Fractional flow reserve and instantaneous wave-free ratio as predictors of the placebo-controlled response to percutaneous coronary intervention in stable single vessel coronary artery disease: the physiology-stratified analysis of ORBITA

Rasha Al-Lamee MA MRCP[1,2] et al

(See Author list)

[1]National Heart and Lung Institute, Imperial College London, London, UK

[2]Imperial College Healthcare NHS Trust, London, UK

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Corresponding author: Rasha Al-Lamee

Correspondence address: International Centre for Circulatory Health, National Heart and Lung Institute, Hammersmith Hospital, Du Cane Rd, London W10 0HS

Tel: +44 (0) 2075945735

Email: r.al-lamee13@imperial.ac.uk

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Abstract

Background

There are no data on how fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are associated with the degree of placebo-controlled efficacy of percutaneous coronary intervention (PCI) in stable single vessel coronary artery disease.

Methods

We report the association between pre-randomization invasive physiology within ORBITA, a randomized placebo-controlled trial which enrolled patients with stable angina and angiographically severe single vessel coronary disease clinically eligible for PCI. Patients underwent a pre-randomization research assessment of FFR and iFR. The operator was blinded to these values. Assessment of response variables, stress echo wall motion, symptom frequency, angina severity, and treadmill exercise time were performed pre-randomization 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.

Results

Invasive physiology data were available in 196 patients (103 PCI and 93 placebo). At pre-randomization the majority of patients had Canadian Cardiovascular Society class II or III symptoms (150/196, 76.5%). 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.

The estimated effect of PCI on pre-randomization-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 ($p_{interaction}$=0.447) and iFR ($p_{interaction}$=0.262).

Stress echo score decreased by 0.92 segment units (SD 1.48) in the PCI arm and had no significant change in the placebo arm (mean change +0.17, SD 1.12). PCI improved stress echo score more than placebo (1.06 segment units, 95% CI 0.69 to 1.43, p<0.00001). The placebo-controlled effect of PCI on the stress echo score increased progressively with decreasing FFR ($p_{interaction}$<0.00001) and with decreasing iFR ($p_{interaction}$<0.00001). PCI did not improve angina frequency score significantly more than placebo (OR 1.62, 95% CI 0.95 to 2.76, p = 0.076) and there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.843) or iFR ($p_{interaction}$=0.780). However, PCI was more likely to result in patient-reported freedom from angina than placebo (49.5% versus 31.5%; OR 2.47, 95% CI 1.30 to 4.72; p = 0.006) but neither FFR ($p_{interaction}$=0.692) nor iFR ($p_{interaction}$=0.759) modified this effect.

Conclusions

In patients with stable angina and severe single vessel coronary stenosis, the blinded effect of PCI was more clearly seen by stress echo score and by freedom from angina than by change in treadmill exercise time. Moreover, the lower the FFR or iFR, the greater the magnitude of stress echocardiographic improvement caused by PCI.

Clinical Trial Registration

URL: https://www.clinicaltrials.gov.

Unique identifier: NCT02062593

Clinical perspective

What is new?

- This report of ORBITA stratified by invasive haemodynamic measures of stenosis severity provides the first placebo-controlled evidence of the association between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) and the magnitude of benefit attributable to percutaneous coronary intervention (PCI).
- PCI improves ischaemia as assessed by dobutamine stress echocardiography.
- PCI delivers freedom from angina to 20 absolute percentage points more patients than placebo (Number Needed to Treat = 5).
- Pre-randomization FFR and iFR predict the placebo-controlled PCI effect on stress echocardiography.
- Pre-randomization FFR and iFR did not predict the placebo-controlled PCI effect on symptoms or treadmill exercise time.

What are the clinical implications?

- PCI renders more patients free of angina than does placebo.
- FFR and iFR can be used to predict the PCI effect on stress echo ischaemia.

Introduction

Percutaneous coronary intervention (PCI) for stable single vessel coronary artery disease is widely accepted to alleviate angina based on unblinded clinical experience and unblinded randomized controlled trials.[1-6] However, in the first placebo-controlled trial of PCI in stable single vessel coronary artery disease with patients and the medical team blinded to treatment allocation, Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA), the placebo-controlled effect of PCI on the pre-specified primary endpoint of exercise time at 6 weeks, by pre-specified statistical methods,[7] unexpectedly[1] did not meet the criteria for statistical significance (point estimate 16.6s, 95% CI -8.9 to 42.0).[8]

ORBITA used conventional, clinical criteria for eligibility for PCI, including symptoms and angiographic assessment. All patients were treated with guideline-directed medical therapy. In ORBITA, 94% of patients had one or more positive ischaemia tests. The unexpected result 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.

PCI had a clearer effect on stress echocardiography than on treadmill exercise time or patient-reported or physician-assessed symptoms. This increases the ability of stress echocardiography to distinguish between the efficacy of PCI across the disease spectrum. In double-blind evaluation, relief of the stenosis and its physiological consequences are the only contributors to symptom and exercise capacity improvement. This contrasts with unblinded

clinical practice and unblinded trials where the patient is told that the lesion is fixed, which may enhance the total therapeutic effect.

A key aim of ORBITA was to document the association between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) and the placebo-controlled response to subsequent PCI. To do this, the trial needed to store values of FFR and iFR before randomization and prevent these values from affecting treatment allocation. Therefore, after the decision for PCI had been made on current conventional clinical criteria, research FFR and iFR measurements were made but their values were not shown to the operator. This report, the physiology-stratified analysis of ORBITA, describes how these blinded FFR and iFR values predict the placebo-controlled effect of PCI on stress echo score, patient-reported and physician-assessed symptoms, quality of life, and treadmill exercise time.

