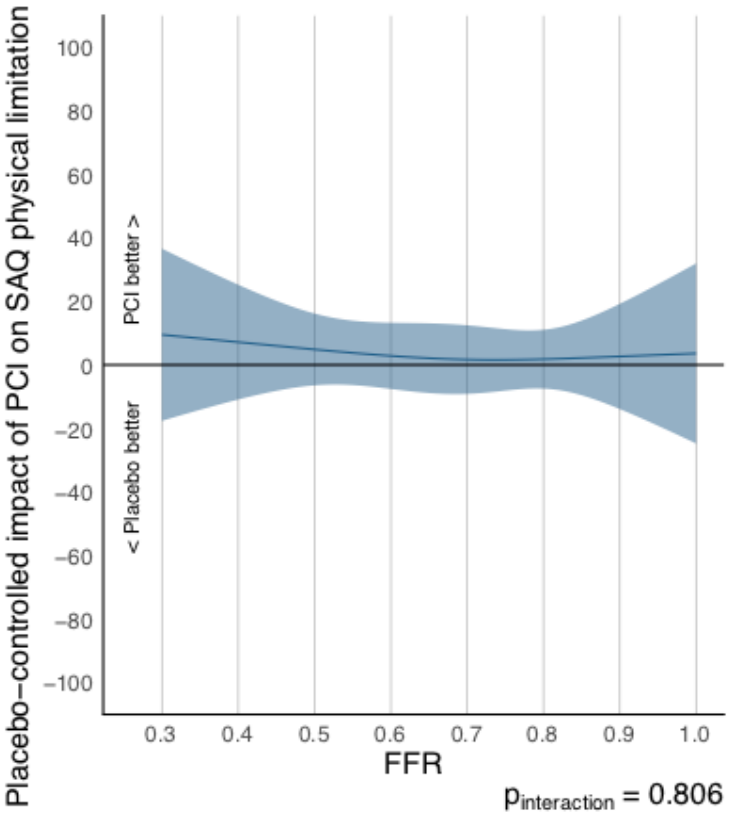


Figure 4.11: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire physical limitation score and pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

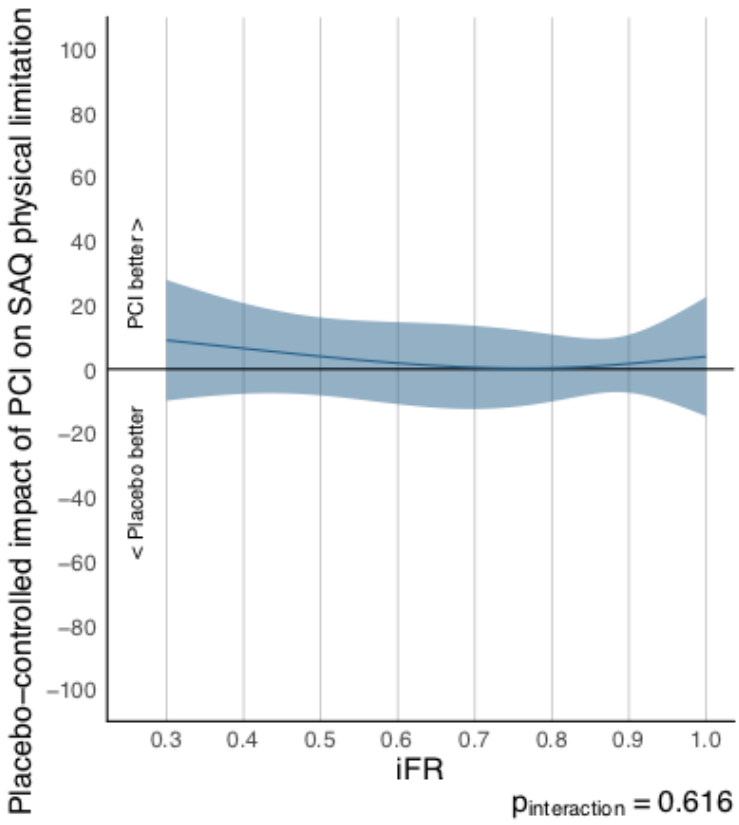


Figure 4.12: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire physical limitation score and pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

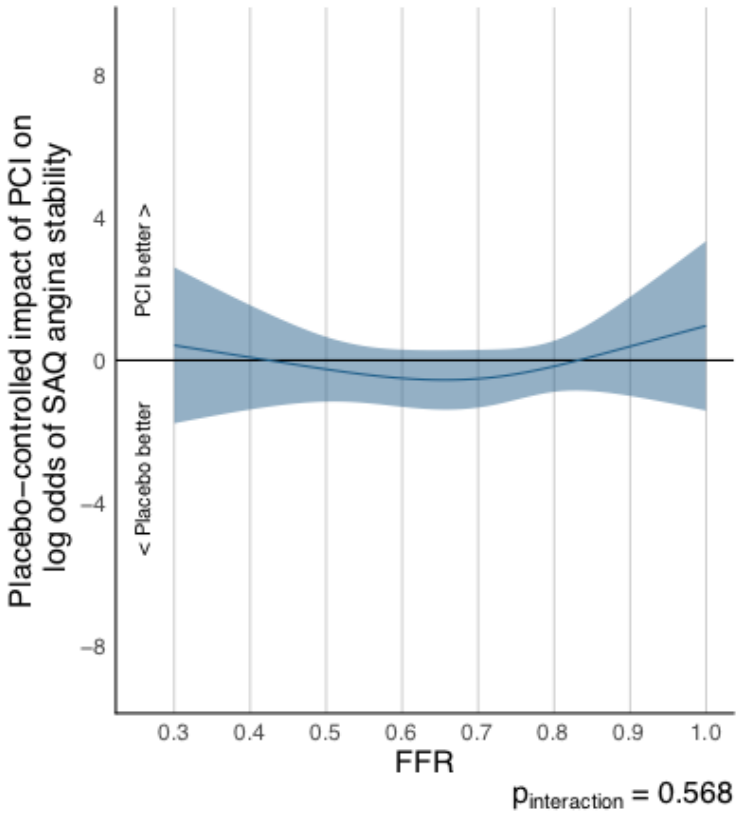


Figure 4.13: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire angina stability score and pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

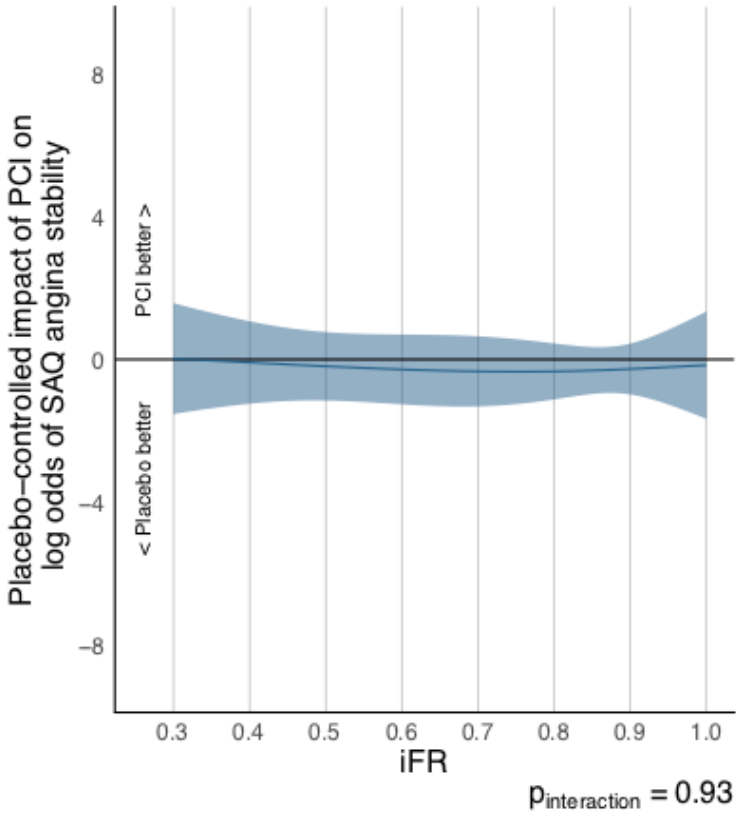


Figure 4.14: ORBITA-PHYSIOLOGY Relationship of treatment difference in Seattle Angina Questionnaire angina stability score and pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

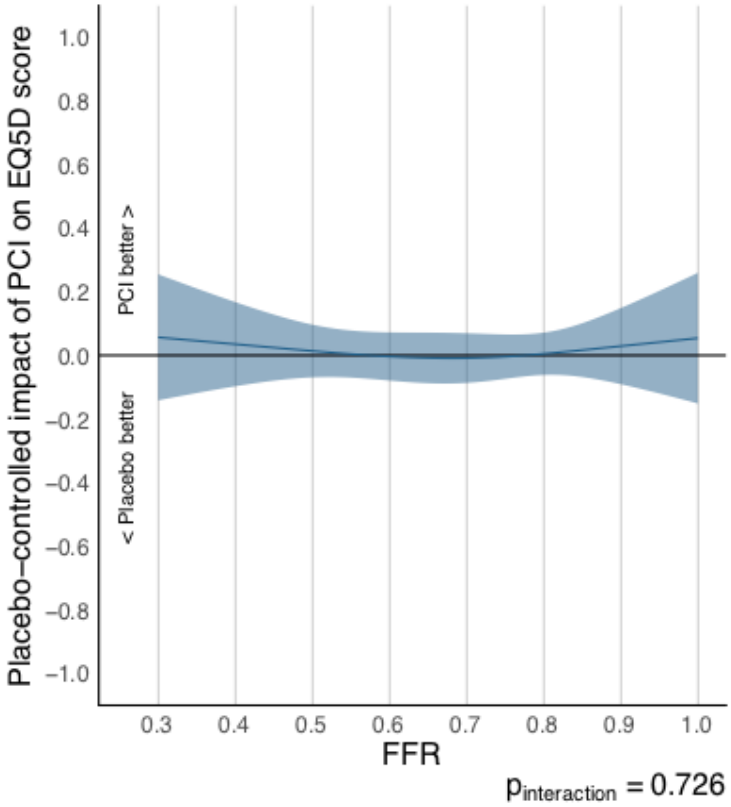


Figure 4.15: ORBITA-PHYSIOLOGY Relationship of treatment difference in EQ-5D-5L quality of life score and pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

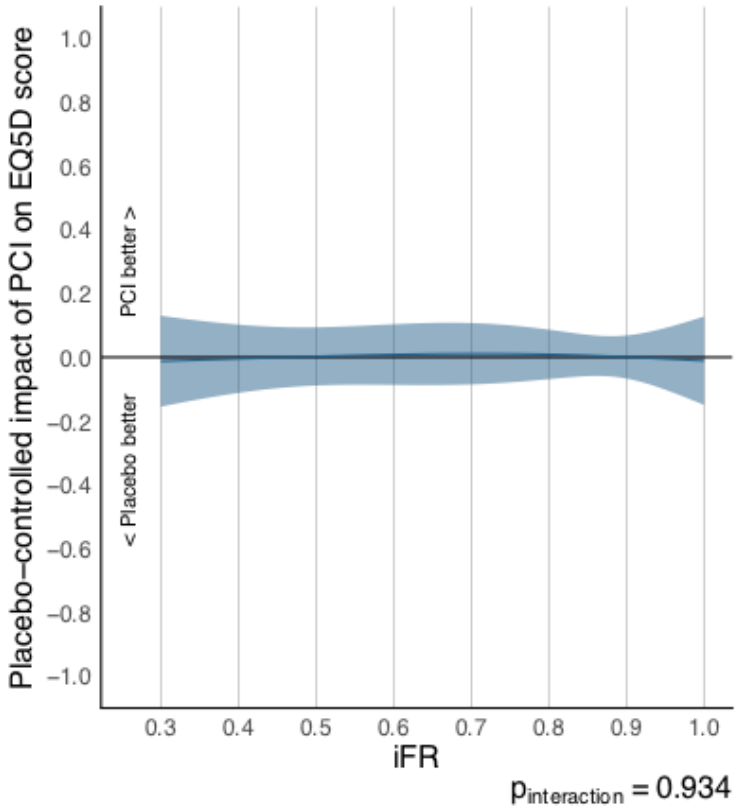


Figure 4.16: ORBITA-PHYSIOLOGY Relationship of treatment difference in EQ-5D-5L quality of life score and pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

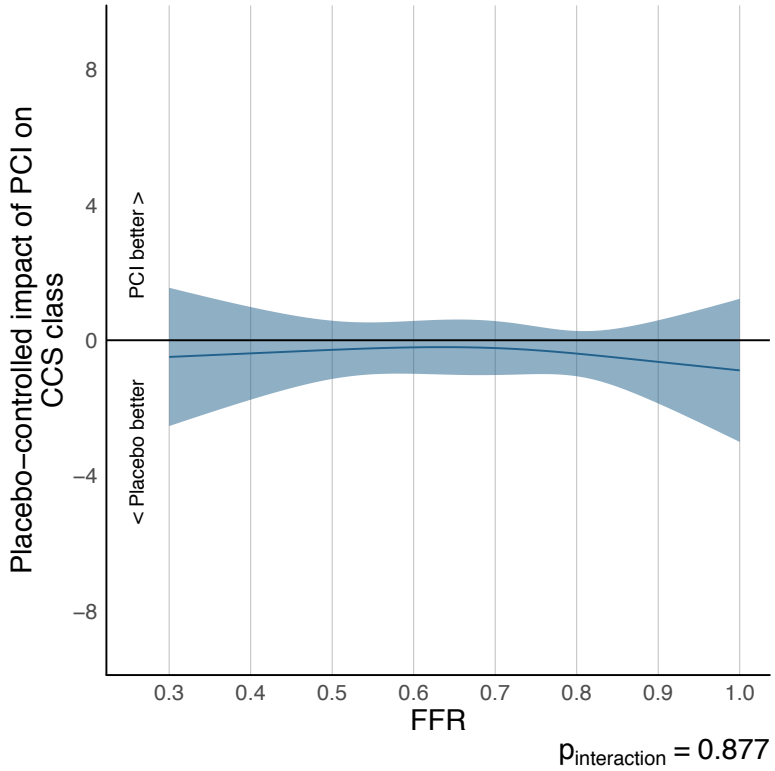


Figure 4.17: ORBITA-PHYSIOLOGY Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society class at follow-up to pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

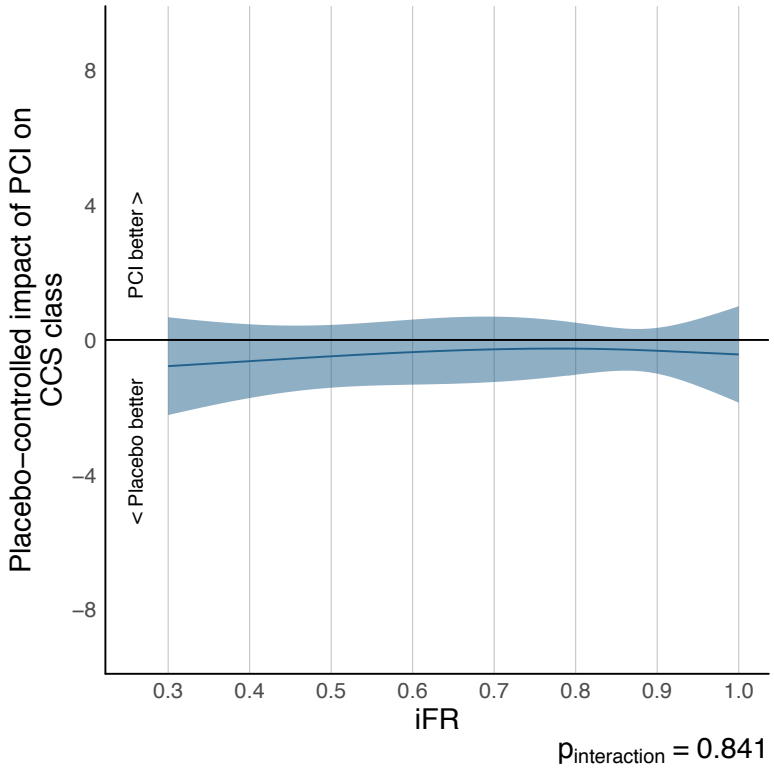


Figure 4.18: ORBITA-PHYSIOLOGY Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society class at follow-up to pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

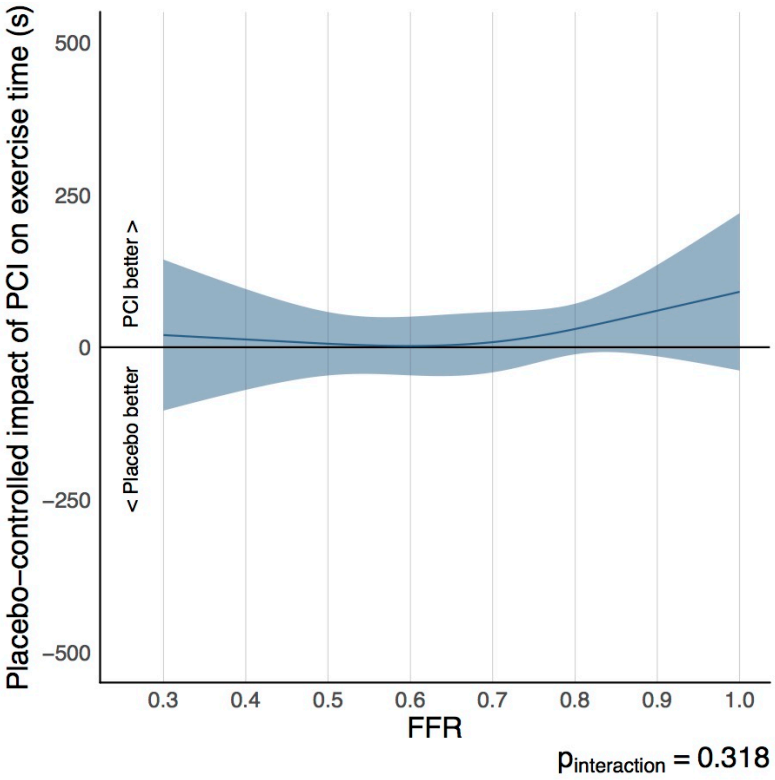


Figure 4.19: ORBITA-PHYSIOLOGY Relationship of change in pre-randomisation to follow up total exercise time and pre-randomisation FFR by randomisation arm

There is no discernible dependency on pre-randomisation FFR.

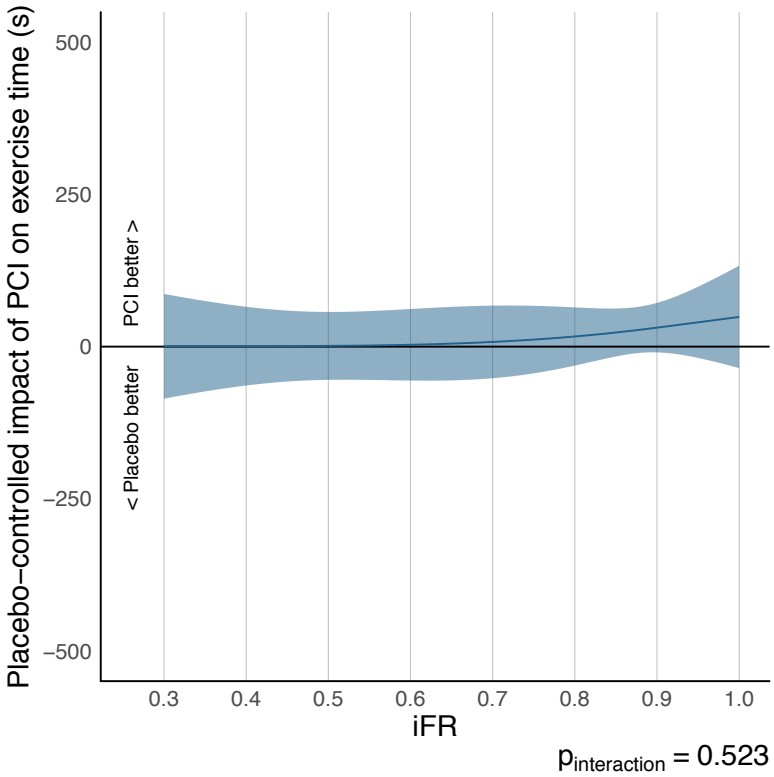


Figure 4.20: ORBITA-PHYSIOLOGY Relationship of change in pre-randomisation to follow up total exercise time and pre-randomisation iFR by randomisation arm

There is no discernible dependency on pre-randomisation iFR.

5 Effect of dobutamine stress echocardiography on placebo-controlled efficacy of percutaneous coronary intervention in stable coronary artery disease: the stress echo-stratified analysis of the ORBITA trial (ORBITA-DSE)

5.1 Abstract

5.1.1 Background

Dobutamine stress echocardiography is widely used to assess the degree of baseline ischaemia in patients with stable CAD. There are no placebo-controlled data on the use of this technique for assessing ischaemia and the efficacy of PCI.

5.1.2 Methods

Two hundred patients with stable angina and single vessel coronary artery disease were enrolled into the double-blinded ORBITA trial. Following a six-week medical optimisation phase, patients underwent pre-randomisation assessment with symptoms and quality of life questionnaires, cardiopulmonary exercise testing, dobutamine stress echocardiography, FFR and iFR. They were then randomised to PCI or placebo procedure. Following a six-week blinded period they had reassessment of the symptoms and quality of life questionnaires, cardiopulmonary exercise testing and dobutamine stress echocardiography. Effects were calculated by analysis of covariance. Each stress echocardiogram was reported twice by six reporters blinded to treatment allocation, time-point of the test, other reporters' opinion and their own first opinion. The ability of pre-randomisation stress echo to predict placebo-controlled changes in response variables was tested using regression modelling.

5.1.3 Results

In this dobutamine stress echo-stratified analysis of the ORBITA trial we report data from 183 of these patients who had pre-randomisation stress echocardiography (98 in the PCI arm, 85 in placebo arm). At pre-randomisation the number of ischaemic segments by stress echo score was 1.57 (SD 1.77) in the PCI arm and 1.62 (SD 1.76) in the placebo arm. Stress echo score strongly correlated with pre-randomisation FFR ($p_{correlation} \leq 0.0001$) and iFR ($p_{correlation} < 0.0001$) with higher stress echo scores at lower values of FFR and iFR. There was a detectable interaction between pre-randomisation stress echo score and the effect of PCI on angina frequency score with a larger placebo-controlled effect in patients with the highest stress echo score ($p_{interaction} = 0.029$). PCI was more likely to result in patient-reported freedom from angina than placebo (OR 0.33; 95% CI 0.17 to 0.66; p=0.002). There was no

interaction between stress echo score and any of the other patient-reported response variables of freedom from angina ($p_{interaction}$=0.109), angina stability ($p_{interaction}$=0.257), physical limitation ($p_{interaction}$=0.292), EQ-5D-5L quality of life score ($p_{interaction}$=0.824), physician-assessed Canadian Cardiovascular Society angina class ($p_{interaction}$=0.733), and treadmill exercise time ($p_{interaction}$=0.426).

