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 (PInteraction=0.318) or iFR (PInteraction=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 (PInteraction<0.00001) and decreasing iFR (PInteraction<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 (PInteraction=0.849) or iFR (PInteraction=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 (PInteraction=0.693) nor iFR (PInteraction=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.

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. 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 presupposed primary end point of exercise time at 6 weeks, by prespecified statistical methods, did not meet the criteria for statistical significance (point estimate 16.6 s; 95% CI, −8.9 to 42.0).

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. 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; (3) quality of life using EuroQOL 5 (EQ-5D-5L) questionnaire; (4) cardiopulmonary exercise testing using the smoothed modified Bruce protocol 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 μg·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 if 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.

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 pre-specified 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
**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 194 (69.4%) had iFR ≤0.89, with mean 0.94 (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...
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
Pairied 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 (Pinteraction=0.318) or iFR (Pinteraction=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 (Pinteraction<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 (Pinteraction<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 (Pinteraction=0.848) or iFR (Pinteraction=0.783) and the effect of PCI on angina frequency score (Figure 3A and 3B).

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics at Enrollment</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society Angina class</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Angina duration, mo</td>
</tr>
<tr>
<td>Positive functional test</td>
</tr>
<tr>
<td>Exercise tolerance test</td>
</tr>
<tr>
<td>Nuclear medicine myocardial perfusion scan</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
</tr>
<tr>
<td>Magnetic resonance imaging perfusion</td>
</tr>
</tbody>
</table>

Values indicate n (%) or mean±SD.
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 (\( P_{\text{interaction}}=0.693 \); Figure 5A and \( P_{\text{interaction}}=0.761 \); 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 (\( P_{\text{interaction}}=0.805 \)) or iFR (\( P_{\text{interaction}}=0.610 \)) 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 (\( P_{\text{interaction}}=0.321 \)) or iFR (\( P_{\text{interaction}}=0.242 \)) and the ef-

### Table 2. Procedural Demographics

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Percutaneous Coronary Intervention (n=103)</th>
<th>Placebo (n=93)</th>
<th>Complete Group (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending</td>
<td>72 (69.9)</td>
<td>65 (70.0)</td>
<td>137 (69.9)</td>
</tr>
<tr>
<td>Ostial/proximal</td>
<td>46 (44.7)</td>
<td>30 (32.3)</td>
<td>76 (38.8)</td>
</tr>
<tr>
<td>Mid</td>
<td>33 (32.0)</td>
<td>38 (40.9)</td>
<td>71 (36.2)</td>
</tr>
<tr>
<td>Distal</td>
<td>4 (3.9)</td>
<td>8 (8.6)</td>
<td>12 (6.1)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>16 (15.5)</td>
<td>15 (16.1)</td>
<td>31 (15.8)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>9 (8.7)</td>
<td>9 (9.7)</td>
<td>18 (9.1)</td>
</tr>
<tr>
<td>First obtuse marginal</td>
<td>3 (2.9)</td>
<td>–</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>First diagonal</td>
<td>2 (1.9)</td>
<td>2 (2.2)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1 (1.0)</td>
<td>2 (2.1)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Serial lesions</td>
<td>17 (16.5)</td>
<td>12 (12.9)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>No. of patients with diameter stenosis ≥50% by quantitative coronary angiography</td>
<td>87 (84.4)</td>
<td>79 (85.0)</td>
<td>166 (84.7)</td>
</tr>
<tr>
<td>Diameter stenosis by quantitative coronary angiography</td>
<td>64.1±13.7</td>
<td>63.7±13.6</td>
<td>63.9±13.6</td>
</tr>
<tr>
<td>Area stenosis by quantitative coronary angiography</td>
<td>84.4±10.1</td>
<td>84.0±10.2</td>
<td>84.2±10.1</td>
</tr>
<tr>
<td>FFR Median (IQR)</td>
<td>0.69±0.16 (0.25)</td>
<td>0.69±0.16 (0.21)</td>
<td>0.69±0.16 (0.24)</td>
</tr>
<tr>
<td>iFR Median (IQR)</td>
<td>0.76±0.22 (0.24)</td>
<td>0.76±0.21 (0.21)</td>
<td>0.76±0.22 (0.22)</td>
</tr>
<tr>
<td>No. of patients with FFR ≤0.80</td>
<td>76 (73.8)</td>
<td>69 (75.8)</td>
<td>145 (74.7)</td>
</tr>
<tr>
<td>No. of patients with iFR ≤0.89</td>
<td>68 (66.0)</td>
<td>68 (73.1)</td>
<td>136 (69.4)</td>
</tr>
<tr>
<td>Stent length, mm Median (IQR)</td>
<td>28.4±14.8 (15)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stent diameter, mm Median (IQR)</td>
<td>3.07±0.46 (0.75)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FFR post-PCI (n=101) Median (IQR)</td>
<td>0.90±0.06 (0.06)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>iFR post-PCI (n=101) Median (IQR)</td>
<td>0.95±0.04 (0.05)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No. of patients with post-FFR&gt;0.80</td>
<td>95 (94.1) (n=101)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No. of patients with post-iFR&gt;0.89</td>
<td>98 (95.1) (n=103)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values indicate n (%) or mean±SD. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and IQR, interquartile range.
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 (\( P_{\text{interaction}} = 0.730 \)) or iFR (\( P_{\text{interaction}} = 0.933 \)) 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 (\( P_{\text{interaction}} = 0.397 \)) or iFR (\( P_{\text{interaction}} = 0.400 \)) 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
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 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. 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 ($P<0.01$), $\beta$-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 they had had PCI.

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

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**Figure 2. Relationship of treatment difference in stress echo score and prerandomization FFR and iFR by randomization arm.**

Left, Relationship of treatment difference in stress echo score and prerandomization FFR by randomization arm. At the right, with $\text{FFR} = 1.0$, the curve is $\approx 0$, 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 $P_{\text{interaction}} < 0.00001$. Right, Relationship of treatment difference in peak stress echo score and prerandomization iFR by randomization arm. At the right, with $\text{iFR} = 1.0$, the curve is $\approx 0$, 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 $P_{\text{interaction}} < 0.00001$. The stress echo score can be converted to classical Wall Motion Score Index as follows. Wall Motion Score Index $= 1 + (\text{stress echo score}) / 17$. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and PCI, percutaneous coronary intervention.
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 3.** Relationship of treatment difference in Seattle Angina Questionnaire angina frequency score and prerandomization FFR and iFR by randomization arm.

Left, 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. Right, 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.

**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.
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 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

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**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.

Left, 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. Right, 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.13 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

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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, Petroca, 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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