Circulation

ORIGINAL RESEARCH ARTICLE

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

Physiology-Stratified Analysis of ORBITA

Rasha Al-Lamee, MA, MRCP
et al

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

METHODS: We report the association between prerandomization invasive physiology within ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina), a placebo-controlled trial of patients who have stable angina with angiographically severe single-vessel coronary disease clinically eligible for PCI. Patients underwent prerandomization research FFR and iFR assessment. The operator was blinded to these values. Assessment of response variables, treadmill exercise time, stress echocardiography score, symptom frequency, and angina severity were performed at prerandomization and 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 by using regression modeling.

RESULTS: Invasive physiology data were available in 196 patients (103 PCI and 93 placebo). At prerandomization, the majority 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% had ≥1 positive ischemia tests. The estimated effect of PCI on between-arm prerandomization-adjusted total exercise time was 20.7 s (95% confidence interval [CI], –4.0 to 45.5; P=0.100) with no interaction of FFR ($P_{interaction}$=0.318) or iFR ($P_{interaction}$=0.523). PCI improved stress echocardiography score more than placebo (1.07 segment units; 95% CI, 0.70–1.44; P<0.00001). The placebo-controlled effect of PCI on stress echocardiography score increased progressively with decreasing FFR ($P_{interaction}$<0.00001) and decreasing iFR ($P_{interaction}$<0.00001). PCI did not improve angina frequency score significantly more than placebo (odds ratio, 1.64; 95% CI, 0.96–2.80; P=0.072) with no detectable evidence of interaction with FFR ($P_{interaction}$=0.849) or iFR ($P_{interaction}$=0.783). However, PCI resulted in more patient-reported freedom from angina than placebo (49.5% versus 31.5%; odds ratio, 2.47; 95% CI, 1.30–4.72; P=0.006) but neither FFR ($P_{interaction}$=0.693) nor iFR ($P_{interaction}$=0.761) modified this effect.

CONCLUSIONS: In patients with stable angina and severe single-vessel disease, the blinded effect of PCI was more clearly seen by stress echocardiography score and freedom from angina than 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.

Key Words: angina, stable ■ clinical trial ■ fractional flow reserve, myocardial ■ ischemia ■ percutaneous coronary intervention

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Clinical Perspective

What Is New?

- This report of ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) stratified by invasive hemodynamic measures of stenosis severity provides the first placebo-controlled evidence of the association between fractional flow reserve and instantaneous wave-free ratio and the magnitude of benefit attributable to percutaneous coronary intervention (PCI).
- PCI improves ischemia 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).
- Prerandomization fractional flow reserve and instantaneous wave-free ratio predict the placebo-controlled PCI effect on stress echocardiography.
- Prerandomization fractional flow reserve and instantaneous wave-free ratio 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.
- Fractional flow reserve and instantaneous wave-free ratio can be used to predict the PCI effect on stress echocardiography ischemia.

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, ORBITA (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina), the placebo-controlled effect of PCI on the prespecified primary end point of exercise time at 6 weeks, by prespecified statistical methods,[7] unexpectedly[1] did not meet the criteria for statistical significance (point estimate 16.6 s; 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 ≥1 positive ischemia 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 echocardiography score (stress echo score), patient-reported and physician-assessed symptoms, quality of life, and treadmill exercise time.

METHODS

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.

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 enrollment, 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) 6-week medical optimization phase of antianginal medication uptitration, ending with prerandomization assessment and the blinded angiography procedure, and (2) 6-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 prerandomization 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] that 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 randomly assigned 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 with high FFR were studied with 1 trial with 1 end point, and patients with low FFR were studied in a different trial with a different end point.[4,11]

After administration of intracoronary nitrate and normalization of the pressure wire, FFR and iFR were measured by using standard techniques with the wire placed at least 3 vessel diameters distal to the most distal stenosis. Intravenous adenosine was then administered (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) 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 readministered, the wire was renormalized and readvanced into the same distal position by 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 renormalized, 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 randomly assigned to receive PCI or placebo procedure.

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

If randomly assigned to PCI, this was performed by using angiographic guidance with drug-eluting stents implanted and complete angiographic revascularization mandated. Postdilatation was recommended, and intravascular ultrasound or optical coherence tomography were used at the operator's discretion.

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

The patient and all subsequent medical caregivers were blinded to the treatment allocation by using the methods described previously.[8]

Study End Points and Follow-Up

At the end of the blinded follow-up period patients reattended 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 by 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 (prerandomization or follow-up), using an online reporting tool. In the original ORBITA publication, analysis had been performed by 2 imaging consultants (R.A. and D.F.).

For the present physiology-stratified analysis of ORBITA, each scan received 12 opinions. Each scan was examined twice by 6 imaging consultants (R.A., D.F., G.C., G.K., J.S., and N.K.) 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 echocardiography results are presented in a manner that represents the number of hypokinetic segments (with akinetic segments scoring double, 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. 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). Cardiopulmonary exercise testing was performed using the smoothed modified Bruce protocol and end points reported as previously described.[8]

Statistical Analysis

For the physiology-stratified analysis of ORBITA, the data available consisted of all patients with at least 1 form of invasive physiological assessment at prerandomization. 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 prespecified method of analysis.[7] However, regression models (a generalized 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 end point, a model was fitted. For the continuous end points 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 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 1 covariate and it is binary. Even if the response variables are normally distributed, the proportional odds model has efficiency of $3/\pi$ or ≈0.95.

For both continuous and categorical outcome variables, we modeled the follow-up value conditioned on the prerandomization value transformed by a restricted cubic spline with 3 parameters and randomization arm. A model was then fitted for each outcome variable with prerandomization FFR or iFR interacting with the randomization arm and the prerandomization value of the outcome variable with a restricted cubic spline with 3 parameters, ie, the shape of effect was allowed to vary over treatments.[12,14] Graphs of the end points against FFR and iFR and the contrast between the arms were generated adjusting for the median value of the prerandomization value.

All analyses were performed using the open-source statistical environment "R,"[15] with the package "rms" for regression modeling[16] and "ggplot2" for graphs.[17]

RESULTS

ORBITA enrolled 230 patients. After the medical optimization phase, 200 patients were randomly assigned to PCI (n=105) versus placebo (n=95). Four patients in the ORBITA data set 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 randomly assigned patients had invasive physiological assessment and were available for the physiology-stratified analysis of ORBITA (103 in the PCI arm and 93 in the placebo arm). Within this data set 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 the PCI arm and 96.8% in the placebo arm) had physician-assessed CCS class II or III angina severity at enrollment.

Medical Therapy

At prerandomization, the majority of patients were taking more than 2 antianginal medications (85.4% in PCI versus 90.3% in placebo, Table I in the online-only Data Supplement); 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 prerandomization, the majority of patients had CCS class II or III symptoms (150/196, 76.5%) (Table II in the online-only Data Supplement) and 83.0% (161/194) of patients reported ≥1 episodes of angina in the past 4 weeks (Table III in the online-only Data Supplement).

Procedural Demographics

Procedural demographics are shown in Table 2. The median time between the first diagnostic angiogram and the prerandomization angiogram was 54 days (interquartile range, 45–64) 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 I and II in the online-only Data Supplement. The mean FFR was 0.69 (SD, 0.16): 145 of 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 of 196 (69.4%) had iFR≤0.89, with mean 0.68 (SD, 0.21); the remainder had mean iFR 0.94 (SD, 0.03).

Overall, 191 patients (97%) had ≥1 positive ischemia tests by the time of randomization; these consisted of a preenrollment clinical test, research stress echocardiography, FFR≤0.80 or iFR≤0.89. The angiographic images of the remaining 5 patients are shown in Figure III in the online-only Data Supplement.

All patients in the PCI arm had drug-eluting stents implanted. Postdilatation was performed with a noncompliant balloon in 86 (83.5%) of these stents. Post-PCI FFR values were available for 101 patients, and post-PCI iFR values were available for 103 patients. Mean post-PCI FFR was 0.90 (SD, 0.06) and post-PCI iFR was 0.95 (SD, 0.04). Six (5.9%) patients had FFR≤0.80

Table 1. Patient Demographics at Enrollment

	Percutaneous Coronary Intervention (n=103)	Placebo (n=93)	Complete Group (n=196)
Age, y	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 mellitus	15 (14.6)	21 (22.6)	36 (18.4)
Previous myocardial infarction	4 (3.9)	7 (7.5)	11 (5.6)
Previous percutaneous coronary intervention	10 (9.7)	14 (14.1)	24 (12.2)
Canadian Cardiovascular Society Angina 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, mo	9.54±15.8	8.45±7.59	9.03±12.6
Positive functional test	55 (53.4)	42 (45.2)	97 (49.5)
Exercise tolerance test	26 (25.2)	17 (18.3)	43 (21.9)
Nuclear medicine myocardial perfusion scan	10 (9.7)	11 (11.8)	21 (10.7)
Dobutamine stress echocardiography	19 (18.4)	13 (14.0)	32 (16.3)
Magnetic resonance imaging perfusion	0 (0)	1 (1.1)	1 (0.5)

Values indicate n (%) or mean±SD.

postprocedure: their mean FFR was 0.76 (SD, 0.06). Five (4.9%) patients had iFR≤0.89 postprocedure: their mean iFR was 0.86 (SD, 0.04).

Study End Points

Exercise Time

Paired exercise time data were available for 190 patients in the physiology-stratified analysis of the ORBITA data set (102 in the PCI arm and 88 in the placebo arm). The estimated effect of PCI over placebo on exercise time using regression modeling was 20.7 seconds (95% CI, –4.0 to 45.5; P=0.100; Table IV in the online-only Data Supplement). 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 1A and 1B).

Dobutamine Stress Echocardiography

The stress echocardiography data set consists of 159 patients (90 PCI, 69 placebo), each with prerandomization 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 (+0.18 segment units; SD, 1.14). Overall, PCI improved the stress echo score in comparison with placebo (difference 1.07 segment units; 95% CI, 0.70–1.44; P<0.00001; Table IV in the online-only Data Supplement).