Methods

Study design

The design of the ORBITA trial has been previously described.[8] In summary, patients with stable angina and angiographically severe single vessel coronary disease were enrolled at 5 UK sites. At enrolment patients had assessment of symptoms by Canadian Cardiovascular Society (CCS) angina class and completed questionnaires on angina and quality of life. The trial consisted of 2 consecutive phases: (1) six-week medical optimization phase of antianginal medication uptitration, ending with pre-randomization 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-randomization assessment included: (1) physician-assessed grading of angina severity (CCS class), (2) patient-reported symptoms using Seattle Angina Questionnaire,[9] (3) quality of life using EuroQOL 5 (EQ-5D-5L) questionnaire, (4) cardiopulmonary exercise testing using the smoothed modified Bruce protocol[10] which incorporates an initial 3 minutes of low level exercise that is not present in the standard Bruce protocol, and (5) dobutamine stress echocardiography.

Invasive physiological assessment

Patients then attended for the invasive procedure, which included research invasive pressure measurements and then randomization. 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 randomized 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 randomized with different protocols for outcome assessment.[4, 11]

After administration of intracoronary nitrate and normalization 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. Intravenous 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-normalized 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-normalized and iFR and FFR measurements were repeated with final drift check.

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

Blinding and randomization

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 randomized to receive PCI or placebo procedure.

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

If randomized to PCI, this was performed using angiographic guidance with drug eluting stents implanted and complete angiographic revascularization 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.[8]

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-randomization or follow up), using an online reporting tool. In the original ORBITA publication, analysis had been performed by 2 imaging consultants (RA and DF).

For the present physiology-stratified analysis of ORBITA, each scan received 12 opinions. Each scan was examined twice by 6 imaging consultants (RA, DF, GC, SK, JS, and NK) 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.[8]

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-randomization. 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.[7] 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.[12]

The Seattle Angina Questionnaire scales for angina frequency, physical limitation and quality of life scores were derived from the patient's answers in accordance with published guidelines.[13] Freedom from angina was calculated from the Seattle Angina Questionnaire.

For each endpoint, a model was fitted. For the continuous endpoints of EQ-5D-5L descriptive system and visual analogue scores, Seattle Angina Questionnaire physical limitation and quality of life scores, total exercise time and stress echo score linear models were used.

For the ordinal variables of Seattle Angina Questionnaire angina frequency and freedom from angina, and CCS class a proportional odds ordinal logistic model was used. The proportional odds ordinal logistic model accommodates the strange statistical distribution (and possible floor and ceiling effects) of variables such as angina frequency. It involves no categorization and is statistically very efficient while only using the rank order of frequency across patients. The commonly used Wilcoxon-Mann-Whitney 2-sample rank-sum test is a special case of this ordinal logistic model when there is only one covariate and it is binary. Even if the response variable were normally distributed, the proportional odds model has efficiency of $3/\pi$ or about 0.95.

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

parameters, i.e. the shape of effect was allowed to vary over treatments.[12] Graphs of the endpoints against FFR and iFR, and the contrast between the arms was generated adjusting for the median value of the pre-randomization value.

All analyses were performed using the open-source statistical environment "R",[14] with the package "rms" for regression modelling,[15] and "ggplot2" for graphs.[16]

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Results

ORBITA enrolled 230 patients. After the medical optimization phase 200 patients were randomized 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 randomized 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.

Patient demographics

Patient demographics are shown in Table 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 enrolment.

Medical therapy

At pre-randomization, the majority of patients were taking more than 2 antianginal medications (85.4% in PCI vs. 90.3% in placebo, Table A1 in Supplementary Appendix). 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. After the medical optimization phase, at pre-randomization, the majority of patients had CCS class II or III symptoms (150/196, 76.5%) (Table A2 in Supplementary Appendix) and the 83.0% (161/194) of patients reported one or more episodes of angina in the last 4 weeks (Table A3 in Supplementary Appendix).

Procedural demographics

Procedural demographics are shown in Table 2. The median time between the first diagnostic angiogram and the pre-randomization angiogram was 54 days (IQR 45 to 64) for the complete group. 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 Figures A1 and A2 in Supplementary Appendix. 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 randomization; these consisted of a pre-enrolment clinical test, research stress echo, FFR≤0.80 or iFR≤0.89. The angiographic images of the remaining 5 patients are shown in Figure A3 in Supplementary Appendix.

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).

Study endpoints

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 -4.04 to 45.5; p=0.100, Table A4 in Supplementary Appendix). For this relatively small effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.447) or iFR ($p_{interaction}$=0.262) and the effect of PCI on exercise time increment (Figures 1A and 1B).

Dobutamine stress echocardiography

The stress echo dataset consists of 159 patients (90 PCI, 69 placebo), each with pre-randomization and follow-up scans, with each scan having reported twice by 6 imaging consultants. Stress echo score decreased by 0.92 segment units (SD 1.48) in the PCI arm and had no significant change in the placebo arm (mean change +0.17, SD 1.12). Overall, PCI improved the stress echo score when compared to placebo (difference 1.06 segment units, 95% CI 0.69 to 1.43; p < 0.00001, Table A4 in the Supplementary Appendix).