5.1.4 Conclusions

In this placebo-controlled trial, PCI in stable CAD results in a significant improvement in ischaemia as assessed by stress echo score. Once the magnitude of the effect of PCI is detectable by an improvement in regional wall motion at stress, a detectable reduction in patient-reported frequency of angina is seen that is greater at higher levels of ischaemia as assessed by stress echo score.

5.2 Introduction

The primary results of the ORBITA showed a smaller than expected effect size of PCI when compared to placebo in single vessel stable CAD on the primary endpoint of change in treadmill exercise time.[85] While there was no significant difference between PCI and placebo groups in the patient-reported and physician-assessed symptom and quality of life endpoints, ischaemia as assessed by dobutamine stress echocardiography wall motion score index was significantly reduced by PCI.

The physiology-stratified analysis of ORBITA built upon these results and showed that the severity of ischaemia assessed by pre-randomisation FFR and iFR predicted the degree of improvement of ischaemia as assessed by dobutamine stress echo score. While the analysis also showed that the proportion of patients becoming free from angina was higher in the PCI than the placebo group there was no interaction of invasive physiology on this outcome or indeed any of the other symptom or quality of life outcomes or on total exercise time.

We proposed a mechanistic pathway that may explain these findings with a sequence of events based on the magnitude of effect size. This pathway begins with the patient presenting with symptoms of angina and the finding of severe angiographic coronary artery disease. Once PCI is performed, angiographic improvement in stenosis is seen immediately (step 1). If PCI is performed adequately, ischaemia reduction is seen by an improvement in invasive physiology (step 2). If ischaemia reduction affects a large enough territory of myocardium, it will result in a reduction in the degree of wall motion abnormalities seen at peak stress on dobutamine stress echocardiography (step 3). If the improvement in regional wall function is large enough it will result in an improvement in patient-reported symptoms (step 4). If patient-reported symptom relief is great enough, it will be reflected in an improvement in the assessment of symptom scores by the physician (step 5). This may then result in an improvement in treadmill exercise time, but it is unlikely to improve by the same mechanism after PCI when compared with anti-anginal therapy (step 6) (Figure 5.1).

The clinical effect of any intervention on a subjective endpoint such as symptom relief is a combination of both the true physical and the placebo effect.[35] In unblinded clinical experience and unblinded clinical trials[13,14,25] a larger effect size was seen for treadmill exercise time, and patient-reported and physician assessed symptom and quality of life endpoints than in the blinded ORBITA trial.[85] This difference is likely to have been due to the impact of telling a patient that a stent had been implanted and that the blood supply to the heart has been fixed in the unblinded examples. The effect of telling will accentuate the magnitude of efficacy of the intervention as it adds to the size of the placebo effect which contributes to the overall clinical improvement that we see.[37,95] In ORBITA this placebo effect was likely to have been smaller than that seen in clinical practice due to blinding of both the patients and the medical team. Telling the patient and the clinical team about the success of the procedure in the ORBITA trial resulted in the effect of ischaemia reduction with PCI being evident along the pathway to step 3 but with little impact on the remaining sequence of steps (Figure 5.2).

The addition of telling the patient that the stenosis is fixed and the blood supply to the heart is improved is likely to accentuate the efficacy of PCI therefore its effects are seen up to step 5 and even step 6 in clinical practice and unblinded clinical trials [13,14,25] (Figure 5.3).

Invasive physiology provides a vessel specific assessment of the severity of ischaemia and was initially validated against non-invasive imaging.[68,96] The results of validation and outcome trials resulted in FFR being considered the "gold standard" for ischaemic assessment.[14,18,70,79,97,98] However, the assessment of accuracy of tests for ischaemia has become rather circular. It is now the same original non-invasive tests that were used to validate FFR that are compared to FFR as the reference standard for their own validation. The sensitivity and specificity of stress echocardiography to predict FFR is considered to be moderate and in the range of 75 to 84% and 77 to 87% respectively.[99-101]

There are no placebo-controlled data on the relationship between ischaemic evaluation by dobutamine stress echocardiography and the efficacy of PCI. The aim

of this analysis is to assess the impact of the severity of ischaemia as assessed by pre-randomisation dobutamine stress echo score on the primary and secondary endpoints of the ORBITA trial.

5.3 Methods

5.3.1 Study design

The design of the ORBITA trial has been reported previously.[85] In brief, the ORBITA trial was a double blind randomised controlled trial comparing PCI to a placebo procedure in patients with stable angina and angiographically severe single vessel coronary artery disease. Intensive medical therapy was given to both groups. Prior to randomisation patients had assessment of symptom and quality of life questionnaires, cardiopulmonary exercise testing using a smoothed modified Bruce protocol, dobutamine stress echocardiography and measurement of FFR and iFR.

5.3.2 Blinding and randomisation

Patients were randomised 1:1 to PCI versus a placebo procedure with patients and the medical team outside of the catheterisation laboratory blinded to treatment allocation as previously described.[85]

5.3.3 Study endpoints and follow-up

At the end of the six-week blinded period patients returned for repeat of all pre-randomisation tests including symptom and quality of life questionnaires, cardiopulmonary exercise testing using a smoothed modified Bruce protocol, and dobutamine stress echocardiography.

5.3.4 Dobutamine stress echocardiography assessment

Patients were instructed to omit beta blockers for at least 24 hours prior to dobutamine stress echocardiography. The test was performed by a physician and sonographer. The patient, physician and sonographer were all blinded to allocation arm.

Echocardiography was performed using contrast agent for all studies. Ultrasound scanners were set to record at frame rates of at least 25 frames per second with contrast presettings used and preset acquisition of at least 3 beats. At heart rates of 20 frames per second for heart rates of >140bpm. The contrast agent used was a commercially available sulphur hexafluoride microbubble preparation, SonoVue (Bracco Imaging SpA, Milan, Italy). This agent was administered in 0.3mL bolus doses intravenously for each image acquisition followed by 1 to 2mL saline flush. After acquisition of resting images to exclude significant valvular disease, IV dobutamine was infused at a starting dose of 10μg/kg/min followed by increasing doses of 20μg/kg/min, 30μg/kg/min, 40μg/kg/min, up to a maximum of 50μg/kg/min in 3-minute stages. IV atropine was administered in 300mcg boluses up to a maximum of 1200mcg for those patients not achieving 85% of the predicted maximal heart rate. Images were taken in the apical 2-chamber, 3-chamber and 4-chamber, and parasternal short axis views at baseline, low dose stress, high dose stress and recovery.

5.3.5 Dobutamine stress echocardiography reporting

Analysis was also performed with reporters blinded to treatment allocation and phase (pre-randomisation or follow up), using an online reporting tool.

Each scan received 12 opinions. Each scan was examined twice by 6 imaging consultants who were blinded to treatment allocation, time-point of the scan, their colleagues' opinions, and (on the second viewing) their own first opinion.

Stress echocardiography results are presented in a manner that represents the number of hypokinetic segments (with akinetic segments scoring double, and dyskinetic scoring triple, and aneurysmal segments scoring quadruple). The left ventricle was divided into the standard 17 segment model. Wall motion was scored as follows: normal = 0, hypokinetic = 1, akinetic = 2, dyskinetic = 3 or aneurysmal = 4. Individual wall abnormality scores at peak stress were summed. Both opinions from all 6 consultants were then averaged. This stress echo score can be converted to classical wall motion score index as follows: wall motion score index = 1+(stress echo score)/17.

5.3.6 Statistical analysis

Summary statistics were presented as appropriate for baseline characteristics.

Models were fitted for each endpoint. Linear models were used for continuous endpoints i.e. Seattle Angina Questionnaire physical limitation score, total exercise time and stress echo score. Proportional odds logistic models were used for ordinal variables i.e. Seattle Angina Questionnaire angina frequency and angina stability scores and Canadian Cardiovascular Society class.

To assess the interaction of pre-randomisation stress echo score with each continuous and categorical outcome variable, the follow-up value was modelled conditioned on the pre-randomisation value transformed by a restricted cubic spline with three parameters, and randomisation arm. A model was then fitted with pre-randomisation stress echo score interacting with the randomisation arm with a restricted cubic spline with three parameters therefore the shape of the effect was allowed to vary over treatments.[86] Graphs are shown of the endpoints against pre-randomisation stress echo score. The contrast between the arms was generated with adjustment for the median value of the pre-randomisation value.

Analyses were performed using the open-source statistical environment "R",[87] with the package "rms" for regression modelling,[88] and "ggplot2" for graphs[89].

5.4 Results

Pre-randomisation stress echo score was available for 183 patients (98 PCI and 85 placebo) that form this stress echocardiography-stratified analysis of the ORBITA trial. Seventeen patients did not have dobutamine stress echocardiography at pre-randomisation as 1 had poor quality echocardiographic imaging windows, 6 had a previous adverse reaction to dobutamine, 6 had a clinical contraindication to dobutamine, and in 4 there were logistical reasons as to why the test was not carried out.

5.4.1 Patient demographics

Table 5.1 shows the patient demographic data. The majority of patients had normal LV systolic function (94.9% in PCI arm and 90.6% in placebo arm). Median angina duration was 5 months in the PCI arm (IQR 4 to 10) and 6 months in the placebo arm (IQR 4 to 9). Fifty-two (53.1%) patients in the PCI arm and 36 (42.4%) in the placebo arm had a positive non-invasive functional test prior to enrollment into the trial. Table 5.2 shows the frequency of angina at enrollment, pre-randomisation and follow-up.

5.4.2 Procedural demographics

Procedural demographics are shown in Table 5.3. The majority of lesions were in the left anterior descending artery (68.4% PCI and 69.4% placebo). 16.3% patients in PCI arm and 11.8% patients in the placebo arm had serial lesions in a single coronary artery. The mean diameter stenosis by quantitative coronary angiography was 64.3% (SD 13.9) in the PCI arm and 64.1% (SD 13.4) in the placebo arm. The mean area stenosis by quantitative coronary angiography was 84.5% (SD 10.2) in the PCI arm and 84.7% (SD 9.7) in the placebo arm. The mean FFR was 0.69 (SD 0.16) for the PCI arm and 0.69 (SD 0.16) for the placebo arm and mean iFR was 0.76 (SD 0.22) for the PCI arm and 0.77 (SD 0.20) for the placebo arm. Following intervention with drug eluting stents implanted in the PCI arm the mean FFR increased to 0.90 (SD 0.05) and iFR increased to 0.94 (SD 0.04).

5.4.3 Relationship between FFR and iFR and stress echo score

Pre-randomisation FFR or iFR and stress echo data were available in 179 patients and 181 patients respectively (in 2 patients we were unable to elicit a hyperemic response to adenosine therefore only iFR data is available).

Figure 5.4 shows the relationship between pre-randomisation FFR and pre-randomisation stress echo score. As the stress echo score became larger with a greater number of ischaemic myocardial segments, the FFR value decreased therefore showing a greater degree of ischaemia ($p_{correlation}$ <0.0001).

Figure 5.5 shows the relationship between pre-randomisation iFR and pre-randomisation stress echo score. Similarly, as the stress echo score became larger

with a greater number of ischaemic myocardial segments, the iFR also decreased showing a greater degree of ischaemia ($p<0.0001$).

5.4.4 Patient-reported symptoms

Seattle Angina Questionnaire angina frequency score

Paired Seattle Angina Frequency Questionnaire data was available for 176 patients in the stress echo-stratified analysis of the ORBITA (96 in the PCI arm and 80 in the placebo arm).

Overall, there was little evidence that PCI improved Seattle Angina Questionnaire angina frequency score more than placebo (OR 0.62, 95% CI 0.36 to 1.08; p=0.091, Table 5.4).

However, there was a detectable interaction between pre-randomisation stress echo score and the effect of PCI on angina frequency score with a larger placebo-controlled effect of PCI in patients with the highest stress echo score ($p_{interaction}=0.029$) (Figure 5.6).

Freedom from angina

Paired Angina Freedom data was available for 175 patients in the stress echo-stratified analysis of the ORBITA (95 in the PCI arm and 80 in the placebo arm).

PCI was more likely to result in patient-reported freedom from angina than placebo (OR 0.33; 95% CI 0.17 to 0.66; p=0.002; Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on freedom from angina ($p_{interaction}=0.109$) (Figure 5.7).

Seattle Angina Questionnaire angina stability score

Paired Seattle Angina Stability Questionnaire data was available for 175 patients in the stress echo-stratified analysis of the ORBITA (96 in the PCI arm and 79 in the placebo arm).

There was no evidence that PCI improved Seattle Angina Questionnaire angina stability score more than placebo (OR 1.49, 95% CI 0.83 to 2.66; p=0.18, Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on angina stability score ($p_{interaction}$=0.257) (Figure 5.8).

Seattle Angina Questionnaire physical limitation score

Paired Seattle Physical Limitation Questionnaire data was available for 171 patients in the stress echo-stratified analysis of the ORBITA (93 in the PCI arm and 78 in the placebo arm).

There was no evidence that PCI improved Seattle Angina Questionnaire physical limitation score more than placebo (OR 0.71, 95% CI 0.41 to 1.21; p=0.21, Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on physical limitation score ($p_{interaction}$=0.292) (Figure 5.9).

EQ-5D-5L quality of life score

Paired EQ-5D-5L data was available for 175 patients (96 in the PCI arm and 79 in the placebo arm).

PCI did not improve EQ-5D-5L quality of life score more than placebo: point estimate -0.007 (95% CI -0.048 to 0.033; p=0.73; Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on quality of life as assessed by EQ-5D-5L ($p_{interaction}$=0.824) (Figure 5.10).

5.4.5 Physician-assessed symptoms

Paired CCS class data was available for 179 patients (98 in the PCI arm and 81 in the placebo arm).

There was no evidence that PCI improved CCS class more than placebo (OR 0.85, 95% CI 0.49 to 1.47; p=0.55, Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on CCS class ($p_{interaction}$=0.733) (Figure 5.11).

5.4.6 Treadmill exercise time

Paired treadmill exercise time data was available for 177 patients (97 in the PCI arm and 80 in the placebo arm).

The estimated effect of PCI over placebo on exercise time using regression modelling was 17.5 seconds (95% CI -7.61 to 42.6; p=0.17, Table 5.4).

There was no detectable interaction between pre-randomisation stress echo score and the effect of PCI on exercise time ($p_{interaction}$=0.426) (Figure 5.12).

5.5 Discussion

5.5.1 Main findings of the stress echo-stratified analysis of ORBITA

In this stress echo-stratified analysis of the ORBITA trial we have shown a strong correlation between pre-randomisation stress echo score and invasive physiology measured by FFR and iFR. The higher the number of ischaemic regional wall segments seen at peak stress, the lower the FFR or iFR value.

In this first placebo-controlled analysis of the relationship of ischaemia assessed by dobutamine stress echocardiography and the efficacy of PCI in stable coronary artery disease, we found evidence of interaction of the pre-randomisation stress echo and the impact of PCI on the improvement in the Seattle Angina Questionnaire angina frequency score. The greater the degree of ischaemia on stress echo before randomisation, the greater the effect of PCI on improving patient-reported symptoms of angina. Furthermore, PCI resulted in a significantly more patients reporting freedom from angina but there was no evidence of interaction between this effect and the pre-randomisation stress echo score.

5.5.2 Mechanistic pathway for ischaemia

We previously proposed a mechanistic pathway from presentation with angina and severe single vessel angiographic coronary disease to improvement in ischaemia assessed invasively and non-invasively, patient-reported and physician-assessed symptom relief and exercise time improvement. The results of this study and the physiology-stratified analysis of ORBITA support this notion.

In the physiology-stratified analysis the placebo-controlled effect of PCI was detectable by ischaemia reduction seen with both invasive physiology and dobutamine stress echocardiography. The later was strongly related to the pre-randomisation FFR and iFR values. It was also seen by an improvement in the proportion of patients reporting freedom from angina but there was no detectable interaction with invasive physiology on this endpoint.

In this stress echo-stratified analysis the magnitude of efficacy of PCI was seen at step 4 of the pathway with an improvement in patient-reported freedom from angina. Additionally, stratification of the data by pre-randomisation stress echo score showed a greater magnitude of effect of PCI on improvement of angina frequency with higher stress echo scores and therefore a tighter link between stress echo score and symptoms.

5.5.3 Comparative assessment of measures of ischaemia

Invasive physiology, in particular FFR, is considered to the "gold standard" for assessment of ischaemia based on robust clinical evidence.[18,68,70,98] Dobutamine stress echocardiography is considered to be a less sensitive assessment tool for ischaemia.[73] However, while FFR and iFR may be a more sensitive in detecting ischaemia as determined using pre-specified thresholds, these data show that the lower the FFR and iFR, the greater the burden of ischaemia on stress echocardiography. It may therefore be reasonable to conclude that for ischaemia to be detected by regional wall motion abnormalities at peak stress, a larger myocardial territory must be affected which is reflected in lower FFR and iFR values. This greater magnitude of ischaemia, the greater the efficacy of PCI in improving patient-reported symptoms of angina.

5.5.4 Limitations of this study

This is a sub-analysis of 183 patients from the ORBITA trial and the sample size may therefore be considered underpowered. However, as the first placebo-controlled data of their kind, they remain of interest.

The follow-up period may be considered short at six weeks. However, the effect of PCI on both angiographic and physiological improvement of a stenosis is immediate, and the effect on reduction of regional wall abnormalities must also occur soon after PCI. In previous trials angina relief was seen at one-month post-PCI,[25] therefore six weeks is an adequate time period to measure symptom endpoints.

Stress echocardiography assessment is known to have inter-observer variability.[102] It is also known to demonstrate significant intra-observer variability when the same images are reported repeatedly by the same operator.[103] To reduce the degree of inter- and intra-observer variability, in order to increase the statistical power of this study, each scan was reported twice by 6 different operators who were each blinded to the treatment allocation and time-point of the scan, and to their own and each other's opinions.

5.6 Conclusions

Stratification of the primary and secondary endpoints of ORBITA by pre-randomisation stress echocardiography showed that the higher the stress echo score, the greater the placebo-controlled efficacy of PCI on improvement in symptoms of angina.

This stress echo-stratified analysis of the ORBITA trial showed a significant increase in the proportion of patients who reported freedom from angina at follow-up in the PCI arm compared to the placebo arm. However, there was no interaction of pre-randomisation stress echo score with this effect.

There was no interaction between pre-randomisation stress echo score and the other patient-reported metrics of angina stability, physical limitation or quality of life, physician-assessed angina severity or treadmill exercise time.

Table 5.1: ORBITA-DSE Patient demographics at enrollment

	PCI (n=98) n (%)	Placebo (n=85) n (%)	Complete group (n=183) n (%)
Age (yrs)	65.9±9.6	65.8±8.5	65.9±9.1
Male	68 (69.4)	65 (76.5)	133 (72.7)
Hypertension	65 (66.3)	58 (68.2)	123 (67.2)
Hypercholesterolemia	74 (75.5)	57 (67.1)	131 (71.6)
Diabetes	14 (14.3)	19 (22.4)	33 (18.0)
Previous MI	4 (4.1)	7 (8.2)	11 (6.0)
Previous PCI	9 (9.2)	15 (17.6)	24 (13.1)
CCS class			
I	2 (2.0)	3 (3.5)	5 (2.7)
II	61 (62.2)	48 (56.4)	109 (59.6)
III	35 (35.7)	34 (40.0)	69 (37.7)
Left ventricular systolic function			
Normal	93 (94.9)	77 (90.6)	170 (92.9)
Mild impairment	3 (3.1)	5 (5.9)	8 (4.4)
Moderate impairment	2 (2.0)	3 (3.5)	5 (2.7)
Severe impairment	0 (0)	0 (0)	0 (0)
Angina duration (months) (median IQR)	5 (4 to 10)	6 (4 to 9)	6 (4 to 9)
Positive functional test	52 (53.1)	36 (42.4)	88 (48.1)
ETT	24 (24.5)	15 (17.6)	39 (21.3)
MIBI	10 (10.2)	8 (9.4)	18 (9.8)
DSE	18 (18.4)	12 (14.1)	30 (16.4)
MRI perfusion	0 (0)	1 (1.2)	1 (0.5)

MI= Myocardial infarction
PCI= Percutaneous coronary intervention
CCS= Canadian Cardiovascular Society Angina Grade
SAQ= Seattle angina questionnaire
ETT= Exercise tolerance test
MIBI= Nuclear medicine myocardial perfusion scan
DSE= Dobutamine stress echocardiography
MRI= Magnetic resonance imaging

Table 5.2: ORBITA-DSE Frequency of angina

		PCI n (%)	Placebo n (%)
Enrollment		n=96	n=82
Frequency of angina	Daily angina	29 (30.2)	25 (30.5)
	Weekly angina	38 (39.6)	31 (37.8)
	Monthly angina	16 (16.7)	12 (14.6)
	Angina free	13 (13.5)	14 (17.1)
Pre-randomisation		n=97	n=84
Frequency of angina	Daily angina	19 (19.6)	20 (23.8)
	Weekly angina	36 (37.1)	31 (36.9)
	Monthly angina	28 (28.9)	14 (16.7)
	Angina free	14 (14.4)	19 (22.6)
Follow-up		n=96	n=81
Frequency of angina	Daily angina	9 (9.4)	8 (9.9)
	Weekly angina	24 (25.0)	32 (39.5)
	Monthly angina	14 (14.6)	16 (19.8)
	Angina free	49 (51.0)	25 (30.9)

Angina is categorised as "daily" if there are one or more episodes of angina per day. The remaining patients are categorised as "weekly" there are one or more episodes of angina per week. The remaining are categorised as "monthly" if there are one or more episodes of angina per week. Below one episode per month is categorised as "angina free".