There was an interaction between FFR and the stress echocardiography improvement from PCI over placebo ($P_{interaction}$<0.00001), with a progressively larger improvement at lower prerandomization FFR values (Figure 2A).

Similarly, there was an interaction between iFR and the stress echocardiography improvement ($P_{interaction}$<0.00001; Figure 2B), with a progressively larger improvement at lower prerandomization iFR values.

Patient-Reported Symptoms and Quality of Life

Paired patient-reported data at prerandomization and follow-up from the Seattle Angina Questionnaire were available in 189 patients (101 in the PCI arm and 88 in the placebo arm).

There was no statistically significant evidence that PCI improved Seattle Angina Questionnaire angina frequency score more than placebo (odds ratio, 1.64; 95% CI, 0.96–2.80; P=0.072; Table IV in the online-only Data Supplement). 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 2 groups, for any nonzero f. For this nonsignificant 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 3A and 3B).

Table 2. Procedural Demographics

	Percutaneous Coronary Intervention (n=103)	Placebo (n=93)	Complete Group (n=196)
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 (14.8)
No. of patients with diameter stenosis ≥50% by quantitative coronary angiography	87 (84.4)	79 (85.0)	166 (84.7)
Diameter stenosis by quantitative coronary angiography	64.1±13.7	63.7±13.6	63.9±13.6
Area stenosis by quantitative coronary angiography	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 0.72 (0.24) (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 0.83 (0.22)
No. of patients with FFR ≤0.80	76 (73.8)	69 (75.8) (n=91)	145 (74.7) (n=194)
No. of patients 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. of patients with post-FFR>0.80	95 (94.1) (n=101)	–	–
No. of patients with post-iFR>0.89	98 (95.1) (n=103)	–	–

Values indicate n (%) or mean±SD.
FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and IQR, interquartile range.

PCI was more likely to result in patient-reported freedom from angina than placebo (odds ratio, 2.47; 95% CI, 1.30–4.72; *P*=0.006; Figure 4, Tables IV and V in the online-only Data Supplement). Complete freedom from angina was achieved in more patients in the PCI arm than in the placebo arm (49.5% versus 31.5%). 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 5A and $P_{interaction}$=0.761; Figure 5B).

PCI did not improve Seattle Angina Questionnaire physical limitation score more than placebo: point estimate 2.59 U (95% CI, –2.93 to 8.10; *P*=0.356; Table IV in the online-only Data Supplement). For this nonsignificant effect, there was no detectable evidence of interaction between either FFR ($P_{interaction}$=0.805) or iFR ($P_{interaction}$=0.610) and the effect of PCI on physical limitation score (Figure IVA and IVB in the online-only Data Supplement).

PCI did not improve Seattle Angina Questionnaire quality-of-life score more than placebo (2.08; 95% CI, –3.85 to 8.01; *P*=0.490; Table IV in the online-only Data Supplement). For this nonsignificant effect, there was no detectable evidence of interaction between either FFR ($P_{interaction}$=0.321) or iFR ($P_{nteraction}$=0.242) and the ef-

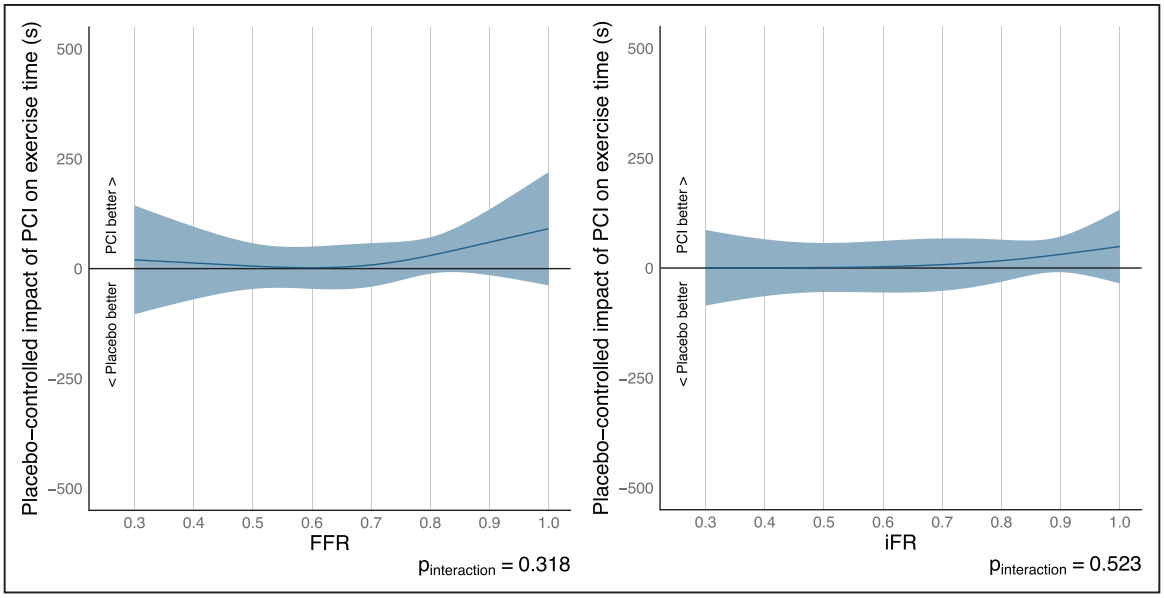

Figure 1. Relationship of change in prerandomization to follow-up total exercise time and prerandomization FFR and iFR by randomization arm. **A,** Relationship of change in prerandomization to follow-up total exercise time and prerandomization FFR by randomization arm. There is no discernible dependence on prerandomization FFR. **B,** Relationship of change in prerandomization to follow-up total exercise time and prerandomization iFR by randomization arm. There is no discernible dependence on prerandomization iFR. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and PCI, percutaneous coronary intervention.

fect of PCI on quality-of-life score (Figure VA and VB in the online-only Data Supplement).

Paired EQ-5D-5L data were 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 IV in the online-only Data Supplement). For this nonsignificant 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 descriptive scale (Figure VIA and VIB in the online-only Data Supplement). 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*=0.609; Table IV in the online-only Data Supplement). For this nonsignificant 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 (Figure VIIA and VIIB in the online-only Data Supplement).

Physician-Assessed Symptoms

Paired CCS data were available for 192 patients in the physiology-stratified analysis of the ORBITA data set (103 in the PCI arm and 89 in the placebo arm). At enrollment, there were no patients with CCS 0, and within this cohort by prerandomization 9 of 103 (8.74%) patients in the PCI arm and 12 of 89 (13.5%) patients in the placebo arm were classified as CCS 0, by follow-up 41 of 103 (39.8%) of patients in the PCI arm and 26 of 89 (29.2%) of patients in the placebo arm were classified as CCS 0 (*P*=0.132; Table II in the online-only Data Supplement). PCI did not improve CCS class more than placebo (odds ratio, 0.73; 95% CI, 0.43–1.25; *P*=0.254; Table IV in the online-only Data Supplement). For this nonsignificant 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 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 VI to IX in the online-only Data Supplement.

In addition, the end point analysis and PCI effects for dichotomous FFR and iFR in only those patients with CCS class I to IV symptoms at prerandomization are presented in Tables X to XIV in the online-only Data Supplement.

DISCUSSION

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

The initial anatomic and hemodynamic effects of PCI were large. The resultant stress echo score was very clearly improved by PCI versus placebo; and the more

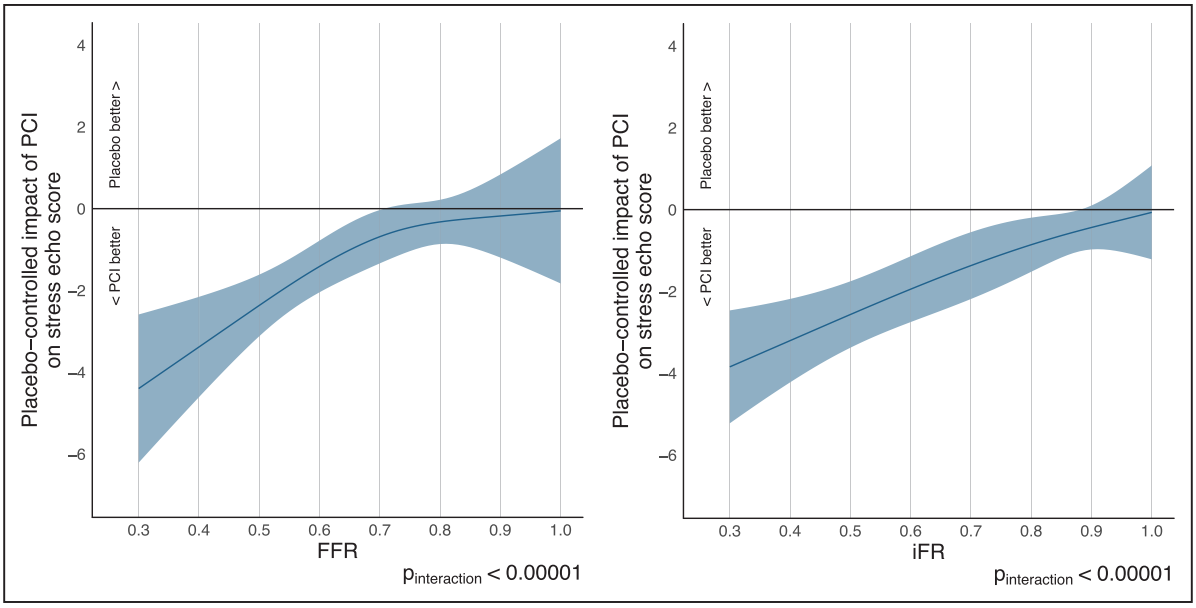

Figure 2. Relationship of treatment difference in stress echo score and prerandomization FFR and iFR by randomization arm.
A, Relationship of treatment difference in stress echo score and prerandomization FFR by randomization arm. At the right, with FFR≈1.0, the curve is ≈0, indicating that there is 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 end point. This progressive tendency for larger effects on stress echo score with lower prerandomization FFR has $P_{interaction}$<0.00001. **B,** Relationship of treatment difference in peak stress echo score and prerandomization 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% confidence interval for the estimate of this mean effect. At progressively lower iFR values, there is a progressively larger difference between PCI and placebo on the end point. This progressive tendency for larger effects on stress echo score with lower prerandomization iFR has $P_{interaction}$<0.00001. The stress echo score can be converted to classical Wall Motion Score Index as follows. Wall Motion Score Index=1+(stress echo score)/17. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and PCI, percutaneous coronary intervention.

severe the FFR and iFR, the larger the PCI effect on the stress echo score.