There was an interaction between FFR and the stress echo improvement from PCI over placebo ($p_{interaction}$<0.00001), with a progressively larger improvement at lower pre-randomization FFR values (Figure 2A)

Similarly, there was an interaction between iFR and the stress echo improvement ($p_{interaction}$<0.00001, Figure 2B), with a progressively larger improvement at lower pre-randomization iFR values.

Patient-reported symptoms and quality of life

Paired patient-reported data at pre-randomization 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 no statistically significant evidence that PCI improved Seattle Angina Questionnaire angina frequency score more than placebo (OR 1.62; 95% CI 0.95 to 2.76; p=0.076, Table A4 in Supplementary Appendix). This odds ratio does not come from a dichotomization of angina frequency but from the proportional odds model and involves the ratio of odds of a frequency > f for two groups, for any non-zero f.

For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.843) or iFR ($p_{interaction}$=0.780) and the effect of PCI on angina frequency score (Figures 3A and 3B).

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; Tables A4 and A5 in Supplementary Appendix). Complete freedom from angina was achieved in more patients in the PCI arm compared to the placebo arm (49.5% versus 31.5%, p=0.006). 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 ($p_{interaction}$=0.692; Figure 5A and $p_{interaction}$=0.759; Figure 5B).

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 A4 in Supplementary Appendix). 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 (Figures A4A and A4B in Supplementary Appendix).

PCI did not improve Seattle Angina Questionnaire quality of life score more than placebo (2.15; 95% CI -3.75 to 8.05; p = 0.474, Table A4 in Supplementary Appendix). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.317) or iFR ($p_{interaction}$=0.240) and the effect of PCI on quality of life score (Figures A5A and A5B in Supplementary Appendix).

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 descriptive scale more than placebo: point estimate 0.001 (95% CI -0.039 to 0.042; p=0.951, Table A4 in Supplementary Appendix). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.726) or iFR ($p_{interaction}$=0.934) and the effect of PCI on EQ-5D-5L descriptive scale (Figures A6A and A6B in Supplementary Appendix).

PCI did not improve EQ-5D-5L visual analogue score more than placebo: point estimate 1.22 (95% CI -3.47 to 5.90; p=0.610, Table A4 in Supplementary Appendix). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.397) or

iFR ($p_{interaction}$=0.400) and the effect of PCI on EQ-5D-5L visual analogue score (Figures A7A and A7B in Supplementary Appendix).

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 enrolment there were no patients with CCS 0, at pre-randomization 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 (p=0.132, Table A2 in Supplementary Appendix). PCI did not improve CCS class more than placebo (OR 0.73, 95% CI 0.43 to 1.25; p = 0.254, Table A4 in Supplementary Appendix). For this non-significant effect, there was no detectable evidence of interaction between either FFR ($p_{interaction}$=0.876) or iFR ($p_{interaction}$=0.841) and the effect of PCI on change in CCS class (Figures 6A and 6B).

Using FFR and iFR dichotomously

Although this study was intended to treat FFR and iFR as continuous variables, some readers may wish to see the PCI effect in patients above and below certain FFR and iFR values. These data are presented in Tables A6 to A9 in the Supplementary Appendix.

Additionally, the endpoint analysis and PCI effects for dichotomous FFR and iFR in only those patients with CCS class I-IV symptoms at pre-randomization are presented in Tables A10 to A14 in the Supplementary Appendix.

Discussion

This physiology-stratified analysis of ORBITA provides placebo-controlled data on the association between pre-randomization invasive physiology and the efficacy of PCI in stable single vessel coronary artery disease. The severe anatomical stenosis was dramatically improved, and there were progressively smaller effects along a notional mechanistic pathway, including invasive haemodynamic measurements, myocardial perfusion and finally symptoms.

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

Of patient-reported change in symptoms, the most binary is absence versus presence of symptoms. On this endpoint of patient-reported freedom from angina, PCI was more effective than placebo. Indeed, one in five more patients became free of angina with PCI than with placebo procedure. However, Seattle Angina Questionnaire physical limitation score and quality of life scores and EQ-5D-5L quality of life score did not show an effect of PCI beyond placebo. Nor could physician-assessment of patient symptoms (CCS) or treadmill exercise time detect the effect of PCI beyond placebo.

Neither exercise time nor symptom endpoints showed any association between FFR or iFR and the effect of PCI. This means that there is no sign of the unexpected primary result of ORBITA[8] being the consequence of enrolling the full spectrum of patients clinically eligible for

single vessel PCI including those who met the criteria despite their blinded research FFR being >0.80.

This analysis of ORBITA was intended to treat FFR and iFR as continuous variables. Dichotomous analysis of continuous variables loses power and precision but is often recommended, reported and discussed. There is no established cut-point for angina. We therefore present in the Supplementary Appendix results for the patients dichotomised using a range of cut-points including those commonly recommended for the decision for PCI.

The blinded effect size calculated from ORBITA is much smaller than the 96s exercise time benefit calculated from the unblinded ACME trial which was of similar size, enrolled patients with similar exercise capacity, and used the same statistical method as pre-specified in ORBITA.[7] One possibility is that patients being told their lesion had been fixed or not fixed makes a difference to their exercise capacity. An alternative possibility is that the ~6-fold larger effect size of ACME was because it used plain balloon angioplasty rather than modern-day stenting or that its 6-month time-point was necessary for the lesion to be properly relieved. Another possibility that has been proposed is that the large effect size was due to differences in medical therapy between arms. We do not believe this is plausible because the ACME PCI arm received less nitrates ($p<0.01$), beta-blockers ($p<0.01$), and calcium channel antagonists ($p<0.01$). A final possibility is that patients in the PCI arm may have reduced their beta-blocker usage or had increased their habitual exercise as a result of knowing had had PCI.[17]

It is still not clear why the objective relief of anatomical, haemodynamic and stress echocardiographic abnormalities did not translate as well as hoped into patient-centred endpoints under blinded conditions. However, on the most unambiguous dichotomous

patient-centred endpoint, freedom from angina, there was a statistically significant improvement with PCI with a large absolute improvement.