Table 5.3: ORBITA-DSE Procedural demographics

	PCI (n=98) n (%)	Placebo (n=85) n (%)	Complete group (n=183) n (%)
Vessel			
Left anterior descending	67 (68.4)	59 (69.4)	126 (69.9)
Ostial/proximal	43 (43.9)	28 (32.9)	71 (38.8)
Mid	31 (31.6)	33 (38.8)	64 (35.0)
Distal	4 (4.1)	6 (7.1)	10 (5.5)
Right coronary	16 (16.3)	13 (15.3)	29 (15.8)
Circumflex	9 (9.2)	9 (10.6)	18 (9.8)
First obtuse marginal	3 (3.1)	0 (0)	3 (1.6)
First diagonal	2 (2.0)	2 (2.4)	4 (2.2)
Intermediate	1 (1.0)	2 (2.4)	3 (1.6)
Serial lesions	16 (16.3)	10 (11.8)	26 (14.2)
No. pts with diameter stenosis ≥50% by QCA	84 (85.7)	73 (85.9)	157 (85.8)
No. pts with area stenosis ≥70% by QCA	81 (82.7)	73 (85.9)	154 (84.2)
Diameter stenosis by QCA	64.3±13.9	64.1±13.4	64.2±13.6
Area stenosis by QCA	84.5±10.2	84.7±9.7	84.6±9.9
Pre-randomisation stress echo score	1.57±1.77	1.62±1.76	1.59±1.76
Mean (SD)	1 (0.42 to 2.17)	1 (0.42 to 2.00)	1 (0.42 to 2.13)
Median (IQR)			
FFR	n=97	n=82	n=179
Mean (SD)	0.69±0.16	0.69±0.16	0.69±0.16
Median (IQR)	0.72 (0.57 to 0.82)	0.73 (0.59 to 0.80)	0.72 (0.58 to 0.81)
iFR	n=97	n=84	n=181
Mean (SD)	0.76±0.22	0.77±0.20	0.76±0.21
Median (IQR)	0.85 (0.68 to 0.92)	0.85 (0.70 to 0.89)	0.85 (0.69 to 0.90)
No. pts with FFR ≤0.80	n=97 71 (73.2)	n=82 63 (76.8)	n=179 134 (74.9)
No. pts with iFR ≤0.89	n=97 63 (64.9)	n=84 62 (73.8)	n=181 125 (69.1)
Stent length (mm) Median (IQR)	24 (18 to 33)	NA	NA
Stent diameter (mm) Median (IQR)	3 (2.75 to 3.5)	NA	NA
FFR post PCI	n=96	NA	NA
Mean (SD)	0.90±0.05		
Median (IQR)	0.90 (0.87 to 0.93)		
iFR post PCI	n=97	NA	NA
Mean (SD)	0.94±0.04		
Median (IQR)	0.95 (0.92 to 0.97)		
No. pts with post FFR>0.80	n=96 91 (94.8)	NA	NA
No. pts with post iFR>0.89	n=97 94 (96.9)	NA	NA

QCA= Quantitative coronary angiography
FFR= Fractional flow reserve
iFR= Instantaneous wave-free ratio

Table 5.4: ORBITA-DSE Endpoint analysis

Endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)
Total exercise time	17.5s (95% CI -7.61 to 42.6; p = 0.17)
SAQ physical limitation score	0.71 (95% CI 0.41 to 1.21; p = 0.21)
EQ-5D-5L	-0.007 (95% CI -0.048 to 0.033; p = 0.73)
Endpoint	**Logistic (proportional odds) ordinal regression model estimate (PCI over placebo)**
CCS class	OR 0.85 (95% CI 0.49 to 1.47; p = 0.55)
SAQ angina frequency	OR 0.62 (95% CI 0.36 to 1.08; p = 0.091)
SAQ angina stability	OR 1.49 (95% CI 0.83 to 2.66; p = 0.18)
Patient-reported freedom from angina	OR 0.33 (95% CI 0.17 to 0.66; p = 0.002)

SAQ= Seattle angina questionnaire
CCS= Canadian Cardiovascular Society angina grade

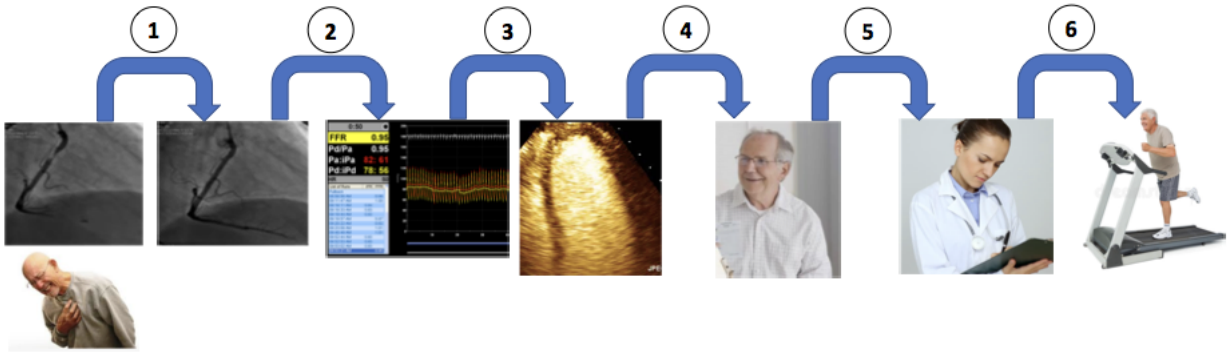


Figure 5.1: Mechanistic ischaemic pathway

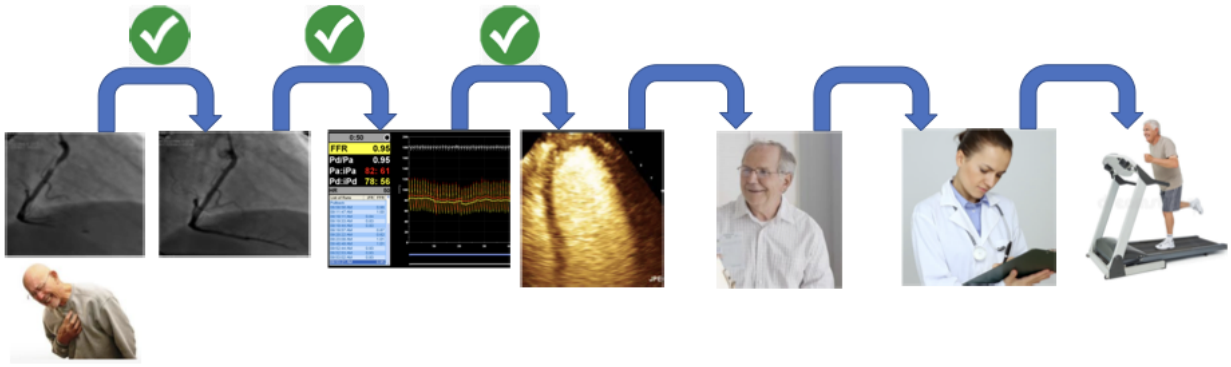


Figure 5.2: Steps of ischaemia improvement seen in blinded placebo-controlled trial



Figure 5.3: Steps of ischaemia improvement seen in unblinded clinical trial and clinical experience

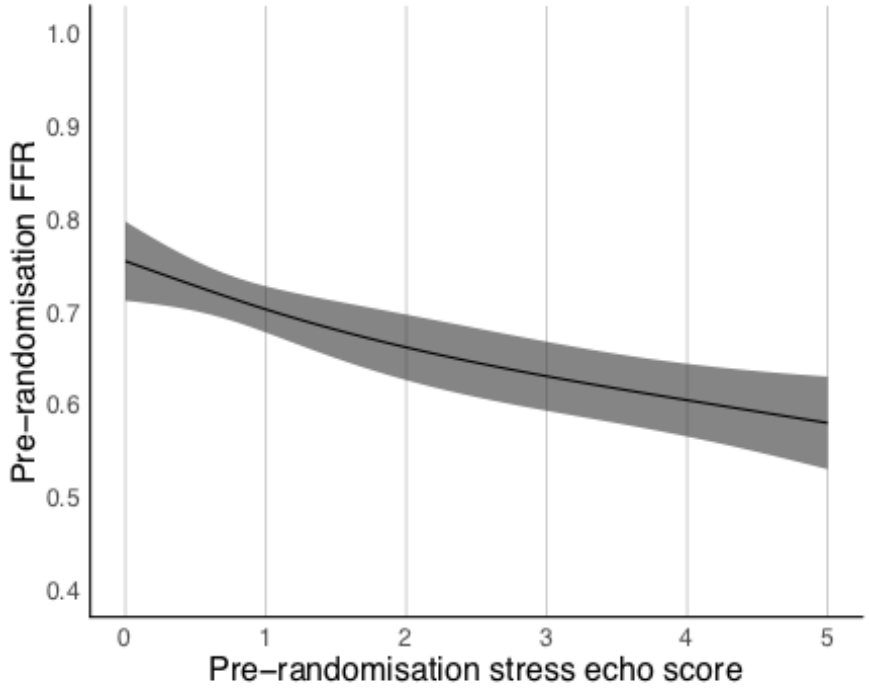


Figure 5.4: ORBITA-DSE Relationship between pre-randomisation stress echo score and pre-randomisation FFR

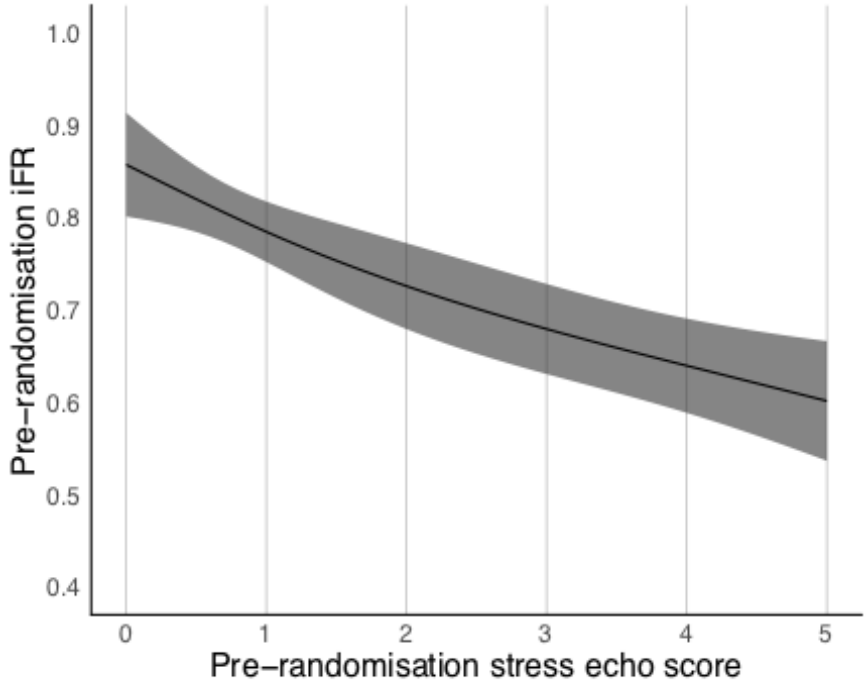


Figure 5.5: ORBITA-DSE Relationship between pre-randomisation stress echo score and pre-randomisation iFR

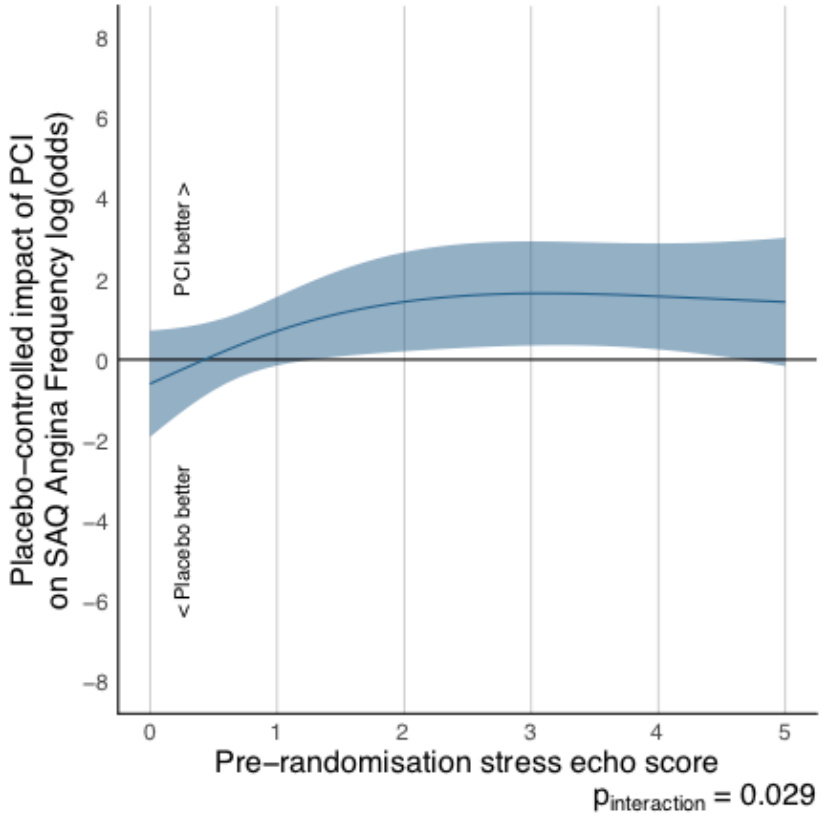


Figure 5.6: ORBITA-DSE Relationship of treatment difference in patient-reported Seattle Angina Questionnaire angina frequency score at follow-up to pre-randomisation stress echo score by randomisation arm

There is a significant interaction between stress echo score and angina frequency score with a progressive tendency for larger effects on angina frequency score with higher stress echo score ($p_{interaction}$=0.029).

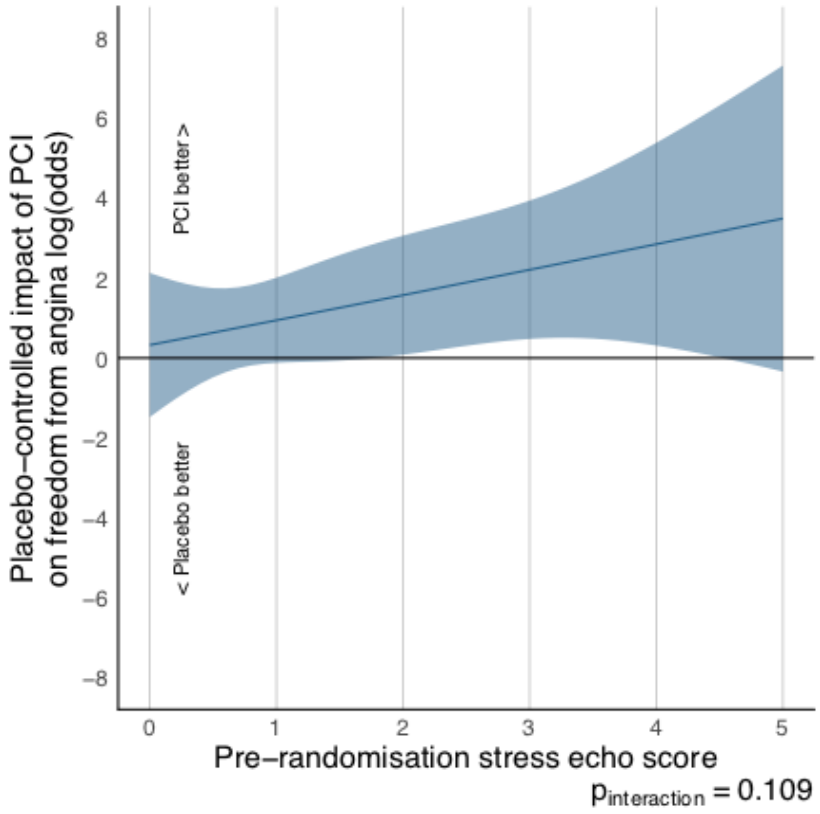


Figure 5.7: ORBITA-DSE Relationship of treatment difference in freedom from angina and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

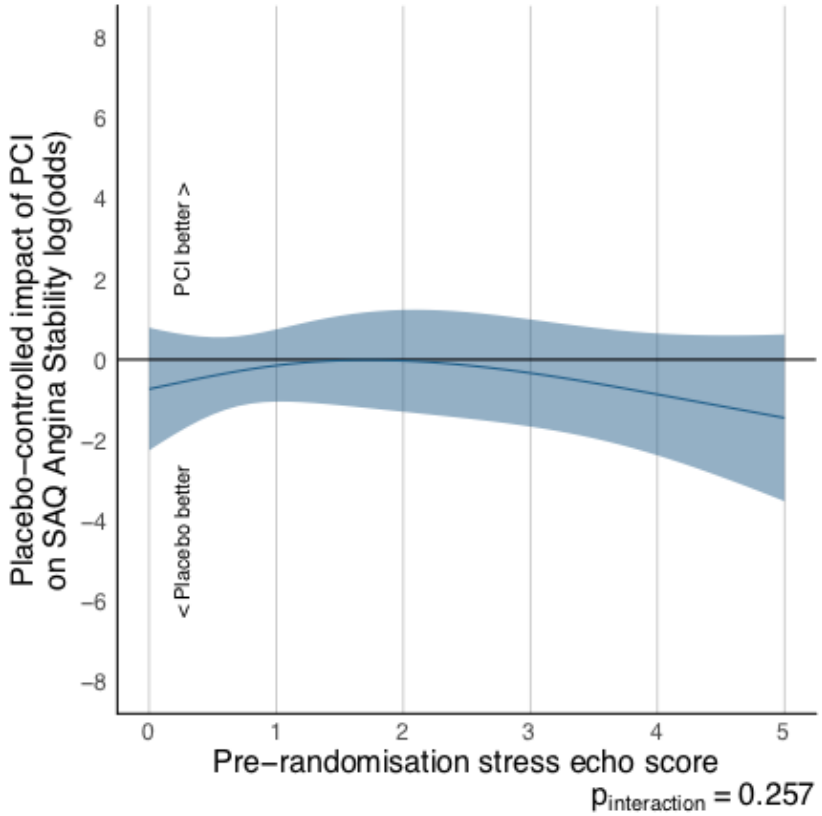


Figure 5.8: ORBITA-DSE Relationship of treatment difference in Seattle Angina Questionnaire angina stability score and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

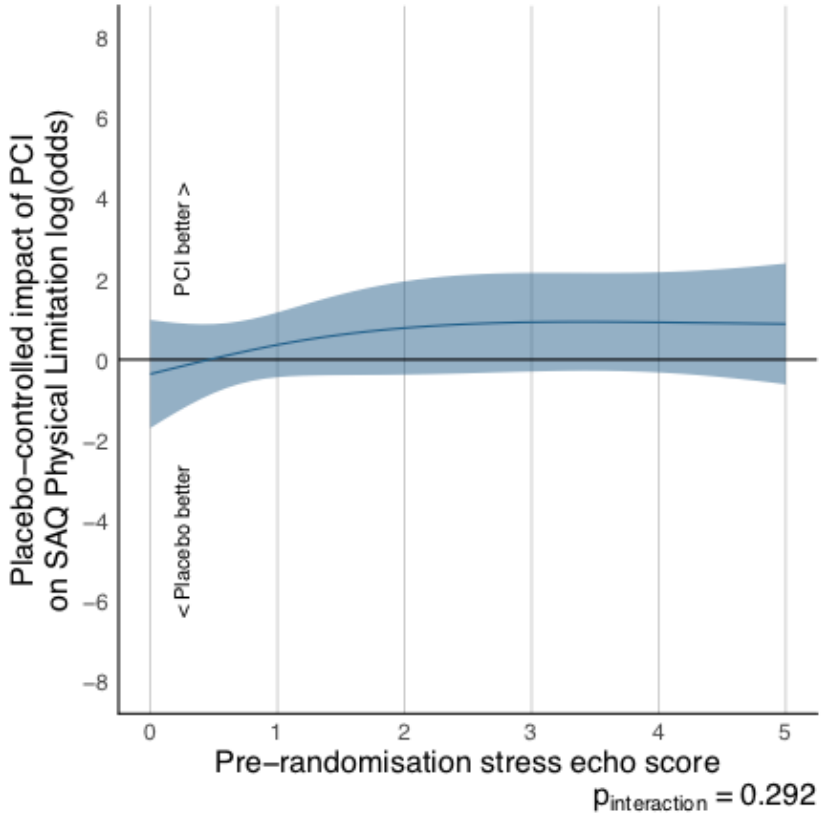


Figure 5.9: ORBITA-DSE Relationship of treatment difference in Seattle Angina Questionnaire physical limitation score and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

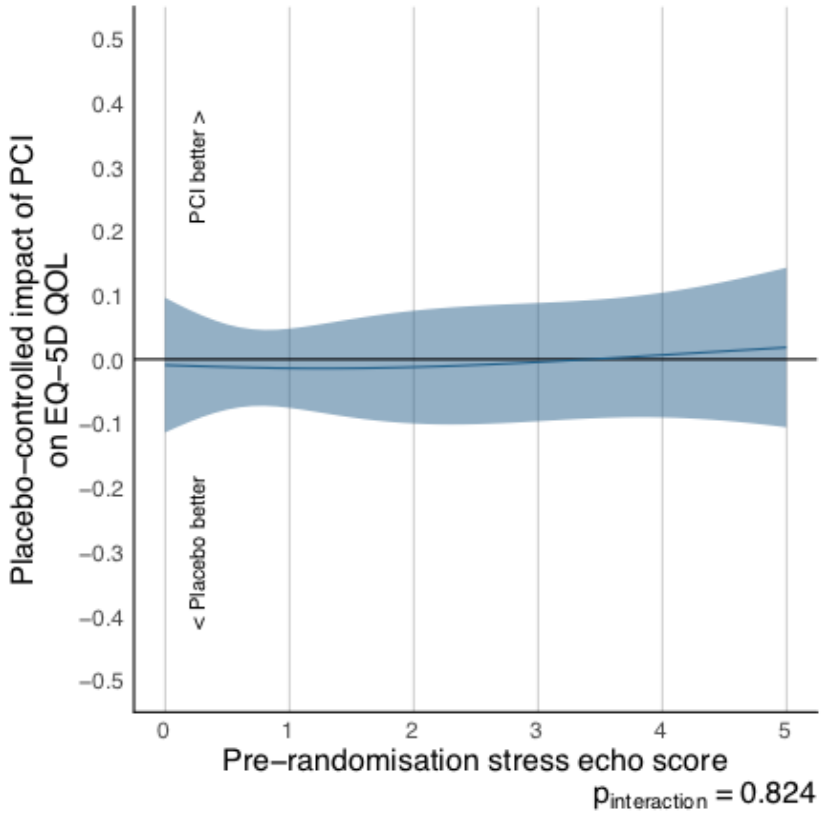


Figure 5.10: ORBITA-DSE Relationship of treatment difference in EQ-5D-5L quality of life score and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