Of patient-reported change in symptoms, the most binary is absence versus presence of symptoms. On this end point of patient-reported freedom from angina, PCI was more effective than placebo. Indeed, 1 in 5 more patients became free of angina with PCI than with the 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 end points 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 online-only Data Supplement, results for the patients dichotomized by 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 (Angioplasty Compared to Medicine), which had a similar size, enrolled patients with similar exercise capacity, and used the same statistical method as prespecified 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 attributable to differences in medical therapy between arms. We do not believe this is plausible because the ACME PCI arm received fewer nitrates (P<0.01), β-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 β-blocker usage or had increased their habitual exercise as a result of knowing they had had PCI.[18]

It is still not clear why the objective relief of anatomic, hemodynamic, and stress echocardiographic abnormalities did not translate as well as hoped into patient-centered end points under blinded conditions. However, on the most unambiguous dichotomous patient-centered end point, freedom from angina, there

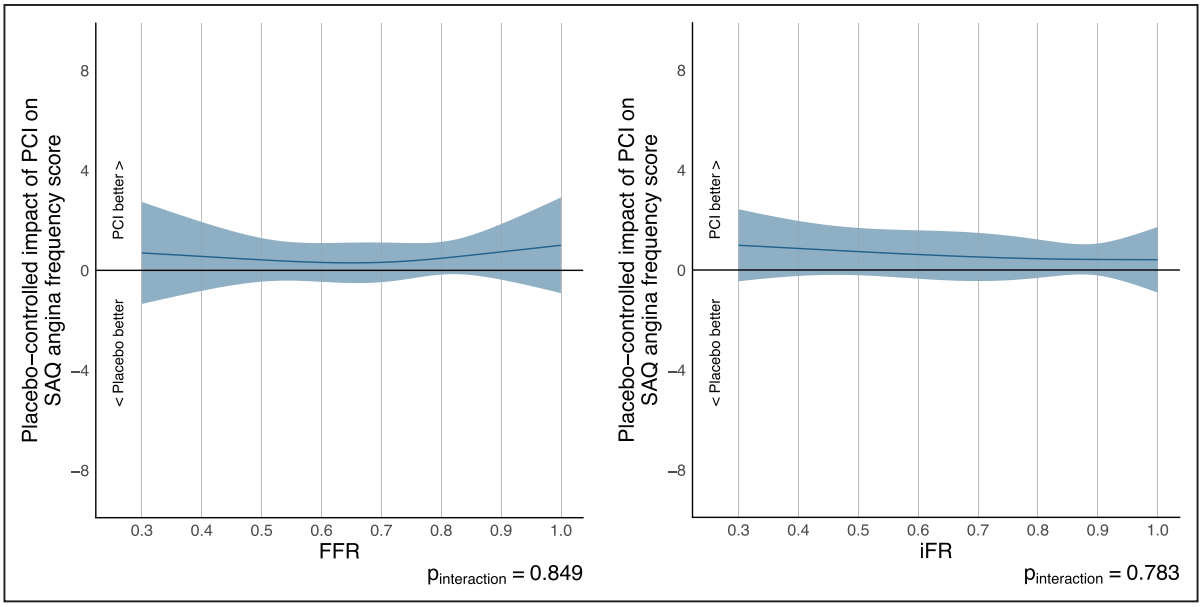

Figure 3. Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and prerandomization FFR and iFR by randomization arm.

A, Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and prerandomization FFR by randomization arm. There is no discernible dependence on prerandomization FFR. **B,** Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and prerandomization iFR by randomization arm. There is no discernible dependence on prerandomization 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 2-fold more favorable with PCI than with placebo. The improvement or deterioration is calculated using an ordinal cumulative probability model.[14] FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

was a statistically significant improvement with PCI with a large absolute improvement.

ORBITA was analyzed as prespecified,[7] with the *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 modeling, which offers advantages including the ability to adjust appropriately for prerandomization 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]

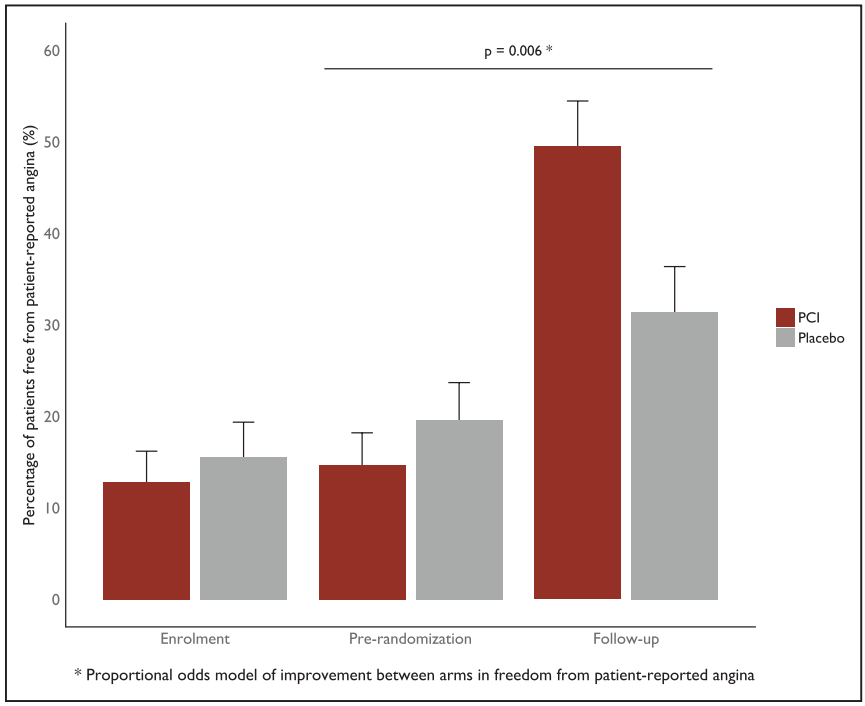

Figure 4. Percentage of patients free of patient-reported angina at enrollment, prerandomization, and follow-up per study arm from Seattle Angina Questionnaire.
Proportional odds model for freedom from angina from prerandomization to follow-up. PCI indicates percutaneous coronary intervention

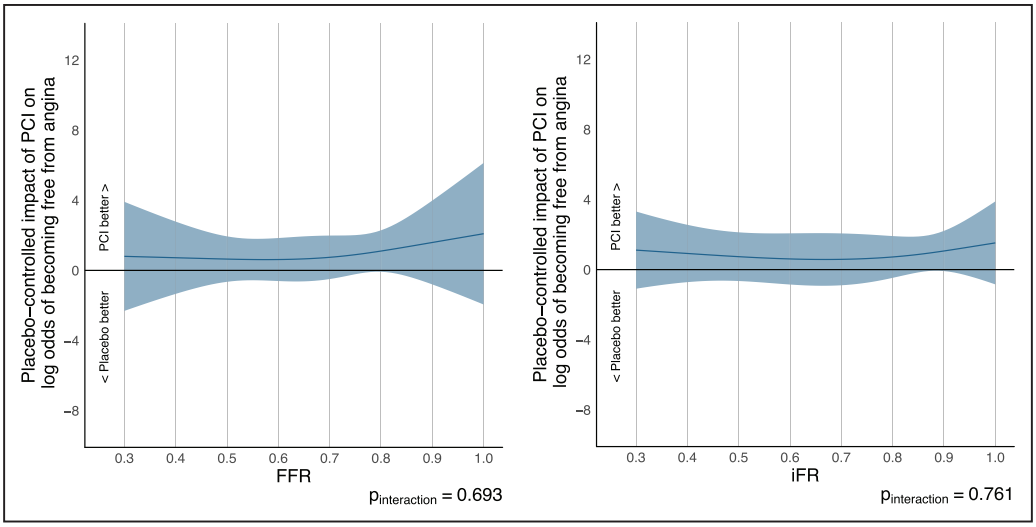

Figure 5. Relationship of treatment difference in patient-reported freedom from angina from Seattle Angina Questionnaire at follow-up to prerandomization FFR and iFR by randomization arm.

A, Relationship of treatment difference in patient-reported freedom from angina from Seattle Angina Questionnaire at follow-up to prerandomization FFR by randomization arm. There is no discernible dependence on prerandomization FFR. **B,** Relationship of treatment difference in patient-reported freedom from angina from Seattle Angina Questionnaire at follow-up to prerandomization iFR by randomization arm. There is no discernible dependence on prerandomization 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 2-fold more favorable with PCI than with placebo. The improvement or deterioration is calculated using an ordinal cumulative probability model.[14] FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and PCI, percutaneous coronary intervention.

Exercise treadmill time has a long track record of detecting the effect of antianginal medication against placebo. However, PCI opens the stenosis and antianginals do not. This may explain why treadmill exercise time under placebo-controlled conditions responds differently to PCI than to antianginal medications.

The patient-centered symptomatic aim is ultimately 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 end point 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.[19]

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 ischemia measured by invasive physiology. In addition, it provides data that patients in the PCI arm were more likely to report freedom from angina at follow-up than patients in the placebo arm, but that this effect was not predicted by prerandomization FFR and iFR values.