ORBITA was analysed as pre-specified,[7] with t-test of change scores in the objective and continuous variable of exercise time. An alternative statistical approach, applied in this stratified analysis of ORBITA, is regression modelling, which offers advantages including the ability to adjust appropriately for pre-randomization values and to measure the interaction between FFR and iFR on the effect size. 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.[1]

Exercise treadmill time has a long track record of detecting the effect of anti-anginal medication against placebo. However, 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 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.[18]

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-randomization FFR and iFR values.

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 randomized 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 association between invasive physiology and placebo-controlled response to PCI.[1] Although it was the pre-specified primary endpoint, exercise time was one of the least influenced markers. The same can be said for symptoms.

This study intentionally included a representative spectrum of patients appropriate for clinical single vessel PCI. Of them, 97% had ischemia documented on one or more non-invasive or invasive tests at the time of randomization, and the 5 remaining angiograms are shown (Supplementary Appendix). FFR was measured not[19] for clinical decision-making (since all patients were already eligible), but rather for research purposes to study the association between FFR and the placebo-controlled effect of PCI.

Dichotomising a continuous variable removes most of its information content[12] but we present the dichotomous analyses because readers may be curious. There has been no previous blinded identification of a “best” threshold of FFR or iFR for angina relief from PCI. We therefore present data for multiple thresholds that include the thresholds recommended from unblinded trials.

No study can exclude the possibility of a weak association between variables. This study merely shows that there is no threshold of FFR or iFR below which PCI consistently improves exercise time (or symptoms) more than placebo and above which it consistently does not. However, there is a marked association between FFR or iFR and change in stress echo score ($p<0.00001$, $p<0.00001$) which indicates that for this endpoint the study is not underpowered.

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 enrolment (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-enrolment 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 pre-randomization were 11.5% in ORBITA, 9% in ACME, 11.2% in FAME-2 and 12.5% in COURAGE.[20, 21]

A significant proportion 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.[8, 22] For comparison, after unblinded PCI, physician-assessed CCS II-III was 57.1% in the second Randomised Intervention Treatment of Angina (RITA-2) at 6 months,[2] 45.5% in Medicine, Angioplasty, or Surgery Study (MASS-II) at 1 year,[23] and 34% in COURAGE at 1 year.[3] The one dramatically different result was from FAME-2 which reported 5.9%.[24]

The trial design only asked patients to remain blinded and randomized for 6 weeks, because we expected a large benefit from PCI and wanted to ensure recruitment of severe coronary stenoses as shown in the ORBITA appendix. All patients were unblinded. The placebo arm patients returned to their normal clinical care. The results of ORBITA were not yet known. Most (77/91, 85%) control patients in ORBITA chose to have PCI. In a placebo-controlled trial the scientific value of symptom assessment is during the blinded period.

Conclusions

PCI relieved not only the anatomical and haemodynamic features of the coronary stenosis but also normalized the stress echocardiography. PCI caused more patients to become free from angina than did placebo.

Progressively lower pre-randomization FFR and iFR predicted a progressively larger effect of PCI versus placebo on stress echo ischaemia. They did not predict the PCI effect on symptoms, quality of life or treadmill exercise time.

The effect of PCI on endpoints, and the extent to which this effect is associated with 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.

Authors

Rasha Al-Lamee MA MRCP[1,2], James Howard MA MRCP[1,2], Matthew Shun-Shin MA MRCP[1,2], David Thompson MCPI[1], Hakim-Moulay Dehbi PhD[3], Sayan Sen MRCP[1,2], Sukhjinder Nijjer MRCP[1,2], Ricardo Petraco MRCP[1,2], John Davies MRCP[4,5], Thomas Keeble MRCP[4,5], Kare Tang FRCP[4], Iqbal Malik FRCP[1,2], Christopher Cook MRCP[1,2], Yousif Ahmad MRCP[1,2], Andrew SP Sharp FRCP[6], Robert Gerber FRCP[7], Christopher Baker FRCP[2], Raffi Kaprielian FRCP[2], Suneel Talwar MRCP[8], Ravi Assomull MRCP[2], Graham Cole MRCP[1,2], Niall G Keenan MRCP[9], Gajen Kanaganayagam MRCP[2], Joban Sehmi MRCP[9], Roland Wensel MRCP[1], Frank E Harrell PhD[10], Jamil Mayet FRCP[1,2], Simon Thom FRCP[1], Justin E Davies MRCP[2], Darrel P Francis FRCP[1,2]

[1]National Heart and Lung Institute, Imperial College London, London, UK

[2]Imperial College Healthcare NHS Trust, London, UK

[3]Cancer Research UK & UCL Cancer Trials Centre, University College London, London, UK

[4]Essex Cardiothoracic Centre, Basildon, UK

[5]Anglia Ruskin University, Chelmsford, UK

[6]Royal Devon and Exeter NHS Trust, Exeter, UK

[7]East Sussex Healthcare NHS Trust, Hastings, UK

[8]Royal Bournemouth and Christchurch NHS Trust, Bournemouth, UK

[9]West Hertfordshire Hospitals NHS Trust, Watford, UK

[10]Vanderbilt University School of Medicine, Department of Biostatistics, Nashville, USA.