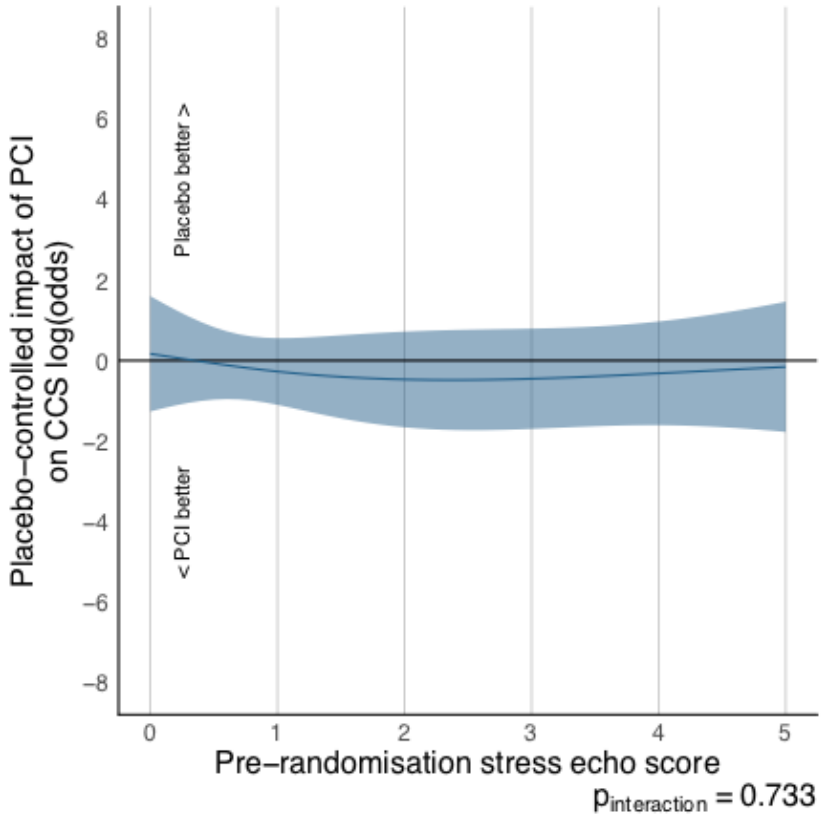


Figure 5.11: ORBITA-DSE Relationship of treatment difference in Canadian Cardiovascular Society class and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

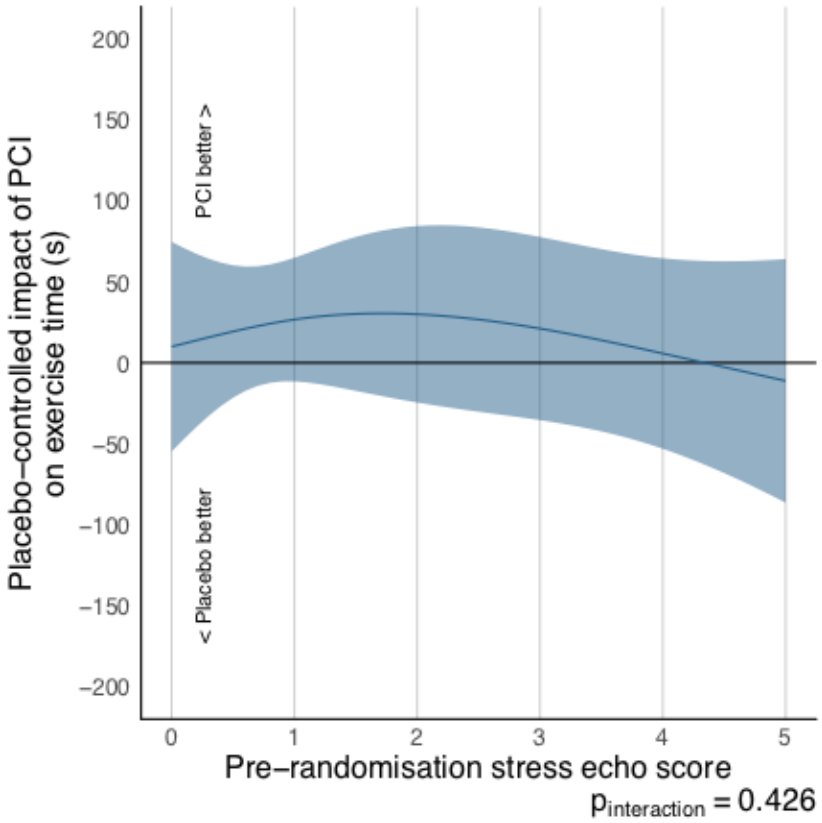


Figure 5.12: ORBITA-DSE Relationship of treatment difference in treadmill exercise time and pre-randomisation stress echo by randomisation arm

There is no discernible dependency on pre-randomisation stress echo score.

6 Synthesis

In this thesis I assessed the placebo-controlled efficacy of PCI in patients with stable CAD. In this condition we use PCI primarily to relieve angina; however, the true incremental contribution of stenting had never been tested before against placebo control with blinding of patients and evaluators.

In the ORBITA trial I investigated the effect of PCI versus placebo on a number of endpoints with a primary endpoint of change in treadmill exercise time. Secondary endpoints were change in wall motion score index, Duke Treadmill score, time to 1mm ST depression, symptomatic endpoints including Seattle Angina Questionnaire angina frequency, angina stability and angina frequency score and change in CCS class and change in EQ-5D-5L quality of life score.

I then assessed the interaction between pre-randomisation FFR and iFR on the placebo-controlled effect of PCI on the study endpoints. Finally, I studied the interaction of pre-randomisation ischaemia as assessed by dobutamine stress echocardiography on the placebo-controlled effect of PCI on the study endpoints.

6.1 The need for blinding

Randomisation prevents allocation bias.[104,105] Blinding prevents bias in assessing the effect size.[106] Unblinded trials of intervention are known to be susceptible to large, unintentional, levels of bias.[41,50,52] Whilst trials such as FAME 2 should be praised for selective PCI to vessels with the most symptomatic stenosis, the consequences of allocation bias introduced by the lack of a placebo control arm remain unresolved.[48,49] It is irresponsible to ignore the importance of blinding in trial design when evaluating interventions.[53 107]

All stable angina trials so far have been open label, and sceptics have rightly pointed to the substantial risk of bias towards overestimated benefits.[47] As illustrated by the Symplicity HTN3 study,[50] large effect sizes may be reported in open trial designs but when tested in blinded placebo controlled manner the true effect size may be much smaller.[51-53]

Calls for a placebo-controlled trial of PCI for stable angina [48,49] have emphasised that the main benefits of intervention for stable angina may be symptom reduction and improvement in quality of life. These endpoints are subjective (unlike death and MI) and therefore require blinding of patient and the entire clinical team.

Prior to this study, a blinded trial comparing PCI to a placebo procedure (on a background of optimum medical therapy) had never been performed. I have presented the first placebo-controlled data of the effect of PCI on exercise capacity, symptoms, quality of life and the non-invasive and invasive assessment of ischaemia.

6.2 The placebo-controlled efficacy of PCI in stable angina

Patients with stable angina come to cardiologists for relief of symptoms. We have effective medications that relieve symptoms, and which now improve prognosis to very low mortality rates. The clinical symptomatic benefit our patients report following PCI is due to a combination of the true physical effect of PCI, the placebo effect of an intervention and other factors such as the effect of medical therapy.[35]

ORBITA was conceived to deliver simple evidence for what Interventional Cardiologists believed to be true, namely that patients severe angiographic stenoses and sufficient angina on medical therapy, would indeed get a large benefit from PCI.[108]

ORBITA was designed to expose no more patients (and for more no more time) to placebo than necessary. The placebo arm needed to be sufficiently acceptable to patients and their clinicians to prevent undue selection bias and high rates of crossover or drop out. In this trial we were keen to avoid the high crossover that were seen in previous trials. In COURAGE, 32% crossed over from the medical therapy arm to the PCI arm.[11] In FAME-2 the crossovers (with neither myocardial infarction nor ECG changes) comprised the majority of events, and indeed almost all occurred soon after the physician had explained there was a haemodynamically significant lesion that had not been stented or at fixed study time points when the patient was reviewed by the study team.[18]

The results of ORBITA were unexpected. I demonstrated that the placebo-controlled effect size of PCI on treadmill exercise time was smaller than expected and did not meet criteria for statistical significance. Similarly, there was no statistically significant difference between the groups for the endpoints of time to 1mm ST depression, Duke treadmill score, and patient-reported and physician-assessed symptomatic and quality of life endpoints.

However, I did show a significant improvement in regional left ventricular systolic function at peak stress as assessed by dobutamine stress echocardiography in the PCI arm compared to the placebo arm. This reflected a significant reduction in myocardial ischaemia.

6.3 Interaction between invasive physiological assessment of ischaemia and the placebo-controlled efficacy of PCI

In the assessment of the influence of pre-randomisation invasive physiology on the trial endpoints in the ORBITA patients I showed that as the level of ischaemia became larger with lower FFR and iFR values, the placebo-controlled efficacy of PCI on reduction of ischaemia as measured by stress echocardiography increased. Therefore, the ability of PCI to reduce the burden of ischaemia was highest in those patients with the greatest degree of ischaemia before randomisation. Whilst I also showed that the proportion of patients who were free from angina at follow-up was greater in the PCI arm than the placebo arm, there was no interaction between this effect and pre-randomisation invasive physiology. Additionally, the level of ischaemia assessed by pre-randomisation FFR and iFR did not interact with any of the other endpoints of ORBITA, notably, exercise time, angina frequency, physical limitation and quality of life.

6.4 Interaction between non-invasive functional assessment of ischaemia and the placebo-controlled efficacy of PCI

I analysed the effect of ischaemia as assessed by pre-randomisation stress echo score on the placebo-controlled efficacy of PCI. I showed that as the burden of ischaemia

increased with a greater number of ischaemic segments, the efficacy of PCI of patient-reported angina frequency improved when compared to placebo. I also showed that while PCI was more effective than placebo at improving the proportion of patients were reported freedom from angina, this effect was not influenced by pre-randomisation stress echo score. The stress echo score also did not interact with the other endpoints of ORBITA including exercise time and quality of life.

6.5 Clinical implications of these results

The results of ORBITA were a surprise to the interventional community. Since the design targeted a conservative expectation of effect size, I expected PCI, with anatomic stenosis resolution, to easily show a statistically significant effect beyond placebo. The results have shown the link between treating a severe epicardial stenosis with stenting and symptomatic relief was more complex than we had supposed. Based on the results of further analysis of the ORBITA data, using pre-randomisation invasive and non-invasive assessment of ischaemia, I proposed a mechanistic pathway for the changes seen in treatment of stable CAD. This begins with the patient presenting with angina and being diagnosed with angiographically severe CAD. PCI will successfully treat the angiographic stenosis which should then lead to an improvement in invasive physiology. If the improvement in ischaemia is great enough this is seen with an improvement in regional wall motion abnormalities on stress echocardiography. This may then result in an improvement in patient-reported symptoms if the magnitude of the effect is great enough. The sequence of events then continues to an improvement in physician-assessed symptoms and treadmill exercise time. The detection of the effects of PCI becomes harder at further points down the pathway and is more likely if the magnitude of effect at the outset is increased or if the placebo component of an interventional procedure is maximised as in unblinded clinical practice and unblinded clinical trials.

While ORBITA showed a smaller than expected effect size on the primary endpoint of treadmill exercise time, PCI certainly did result in improvement in ischaemia, and in those patients with the greatest ischaemic burden on stress echocardiography there was a significant impact of PCI on angina frequency. Additionally, more patients

became free of angina in the PCI arm. There has been paucity of research focusing on reliable quantification of the effect of PCI on symptoms, this data provides more information which can be used to guide treatment.

Millions of patients continue to experience inadequately controlled angina because medication has incomplete efficacy, can be difficult to adhere to or leads to side effects.[10] We now have data that allows us to consider which patients may have the greatest benefit from PCI. For many of our patients, improvement in the blood supply to the heart maybe be enough to make the decision for PCI regardless of the symptomatic benefit they might see. For those patients with the greatest level of ischaemia at the outset, there may be more symptomatic benefit to be offered by PCI.

6.6 Dissemination of Results

I presented the primary results of ORBITA as a late breaking clinical trial at the Transcatheter Therapeutics Conference in November 2017 with simultaneous publication in The Lancet[85] with an accompanying editorial[109]. The results of the trial were widely publicised with articles in both the lay press and medical literature including The Wall Street Journal, New York Times and Time Magazine (Appendix 8.6).

6.7 Reaction to ORBITA

The reaction to the results of the trial were certainly a surprise. The lay press, medical "key opinion leaders" and social media commentators competed to voice their opinions. Some over-extrapolated the results to undermine PCI as a whole for stable angina. Others were just as quick to undermine the trial.

In decades of PCI, lesions have been stented that may have been better left alone and the entire credibility of Interventional Cardiology has been called into question as adverse events may be more likely in those patients who have had inappropriate PCI. Guidelines already reserve PCI for patients with objective evidence of ischaemia or symptoms refractory to medical therapy.[9]

The reception experienced by ORBITA, and by COURAGE a decade ago, emphasises the polarity of opinions and reflects a need for more such trials. As clinical trialists we should be the first to acknowledge the limitations of our research and put our own results into perspective. However, every step in medical research should be seen as exactly that, "one more step" forward. The equal servings of praise and ridicule may continue for some time but ORBITA has undoubtedly shown that placebo-controlled interventional trials can be done, do provide new information, and should be as standard for interventional procedures as they are for pharmacotherapy.

6.8 Critical appraisal of the ORBITA trial

Through the retrospectoscope, critics suggested modifications that might have made the effect size larger; but we planned the trial without knowing its results. In the four years of conception, design, execution and completion of the ORBITA trial, we fell into the trap of expecting the data to speak for itself.[85] We failed to anticipate the number of voices that would drown out ORBITA with competing choruses of over-extrapolation and denigration. I have highlighted a selection of some of the criticisms the trial has received and discuss each of these points in turn.

6.8.1 Was the trial ethical?

Many interventionists were surprised that we obtained ethical approval for this trial. In fact, the appraisal by the national ethics committee was very enlightening as they raised the following questions:

1. "Is it possible that we may be implanting unnecessary stents?"
2. "Does an angioplasty procedure have risks?"
3. "Are there long-term complications following angioplasty?"

When my answer to each of these questions was affirmative, their final question was, "Then why not been done before?" To that, I had no response.

The ORBITA patients were consented to the 50:50 chance of having a placebo procedure. They understood that, if randomised to placebo, this procedure would carry risks, and that they may require another procedure to have clinical PCI after trial

end. They were also willing to measure their heart rate and blood pressure at home and have telephone consultations several times per week with a consultant cardiologist, to introduce and up-titrate anti-anginal medications. The ORBITA patients showed that, with the commitment of an academic team and participants, placebo-controlled trials of procedures can indeed be done.

6.8.2 Was the primary endpoint the correct choice?

The primary endpoint of ORBITA was selected to mirror the US Food and Drug Administration and European Medicines Agency recommendations for anti-anginal medications: treadmill exercise time.[74,75] The exercise protocol was based on the modified Bruce protocol, which is standard for anti-anginal therapies.[13,75] Other endpoints can now be suggested but the primary endpoint of any trial cannot be changed at any time after the first patient has been enrolled.

6.8.3 Was the trial underpowered?

The sample size was designed to be correct to address the question. Sample size calculations can only be performed prospectively. Anti-anginal drug trials had shown placebo-controlled exercise time improvements of 48 to 55 seconds.[74,75] Plain balloon angioplasty provided a +96 second exercise time improvement in the unblinded ACME trial.[13] ORBITA was designed to detect a 30 second effect size beyond placebo and needed ~200 patients. The sample size of ORBITA seems smaller than trials studying rarer events such as MI and death but is similar to other trials that have assessed similar continuous endpoints.[13,60,62,75] The sample size required for any trial falls with the *square* of the effect size one is trying to detect. To design a trial to detect 90 seconds (3-fold larger), would need 3^2-fold fewer, i.e. only ~24 patients. The only reason to do a larger study would have been the belief that a smaller effect size than 30 seconds was clinically relevant. To detect a 15 second effect size (similar to the point estimate of ORBITA) would need 2^2 (4-fold) more patients, i.e. a trial size of 800 patients. Randomising the additional 300 patients to placebo would only be justified if we would be prepared to recommend PCI for an average clinical benefit of 15 seconds.

6.8.4 Should evidence of ischaemia on non-invasive or invasive testing have been part of the inclusion criteria?

94% of ORBITA patients had evidence of ischaemia on one or more non-invasive or invasive tests. However, this was not an entry requirement because the majority of PCI worldwide is based on symptoms and angiographically evidenced disease with approximately 90% of PCI performed without invasive pressure measurements.[110] Enrollment to ORBITA was designed to be representative of appropriate single vessel elective PCI.[29]

6.8.5 Do the results apply to multi-vessel coronary artery disease?

In order to ensure complete revascularisation in the PCI arm and to simplify the correlation of pre-randomisation ischaemic assessment to outcomes, only patients with single vessel coronary disease were enrolled. Extrapolation of these findings to patients with multi-vessel disease or more complex disease is difficult. ORBITA did not show no effect from PCI: it merely found that the effect (in single vessel disease) was smaller than expected from unblinded studies. In multi-vessel disease there may be a several-fold larger effect. Almost half of the patients having PCI for stable angina in the USA have multi-vessel disease.[111]

6.8.6 Was the medical therapy realistic in clinical practice?

After the medical therapy optimisation phase in ORBITA, 12% of patients had class 0 and 13% had class 1 angina. The incremental benefit of any therapy including PCI on symptom resolution after significant improvement in symptoms may be attenuated once it is added in as third or even fourth line therapy in some cases. Whether PCI is different because it eradicated the lesion is not known. Patients in the PCI arm had a spectacular improvement in ischaemia as assessed by stress echocardiography so while symptoms did not continue to improve, objectively measured markers of ischaemia certainly did improve and this may have long term consequences for our patients. PCI did everything it could reasonably be expected to do, at a technical level.

While aggressive pursuit of medical therapies is entirely reasonable, questions remain about the applicability and scalability of the ORBITA medical care model in common practice. Providing the level of care described in ORBITA would be logistically and

financially challenging outside of a clinical trial. If ORBITA-like medical engagement cannot be assured, then the wisdom and ethics of withholding symptom-relieving PCI from patients with limiting angina despite OMT may be questioned.

The issue of patient preference must also be considered. Many patients find it difficult to comply with medical therapies; the greater the number of medications, the lower the likelihood of adherence.[112] ORBITA cannot be considered inapplicable on the grounds of frequency of contact during medical uptitration. That frequency of contact was to ensure PCI was not unacceptably delayed within the setting of a clinical trial. However, its applicability can be doubted on the grounds that in the longer term many patients may not stay on the medications at the level present in ORBITA. If so, PCI might have a larger effect.

Some patients express a strong preference for percutaneous revascularisation to minimise drug exposure and side effects. Guidelines acknowledge the right of patients to choose their treatment, even to select PCI over increased medical therapies, providing they have been adequately informed of risks, benefits and options.[27] Many patients would prefer an upfront procedure with low levels of associated risk to avoid the side effects and long-term pill burden of anti-anginal therapy.

6.8.7 Was the follow up period long enough?

Patients and their clinicians were only asked to remain blinded to treatment allocation for six weeks. Forty years of experience of PCI for stable angina and the previously reported dramatic symptom relief meant it seemed unethical to ask patients to commit to a longer time period in this first blinded trial. Additionally, ORBITA needed to mirror clinical practice by including patients with high-grade stenoses in major epicardial vessels. While such patients would be expected to have the greatest angina relief from PCI, they may also have faced a greater risk of events. Therefore, a realistic blinded period had to be set in advance, to ensure the inclusion of lesions such as those in ORBITA.

6.8.8 Was the statistical analysis correct?

The pre-specified published statistical analysis of ORBITA stated that endpoint analysis would use unpaired, two-tailed Student's t test, with a 5% threshold level of significance.[58] This was similar to other trials assessing a similar placebo-controlled endpoint[60] and was reviewed by an independent statistician and peer-reviewer, and subsequently published online.[58] In order to more adequately adjust for baseline differences between the two groups, regression modelling using a generalised form of analysis of covariance can be used to increase statistical power. In order to meet with the guidelines of medical reporting we reported data using only pre-specified methods in the primary manuscript. However, for subsequent analyses we have used regression modelling.

6.8.9 Was there selection bias in recruitment into the trial?

Selection of ORBITA investigators was key to successful conduct of the trial. Recruitment of ORBITA participants required commitment from the investigators. These interventionists had to understand the need for this trial and be driven by the curiosity to answer this clinical question. Their hospitals made an economic loss on each patient enrolled. They were prepared to enroll all eligible patients including those with severe lesions that may have been excluded from previous trials. A consultant cardiologist approached patients after the diagnostic angiogram. Explaining the rationale and design of ORBITA took time and dedication. The accusations of selection bias are disappointing because of the time taken to enroll 230 patients; in reality it took time because unquestionably single-vessel coronary disease, with stable angina, is rarer than we had thought. We were fortunate that the majority of eligible patients understood the importance of this trial, and a respectable 63% of all eligible patients were recruited.

7 Conclusion

All science builds on the science that has been done before. In the case of the placebo-controlled assessment of the efficacy of modern stenting in angina relief, the science that had been done before was non-existent.

The main indication for PCI for stable angina remains symptom relief and improvement in quality of life. Although angina relief is our primary aim, this is a subjective endpoint. Experience with other interventional procedures has taught us that placebo-controlled trials are essential for reliably evaluating effects on such endpoints. The ORBITA trial was been designed to investigate changes in symptom and functional capacity following PCI when compared to a placebo procedure and to ascertain whether PCI for stable CAD offers an incremental benefit. It was also designed to investigate which patients, if any, would gain the greatest improvement after placebo-controlled PCI.

The primary results were surprising as the effect size of PCI on treadmill exercise time and symptomatic endpoints was smaller than expected. However, PCI did significantly improve ischaemia as assessed by dobutamine stress echocardiography. Further analyses allow a greater understanding for the impact of PCI and show that the degree of ischaemia as assessed by invasive physiology predicts the degree of stress echo improvement with PCI. Also, the degree of ischaemia as assessed by stress echocardiography predicts the extent to which PCI results in an improvement in patient-reported angina frequency.

These placebo-controlled data have enhanced our understanding of stable CAD and its treatment. If we are to ensure that an objective assessment of the impact of interventional procedures are made in future, we must follow the principles that are now standard practice in pharmacological trials. To obtain the highest level of evidence to support the use of any therapy or device with subjective endpoints, it is important to test that intervention against placebo control in a double-blind randomised design.

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9 Appendix

9.1 Publications arising from this thesis

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

Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP; ORBITA investigators.
Lancet. 2018 Jan 6;391(10115):31-40.

Swimming against the tide: insights from the ORBITA trial.

Al-Lamee R, Francis DP.
EuroIntervention. 2017 Dec 8;13(12):e1373-e1375

What is the role of coronary angioplasty and stenting in stable angina?

Al-Lamee R, Davies J, Malik IS
British Medical Journal 2016 Feb 5;352:i205

An unusual complication of radial angiography

Al-Lamee R, Davies JE, Gerber R
European Heart Journal 2016 Jan 21;37(4):385

Effects of fractional flow reserve and instantaneous wave-free ratio on the placebo-controlled response to percutaneous coronary intervention in stable coronary artery disease: the physiology-stratified analysis of ORBITA

Al-Lamee R, Howard J, Shun-Shin M, Thompson D, Dehbi H-M, Sen S, Nijjer S, Petraco R, Davies J, Keeble T, Tang K, Malik I, Cook C, Ahmad Y, Sharp ASP, Gerber R, baker C, Kaprielian R, Talwar S, Assomull R, Cole G, Keenan NG, Kanaganayagam S, Sehmi J, Wensel R, Wensel R, Harrell FE, Mayet J, Thom S, Davies JE, Francis DP
Circulation: Under review

9.2 Other publications during PhD studies

Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements.