Study Limitations

This physiology-stratified analysis of ORBITA is a subanalysis describing the 196 patients for whom invasive physiology measurements were available, only 98% of the 200 randomly assigned 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 end point is not powered for probing the association between invasive physiology and placebo-controlled response to PCI.[1] Although it was the prespecified primary end point, 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 ≥1 noninvasive or invasive tests at the time of randomization, and the 5 remaining angiograms are shown (online-only Data Supplement). FFR was measured not[20] for clinical decision making (because all patients were already eligible), but rather for research purposes to study the association between FFR and the placebo-controlled effect of PCI.

Dichotomizing 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 end point, the study is not underpowered.

In the primary ORBITA report, stress echocardiography data were presented, as prespecified, in the form of wall

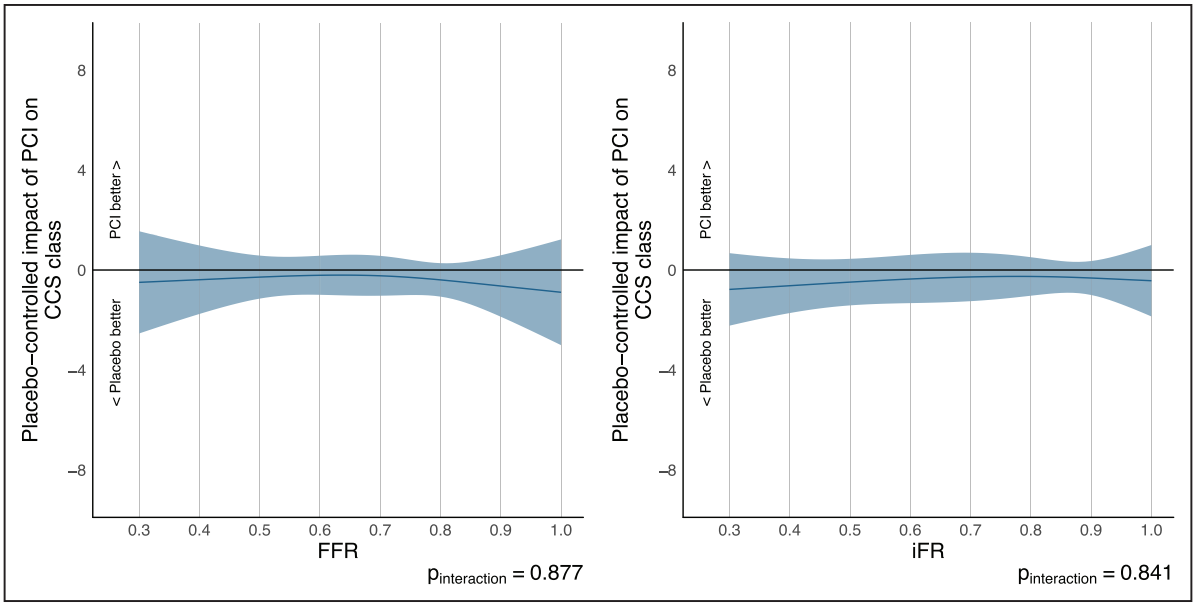

Figure 6. Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society class at follow-up to prerandomization FFR and iFR by randomization arm.

A, Relationship of treatment difference in physician-assessed Canadian Cardiovascular Society (CCS) class at follow-up to prerandomization FFR by randomization arm. There is no discernible dependence on prerandomization FFR. **B,** Relationship of treatment difference in physician-assessed CCS class at follow-up to prerandomization iFR by randomization arm. There is no discernible dependence on prerandomization 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.[14] FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and PCI, percutaneous coronary intervention.

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 nonimaging 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 maximizes the statistical power of the analysis.

All patients were considered by the physician to have angina at enrollment (ie, were CCS class ≥1), 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 4 weeks. We cannot tell whether this was caused by preenrollment antianginal 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 prerandomization were 11.5% in ORBITA, 9% in the ACME study, 11.2% in the FAME-2 study (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation2), and 12.5% in the COURAGE study (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).[21,22]

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 to III in the PCI arm was 47% in ORBITA.[8,23] For comparison, after unblinded PCI, physician-assessed CCS II to III was 57.1% in the second RITA-2 study (Randomised Intervention Treatment of Angina) at 6 months,[2] 45.5% in the MASS-II study (Medicine, Angioplasty, or Surgery Study) at 1 year,[24] and 34% in COURAGE at 1 year.[3] The one dramatically different result was from FAME-2, which reported 5.9%.[25]

The trial design only asked patients to remain blinded and randomly assigned for 6 weeks, because we expected a large benefit from PCI and wanted to ensure the recruitment of severe coronary stenoses as shown in the ORBITA appendix. All patients were unblinded. The patients in the placebo arm 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 anatomic and hemodynamic 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 prerandomization FFR and iFR predicted a progressively larger effect of PCI versus placebo on stress echocardiography ischemia. They did not predict the PCI effect on symptoms, quality of life, or treadmill exercise time.

The effect of PCI on end points, and the extent to which this effect is associated with FFR and iFR, declines progressively along the pathway from resolution of angiographic stenosis, through hemodynamics and myocardial performance, through to patient-experienced symptoms and their downstream consequences.

ARTICLE INFORMATION

Received February 21, 2018; accepted April 20, 2018.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.118.033801/-/DC1.

Authors

Rasha Al-Lamee, MA; James P. Howard, MA; Matthew J. Shun-Shin, MA; David Thompson, MCPI; Hakim-Moulay Dehbi, PhD; Sayan Sen; Sukhjinder Nijjer; Ricardo Petraco; John Davies; Thomas Keeble; Kare Tang; Iqbal S. Malik; Christopher Cook; Yousif Ahmad; Andrew S.P. Sharp; Robert Gerber; Christopher Baker; Raffi Kaprielian; Suneel Talwar; Ravi Assomull; Graham Cole; Niall G. Keenan; Gajen Kanaganayagam; Joban Sehmi; Roland Wensel; Frank E. Harrell, PhD; Jamil Mayet; Simon A. Thom; Justin E. Davies; Darrel P. Francis

Correspondence

Rasha Al-Lamee, MA, National Heart and Lung Institute, Hammersmith Hospital, Du Cane Road, London W10 0HS, United Kingdom. E-mail r.al-lamee13@imperial.ac.uk

Affiliations

National Heart and Lung Institute, Imperial College London, United Kingdom (R.A-L., J.H., M.S.-S., D.T., S.S., S.N., R.P., I.M., C.C., Y.A., G.C., R.W., J.M., S.A.T., D.P.F.). Imperial College Healthcare NHS Trust, London, United Kingdom (R.A.-L., J.H., M.S.-S., S.S., .SN., R.P., I.M.,K C.C., Y.A., C.B., G.C., G.K., J.M., J.E.D., D.P.F.). Cancer Research UK and UCL Cancer Trials Centre, University Col-lege London (H.-M.D.). Essex Cardiothoracic Centre, Basildon, United Kingdom (J.D., T.K., K.T.). Anglia Ruskin University, Chelmsford, United Kingdom (J.D., T.K.). Royal Devon and Exeter NHS Trust, United Kingdom (A.S.P.S.). East Sussex Healthcare NHS Trust, Hastings, United Kingdom (R.G.). Royal Bournemouth and Christchurch NHS Trust, United Kingdom (S.T.). West Hertfordshire Hospi-tals NHS Trust, Watford, United Kingdom (N.G.K.). Vanderbilt University School of Medicine, Department of Biostatistics, Nashville, TN (F.E.H.).

Acknowledgments

ORBITA was an investigator-led trial sponsored by Imperial College London. The authors thank our patients and their families for their dedication and support for the ORBITA trial. Special thanks to N. Bual for performing the stress echo-cardiography investigations. The authors thank the research and administrative teams at Imperial College Healthcare NHS Trust, Essex Cardiothoracic Center, East Sussex Healthcare NHS Trust, Royal Devon and Exeter NHS Trust, and Royal Bournemouth and Christchurch NHS Trust for their dedication and support.

Sources of Funding

The trial was funded by grants from National Institute for Health Research Imperial Biomedical Research Center, Foundation for Circulatory Health, and Imperial Col-lege Healthcare Charity. J. Howard is a PhD Training Fellow at the Wellcome Trust. Philips Volcano supplied the coronary pressure wires. The authors acknowledge the support of the National Institute for Health Research Clinical Research Network.

Disclosures

Drs Justin E. Davies and Mayet hold patents pertaining to the iFR technology. Drs Justin E. Davies and Sharp are consultants for Philips Volcano. Drs Al-Lamee, Sen, Petraco, Cook, and Nijjer have received speaker's honoraria from Philips Volcano. Drs Justin E. Davies and Keeble have received research grants from Philips Volcano. All other authors declare no competing interests.

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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: Physiology-Stratified Analysis of ORBITA

Rasha Al-Lamee, James P. Howard, Matthew J. Shun-Shin, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Sukhjinder Nijjer, Ricardo Petraco, John Davies, Thomas Keeble, Kare Tang, Iqbal S. Malik, Christopher Cook, Yousif Ahmad, Andrew S.P. Sharp, Robert Gerber, Christopher Baker, Raffi Kaprielian, Suneel Talwar, Ravi Assomull, Graham Cole, Niall G. Keenan, Gajen Kanaganayagam, Joban Sehmi, Roland Wensel, Frank E. Harrell, Jamil Mayet, Simon A. Thom, Justin E. Davies and Darrel P. Francis

Circulation. published online May 22, 2018;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

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

Supplemental tables

Table 1
Medical therapy

	PCI (n=103) n (%)	Placebo (n=93) n (%)
Enrolment		
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-randomization		
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 2
Physician-assessed severity of angina

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

CCS = Canadian Cardiovascular Society

Table 3
Seattle Angina Questionnaire frequency of angina

		PCI n (%)	Placebo n (%)
Enrolment		n=101	n=90
Frequency of angina	≥4x/day	3 (3.0)	7 (7.8)
	1-3x/day	29 (28.7)	20 (22.2)
	≥3x/week but not every day	22 (21.8)	20 (22.2)
	1-2x/week	16 (15.8)	13 (14.4)
	<1x/week	18 (17.8)	16 (17.8)
	None in last 4 weeks	13 (12.9)	14 (15.6)
Pre-randomization		n=102	n=92
Frequency of angina	≥4x/day	2 (2.0)	4 (4.3)
	1-3x/day	18 (17.6)	17 (18.5)
	≥3x/week but not every day	14 (13.7)	17 (18.5)
	1-2x/week	25 (24.5)	18 (19.6)
	<1x/week	28 (27.5)	18 (19.6)
	None in last 4 weeks	15 (14.7)	18 (19.6)
Follow-up		n=101	n=89
Frequency of angina	≥4x/day	2 (2.0)	4 (4.5)
	1-3x/day	7 (6.9)	8 (9.0)
	≥3x/week but not every day	12 (11.9)	10 (11.2)
	1-2x/week	14 (13.9)	21 (23.6)
	<1x/week	16 (15.8)	18 (20.2)
	None in last 4 weeks	50 (49.5)	28 (31.5)

These were the answers provided by the patients to the following written question from the Seattle Angina Questionnaire: “Over the past 4 weeks, how many times have you had chest pain, chest tightness or angina?”