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Disclosures

JED and JM hold patents pertaining to the iFR technology. JED and AS are consultants for Philips Volcano. RA-L, SS, RP, CC, and SSN have received speaker's honoraria from Philips Volcano. JED and TK have received research grants from Philips Volcano. All other authors declare no competing interests.

References

1. Parisi AF, Folland ED and Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *The New England journal of medicine*. 1992;326:10-6.
2. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet*. 1997;350:461-8.
3. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, Zhang W, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB, Deaton C, Kaufman S, O'Rourke RA, Goeree R, Barnett PG, Teo KK, Boden WE, Group CTR and Mancini GB. Effect of PCI on quality of life in patients with stable coronary disease. *The New England journal of medicine*. 2008;359:677-87.
4. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nuesch E, Juni P and Investigators FT. Fractional flow reserve-guided PCI for stable coronary artery disease. *The New England journal of medicine*. 2014;371:1208-17.
5. Dagenais GR, Lu J, Faxon DP, Kent K, Lago RM, Lezama C, Hueb W, Weiss M, Slater J, Frye RL and Bypass Angioplasty Revascularization Investigation 2 Diabetes Study G. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation*. 2011;123:1492-500.
6. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC and Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation*. 2010;122:949-57.
7. Al-Lamee R, Thompson D, Thom S, Wensel R, Tang K, Davies J, Keeble T, Talwar S, Sharp A, Gerber RT, Davies JE and Francis D. Protocol 15PRT/06897: Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA trial) - NCT02062593. *The Lancet*. 2016;http://www.thelancet.com/doi/story/10.1016/html.2016.10.12.4214.
8. 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 and investigators O. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391:31-40.
9. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M and Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *Journal of the American College of Cardiology*. 1995;25:333-41.
10. Scott AC, Francis DP, Davies LC, Coats AJ and Piepoli MF. Validation of a treadmill exercise test protocol with improved metabolic plateau formation in patients with chronic congestive heart failure. *The American journal of cardiology*. 2001;87:1328-31.
11. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, Stella PR, van Schaardenburgh P, Bech GJ, De

Bruyne B and Pijls NH. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *European heart journal*. 2015;36:3182-8.
12. Harrell FE. *Regression Modelling Strategies*. Switzerland: Springer International Publishing; 2015.
13. Garratt AM, Hutchinson A, Russell I, Network for Evidence-Based Practice in N and Yorkshire. The UK version of the Seattle Angina Questionnaire (SAQ-UK): reliability, validity and responsiveness. *J Clin Epidemiol*. 2001;54:907-15.
14. Team RDC. *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2010.
15. Harrell FE. rms: Regression Modeling Strategies. R package version 3.4.3. *http://biostatmcvanderbiltedu/rms*. 2018.
16. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*: Springer-Verlag New York; 2009.
17. Rajkumar CA, Nijjer SS, Cole GD, Al-Lamee R and Francis DP. 'Faith healing' and 'subtraction anxiety' in unblinded trials of procedures: Lessons from DEFER and FAME-2 for end points in the ISCHEMIA trial. *Circulation Cardiovascular quality and outcomes*. 2018;11:e004665.
18. Christensen HW, Haghfelt T, Vach W, Johansen A and Hoilund-Carlsen PF. Observer reproducibility and validity of systems for clinical classification of angina pectoris: comparison with radionuclide imaging and coronary angiography. *Clin Physiol Funct Imaging*. 2006;26:26-31.
19. Byrne RA. Fallout from the ORBITA trial - is angioplasty in a spin? *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2017;13:1253-1254.
20. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS and Group CTR. Optimal medical therapy with or without PCI for stable coronary disease. *The New England journal of medicine*. 2007;356:1503-16.
21. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF and Investigators FT. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *The New England journal of medicine*. 2012;367:991-1001.
22. Al-Lamee R. Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA). *Late breaking clinical trial presentation, Transcathetheter Therapeutics Conference*. 2017;https://www.tctmd.com/slide/orbita-randomized-sham-controlled-trial-pci-patients-coronary-artery-disease.
23. Hueb W, Soares PR, Gersh BJ, Cesar LA, Luz PL, Puig LB, Martinez EM, Oliveira SA and Ramires JA. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *Journal of the American College of Cardiology*. 2004;43:1743-51.
24. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Juni P, Pijls NHJ, Hlatky MA and Investigators FT. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary

Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation*. 2018;137:480-487.
25. Harrel FE. Ordinal regression model. 2017.

Tables

Table 1: Patient demographics at enrolment

	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 2: 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)
Diameter stenosis by QCA Mean (SD)	64.1±13.7	63.7 ±13.6	63.9±13.6
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)	-	-