Cook CM, Jeremias A, Petraco R, Sen S, Nijjer S, Shun-Shin MJ, Ahmad Y, de Waard G, van de Hoef T, Echavarria-Pinto M, van Lavieren M, **Al-Lamee R**, Kikuta Y, Shiono Y, Buch A, Meuwissen M, Danad I, Knaapen P, Maehara A, Koo BK, Mintz GS, Escaned J, Stone GW, Francis DP, Mayet J, Piek JJ, van Royen N, Davies JE.

JACC Cardiovasc Interv. 2017 Dec 26;10(24):2514-2524.

Non-Newtonian pulsatile shear stress assessment: a method to differentiate bioresorbable scaffold platforms.

Tenekecioglu E, Torii R, Bourantas CV, **Al-Lamee R**, Serruys PW.

Eur Heart J. 2017 Sep 1;38(33):2570.

Effect of strut thickness on shear stress distribution in a preclinical model.

Tenekecioglu E, Torii R, Bourantas C, Miyazaki Y, Collet C, **Al-Lamee R**, Al-Lamee K, Onuma Y, Serruys PW.

Int J Cardiovasc Imaging. 2017 May 31

Diagnostic Accuracy of Computed Tomography-Derived Fractional Flow Reserve: A Systematic Review.

Cook CM, Petraco R, Shun-Shin MJ, Ahmad Y, Nijjer S, **Al-Lamee R**, Kikuta Y, Shiono Y, Mayet J, Francis DP, Sen S, Davies JE.

JAMA Cardiol. 2017 Jul 1;2(7):803-810

Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI.

Davies JE, Sen S, Dehbi HM, **Al-Lamee R**, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB,

Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp AS, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J
N Engl J Med. 2017 May 11;376(19):1824-1834

Bioresorbable vascular scaffold radial expansion and conformation compared to a metallic platform: insights from in vitro expansion in a coronary artery lesion model.

Foin N, Lee R, Bourantas C, Mattesini A, Soh N, Lim JE, Torii R, Ng J, Liang LH, Caiazzo G, Fabris E, Kilic D, Onuma Y, Low AF, Nijjer S, Sen S, Petraco R, **Al Lamee R**, Davies JE, Di Mario C, Wong P, Serruys PW.
EuroIntervention. 2016 Sep 18;12(7):834-44

Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa.

Cook CM, Ahmad Y, Shun-Shin MJ, Nijjer S, Petraco R, **Al-Lamee R**, Mayet J, Francis DP, Sen S, Davies JE.
Circ Cardiovasc Interv 2016 Apr;9(4)

Distribution of lifespan gain from primary prevention intervention.

Finegold JA, Shun-Shin MJ, Cole GD, Zaman S, Maznyczka A, Zaman S, **Al-Lamee R**, Ye S, Francis DP.
Open Heart 2016 Mar 11;3(1):e000343

Estimation of coronary wave intensity analysis using non-invasive techniques and its application to exercise physiology.

Broyd CJ, Nijjer S, Sen S, Petraco R, Jones S, **Al-Lamee R**, Foin N, Al-Bustami M, Sethi A, Kaprielian R, Ramrakha P, Khan M, Malik IS, Francis DP, Parker K, Hughes AD, Mikhail GW, Mayet J, Davies JE.
Am J Physiol Heart Circ Physiol 2016 Mar 1;310(5):H619-27

ECG-Independent Calculation of Instantaneous Wave-Free Ratio.

Petraco R, Sen S, Nijjer S, Malik IS, Mikhail GW, Al-Lamee R, Cook C, Baker C, Kaprielian R, Foale RA, Mayet J, Francis DP, Davies JE.

JACC Cardiovasc Interv 2015 Dec 28;8(15):2043-6

Change in Coronary Blood Flow After Percutaneous Coronary Intervention in Relation to Baseline Lesion Physiology: Results of the JUSTIFY-PCI Study.

Nijjer SS, Petraco R, van de Hoef TP, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, **Al-Lamee R**, Foin N, Sethi A, Malik IS, Mikhail GW, Hughes AD, Mayet J, Francis DP, Di Mario C, Escaned J, Piek JJ, Davies JE.

Circ Cardiovasc Interv. 2015 Jun;8(6):e001715.

Intra-aortic Balloon Pump Therapy for Acute Myocardial Infarction: A Meta-analysis.

Ahmad Y, Sen S, Shun-Shin MJ, Ouyang J, Finegold JA, **Al-Lamee RK**, Davies JE, Cole GD, Francis DP.

JAMA Intern Med. 2015 Mar 30

Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease.

Nijjer SS, Sen S, Petraco R, Escaned J, Echavarria-Pinto M, Broyd C, **Al-Lamee R**, Foin N, Foale RA, Malik IS, Mikhail GW, Sethi AS, Al-Bustami M, Kaprielian RR, Khan MA, Baker CS, Bellamy MF, Hughes AD, Mayet J, Francis DP, Di Mario C, Davies JE.

JACC Cardiovasc Interv. 2014 Dec;7(12):1386-96. Epub 2014 Nov 20

Real-time use of instantaneous wave-free ratio: results of the ADVISE in-practice: an international, multicenter evaluation of instantaneous wave-free ratio in clinical practice.

Petraco R, **Al-Lamee R**, Gotberg M, Sharp A, Hellig F, Nijjer SS, Echavarria-Pinto M, van de Hoef TP, Sen S, Tanaka N, Van Belle E, Bojara W, Sakoda K, Mates M,

Indolfi C, De Rosa S, Vrints CJ, Haine S, Yokoi H, Ribichini FL, Meuwissen M, Matsuo H, Janssens L, Katsumi U, Di Mario C, Escaned J, Piek J, Davies JE.
Am Heart J. 2014 Nov;168(5):739-48. Epub 2014 Jul 21

Influence of gender on clinical outcomes following transcatheter aortic valve implantation from the UK transcatheter aortic valve implantation registry and the National Institute for Cardiovascular Outcomes Research.
Al-Lamee R, Broyd C, Parker J, Davies JE, Mayet J, Sutaria N, Ariff B, Unsworth B, Cousins J, Bicknell C, Anderson J, Malik IS, Chukwuemeka A, Blackman DJ, Moat N, Ludman PF, Francis DP, Mikhail GW.
American Journal of Cardiology 2014 Feb 1;113(3):522-8

9.3 Abstracts presented at international conferences

The ORBITA trial. Late breaking clinical trial presentation
Transcatheter Cardiovascular Therapeutics conference
2nd Nov 2017
Denver, US

Reshaping the endpoints: insights from the ORBITA study
American College of Cardiology conference
14th March 2015
San Diego, US

Protocol for the Objective Randomised Blinded Investigation of optimal medical Therapy versus Angioplasty for stable angina (ORBITA) trial
EuroPCR conference
21st May 2014
Paris, France

9.4 Awards

Young Leader Cardiovascular Research Technologies 2018
Washington, US

Young Leader Cardiovascular Research Technologies 2016
Washington, US

Imperial College Healthcare Charity Research award 2013

9.5 ORBITA editorials

Last nail in the coffin for PCI in stable angina?

Brown D and Redberg RF

Lancet. 2018 Jan 6;391(10115):3-4

Sham-controlled trials for coronary interventions: ethically acceptable and ethically important

Dickert NW and Miller FG

Journal of American College of Cardiology. 2018 Jan 2;71(1):95-97

Fallout from the ORBITA trial – is angioplasty in a spin?

Byrne R.

EuroIntervention. 2017 Dec 20;13(11):1253-1254

Is Exercise Treadmill Time or Reduction in Myocardial Ischemia the Appropriate Primary Endpoint to Assess Success of Percutaneous Coronary Intervention in Stable Angina (ORBITA)?

Dilsizian V and Erario M.

Journal of Nuclear Medicine. 2018 Jan;59(1):1-2

Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina

Dambalkar A and Singh AI

Journal of the Practice of Cardiovascular Sciences. 2017;3:160-2

The Less-Is-More Crusade — Are We Overmedicalizing or Oversimplifying?

Rosenbaum L

New England Journal of Medicine. 2017 Dec 14;377(24):2392-2397.

ORBITA revisited: what it really means and what it does not?

Chaitman BR, Brooks MM, Fox K, and Luscher T

European Heart Journal. 2018 Jan 6. doi: 10.1093/eurheartj/ehx796

Overuse of Percutaneous Coronary Interventions

Redberg R

JAMA Internal Medicine. 2018 Feb 1;178(2):247.

9.6 ORBITA press articles

Multiple news articles have been written about the ORBITA trial. A selection is listed here.

1. http://www.cardiobrief.org/2017/09/18/what-if-pci-is-just-a-sham/
2. https://www.tctmd.com/news/tct-2017-high-hopes-denver-complex-pci-shorter-dapt-durations-tavr-qol-and-more
3. https://www.tctmd.com/videos/on-record-looking-ahead-to-tct-2017.30d021bbe17e48a2bd5e05a4927ab8bd
4. https://www.medpagetoday.com/MeetingCoverage/TCT/68808
5. https://www.medscape.com/viewarticle/887953?src=soc_tw_170728-pm_mscpedt_news_card&faf=1
6. https://www.medpagetoday.com/cardiology/cardiobrief/68985
7. https://www.tctmd.com/news/orbita-pci-offers-no-symptom-improvement-over-sham-procedure?utm_source=TCTMD&utm_medium=email&utm_campaign=Newsletter110617
8. https://www.medscape.com/viewarticle/888115?nlid=118959_3861&src=WNL_mdplsfeat_171107_mscpedit_card&uac=14100HT&spon=2&impID=1476467&faf=1
9. https://www.medpagetoday.com/cardiology/cardiobrief/69147?xid=nl_mpt_DHE_2017-11-10&eun=g
10. https://www.tctmd.com/news/circling-back-orbita-sham-controlled-pci-trial-makes-best-2017-list?utm_source=TCTMD&utm_medium=email&utm_campaign=Newsletter111317
11. https://imperialbrc.nihr.ac.uk/2017/11/09/potential-placebo-effect-of-heart-stents/
12. https://cardiovascularnews.com/bold-new-study-alter-orbit-elective-pci/
13. https://cardiovascularnews.com/tct-2017-sham-controlled-trial-raises-doubts-benefit-angiography-guided-pci-stable-angina/

14. https://www.invasivecardiology.com/news/tct-2017-orbita-trial-%E2%80%94-scai-examines-strengths-and-weaknesses-sham-pci-trial
15. https://sciencebasedmedicine.org/orbita-another-clinical-trial-demonstrating-the-need-for-sham-controls-in-surgical-trials/
16. https://www.medpagetoday.com/cardiology/cardiobrief/68988
17. https://www.medpagetoday.com/meetingcoverage/tct/68974
18. https://www.tctmd.com/slide/orbita-randomized-sham-controlled-trial-pci-patients-coronary-artery-disease
19. https://www.medscape.com/viewarticle/888115
20. https://www.medscape.com/viewarticle/888011
21. https://www.news-medical.net/news/20171106/ORBITA-trial-on-heart-stents-for-stable-angina-indicates-placebo-effect-potential.aspx
22. https://www.dicardiology.com/article/orbita-study-finds-no-improvement-exercise-time-over-placebo-pci-patients
23. https://www.hayesinc.com/hayes/resource-center/news-service/HNS-20171006-682/
24. https://emcrit.org/emnerd/em-nerd-case-inert-remedy/
25. https://www.obgproject.com/2017/11/03/orbita-trial-stents-useful-stable-angina/
26. https://www.linkedin.com/pulse/think-before-you-stent-orbita-trial-mayooran-shanmuganathan
27. http://www.utswmedicine.org/stories/articles/year-2017/stent-PCI-ORBITA.html
28. https://drsvenkatesan.com/tag/orbita-trial-review-and-comments/
29. http://www.crf.org/crf/news-and-events/news/news/2244-announcing-the-tct-2017-late-breaking-trials-and-first-report-investigations
30. https://respectfulinsolence.com/2017/11/13/angioplasties-coronary-stenting-improve-symptoms-patients-angina/
31. http://roguemedic.com/2017/11/is-placebo-better-than-aggressive-medical-treatment-for-patients-not-having-a-heart-attack/
32. https://www.peoplespharmacy.com/2017/11/09/the-shocking-results-of-a-heart-stent-experiment/

33. http://thehealthcareblog.com/blog/2017/11/07/12-seconds-of-placebo-an-outsiders-view-of-orbita/
34. https://www.clinicalcorrelations.org/?p=13003
35. https://sciencebasedmedicine.org/orbita-another-clinical-trial-demonstrating-the-need-for-sham-controls-in-surgical-trials/
36. http://www.massdevice.com/study-pci-procedures-ineffective-treating-chest-pain/
37. http://www.scai.org/Press/detail.aspx?cid=10e25907-9ad2-4bc8-815a-02eb9cd54c4c#.WhM7hbTQqL8
38. http://www.cardiobrief.org/2017/11/08/orbita-trial-puts-interventional-cardiologists-on-the-defensive/
39. http://montrealgazette.com/opinion/opinion-orbita-angioplasty-trial-provides-food-for-thought
40. https://drsvenkatesan.com/2017/11/06/orbita-trial-first-let-us-do-some-harm-second-we-shall/
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9.7 Standard operating procedure for cardiopulmonary exercise testing

1. Calibration of the metabolic cart
   - the gas (CO2 and O2) calibration is performed every day before the first CPET procedure
   - the flow calibration is performed before every CPET
2. Setup of the patient
   - the patient is prepared in a sitting or standing position
   - to ensure a reliable ECG signal, the skin needs to be degreased before attaching the electrodes – only proceed if the ECG signal is free of artefact, otherwise check electrodes (contact gel dry? skin prep ok, consider using electrodes from a new bag, as the electrode contact gel dries quickly once bag has been opened)
   - the facemask for air leak during gentle expiration
3. Resting measurements
   - performed resting measurement in standing position
   - duration of resting measurements at least for 3 min
   - the purpose of that is for potential hyperventilation to settle and to get stable baseline conditions
   - check resting gas exchange data for plausibility
   - RER should be between 0.75 – 0.85 (if less than 0.7 consider recalibrating the cart)
   - take blood pressure and document on the cart before start of exercise.
4. Exercise Protocol
   - the protocol “xxx” is chosen for every test
   - every 2 min the blood pressure is measured and recorded
   - the gas exchange data monitoring can be terminated after 3 min of recovery
   - the ECG monitoring can be terminated after 6 min of recovery, assuming there are no major arrhythmic events or ischaemia seen
5. Criteria for termination of the test
   - the test should be symptom limited, i.e. terminated at the patient’s request

Reasons to end the test prematurely are:

- Systolic blood pressure is above 240mmHg, diastolic blood pressure >120mmHg
- Clinically significant ECG abnormalities are seen (e.g. ischaemia, ventricular dysrhythmias, new second or third-degree heart block)
- Symptomatic hypotension
- Neurological impairment (e.g. confusion or altered conscious state)

6. Documentation:
   - relevant comments/narratives should be recorded immediately after each test in the CPET operator notes spreadsheet
   - the saved data need to be reviewed immediately, with particular attention to plausibility of manually entered blood pressure data.

9.8 Standard protocol for dobutamine stress echocardiography

1. β-blockers should be omitted for 72hr before the DSE.
2. 2 persons required to record and monitor stress echocardiography.
3. Recordings performed by skilled echocardiographer (physiologist or physician).
4. All patients will receive SonoVue contrast to improve endocardial border definition unless contraindicated.
5. Graded Dobutamine infusion starting with 10μg/kg/min followed by 20μg/kg/min, 30μg/kg/min and 40μg/kg/min in 3 minute stages.
6. In patients who have an "inadequate" heart rate response to Dobutamine, atropine can be used to increase the heart rate. Atropine should be given at the minimum effective dose (≤1200mcg) and administered in 300mcg increments.
7. Imaging: Pre-stress echo at baseline to exclude aortic stenosis graded as moderate or above based on dimensionless index and aortic valve area or any other significant valve disease. For contrast echo the contrast presets of the ultrasound machine are recommended. The frame rate should be at least 25 frames per second. However, with heart rate >140bpm, the frame rate should be increased to 20 frames per second. Preset acquisition to 3 beats. Images should be recorded in the following 4 views:
   - Apical 4 chamber view
   - Apical 2 chamber view
   - Apical 3 chamber view
   - Parasternal short axis view

   All images should be recorded at the following intervals:
   - Baseline
   - Low dose stress (10% increase in heart rate)
   - High dose stress (85% of age predicted heart rate)
   - Recovery

Criteria for consideration of termination of test:

- HR>85% max predicted (220- age)
- Systolic BP <85mmHg or >220mmHg
- Chest pain or shortness of breath if severe or accompanied by regional wall motion abnormalities or ECG changes
- Onset of new arrhythmia: SVT, AF, NSVT (>5 consecutive VEs)
- Patient unable to tolerate the test
- Symptomatic vasovagal response
- Symptomatic bradycardia or hypotension

Further points:

1) Patients with pacemakers in situ: Will be included if they are not pacing dependent and is not programmed in a way that would cause ventricular pacing during a stress echo protocol.

2) Patients with left bundle branch block: Will be included in the analysis but statistical analysis will be performed with both these patients included and excluded in the final analysis as we may find that their data skews the overall result as a result of its intrinsic variability.

3) Patients in atrial fibrillation: Will be included in the analysis but statistical analysis will be performed with both these patients included and excluded in the final analysis as we may find that their data skews the overall result as a result of its intrinsic variability.

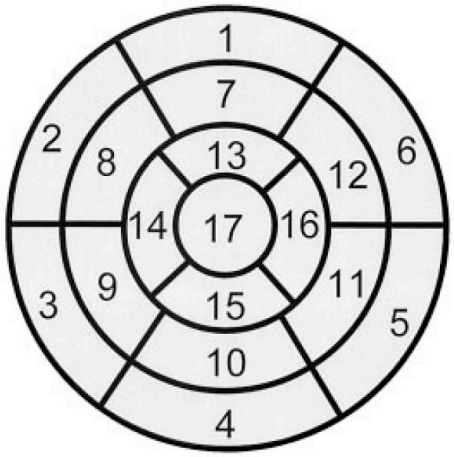
Analysis:

Comprehensive analysis is made after stress test with side by side comparisons or recordings.

Use 17 segment model (Figure 9.1) to perform wall motion scoring

Wall motion is graded in each segment as:

a) Normal=1
b) Hypokinetic=2
c) Akinetic=3
d) Dyskinetic=4
e) Aneursymal=5



1. basal anterior
2. basal anteroseptal
3. basal inferoseptal
4. basal inferior
5. basal inferolateral
6. basal anterolateral
7. mid anterior
8. mid anteroseptal
9. mid inferoseptal
10. mid inferior
11. mid inferolateral
12. mid anterolateral
13. apical anterior
14. apical septal
15. apical inferior
16. apical lateral
17. apex

Figure 9.1: Seventeen-segment regional wall motion model

9.9 Standard protocol for iFR/FFR assessment:

See Figure 9.2

1. Flush the guide wire with enough saline to fill the dispenser hoop and let sit for at least 2 minutes.
2. Connect the ECG and BP cables from the s5 (if applicable) to the haemosystem (this is already done on an s5i).
3. Enter patient information on imaging system.
4. Select iFR on the bottom right hand corner of the screen.
5. Select the Settings tab on the bottom of the screen.

- Make sure the ECG Trace box is ON.

6. Select the Pressure tab on the s5 or s5i.

- Make sure the s5 or s5i has the MAP reading at 3 beats. 7. Once the ECG trace is on and the MAP reading is at 3 beats, select the HOME tab on the bottom of the screen to go to the "LIVE" screen.
- Make sure there is an ECG signal on the top of the HOME screen.

7. Plug the guide wire into the Volcano pimette and allow it to zero.

- It will take 10 to 15 seconds for the wire to "zero".
- Once wire has zeroed, the machine will display a message at the bottom of the screen that states, "Wire zeroed, ready to insert."
- The wire can now be taken out of the dispenser hoop.

8. Administer 300 mcg IC Nitro through the guide catheter, per standard lab procedures.
9. Shape the guide wire (if needed), insert and advance transducer to the end of the guide catheter.
10. Flush catheter with saline.

- Make sure guide catheter is coaxial with vessel and AO pressure is not damped.
- If the AO pressure trace appears damped, ideally disengage the guide catheter to ensure an optimum AO pressure trace. If this is

11. Remove wire introducer.

12. Tighten Tuohy manually, even if the Tuohy has a haemostatic valve.
13. Wait 10 seconds, then press NORMALISE on the sS5 /S5i.

- Make sure Pd/Pa equals 1.00.
- If Pd/Pa does not equal 1.00, wait 10 seconds and then press NORMALISE again.
- If the Pd/Pa ratio still does not equal 1.00, then check the height of the AO transducer to make sure it is midline to the patient and NORMALISE again.
- If Pd/Pa ratio still will not equal 1.00, then open new wire and contact the Volcano study team member to obtain instructions on returning the guide wire to Volcano.

14. Press RECORD on the Volcano system to acquire 5-10 beats of normalisation.
15. Position the wire and pressure sensor at least 3 vessel diameters distal to the lesion to be evaluated.

- Flush the guide catheter with saline (to prevent pressure damping).
- Remove wire introducer.
- Close Tuohy manually, even if it is a Tuohy with a haemostatic valve.
- Turn transducer back on to pressure and make sure Pa pressure is not damped.

- Press RECORD on the Volcano system and make an iFR measurement. Repeat this measurement 3 times and record each of these values.
- Once iFR measurements are complete, pull the guide wire back to the guide catheter and assess for drift of the Pd/Pa recording. If this remains at 1.00 ± 0.02, continue to perform FFR. If the Pd/Pa does not equal 1.00 ± 0.02, repeat the normalisation process until it equals 1.00, and repeat steps 12-13 to obtain drift-free iFR measurements.

15. Select FFR on the bottom left hand corner of the screen.
16. Position the wire and pressure sensor distal to the lesion to be evaluated.

- Flush the guide catheter with saline (to prevent pressure damping).
- Remove wire introducer.
- Close Tuohy manually, even if it is a Tuohy with a haemostatic valve.

- Turn transducer back on to pressure and make sure Pa pressure is not damped.

17. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 20 seconds. Continue recording and make an FFR assessment at the same location using Adenosine infusion through a peripheral vein at 140 mcg/kg/min up to 3 minutes in duration or until stable hyperemia as determined by the physician.
- Make sure the recording is uninterrupted for the entire duration, no injection of contrast, or saline, or disruption to the aortic pressure transducer should be made during this recording phase. A 3 beat moving Pd/Pa average window will be used to obtain FFR.
- For patients greater than 100kg, but less than or equal to 220kg, please follow hospital protocol (found in pharmacy) for non-invasive cardiac stress testing using Adenosine and make note of it in the case log. Data from patients greater than 441 pounds (200 kg) will be excluded.
- Without interruption of adenosine infusion and without opening the Tuohy haemostatic valve, perform a manual pullback manoeuvre under fluoroscopic guidance at an estimated velocity of 0.5mm/sec until the guide wire sensor has reached the tip of the guide catheter. Once the guide wire is into the guide catheter, wait for 20 seconds to check normalisation. Make sure the recording is uninterrupted for the entire duration of the pullback manoeuvre.
18. Check normalisation. If Pd/Pa is outside of 1.00 ± 0.02, then re-NORMALISE and repeat steps 12-17 to obtain a drift-free comparison. Ensure that you record at least 5-10 beats of normalisation.
19. Wait 10 minutes and repeat steps 12-18 to obtain repeat iFR and FFR measurements before randomisation.
20. Randomise patient to PCI+OMT or OMT alone arm.
21. If the patient is then randomised to PCI, pullback the wire, re-administer 300 mcg IC Nitro through the guide catheter and repeat steps 12-18 to repeat iFR and FFR post-PCI.
22. Complete an entry on the Case Report Form for each Baseline/iFR/FFR comparison run. 23. At the conclusion of the case, archive the case to DVD

by selecting the Patient Tab, then the ARCHIVE button, the DVD location, and finally the SAVE button.

23. The site should then remove patient-specific identifiers and assign an ID number to the DVD that matches the Case Report Form).

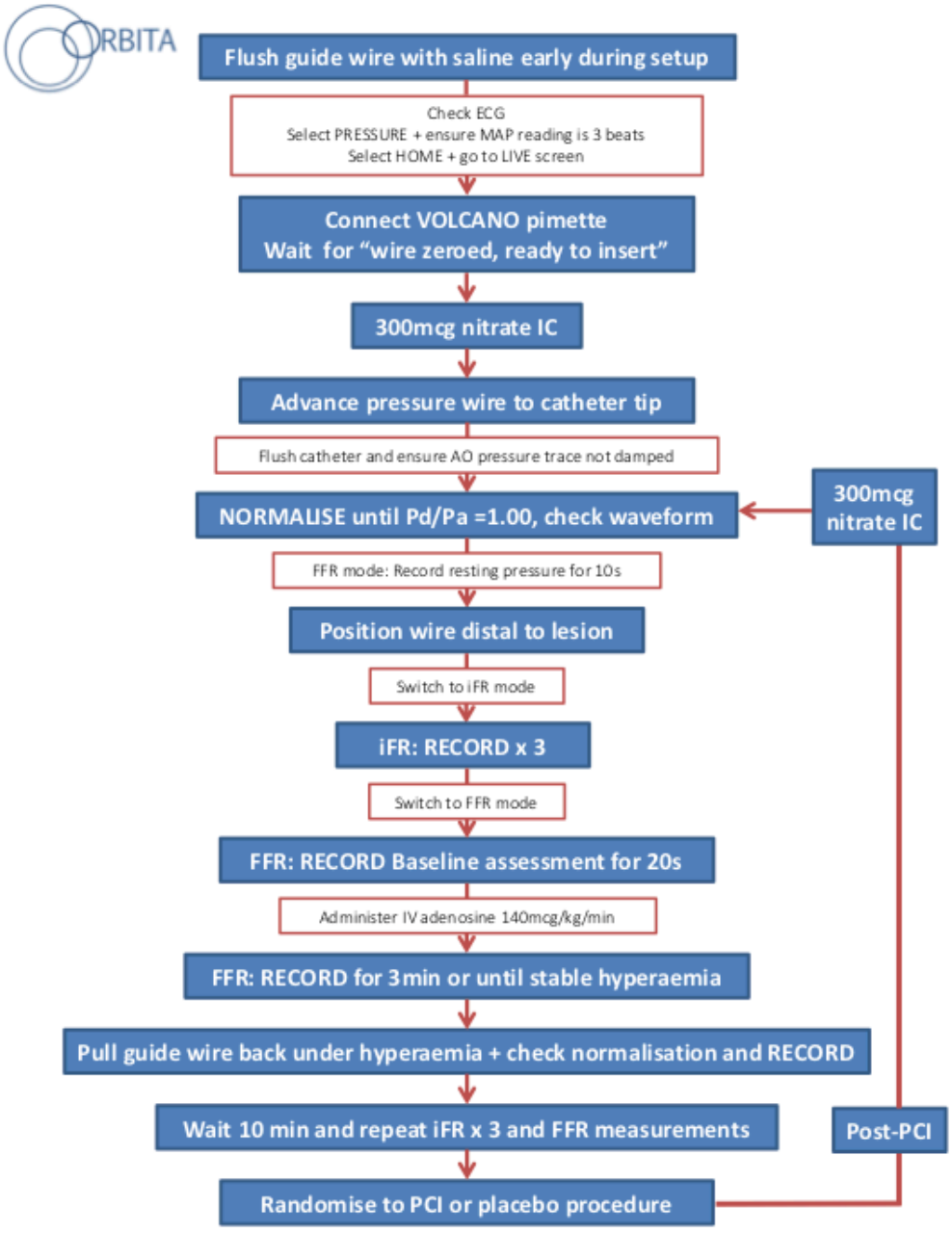
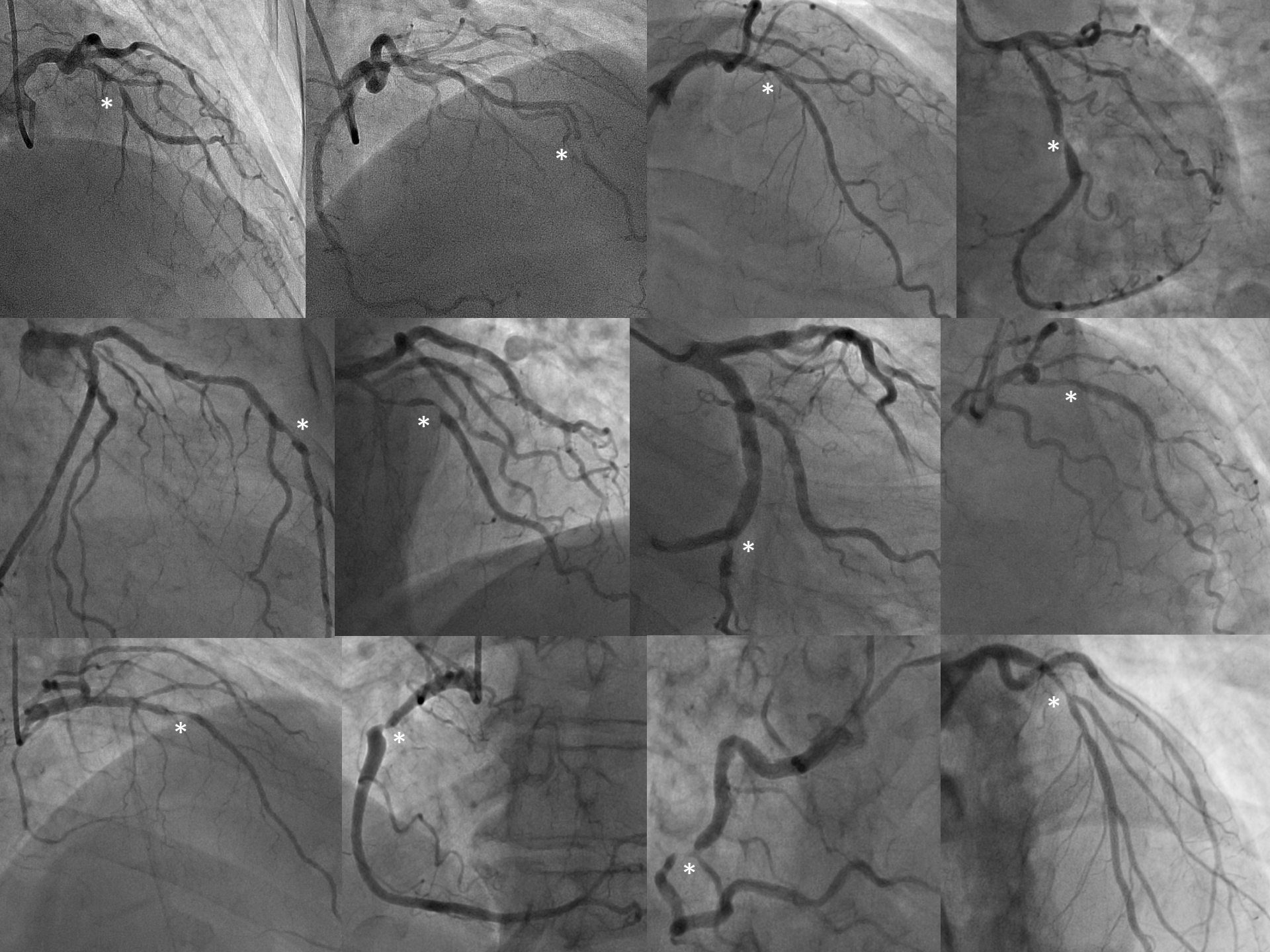


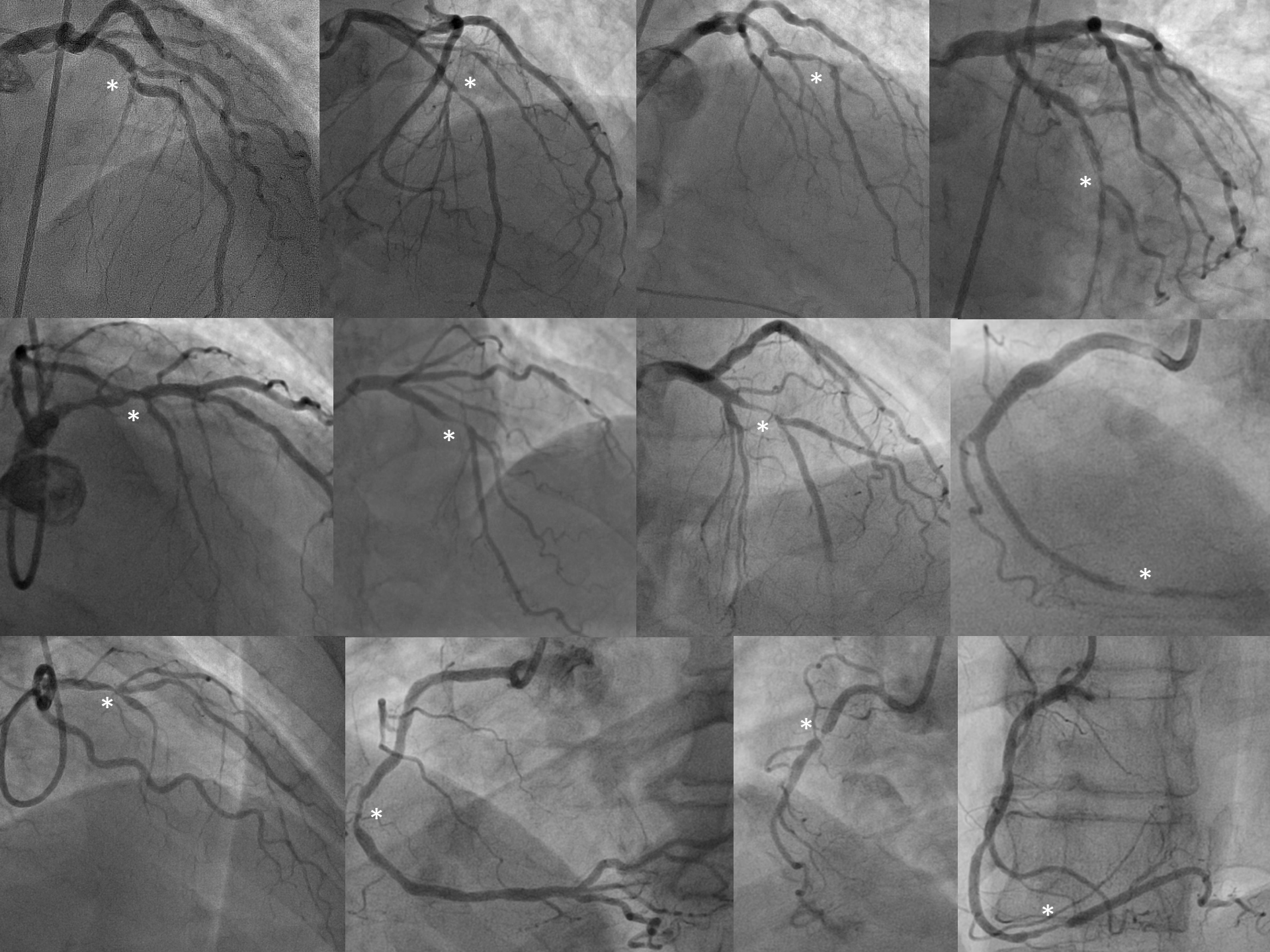
Figure 9.2: ORBITA Flowchart for measurement of invasive physiology

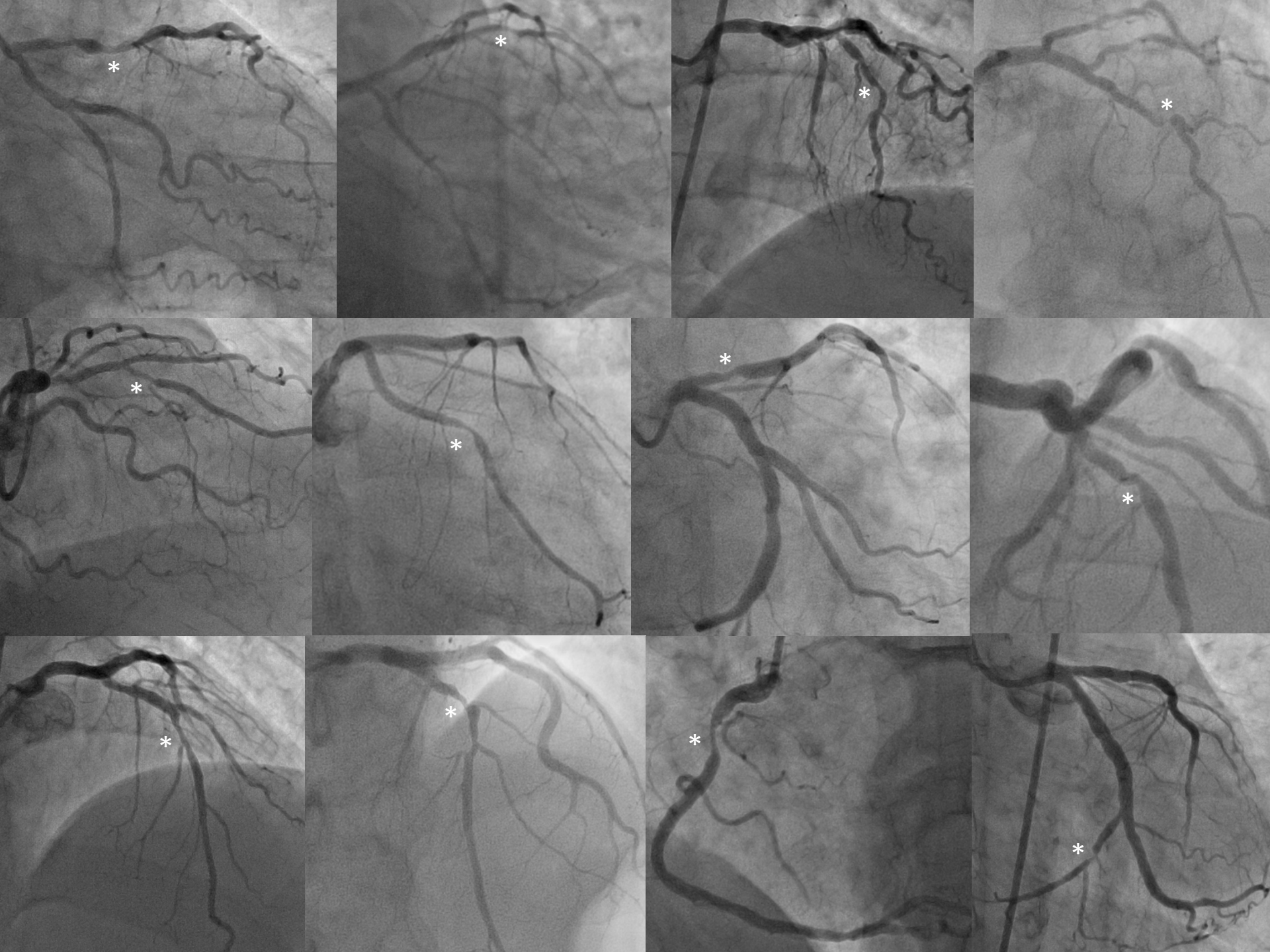
Figure 9.3: Diagnostic angiogram pictures of all 200 randomised ORBITA patients

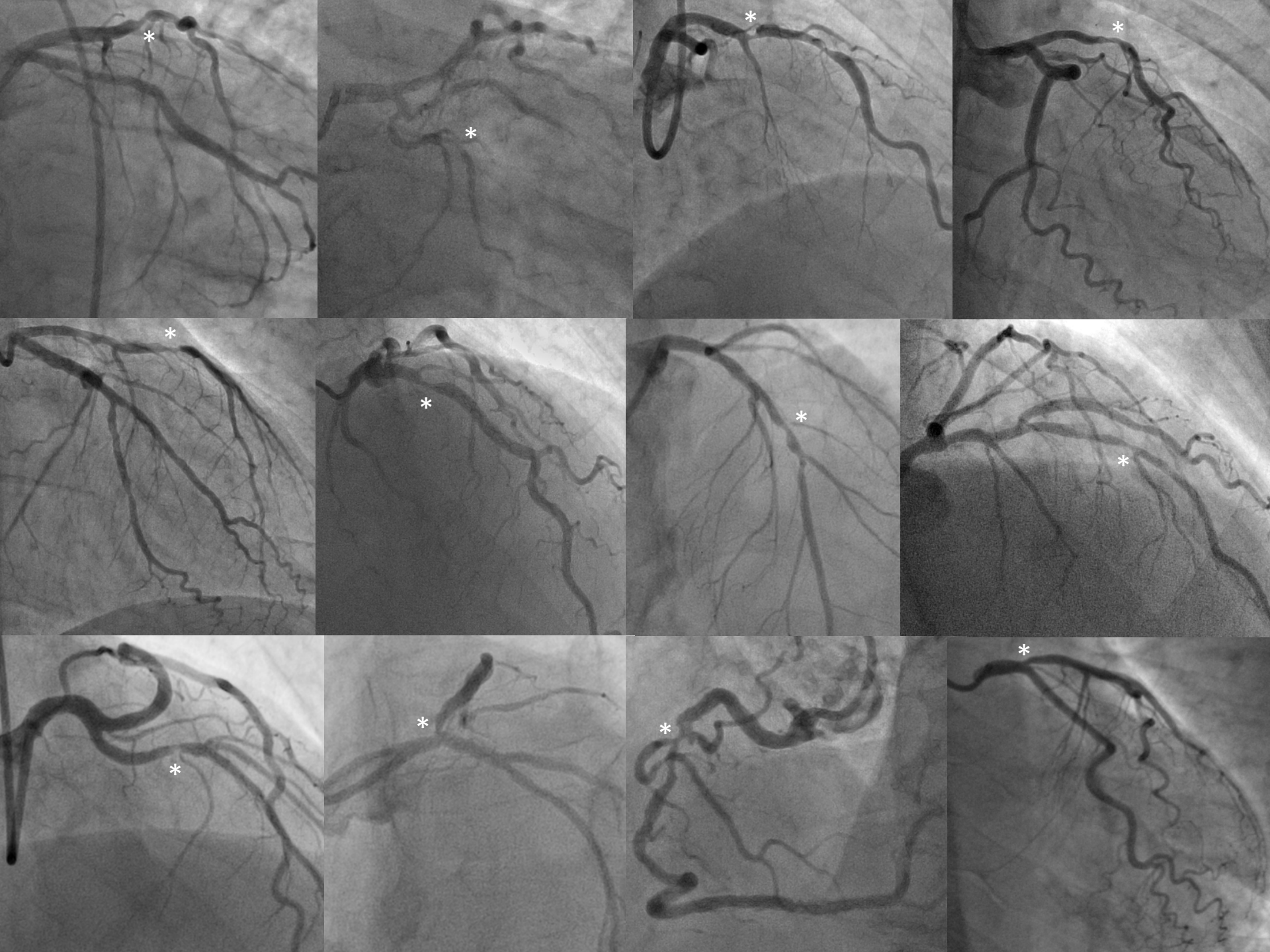
Diagnostic coronary angiogram pictures of all 200 patients randomised into ORBITA. The 6th patient on slide 11 had a tight ostial RCA lesion which is best displayed from the randomisation visit angiogram in which the pressure wire stabilised the catheter position.

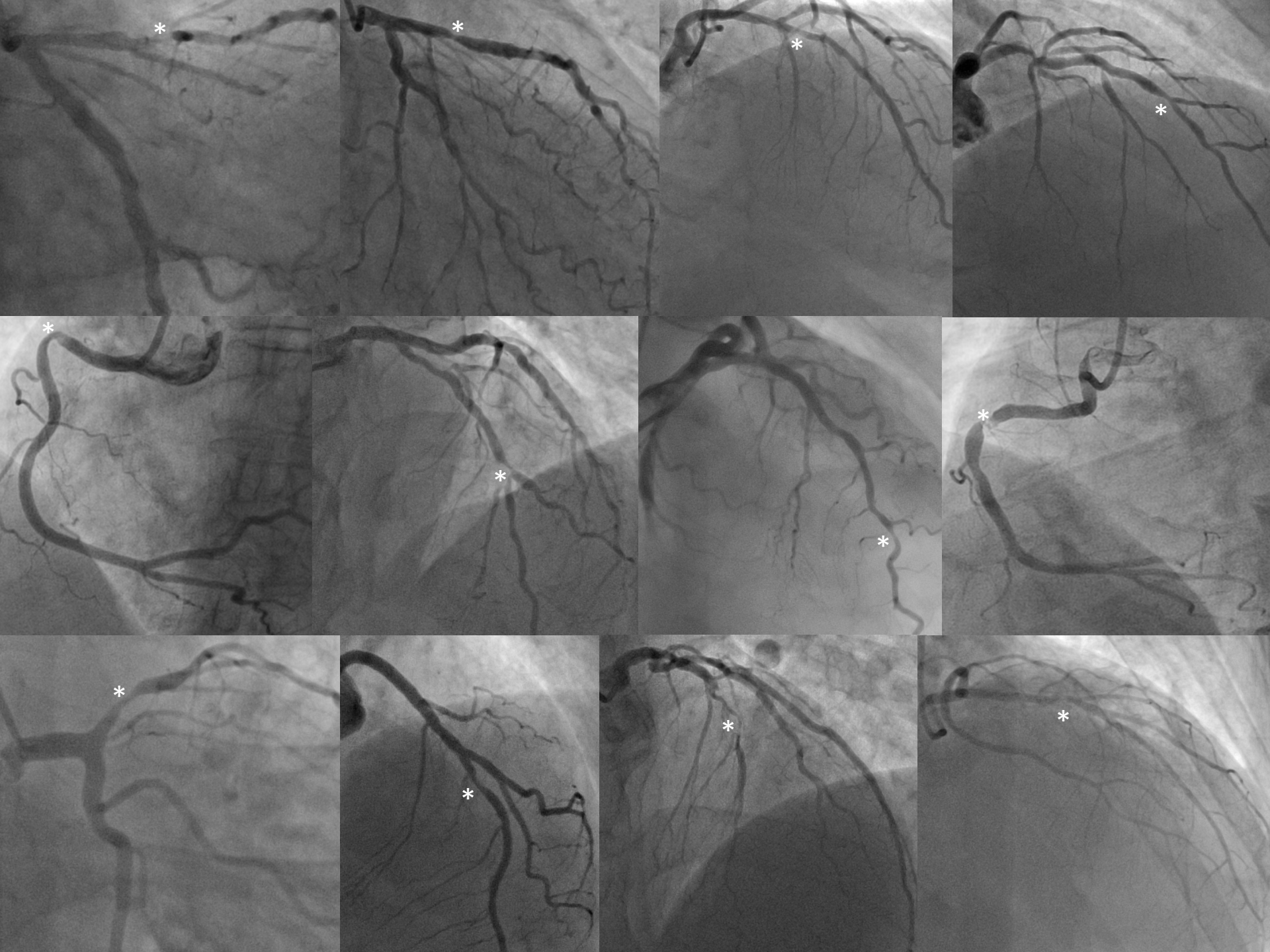
The target vessel is marked with an asterisk.