Table 4
Endpoint analysis for all patients

Endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)
Total exercise time	20.7s (95% CI -4.0 to 45.5; p=0.100)
Dobutamine stress echo score	1.07 (95% CI 0.70 to 1.44; p<0.00001)
SAQ physical limitation score	2.59 (95% CI -2.93 to 8.10; p=0.356)
SAQ quality of life score	2.08 (95% CI -3.85 to 8.01; p=0.490)
EQ-5D-5L descriptive system	0.001 (95% CI -0.039 to 0.042; p=0.951)
EQ-5D-5L visual analogue scale	1.22 (95% CI -3.47 to 5.90; p=0.609)
Endpoint	**Logistic (proportional odds) ordinal regression model estimate* (PCI over placebo)**
SAQ angina frequency score	OR 1.64 (95% CI 0.96 to 2.80; p=0.072)
SAQ freedom from angina	OR 2.47 (95% CI 1.30 to 4.72; p=0.006)
CCS class	OR 0.73 (95% CI 0.43 to 1.25; p=0.254)

SAQ= Seattle Angina Questionnaire, CCS= Canadian Cardiovascular Society Class
* In this proportional odds estimate, an OR of 1 indicates neutrality i.e. that PCI is equivalent to placebo on this endpoint. For example, for CCS class, an OR of ½ (0.5) would indicate that the odds of reduction rather than increase of CCS class are 2-fold better with PCI rather than placebo. Please note that since high SAQ angina frequency scores represent lower actual angina frequency, for SAQ angina frequency scores an OR>1 indicates a tendency for PCI to reduce actual angina frequency more than placebo.

Table 5
Patient-reported presence of angina

		PCI n (%)	Placebo n (%)
Enrolment		n=101	n=90
Presence of angina	Angina present	88 (87.1)	76 (84.4)
	Angina free	13 (12.9)	14 (15.6)
Pre-randomization		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 categorized as “angina present”. Below one episode per month is categorized as “angina free”.

Table 6
Exercise time stratified by FFR and iFR for complete group

Threshold	FFR ≤ threshold				FFR > threshold			
	n	Point Estimate (sec)	95% CI	p value	n	Point estimate (sec)	CI	p value
0.65	75	-3.18	-48.9 to 42.5	0.890	113	34.1	4.27 to 64.0	0.0255
0.70	85	1.49	-39.5 to 42.5	0.943	103	33.0	0.667 to 65.2	0.0455
0.75	113	6.63	-27.5 to 40.7	0.701	75	38.8	0.440 to 77.1	0.0475
0.80	142	9.60	-20.5 to 39.7	0.530	46	48.8	1.42 to 96.3	0.0438
0.85	161	17.9	-10.6 to 46.5	0.217	27	55.0	6.44 to 104	0.0282
0.90	177	19.2	-7.15 to 45.6	0.152	11	76.1	-2.10 to 154	0.0549
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**Point estimate (sec)**	**95% CI**	**p value**	**n**	**Point estimate (sec)**	**CI**	**p value**
0.73	61	11.1	-38.4 to 60.6	0.656	129	24.6	-4.51 to 53.7	0.0969
0.77	66	2.56	-44.2 to 49.4	0.913	124	29.1	-0.445 to 58.7	0.0535
0.81	77	2.93	-39.2 to 45.1	0.890	113	31.8	0.560 to 63.1	0.0461
0.85	96	3.33	-34.0 to 40.7	0.860	94	37.5	3.82 to 71.1	0.0295
0.89	133	5.78	-25.8 to 37.4	0.718	57	60.0	17.3 to 103	0.00674
0.93	161	14.3	-13.4 to 42.1	0.310	29	66.0	3.58 to 128	0.0391

Table 7
Stress echocardiography analysis stratified by FFR and iFR for complete group

Threshold	FFR ≤ threshold				FFR > threshold			
	n	Point estimate (stress echo units)	95% CI	p value	n	Point estimate (stress echo units)	95% CI	p value
0.65	58	-1.73	-2.47 to -0.979	0.0000229	99	-0.504	-0.882 to -0.126	0.00957
0.70	67	-1.80	-2.46 to -1.15	0.000000787	90	-0.388	-0.773 to -0.00235	0.0487
0.75	92	-1.64	-2.22 to -1.07	0.000000162	65	-0.177	-0.483 to 0.129	0.253
0.80	116	-1.30	-1.78 to -0.827	0.000000337	41	-0.192	-0.532 to 0.149	0.261
0.85	133	-1.18	-1.60 to -0.764	0.000000139	24	0.0117	-0.413 to 0.436	0.955
0.90*	148	-1.08	-1.46 to -0.698	0.000000102	9	0.164	-0.614 to 0.942	0.625
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**Point estimate (stress echo units)**	**95% CI**	**p value**	**n**	**Point estimate (stress echo units)**	**95% CI**	**p value**
0.73	45	-2.42	-3.36 to -1.49	0.00000531	114	-0.485	-0.823 to -0.146	0.00537
0.77	50	-2.21	-3.07 to -1.34	0.00000544	109	-0.490	-0.843 to -0.136	0.00709
0.81	60	-2.29	-3.09 to -1.50	0.000000367	99	-0.318	-0.602 to -0.0345	0.0284
0.85	77	-1.71	-2.39 to -1.04	0.00000315	82	-0.407	-0.709 to -0.106	0.00877
0.89	106	-1.40	-1.92 to -0.881	0.000000526	53	-0.312	-0.695 to 0.0715	0.108
0.93	133	-1.25	-1.69 to -0.808	0.000000118	26	0.088	-0.385 to 0.561	0.703

*****This stratification for FFR > threshold was modelled without the use of a restricted cubic spline on the pre-randomisation value due to sample size constraints.

Table 8
Seattle angina frequency score stratified by FFR and iFR for complete group

Threshold	FFR ≤ threshold				FFR > threshold			
	n	OR	95% CI	p value	n	OR	CI	p value
0.65	75	1.66	0.691 to 3.97	0.258	112	1.46	0.731 to 2.93	0.282
0.70	85	1.46	0.625 to 3.39	0.384	102	1.51	0.737 to 3.10	0.260
0.75	113	1.38	0.678 to 2.81	0.375	74	1.76	0.748 to 4.13	0.196
0.80	141	1.68	0.892 to 3.15	0.109	46	1.44	0.488 to 4.28	0.506
0.85	160	1.65	0.915 to 2.97	0.0960	27	1.39	0.322 to 6.00	0.660
0.90	176	1.61	0.920 to 2.82	0.0952	11	5.74	0.179 to 184	0.323
Threshold								
	n	**OR**	**95% CI**	**p value**	**n**	**OR**	**CI**	**p value**
0.73	61	1.76	0.655 to 4.71	0.263	128	1.61	0.845 to 3.09	0.147
0.77	66	1.82	0.706 to 4.69	0.215	123	1.59	0.819 to 3.07	0.171
0.81	77	1.69	0.714 to 3.98	0.233	112	1.55	0.771 to 3.11	0.22
0.85	96	1.63	0.762 to 3.51	0.207	93	1.83	0.844 to 3.96	0.126
0.89	133	1.74	0.918 to 3.3	0.0898	56	1.62	0.583 to 4.47	0.356
0.93	159	1.99	1.1 to 3.61	0.023	30	1.35	0.294 to 6.25	0.697

Table 9
Seattle Angina Questionnaire freedom from angina stratified by FFR and iFR for complete group

Threshold	FFR ≤ threshold				FFR > threshold			
	n	OR	95% CI	p value	n	OR	95% CI	p value
0.65	75	2.14	0.776 to 5.90	0.141	111	2.46	1.05 to 5.75	0.0382
0.70	85	2.22	0.849 to 5.78	0.104	101	2.37	0.966 to 5.80	0.0594
0.75	113	1.92	0.865 to 4.27	0.109	73	3.50	1.10 to 11.1	0.0334
0.80	140	2.27	1.10 to 4.67	0.0265	46	4.25	0.769 to 23.5	0.0971
0.85	159	2.33	1.16 to 4.66	0.0174	27	6.00	0.596 to 60.4	0.128
0.90	175	2.54	1.30 to 4.95	0.00632	11	1000	2.39e-22 to 4.2e+27	0.811
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**OR**	**95% CI**	**p value**	**n**	**OR**	**95% CI**	**p value**
0.73	61	2.35	0.775 to 7.15	0.131	127	2.50	1.10 to 5.65	0.0279
0.77	66	2.90	1.00 to 8.41	0.0495	122	2.23	0.974 to 5.11	0.0579
0.81	77	2.62	0.982 to 6.99	0.0544	111	2.32	0.971 to 5.55	0.0582
0.85	96	2.76	1.15 to 6.62	0.0232	92	2.21	0.838 to 5.83	0.109
0.89	133	2.34	1.10 to 4.97	0.0269	55	3.19	0.868 to 11.8	0.0806
0.93	158	2.56	1.27 to 5.17	0.00854	30	4.87	0.506 to 46.8	0.171

Table 10
Endpoint analysis for only patients with CCS I-IV at pre-randomization

Endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)
Dobutamine stress echo score	-1.08 (95% CI -1.48 to -0.685; p<0.00001)
Total exercise time	22.0 (95% CI -4.60 to 48.5; p=0.104)
Endpoint	**Logistic (proportional odds) ordinal regression model estimate* (PCI over placebo)**
SAQ angina frequency score	1.49 (95% CI 0.85 to 2.62; p=0.161)
SAQ freedom from angina	2.35 (95% CI 1.19 to 4.64; p=0.0136)

* In this proportional odds estimate, an OR of 1 indicates neutrality i.e. that PCI is equivalent to placebo on this endpoint. Please note that since high SAQ angina frequency scores represent lower actual angina frequency, for SAQ angina frequency scores an OR>1 indicates a tendency for PCI to reduce actual angina frequency more than placebo.