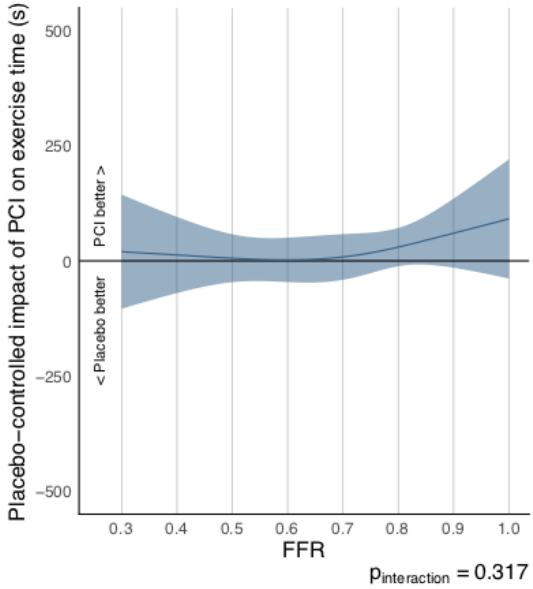
FFR post PCI (n=101) **Median (IQR)**	0.90±0.06 0.9 (0.06)	-	-
iFR post PCI **Median (IQR)**	0.95±0.04 0.95 (0.05)	-	-
No. pts with post FFR>0.80	95 (94.1) (n=101)	-	-
No. pts with post iFR>0.89	98 (95.1) (n=103)	-	-

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

Figures

Figure 1

A:



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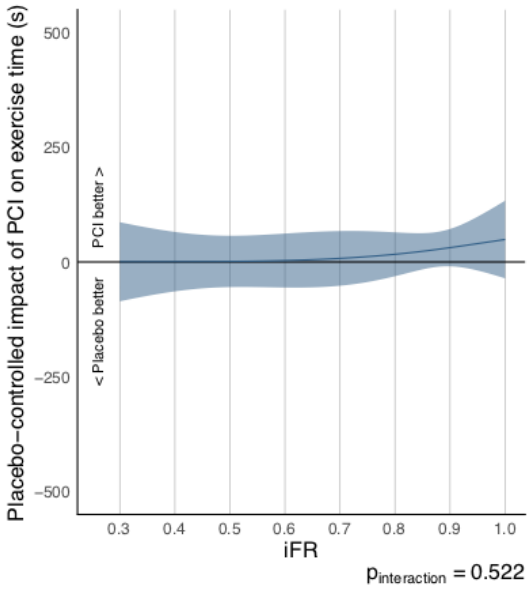


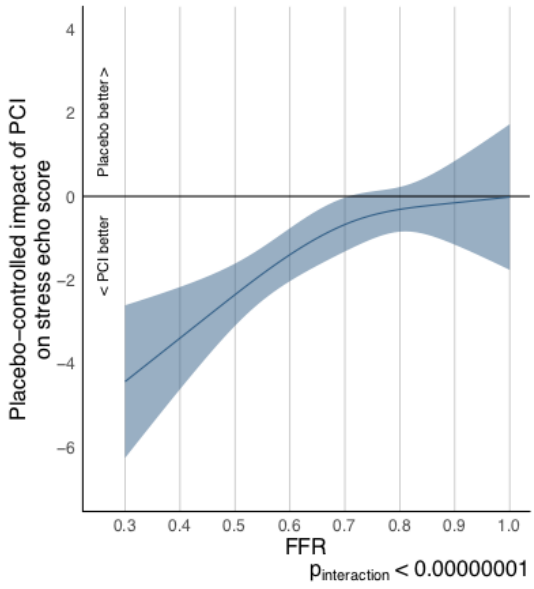
Figure 1.

A. Relationship of change in pre-randomization to follow up total exercise time and pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of change in pre-randomization to follow up total exercise time and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

Figure 2:

A:



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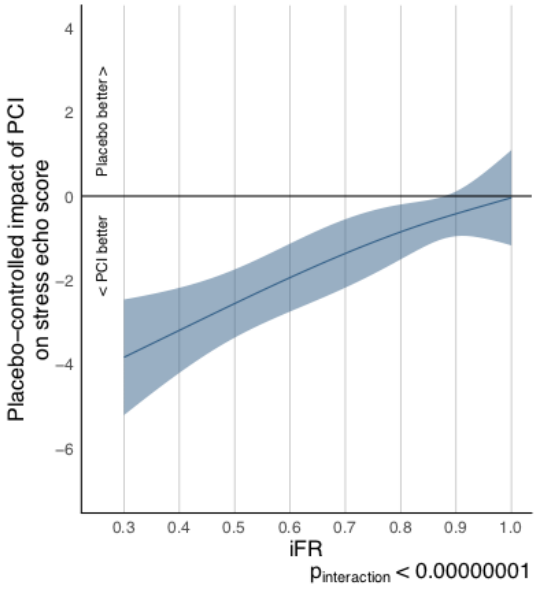


Figure 2.

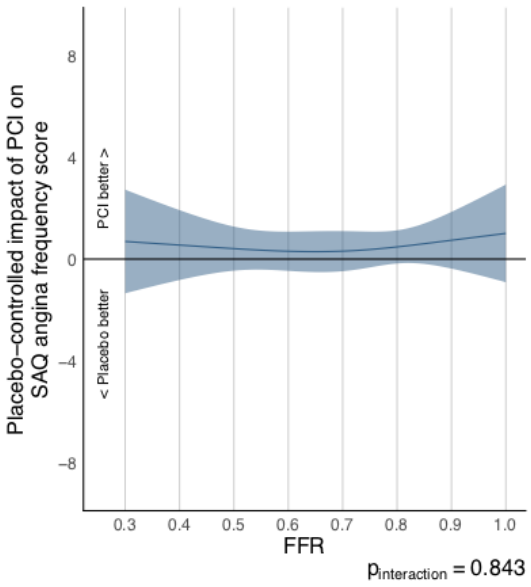
A. Relationship of treatment difference in stress echo score and pre-randomization FFR by randomization arm. At the right, with FFR≈1.0, the curve is ≈0, indicating that there is no difference between PCI and placebo. The shaded area represents the 95% CI for the estimate of this mean effect. At progressively 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-randomization FFR has $p_{interaction}<0.00000001$.