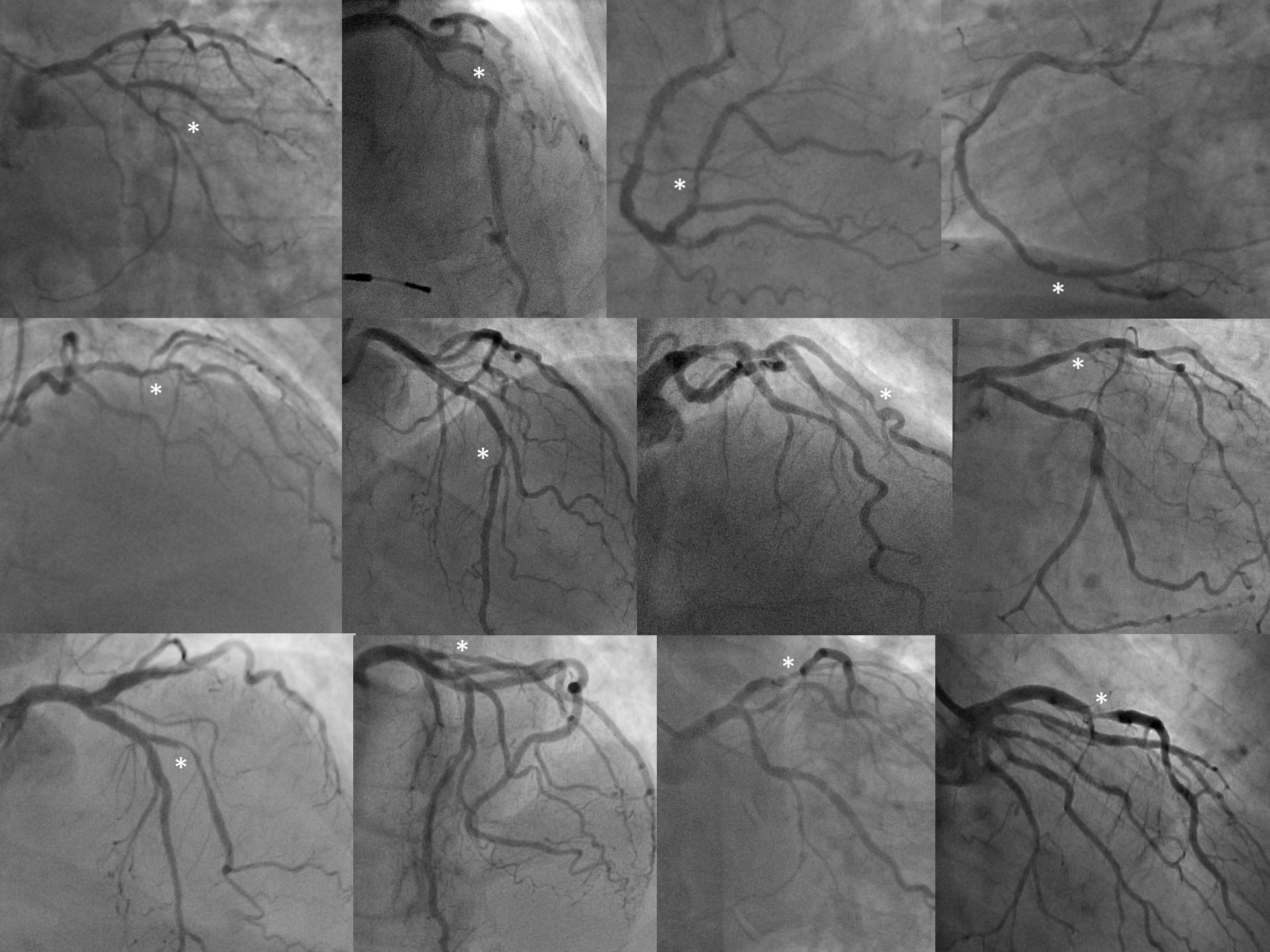


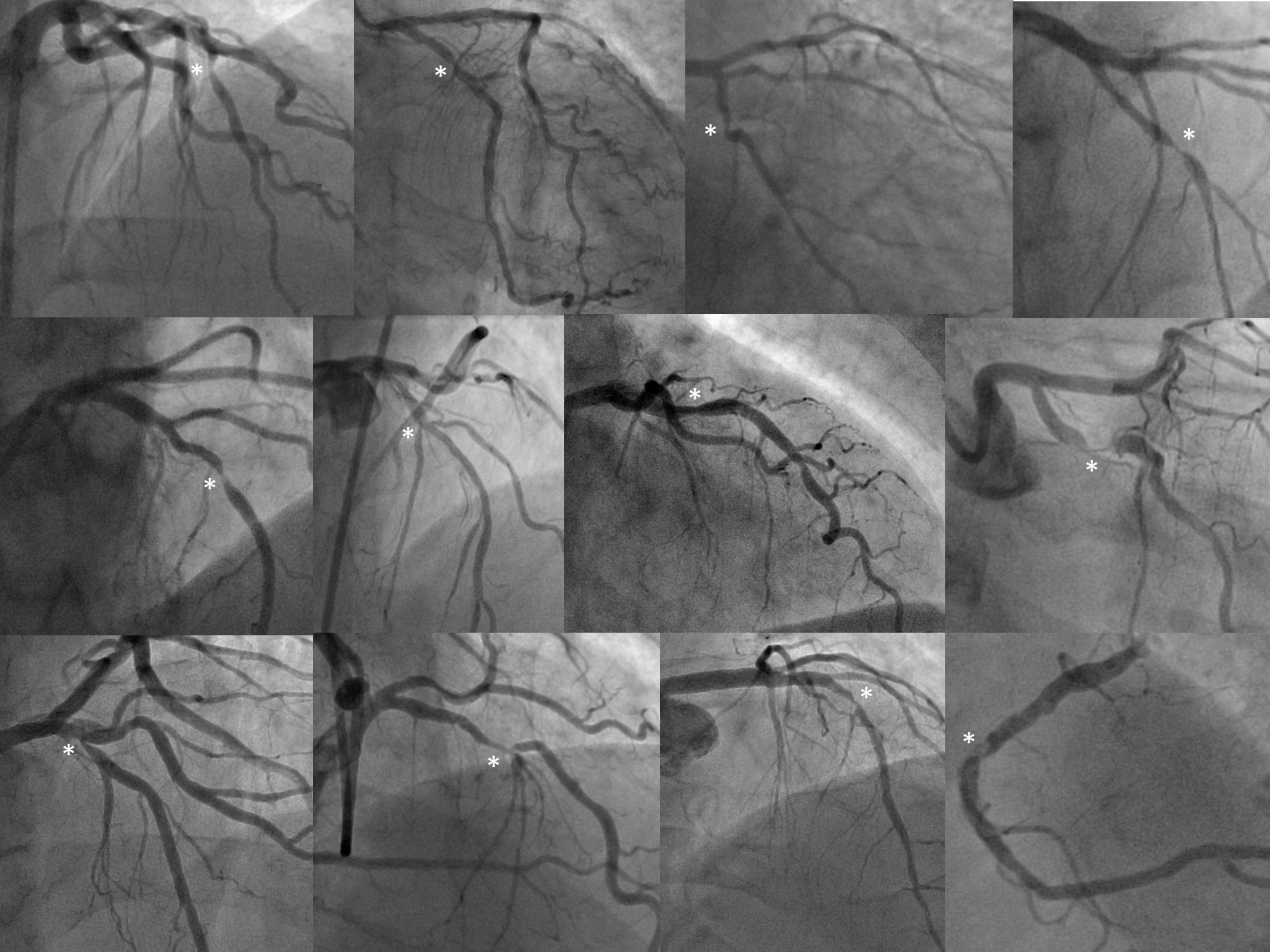


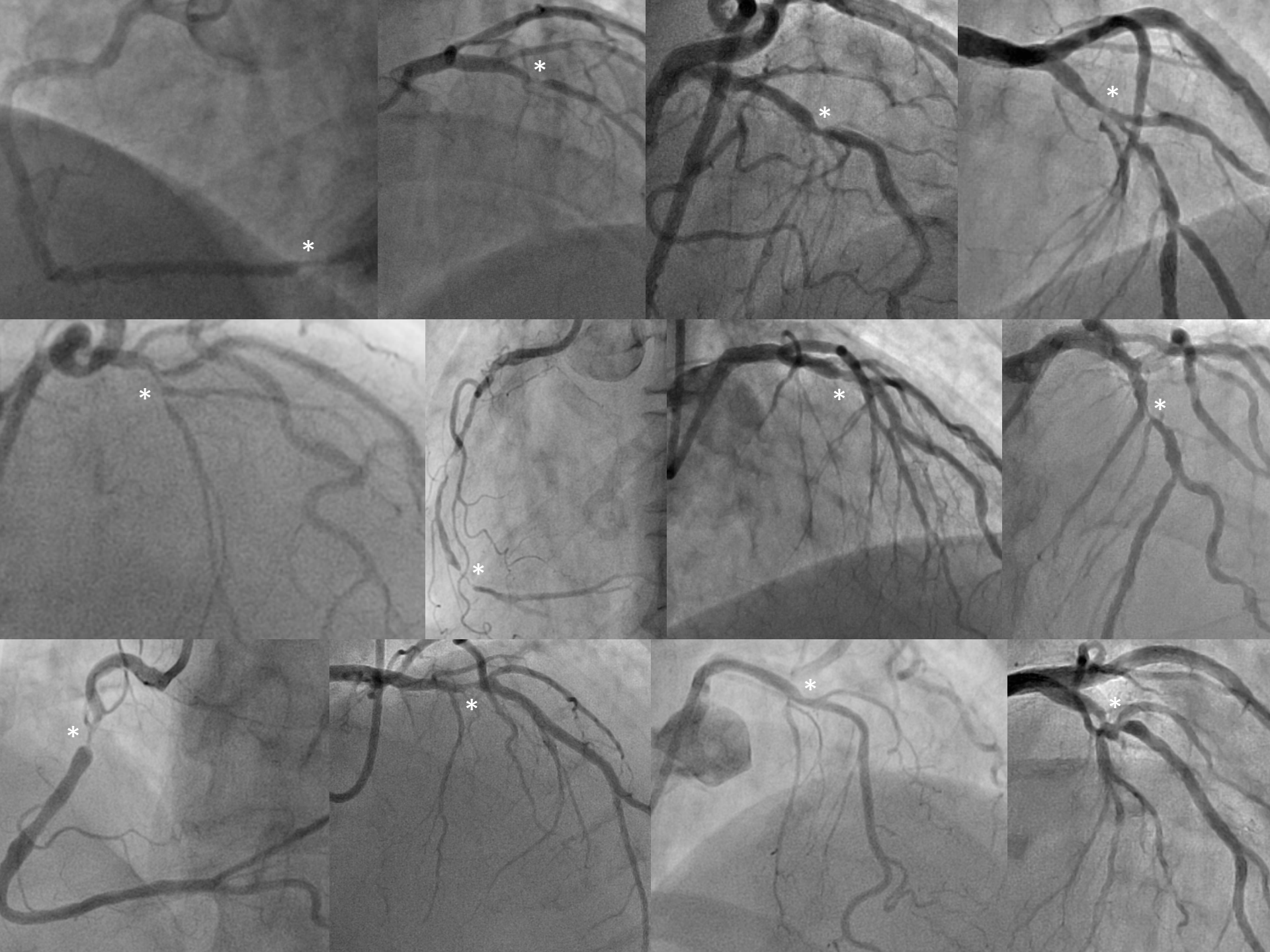


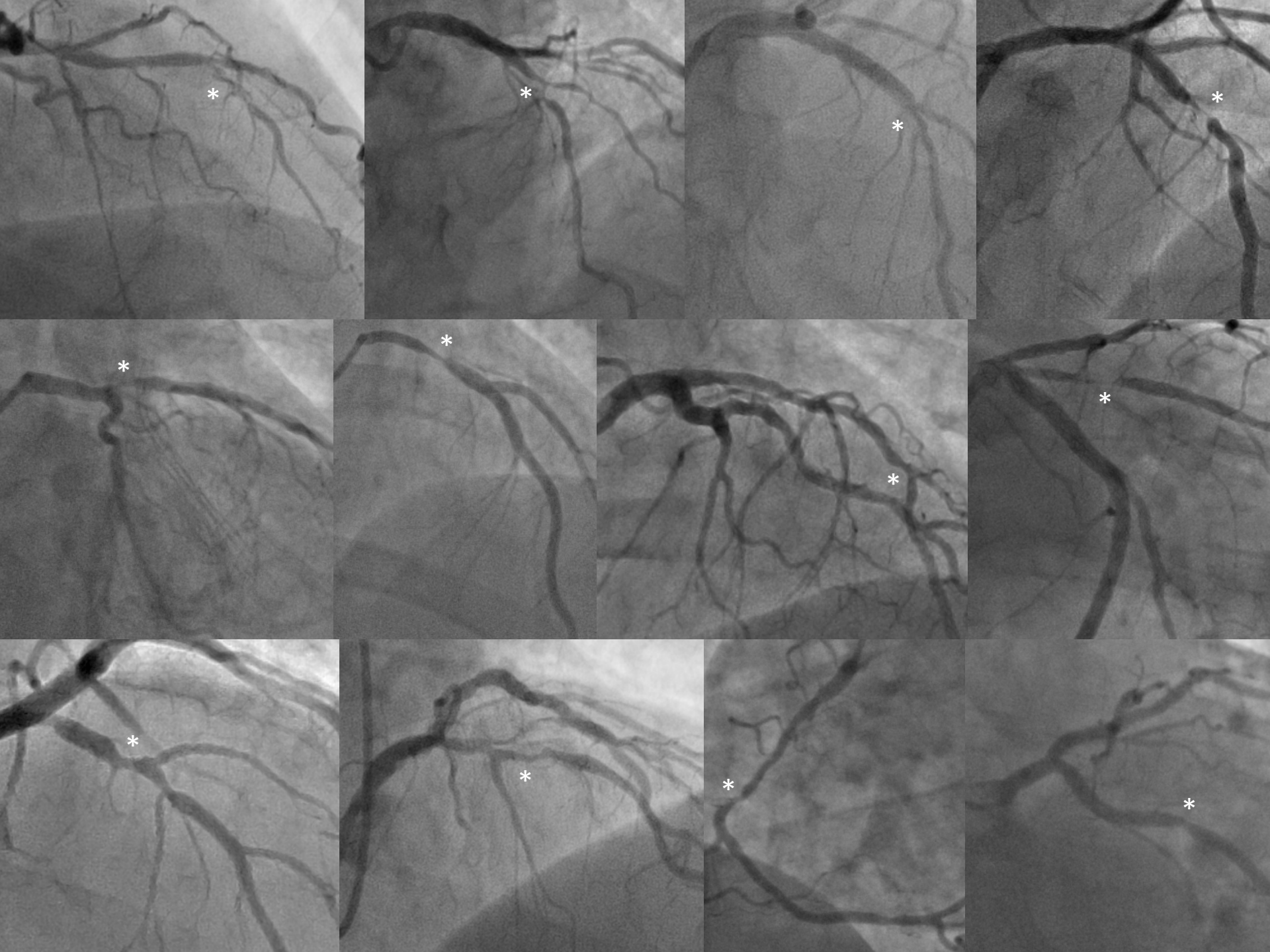


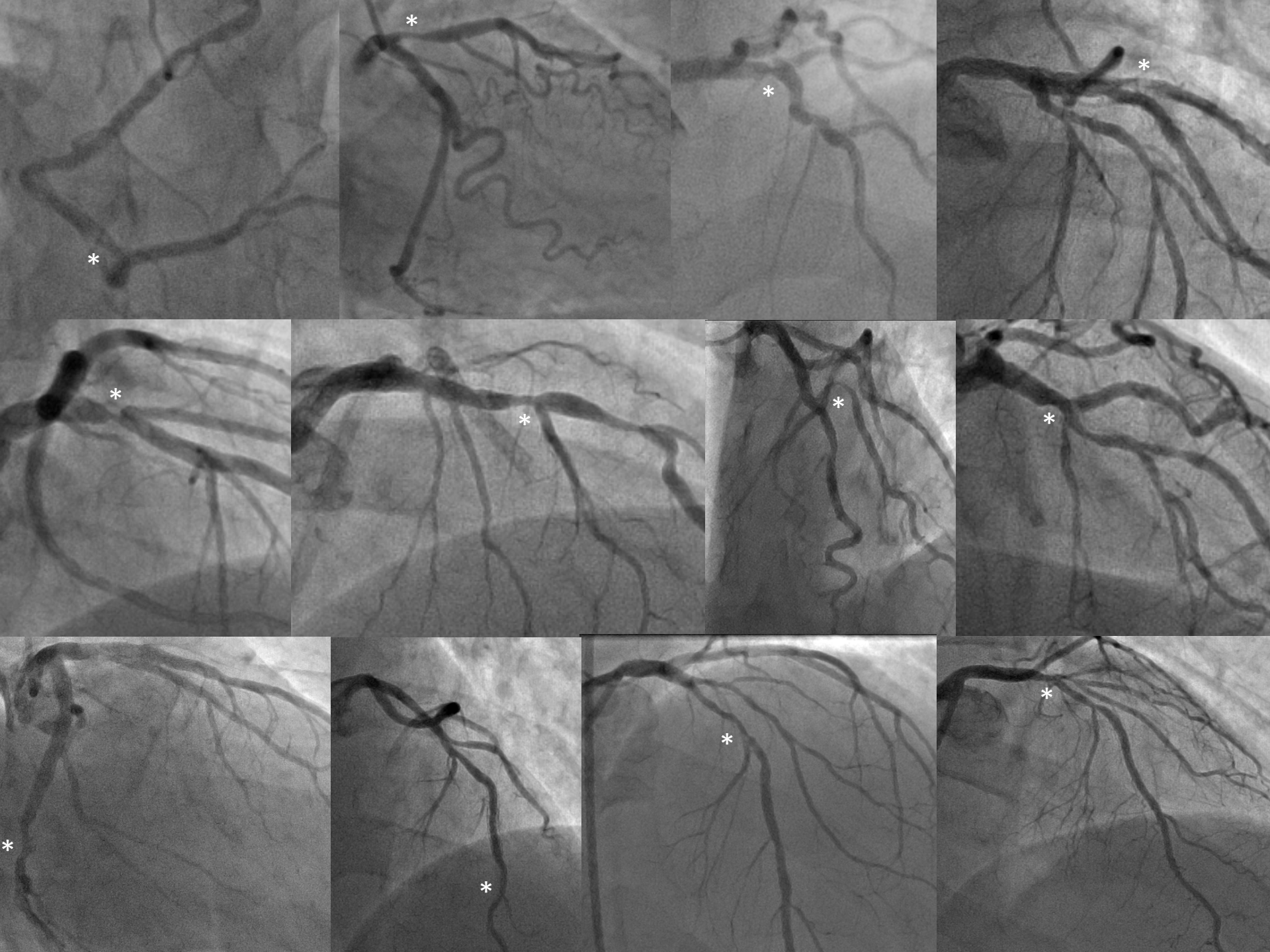






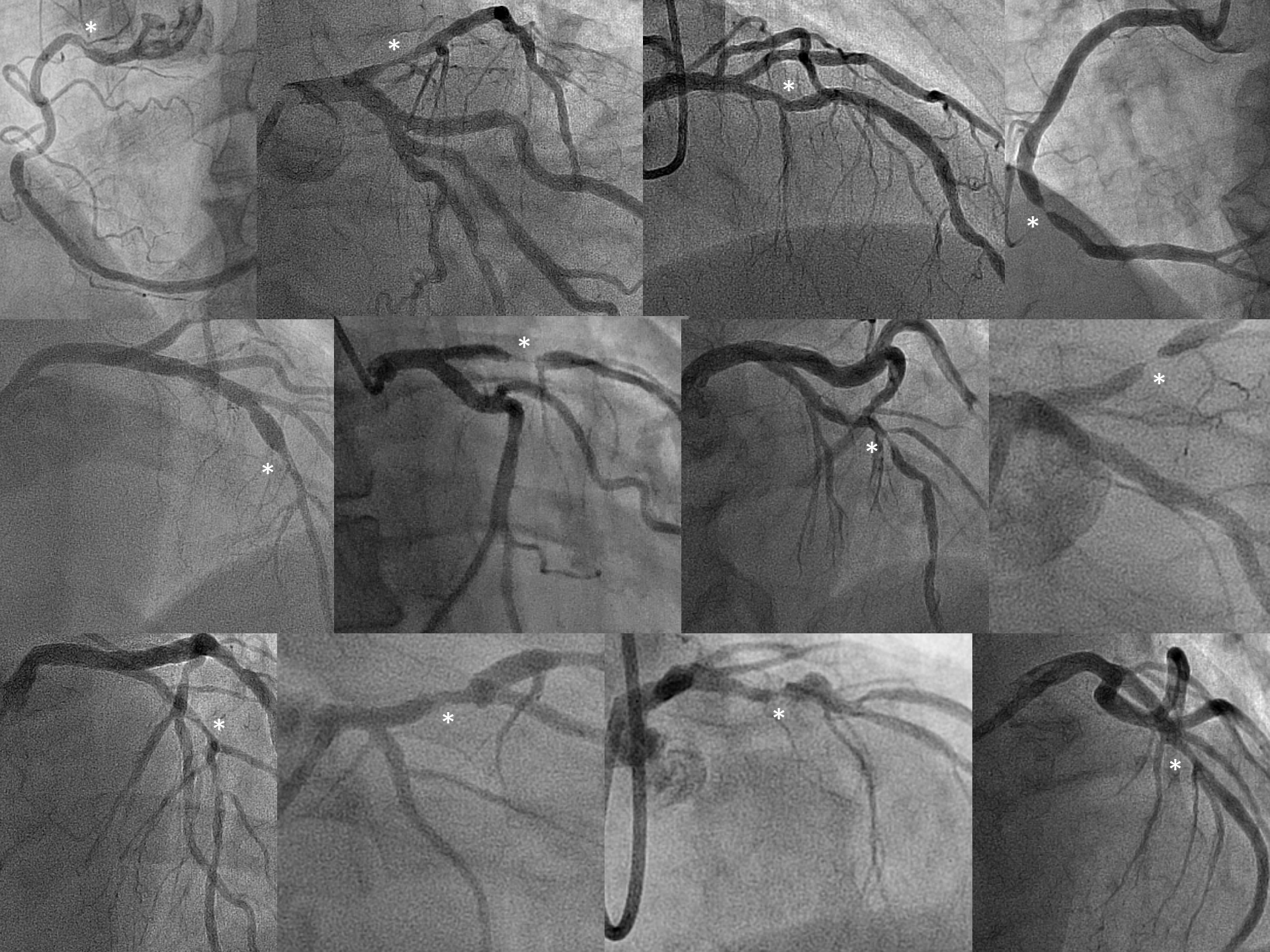


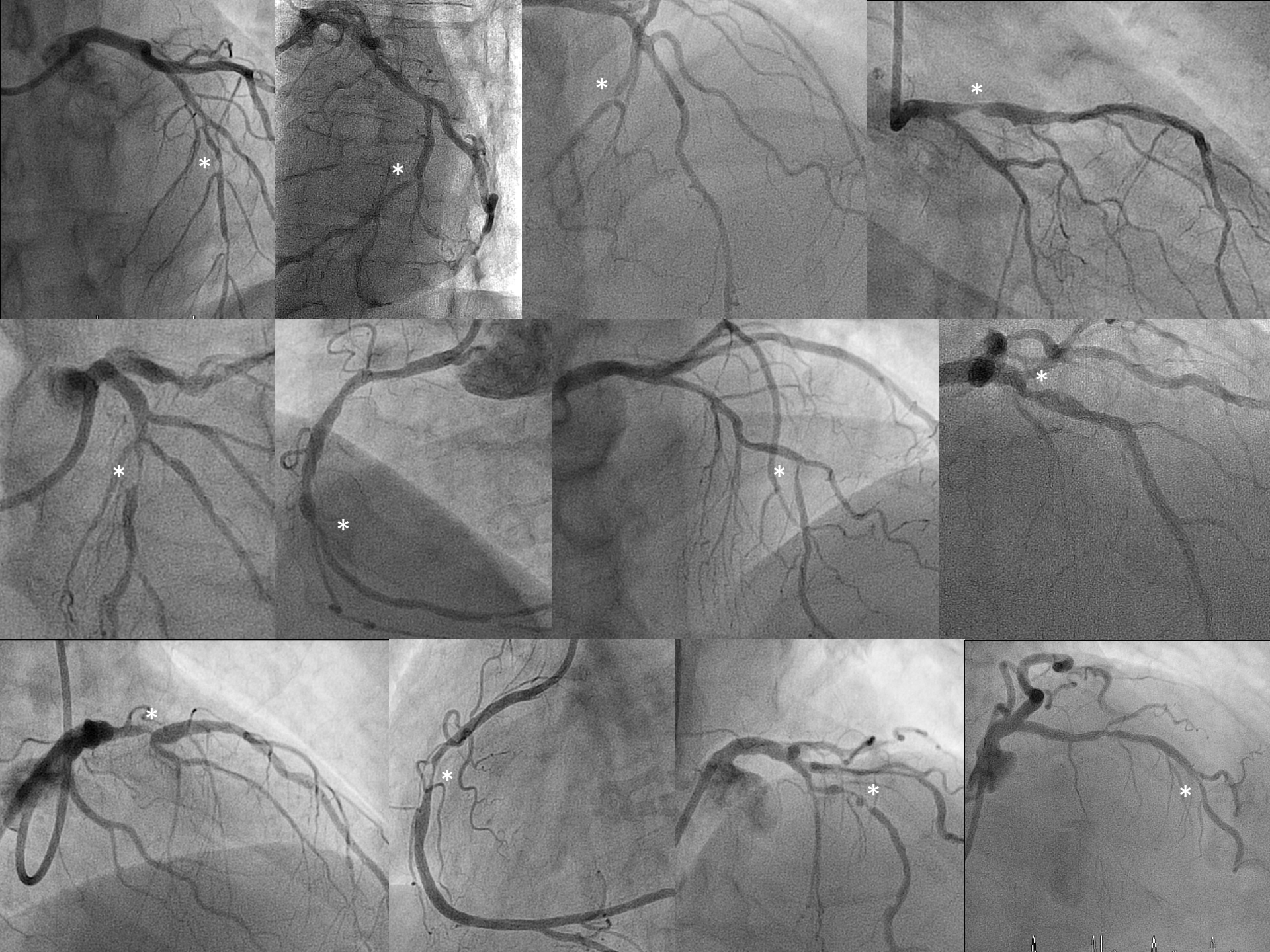


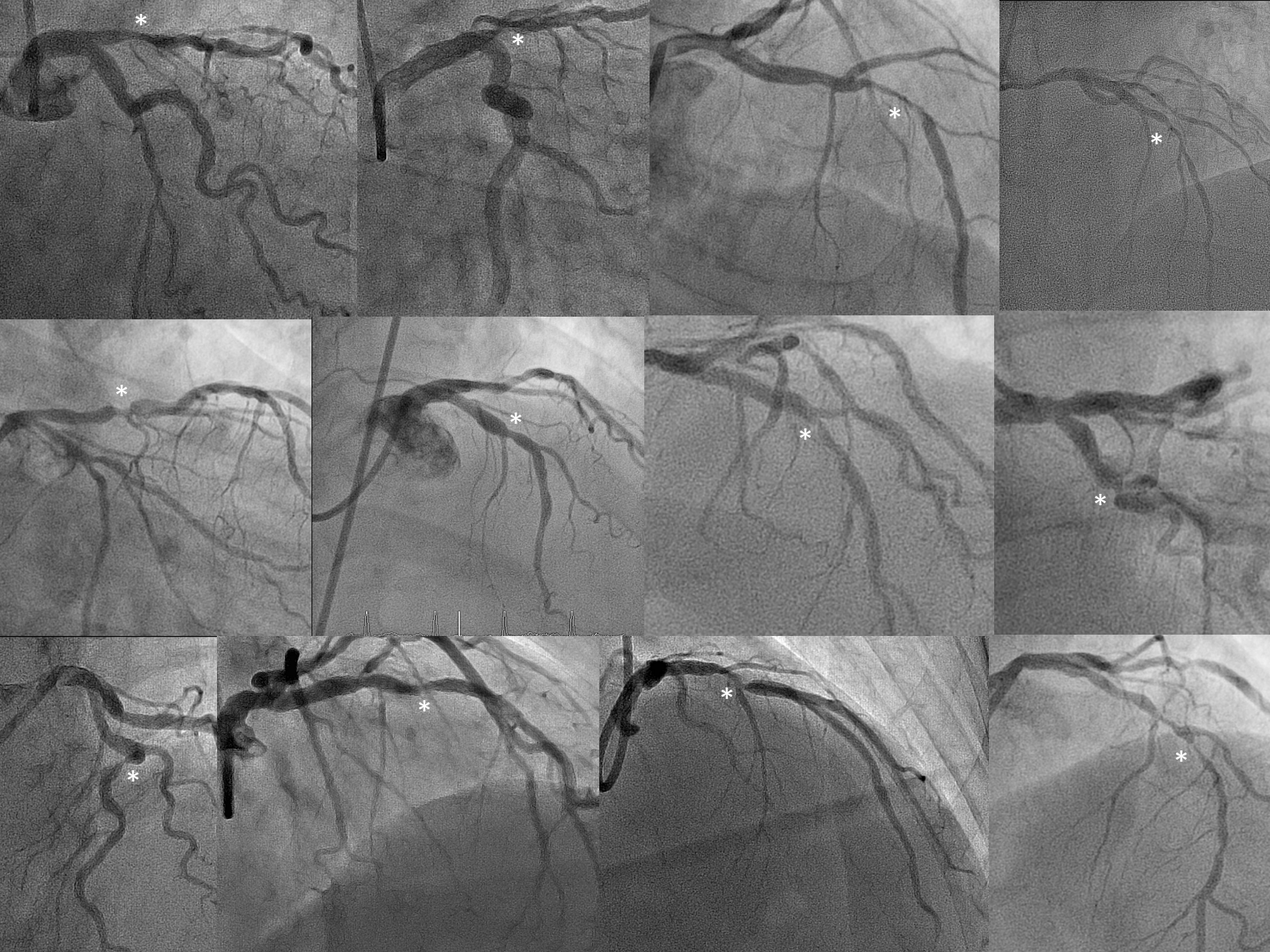
















9.10 Patient information sheet

Imperial College
London

Imperial College Healthcare NHS
NHS Trust

International Centre of Circulatory Health
St Mary's Hospital & Imperial College London
59-61 North Wharf Road
Paddington
London W2 1LA
Tel No: 0207 594 1264

Patient Information Leaflet

For patients undergoing coronary angioplasty

Defining a gold standard for ischaemia: Effects of interventional revascularisation versus optimum medical therapy on exercise capacity in patients with stable coronary artery disease

Chief Investigator: Dr Justin Davies

Version 1.6 15/08/2014

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. 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 one of your heart arteries. These symptoms occur when you exert

yourself. Currently we are not sure whether this is best treated by angioplasty (a procedure in which we open up the narrowing in your heart arteries using inflation of a balloon and a stent) or with medication alone. In this study we will investigate which of these treatments is best in improving your functional capacity; this is a combination of symptoms of chest pain and shortness of breath (which often accompany narrowing in coronary blood vessels), and the ability to exert oneself and overall quality of life.

Previous studies have found conflicting results; the main reason for this is that the participants and investigators were always aware of whether they had received coronary angioplasty or medication alone. This is a major limitation as we know that sometimes the effects of having a treatment can cause a placebo effect in which we perceive that there is an improvement when actually very little has changed. In order to assess whether coronary 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 a combination of coronary angioplasty and medication or medication alone. For a period of 6 weeks after the procedure both the participants and the medical team will not be told whether or not they received coronary angioplasty. This will allow us to answer a very important clinical question which may change the treatment of many patients with coronary artery disease worldwide. The control arm in this study is the group that will receive medication only and this group will be offered coronary angioplasty 6 weeks after the coronary procedure if it is still necessary.

In addition we will use tests to measure the pressure across the narrowing to assess whether these tests can be used to predict which patients will benefit most from coronary angioplasty. These are called Fractional Flow Reserve (FFR) and the Instantaneous wave-Free Ratio (iFR). iFR is an alternative way of assessing blood flow in the heart arteries which we have developed and will be used to assess the severity of the narrowing in your arteries. The main benefits of iFR are that it takes less time to perform than FFR and it does not require administration of adenosine (a drug which can cause side effects). iFR takes 5 seconds to record, and will be performed immediately before measuring FFR. In the future we may be able to

perform iFR as an alternative to FFR which will improve the efficiency of coronary angioplasty and will improve the experience of patients undergoing this procedure.

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. In this study, no clinical decisions will be made using iFR.

Why have I been chosen?

You have been chosen because you are scheduled to have angioplasty. As a normal part of this procedure, a small tube will be inserted into the main artery in the groin. This means that at the time of your procedure, we can use this tube to pass our wires into your heart arteries and safely take measurements in your heart's blood vessels.

Do I have to take part?

No. Your decision whether to participate in this study is entirely voluntary. After you have been given this information leaflet, you will have at least 24 hours to consider whether or not you would like to take part. 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?

You will undergo the routine investigations required prior to angioplasty at St. Mary's Hospital in London which include an ultrasound of the heart (dobutamine stress echocardiogram), an ECG and heart rate measurement, a treadmill exercise and breathing test and blood and urine investigations. After we have performed the procedure and obtained all the necessary information to assess your symptoms we will perform a coronary angiogram at your local hospital. Local anaesthetic will be used and this should not cause any discomfort. We will enter the artery at the top of your leg via a tube that is required for the angiogram. We will also pass a small tube into the vein at the top of your leg. Wires will then be passed into the heart arteries and measurements of pressure will be taken both with and without an adenosine

infusion via the tube within the vein in the leg. Adenosine is a drug which is routinely used to open up the small blood vessel within the heart muscle to stimulate exercise. In total the process will add 10 minutes to the procedure. The measurements will not prolong your recovery from the procedure. We will then randomly allocate you to receive either implantation of a coronary stent along with medication or medication treatment alone to treat your coronary artery disease.

If you are allocated to receive medical treatment alone, the procedure will end at this stage and the wires and tubes will be removed. If you are allocated to receive stenting we will proceed to inflate a balloon within the narrowing in your coronary artery to widen the artery and will then place a coronary stent within the narrowing to keep the artery open. We will then repeat the pressure measurements both with and without an adenosine infusion. At the end of this procedure the wires and tubes will be removed.

You will then receive routine care on the cardiology ward. However 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 discharged home with medication.

You will then be invited to return to St Mary's Hospital for a repeat dobutamine stress echocardiogram after having worn a physical activity belt which we will give you for one week, ECG and heart rate measurement, an exercise and breathing treadmill test and blood and urine investigations 6 weeks after the procedure. After these investigations have been completed, both you and the medical team looking after you will be told whether you received a coronary stent at the time of the procedure. If you did not receive a coronary stent and had medical treatment alone, you will be offered the opportunity to have a third coronary angiogram at this stage at which stage you will have coronary stenting. 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 groin 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.

What are the possible side effects, risks and disadvantages of taking part?
We do not expect you to experience any significant side effects as a result of participating in this study.

During the measurements 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 second tube at the top of the leg using local anaesthetic which should not cause any discomfort. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic which should not cause any discomfort. The measurements extend the length of the procedure by 10 minutes.

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). In the very rare event that the wire causes damage to your coronary arteries we will not proceed to randomisation as we will need to perform coronary stenting. 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 4.4 years of natural background radiation.

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 medication only group may require a third procedure in which they have coronary stenting. This will be an additional risk and 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 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. 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.

As part of the study you will also have one dobutamine stress echocardiogram before the coronary procedure and one after the procedure. This involves having an ultrasound scan of your heart. We will then inject a medication 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 blood flow to the heart muscle is affected in 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 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 the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Justin Davies 020 7594 1264). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?

If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in an anonymous 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.

What will happen to the results of the research study?

This study will form the basis of a PhD research programme for Dr Rasha Al-Lamee. 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 a charitable donation to the International Centre for Circulatory Health, Imperial College Healthcare NHS Trust.

Who has reviewed the study?