Table 11: Exercise time stratified by FFR and iFR for patients with CCS I-IV at pre-randomization

Threshold	FFR ≤ threshold				FFR > threshold			
	n	Point Estimate (sec)	95% CI	p value	n	Point Estimate (sec)	95% CI	p value
0.65	65	-3.13	-52.6 to 46.3	0.900	102	34.0	1.99 to 66.1	0.0376
0.70	74	2.33	-41.7 to 46.4	0.916	93	32.7	-1.94 to 67.4	0.064
0.75	101	5.70	-30.5 to 41.9	0.756	66	43.4	2.04 to 84.8	0.0400
0.80	125	9.13	-23.3 to 41.6	0.578	42	49.8	-2.38 to 102	0.0608
0.85	142	20.3	-10.7 to 51.2	0.197	25	53.8	-3.45 to 111	0.0641
0.90	157	20.7	-7.61 to 49.1	0.151	10	86.7	-18.9 to 192	0.0913
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**Point estimate (sec)**	**95% CI**	**p value**	**n**	**Point estimate (sec)**	**CI**	**p value**
0.73	53	10.4	-42.9 to 63.8	0.697	116	26.8	-4.47 to 58.2	0.0922
0.77	58	-0.310	-50.0 to 49.4	0.990	111	31.7	-0.224 to 63.7	0.0516
0.81	69	0.214	-44.2 to 44.6	0.992	100	34.6	0.37 to 68.7	0.0476
0.85	88	2.51	-36.3 to 41.3	0.898	81	42.3	5.23 to 79.3	0.0259
0.89	117	7.47	-26.7 to 41.6	0.665	52	60.4	12.8 to 108	0.0139
0.93	142	16.3	-13.7 to 46.3	0.284	27	59.5	-12.2 to 131	0.0995

Table 12: Dobutamine stress echocardiography analysis for patients with CCS I-IV at pre-randomization

Threshold	FFR ≤ threshold				FFR > threshold			
	n	Point estimate (stress echo units)	95% CI	p value	n	Point estimate (stress echo units)	95% CI	p value
0.65	49	-1.64	-2.44 to -0.831	0.000176	91	-0.574	-0.984 to -0.164	0.00665
0.70	57	-1.77	-2.47 to -1.06	6.16E-06	83	-0.442	-0.859 to -0.0245	0.0382
0.75	81	-1.60	-2.21 to -0.992	1.45E-06	59	-0.223	-0.560 to 0.115	0.192
0.80	101	-1.32	-1.83 to -0.805	1.72E-06	39	-0.216	-0.584 to 0.152	0.242
0.85	116	-1.20	-1.65 to -0.745	7.98E-07	24	0.0117	-0.413 to 0.436	0.955
0.90*	131	-1.09	-1.49 to -0.680	5.14E-07	9	0.164	-0.614 to 0.942	0.625
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**Point estimate (stress echo units)**	**95% CI**	**p value**	**n**	**Point estimate (stress echo units)**	**95% CI**	**p value**
0.73	38	-2.32	-3.36 to -1.29	6.33E-05	104	-0.55	-0.919 to -0.181	0.00385
0.77	43	-2.08	-3.02 to -1.15	5.97E-05	99	-0.543	-0.928 to -0.159	0.00613
0.81	53	-2.19	-3.04 to -1.33	5.1E-06	89	-0.382	-0.695 to -0.0681	0.0176
0.85	70	-1.59	-2.30 to -0.884	2.91E-05	72	-0.497	-0.838 to -0.155	0.00496
0.89	92	-1.41	-1.97 to -0.847	3.17E-06	50	-0.333	-0.752 to 0.0867	0.117
0.93	116	-1.27	-1.75 to -0.791	6.85E-07	26	0.088	-0.385 to 0.561	0.703

*This stratification for FFR > threshold was modelled without the use of a restricted cubic spline on the pre-randomisation value due to sample size constraints.

Table 13: Seattle Angina Questionnaire angina frequency score analysis for patients with CCS I-IV at pre-randomization

Threshold	FFR ≤ threshold				FFR > threshold			
	n	OR	95% CI	p value	n	OR	CI	p value
0.65	65	1.45	0.575 to 3.64	0.433	101	1.36	0.663 to 2.80	0.400
0.70	74	1.21	0.496 to 2.97	0.672	92	1.46	0.690 to 3.07	0.324
0.75	101	1.26	0.600 to 2.63	0.546	65	1.74	0.706 to 4.26	0.229
0.80	124	1.56	0.810 to 3.01	0.184	42	1.56	0.491 to 4.97	0.450
0.85*	141	1.49	0.807 to 2.75	0.202	25	1.32	0.277 to 6.27	0.729
0.90*	156	1.48	0.826 to 2.66	0.187	10	1.58	0.0213 to 117	0.836
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**OR**	**95% CI**	**p value**	**n**	**OR**	**CI**	**p value**
0.73	53	1.61	0.568 to 4.59	0.368	115	1.45	0.737 to 2.85	0.283
0.77	58	1.71	0.630 to 4.62	0.293	110	1.41	0.708 to 2.82	0.327
0.81	69	1.58	0.640 to 3.87	0.322	99	1.38	0.665 to 2.87	0.387
0.85	88	1.62	0.736 to 3.56	0.231	80	1.64	0.719 to 3.73	0.240
0.89	117	1.57	0.807 to 3.07	0.184	51	1.70	0.576 to 5.04	0.336
0.93	140	1.83	0.987 to 3.39	0.055	28	1.65	0.282 to 9.65	0.578

*****This stratification for FFR > threshold was modelled without the use of a restricted cubic spline on the pre-randomisation value due to sample size constraints.

Table 14: Seattle Angina Questionnaire freedom from angina analysis for patients with CCS I-IV at pre-randomization

Threshold	FFR ≤ threshold				FFR > threshold			
	n	OR	95% CI	p value	n	OR	CI	p value
0.65	65	2.16	0.733 to 6.36	0.162	100	2.30	0.943 to 5.61	0.067
0.70	74	2.21	0.798 to 6.09	0.127	91	2.31	0.898 to 5.96	0.0823
0.75	101	1.89	0.823 to 4.35	0.133	64	3.42	0.967 to 12.1	0.0563
0.80	123	2.26	1.06 to 4.85	0.0355	42	3.23	0.576 to 18.1	0.183
0.85	140	2.24	1.07 to 4.67	0.0320	25	4.67	0.451 to 48.2	0.196
0.90	155	2.44	1.21 to 4.94	0.0129	10	925	1.02e-26 to 8.41e+31	0.841
Threshold	**iFR ≤ threshold**				**iFR > threshold**			
	n	**OR**	**95% CI**	**p value**	**n**	**OR**	**CI**	**p value**
0.73	53	2.89	0.91 to 9.17	0.0719	114	2.17	0.919 to 5.12	0.0773
0.77	58	3.47	1.14 to 10.6	0.0286	109	1.91	0.8 to 4.58	0.145
0.81	69	2.92	1.05 to 8.16	0.0404	98	1.99	0.792 to 5.0	0.143
0.85	88	3.02	1.21 to 7.51	0.0175	79	1.80	0.639 to 5.1	0.266
0.89	117	2.30	1.03 to 5.11	0.0417	50	2.86	0.742 to 11.0	0.127
0.93	139	2.51	1.20 to 5.25	0.0149	28	3.81	0.385 to 37.8	0.253