B. Relationship of treatment difference in peak stress echo score and pre-randomization iFR by randomization 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-randomization 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 3:

A:



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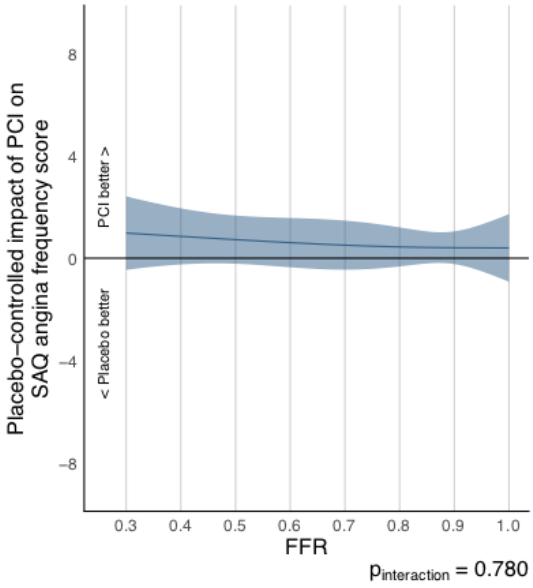


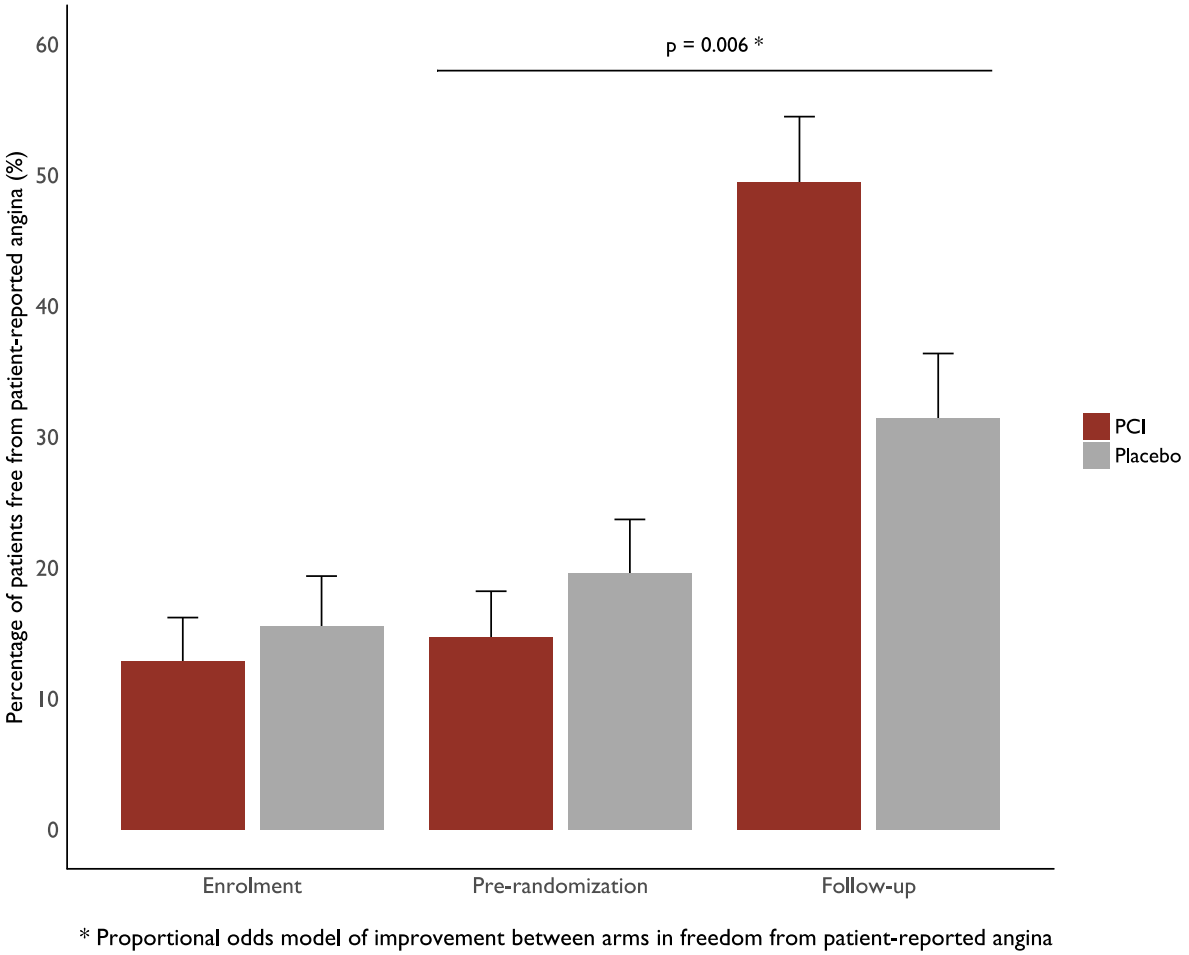
Figure 3.

A. Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

The vertical axis shows the impact of PCI rather than placebo on the natural logarithm of the odds ratio for improvement versus deterioration. Upward indicates greater odds of improvement with PCI than with placebo. An odds ratio of 1 means no difference between arms. An odds ratio of 2 would indicate the odds are two-fold more favourable with PCI than with placebo. The improvement or deterioration is calculated using an ordinal cumulative probability model.[25]

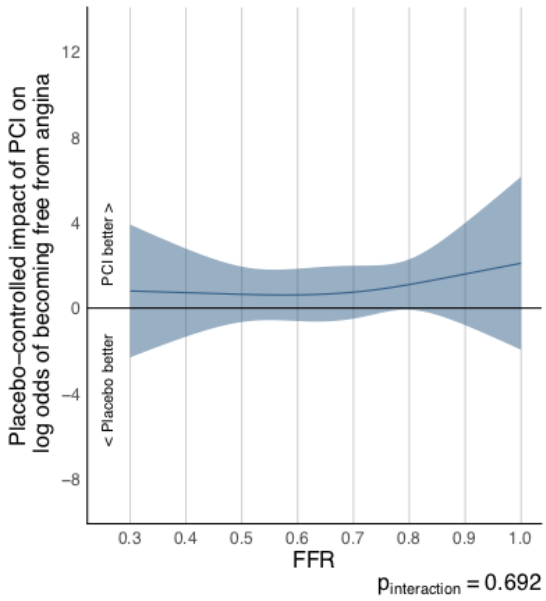
Figure 4



Percentage of patients free of patient-reported angina at enrolment, pre-randomization and follow-up per study arm from Seattle Angina Questionnaire. Proportional odds model for freedom from angina from pre-randomization to follow-up

Figure 5

A:



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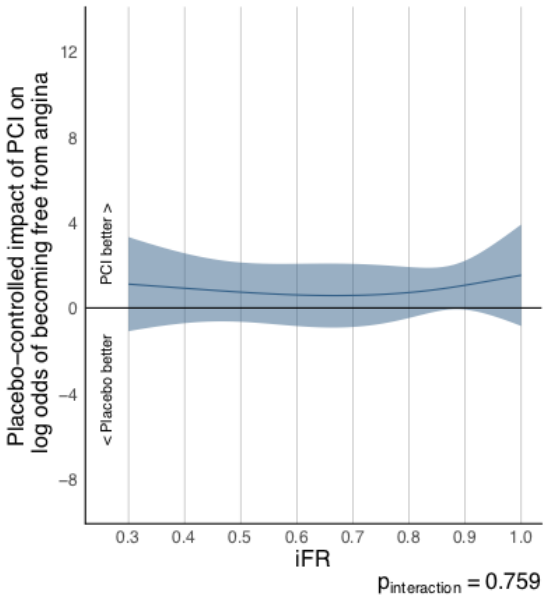


Figure 5.

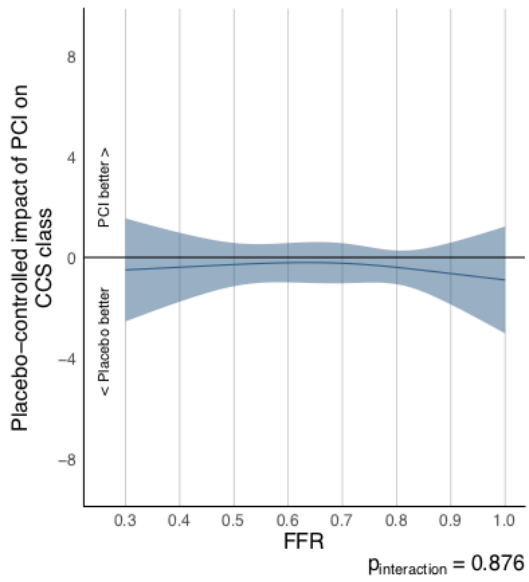
A. Relationship of treatment difference in patient-reported freedom from angina from Seattle Angina Questionnaire at follow-up to pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of treatment difference in patient-reported freedom from angina from Seattle Angina Questionnaire at follow-up to pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

Upward indicates greater odds of achievement of angina freedom with PCI than with placebo. An odds ratio of 1 means no difference between arms. An odds ratio of 2 would indicate the odds are two-fold more favourable with PCI than with placebo. The improvement or deterioration is calculated using an ordinal cumulative probability model.[25]

Figure 6

A:



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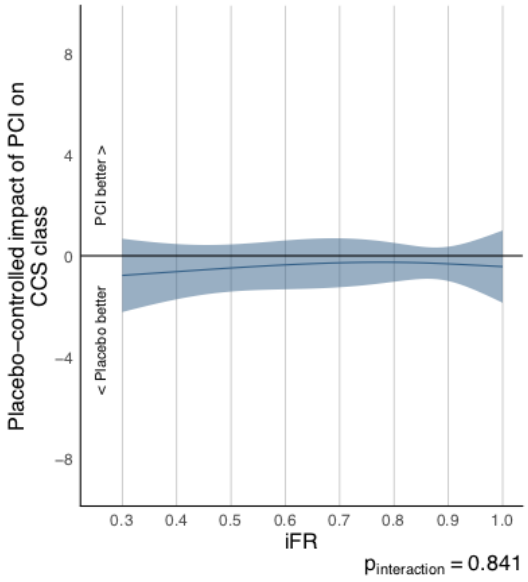

Figure 6.

A. Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society class (CCS) at follow-up to pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society class (CCS) at follow-up to pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

The vertical axis shows the impact of PCI rather than placebo on the natural logarithm of the odds ratio for increase versus decrease in CCS class. Upward indicates greater odds of increase with PCI than with placebo. An odds ratio of 1 means no difference between arms. The increase or decrease is calculated using an ordinal cumulative probability model.[25]