This study has been reviewed and given a favourable ethical opinion by the Outer London Research Ethics Committee.

If you have any further questions please do not hesitate to contact:
Dr Rasha Al-Lamee on 0207 594 1264, rasha.al-lamee@imperial.nhs.uk, or Dr Justin Davies on 0207 594 1264, justin.davies@imperial.ac.uk

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

9.11 Patient consent form

Version 1.6 15/08/2014

Imperial College London

Imperial College Healthcare NHS Trust

International Centre of Circulatory Health
St Mary's Hospital & Imperial College London
59-61 North Wharf Road
Paddington
London W2 1LA

Tel No: 0207 594 1264

CONSENT FORM

(Patients scheduled for pressure-flow wire measurements during coronary angioplasty)
Defining a gold standard for ischaemia: Effects of interventional revascularisation versus optimum medical therapy on exercise capacity in patients with stable coronary artery disease
Chief Investigator: Dr Justin Davies, Dept of Cardiology, ICCH St Mary's NHS Trust

		Please initial as applicable
1.	I have read the Patient Information Sheet (Version 1.6 Date 15/08/2014) .	Yes ..... No.....
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.	Yes ..... No.....
3.	I have spoken to Dr.....	
4.	I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care.	Yes ..... No.....
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.	Yes ..... No.....
6.	I agree to take part in this research study.	Yes ..... No.....
7.	I agree to my GP being informed about my participation in this research study.	Yes ..... No.....
	Signature.....	Yes ..... No.....
	Name (block capitals).....	Date.....
	Signature of Study Investigator.....	
	Name (block capitals).....	Date.....

1 Copy to Patient/ 1 Copy for Investigator/ 1 Copy for Notes

9.12 GP information sheet

Imperial College
London

Imperial College Healthcare NHS
NHS Trust

International Centre of Circulatory Health
St Mary's Hospital & Imperial College London
59-61 North Wharf Road
Paddington
London W2 1LA

Tel No: 0207 594 1264

General Practitioner Information Sheet

Dear Doctor

Re:
Name:
DOB:
Address:

Your patient has agreed to participate in the following research study at the International Centre for Circulatory Health, 59-61 North Wharf Road, St Mary's Hospital, London W2 1LA:

Defining a gold standard for ischaemia: Effects of interventional revascularisation versus optimum medical therapy on exercise capacity in patients with stable coronary artery disease

Background and Aims

Previous studies have suggested that there is no added benefit to performing percutaneous coronary intervention (PCI) above treatment with medical therapy alone in patients with stable angina. However these data were based on subjective measures of angina symptoms and there was no attempt to blind investigators or patients to the treatment they had received which may have biased the results. As yet no study has investigated the effect of PCI on symptoms as measured by objective measures of exercise capacity and non-invasive and invasive measures of coronary ischaemia under blinded conditions.

Fractional flow reserve (FFR) has been used to measure the physiological significance of coronary stenosis for many years. PCI was shown to be superior to medical therapy in patients with functionally significant FFR values; however, while the study was halted prematurely due to a significantly higher rate of urgent revascularization in the medical therapy arm, a significant limitation was the lack of blinding between the 2 study arms. A novel invasive approach for assessing coronary stenosis severity, the instantaneous wave free ratio (iFR) has been developed, and has been shown to correlate well with FFR. It is likely that a positive physiological assessment using these techniques will be associated with a larger improvement in exercise capacity following PCI. Exercise capacity in patients on optimal medical therapy (OMT) will be most limited in those with positive functional tests.

The aim of this study is to assess the improvement in exercise capacity and burden of myocardial ischaemia following PCI and optimum medical therapy versus optimum medical therapy alone as assessed by cardiopulmonary exercise testing and non-invasive and invasive measures of ischaemia respectively.

What is involved for your patient

Your patient will have weekly clinic visits to optimise their medical therapy.
Patients will then attend Imperial College Healthcare NHS Trust for blood and urine investigation for biochemical markers of ischaemia, dobutamine stress echocardiography, an ECG and heart rate variability measurement, a cardiopulmonary exercise test and a clinical questionnaire set.
We will then perform a coronary angiogram one week later with invasive assessment of coronary ischaemia using FFR and iFR. Patients will then be randomised to receiving coronary angioplasty and optimum medical therapy or optimum medical therapy alone. Patients and researchers will be blinded to the treatment strategy at this stage. The data collected will be stored a computer and analysed later.
Patients will then return for a follow-up visit at Imperial College Healthcare NHS Trust 6 weeks after the procedure during which they will wear a physical activity belt. At this stage we will repeat blood and urine investigations for biochemical markers of ischaemia, dobutamine stress echocardiography, ECG and heart rate variability measurement, a cardiopulmonary exercise 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 optimum medical therapy alone group will be given the option to receive coronary angioplasty.
All of the information that we take will be fully anonymised.
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 diagnosis and management of patients with pulmonary hypertension.

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 OMT alone

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.

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

Dr Rasha Al-Lamee
Interventional Research Fellow
International Centre for Circulatory Health
Imperial College and Imperial College NHS Trust
59-61 North Wharf Road
W2 1LA

Telephone. 0207 594 1264
E-mail. rasha.al-lamee@imperial.nhs.uk

9.13 Patient prescription letter

Imperial College London

Imperial College Healthcare NHS Trust

International Centre of Circulatory Health
St Mary's Hospital & Imperial College London
59-61 North Wharf Road
Paddington
London W2 1LA

Tel No: 0207 594 1264

General Practitioner Information Sheet

Dear Doctor

Re:
Name:
DOB:
Address:

Your patient has agreed to participate in the following research study at the International Centre for Circulatory Health, 59-61 North Wharf Road, St Mary's Hospital, London W2 1LA:

Defining a gold standard for ischaemia: Effects of interventional revascularisation versus optimum medical therapy on exercise capacity in patients with stable coronary artery disease

As part of this study your patient will undergo a six-week period of medical therapy optimisation in order to ensure that they receive optimal medical therapy for stable coronary artery disease. This will be done by weekly telephone consultations with the research team with regular blood pressure and pulse monitoring. We would therefore appreciate it if you could prescribe the following cardiac medications required for the treatment of stable coronary artery disease, these medications will then be started by the research team as guided by symptoms and blood pressure and pulse measurements:

Please do not hesitate to contact me at the following address:

Dr Rasha Al-Lamee
Interventional Research Fellow
International Centre for Circulatory Health
Imperial College and Imperial College NHS Trust
59-61 North Wharf Road
W2 1LA

Telephone. 0207 594 1264
E-mail. rasha.al-lamee@imperial.nhs.uk

9.14 Standardised patient discharge letter

Imperial College London

Imperial College Healthcare NHS Trust

International Centre of Circulatory Health
St Mary's Hospital & Imperial College London
59-61 North Wharf Road
Paddington
London W2 1LA

Tel No: 0207 594 1264

General Practitioner Information Sheet

Dear Doctor

Re:
Name:
DOB:
Address:

Procedure date:

Your patient has agreed to participate in the following research study at the International Centre for Circulatory Health, 59-61 North Wharf Road, St Mary's Hospital, London W2 1LA:

Defining a gold standard for ischaemia: Effects of interventional revascularisation versus optimum medical therapy on exercise capacity in patients with stable coronary artery disease (ORBITA study)

As part of the ORBITA study, your patient attended for coronary angiography today and was randomised to receive either coronary angioplasty or a placebo procedure. The study is a double blinded randomised controlled trial therefore both the patient and all medical professionals will not be told the treatment allocation arm until follow-up is complete at 6 weeks. At this stage, we will write to you with the full details of the procedure. In the interim period please continue dual antiplatelet therapy and post-angioplasty standard care.

Please continue on the following medications until trial completion or further information:

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

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

Dr Rasha Al-Lamee
Interventional Research Fellow
International Centre for Circulatory Health
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