Supplemental figures

Figure 1

Distribution of FFR Values

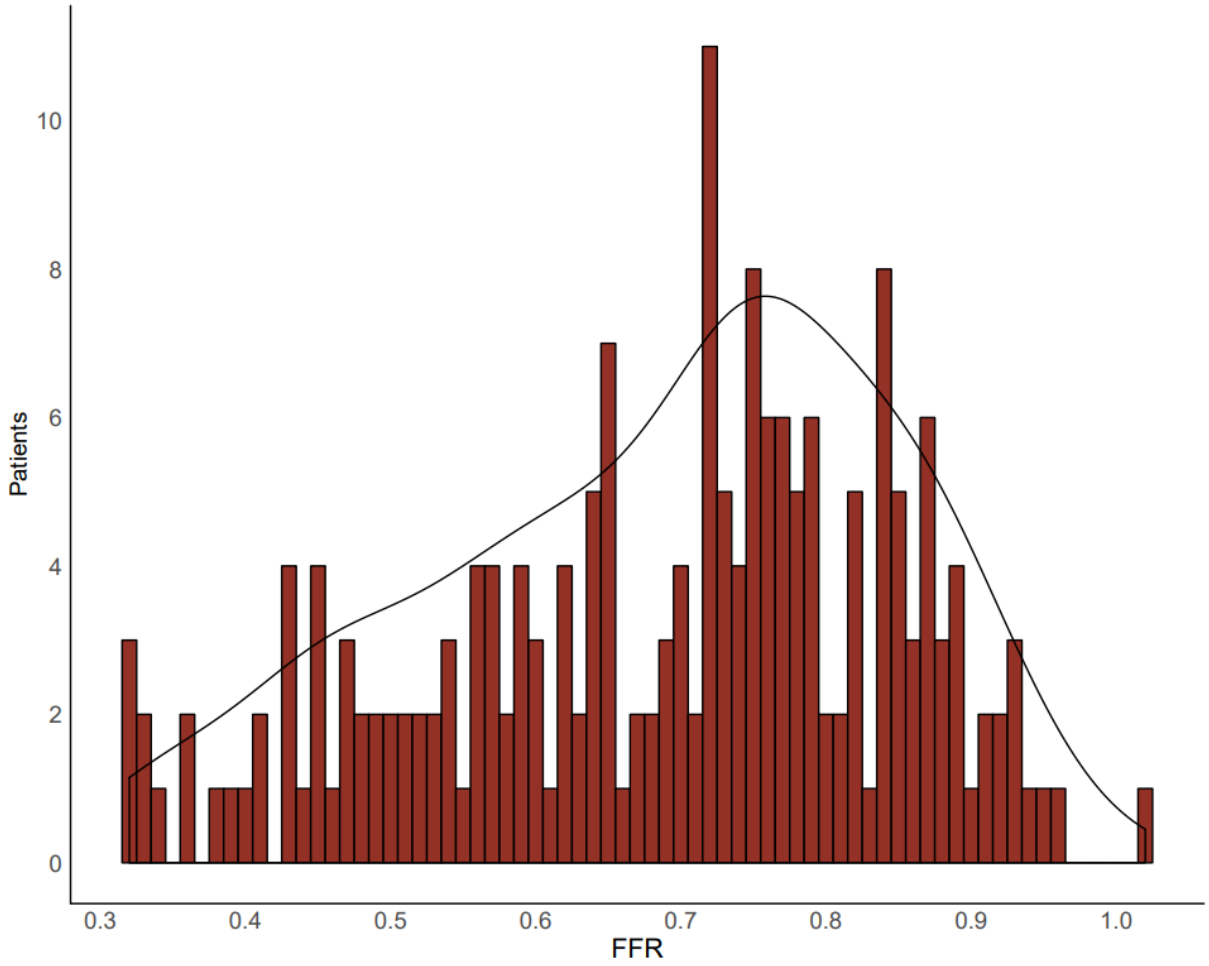

Figure 2

Distribution of iFR values

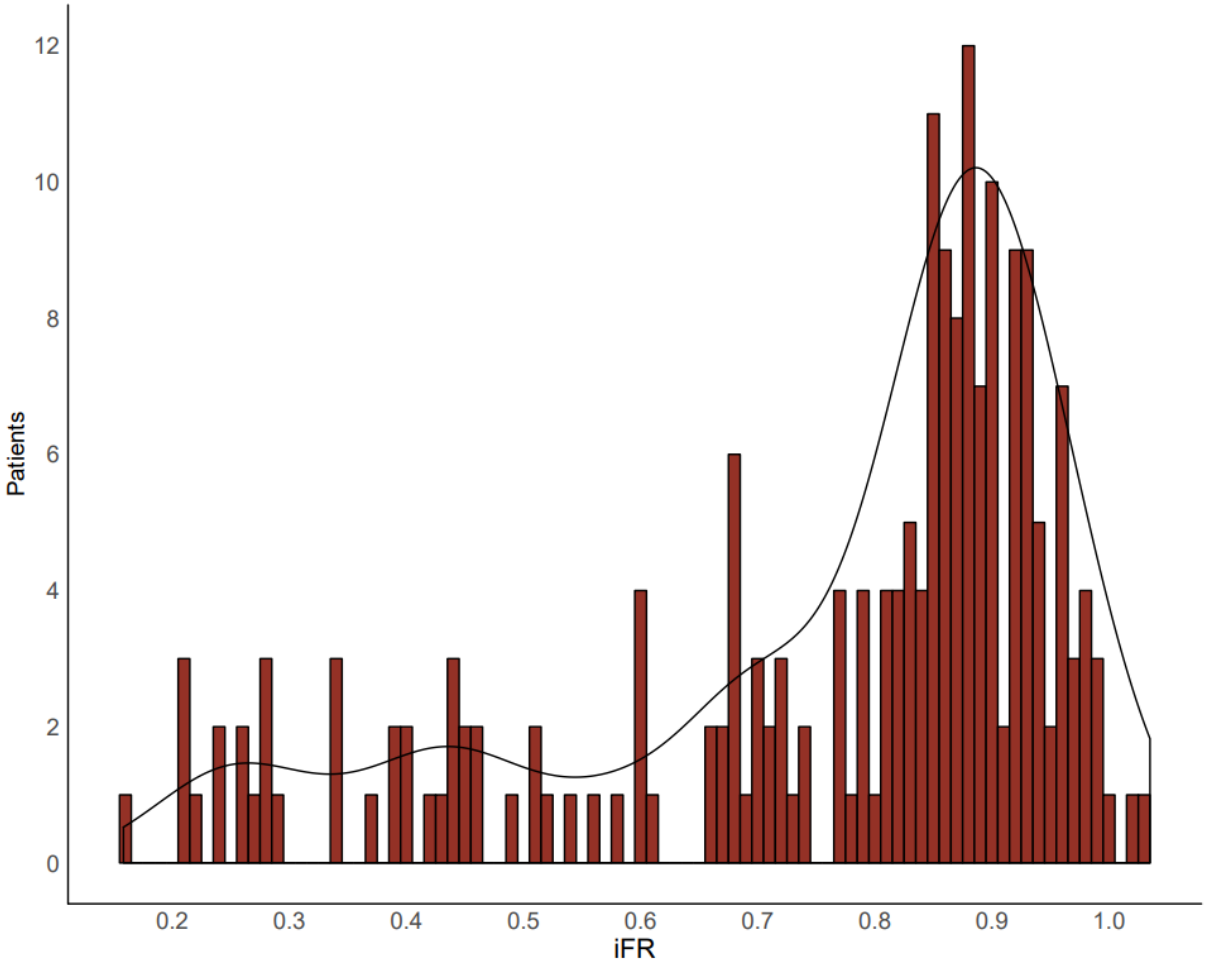

Figure 3

Angiographic images of patients with symptoms of stable angina with no evidence of ischaemia on non-invasive or invasive functional test

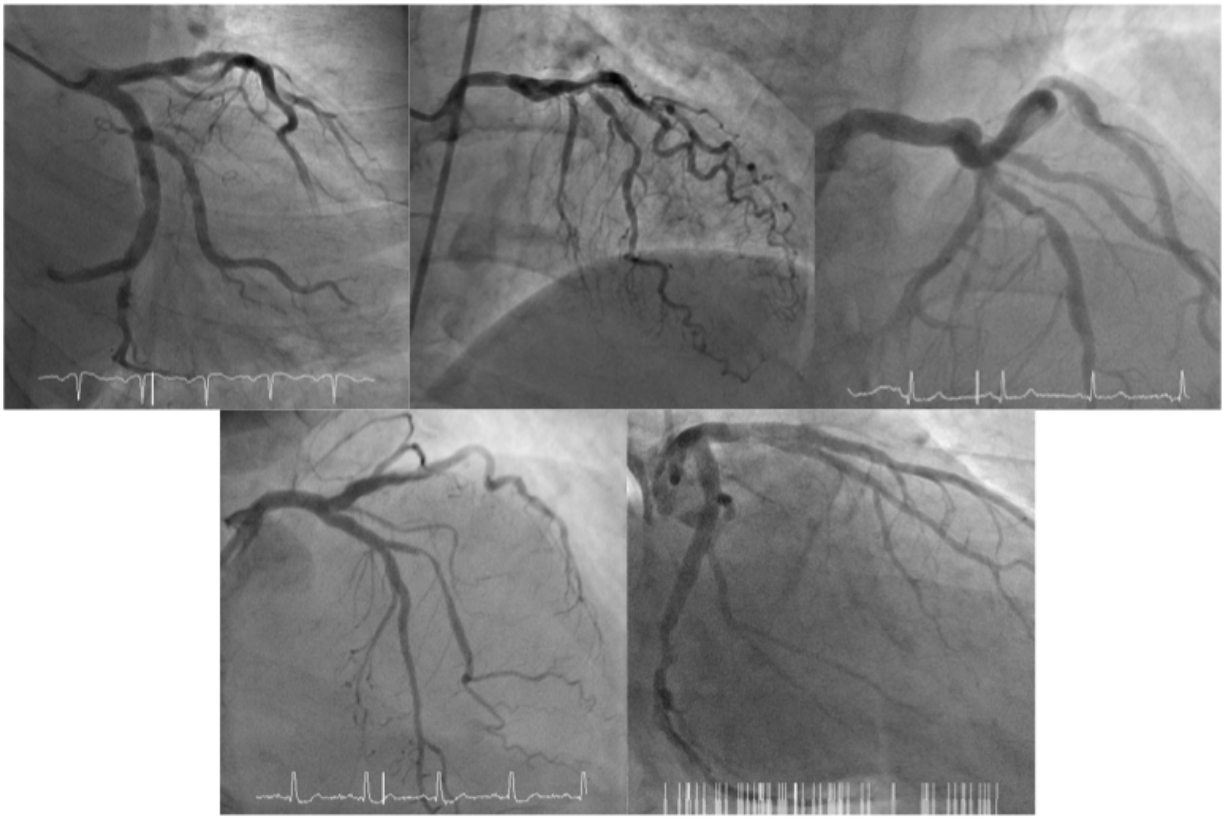

Figure 4

Relationship of treatment difference in Seattle Angina Questionnaire physical limitation score and pre-randomization FFR and iFR by randomization arm.

A: **B:**

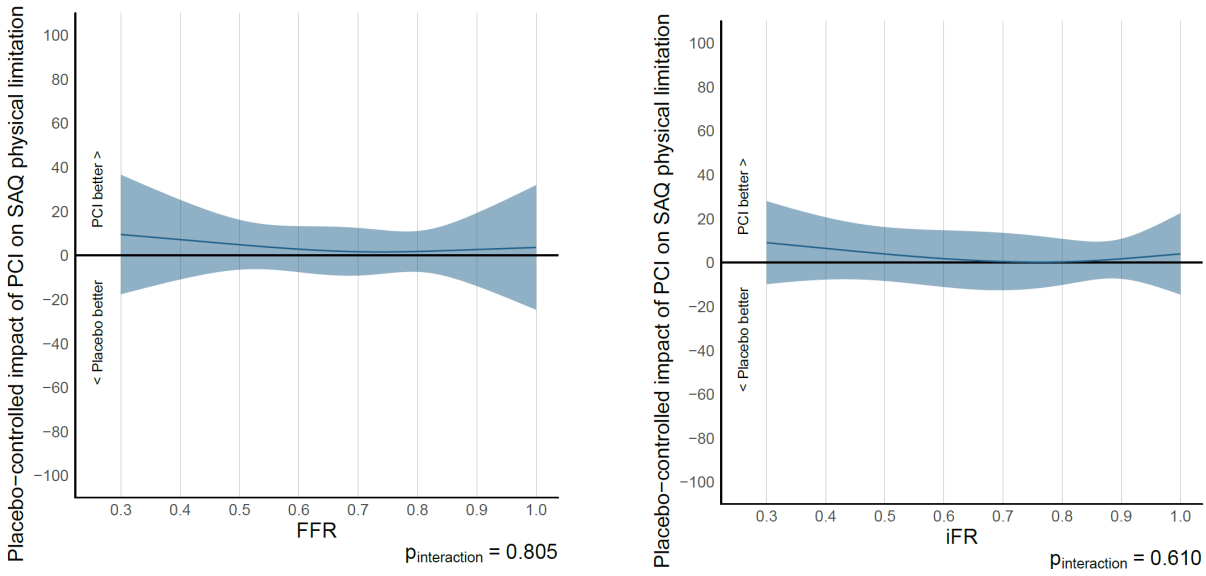

Figure 4.

A. Relationship of treatment difference in Seattle Angina Questionnaire physical limitation 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 physical limitation score and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

Figure 5

Relationship of treatment difference in Seattle Angina Questionnaire quality of life score and pre-randomization FFR and iFR by randomization arm.

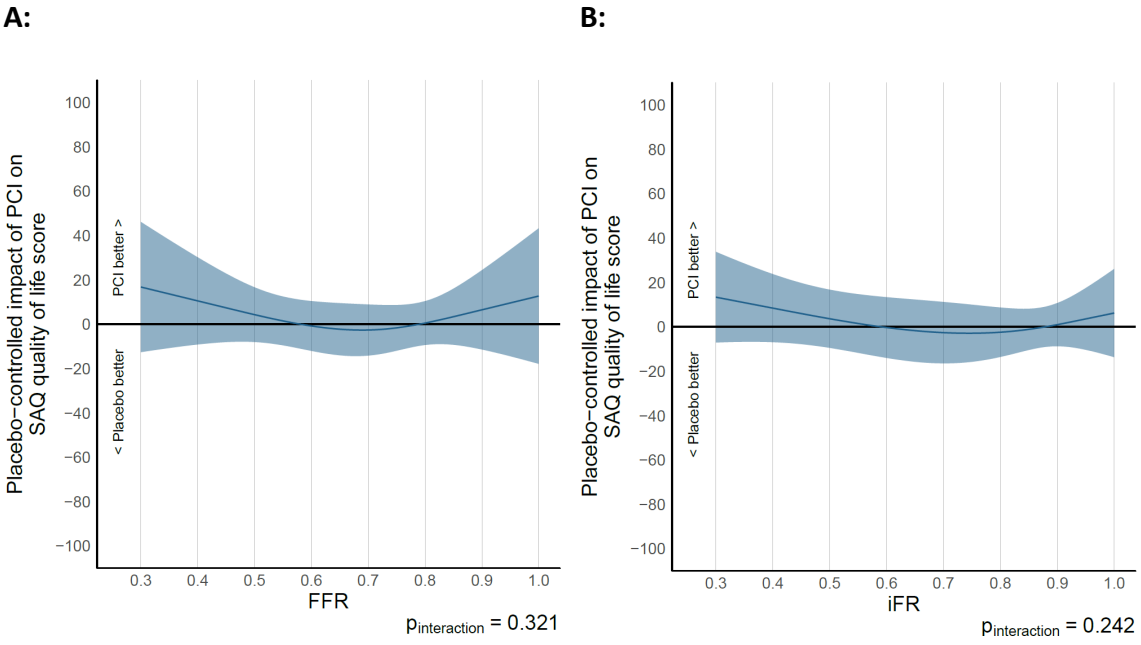

Figure 5.

A. Relationship of treatment difference in Seattle Angina Questionnaire quality of life 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 quality of life score and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

Figure 6

Relationship of treatment difference in EQ-5D-5L descriptive scale and pre-randomization FFR and iFR by randomization arm.

A: **B:**

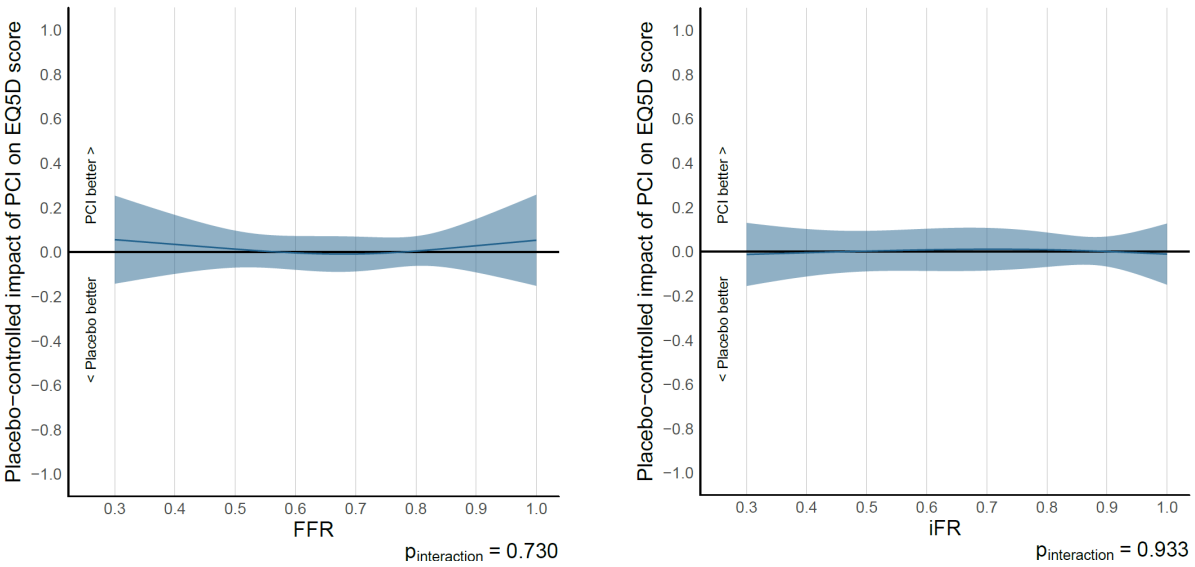

Figure 6.

A. Relationship of treatment difference in EQ-5D-5L descriptive scale and pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of treatment difference in EQ-5D-5L descriptive scale and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.

Figure 7

Relationship of treatment difference in EQ-5D-5L visual analogue score and pre-randomization FFR and iFR by randomization arm.

A: **B:**

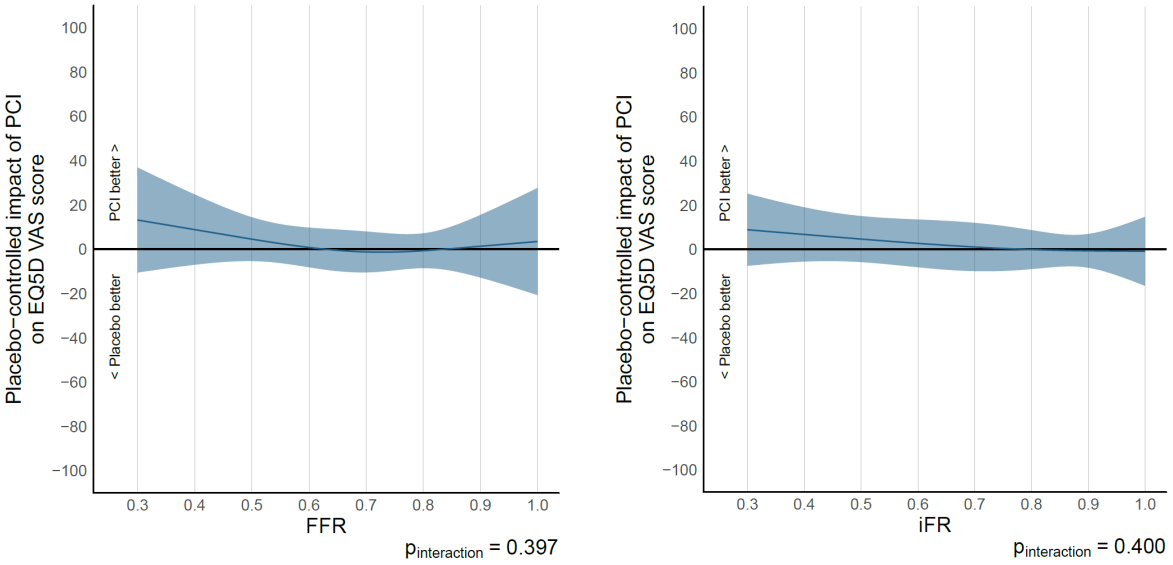

Figure 7.

A. Relationship of treatment difference in EQ-5D-5L visual analogue score and pre-randomization FFR by randomization arm. There is no discernible dependency on pre-randomization FFR.

B. Relationship of treatment difference in EQ-5D-5L visual analogue score and pre-randomization iFR by randomization arm. There is no discernible dependency on pre-randomization iFR.