ORIGINAL ARTICLE

A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina

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ABSTRACT

BACKGROUND

Percutaneous coronary intervention (PCI) is frequently performed to reduce the symptoms of stable angina. Whether PCI relieves angina more than a placebo procedure in patients who are not receiving antianginal medication remains unknown.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of PCI in patients with stable angina. Patients stopped all antianginal medications and underwent a 2-week symptom assessment phase before randomization. Patients were then randomly assigned in a 1:1 ratio to undergo PCI or a placebo procedure and were followed for 12 weeks. The primary end point was the angina symptom score, which was calculated daily on the basis of the number of angina episodes that occurred on a given day, the number of antianginal medications prescribed on that day, and clinical events, including the occurrence of unblinding owing to unacceptable angina or acute coronary syndrome or death. Scores range from 0 to 79, with higher scores indicating worse health status with respect to angina.

RESULTS

A total of 301 patients underwent randomization: 151 to the PCI group and 150 to the placebo group. The mean (±SD) age was 64±9 years, and 79% were men. Ischemia was present in one cardiac territory in 242 patients (80%), in two territories in 52 patients (17%), and in three territories in 7 patients (2%). In the target vessels, the median fractional flow reserve was 0.63 (interquartile range, 0.49 to 0.75), and the median instantaneous wave-free ratio was 0.78 (interquartile range, 0.55 to 0.87). At the 12-week follow-up, the mean angina symptom score was 2.9 in the PCI group and 5.6 in the placebo group (odds ratio, 2.21; 95% confidence interval, 1.41 to 3.47; P<0.001). One patient in the placebo group had unacceptable angina leading to unblinding. Acute coronary syndromes occurred in 4 patients in the PCI group and in 6 patients in the placebo group.

CONCLUSIONS

Among patients with stable angina who were receiving little or no antianginal medication and had objective evidence of ischemia, PCI resulted in a lower angina symptom score than a placebo procedure, indicating a better health status with respect to angina. (Funded by the National Institute for Health and Care Research Imperial Biomedical Research Centre and others; ORBITA-2 ClinicalTrials.gov number, NCT03742050.)

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*A complete list of the ORBITA-2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Relief from angina is the primary reason that patients with stable coronary artery disease undergo percutaneous coronary intervention (PCI).[1-3] The evidence that PCI reduces angina comes from unblinded clinical trials[1,4-6] in which the overall effect of PCI on symptoms is the result of a physical component as well as a placebo effect.[7] The size of the physical component, calculated by subtracting the placebo effect, is essential knowledge in clinical decision making, especially for procedures with nonnegligible risks and costs.[8]

The results of ORBITA (Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina), a placebo-controlled trial of PCI in which the use of guideline-directed antianginal medications was mandated, showed no significant effect of PCI on treadmill exercise time.[9] However, it is possible that the absence of a difference between PCI and placebo was attributable to the high number of background antianginal medications. Intensive antianginal medical therapy can be difficult to achieve in clinical practice, in part owing to side effects and nonadherence to the prescribed treatment, and there are instances in which patients may prefer PCI over increased medical therapy. The ORBITA-2 trial was designed to evaluate the effect of PCI as compared with a placebo procedure in patients with stable angina who are not receiving background antianginal medication.

Methods

Trial Design and Oversight

The ORBITA-2 trial was an investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial that was conducted at 14 sites in the United Kingdom (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol has been published previously[10] and is available at NEJM.org. The trial was approved by the London Central Research Ethics Committee. All the patients provided written informed consent. A steering committee and an independent data and safety monitoring board oversaw the conduct of the trial; a list of members is provided in the Supplementary Appendix. The first and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Neither the sponsor nor the funders had any role in the design of the trial; in the collection, analysis, or interpretation of the data; or in the preparation of the manuscript.

Patients

Patients were eligible for participation if they were considered to be clinically suitable for PCI by the referring heart team, had angina or symptoms equivalent to those with angina, had anatomical evidence of at least one severe coronary stenosis that was identified on invasive diagnostic coronary angiography or coronary computed tomographic angiography, and had evidence of ischemia on the basis of noninvasive imaging or invasive coronary physiological tests. Additional details regarding these criteria are provided in the Supplementary Appendix.

Trial Procedures and Randomization

At enrollment, patients ceased treatment with antianginal medications. Antihypertensive medications with antianginal properties were replaced with alternative agents that had no antianginal effects. Medications with antianginal properties that patients were receiving for other clinical indications, such as heart failure or heart-rate control for atrial fibrillation, were continued and were incorporated in the statistical analysis. Medications including dual antiplatelet agents and high-intensity statins were prescribed for risk reduction.

The patients were instructed to use a dedicated smartphone application to report the presence or absence of angina and the number of angina episodes on a daily basis. The design, features, and validation of the smartphone application have been described previously[11,12]; Figure S1 shows screenshots from the application. The patients completed the Seattle Angina Questionnaire (SAQ) and the EuroQol Group 5-Dimensions 5-Level questionnaire (EQ-5D-5L). The Canadian Cardiovascular Society (CCS) class was assessed. A treadmill exercise test was performed with the use of the modified Bruce protocol; dobutamine stress echocardiography was also performed. The patients then entered a 2-week prerandomization symptom assessment phase during which they reported the number of episodes of angina each day with the use of the smartphone application. During this phase, patients had 24-hour access to trial personnel, and treatment with antianginal medications was initiated according

to a prespecified treatment protocol in response to angina that had resulted in patient-triggered contact. Patients were eligible to proceed to randomization if they reported at least one episode of angina during the symptom assessment phase. Asymptomatic patients were withdrawn from further participation in the trial.

Patients then underwent coronary angiography while wearing over-the-ear headphones with music playing for auditory isolation throughout the procedure. Prerandomization invasive physiological assessments were performed in each vessel with a stenosis of at least 50% of the vessel diameter on the basis of visual estimation. Operators used the invasive physiological assessments to identify the target vessels. Patients who had evidence of ischemia in at least one cardiac territory were eligible to undergo randomization. Patients who did not meet this criterion were withdrawn from the trial.

Eligible patients received incremental doses of intravenous benzodiazepines and opiates to achieve a deep level of conscious sedation until they were unresponsive to verbal and tactile stimuli. Patients were then randomly assigned in a 1:1 ratio to undergo PCI or a placebo procedure by means of computer-generated randomization with a block size between 8 and 16 and with no stratification.

INTERVENTIONS AND BLINDING

For the PCI group, angiographic and physiological complete revascularization of the target vessels was mandated, and intravascular imaging was encouraged. In patients with multivessel coronary artery disease, all the vessels were treated during the index procedure. The patients in the placebo group remained sedated, without any further intervention, for at least 15 minutes after randomization.

There was no transfer of information regarding the trial-group assignments to the recovery-room staff. All subsequent medical caregivers were also unaware of the trial-group assignments. The operator and research staff who had been present during the randomization procedure had no further patient contact. Each patient and the recovery team underwent a test of blinding before the patient was discharged; details of the blinding framework have been reported previously (Table S2),[13] and information regarding the testing of its efficacy in this trial are provided in the Supplementary Appendix. All the patients were discharged with standardized discharge documentation and a prescription for dual antiplatelet medication on the day of randomization unless otherwise clinically indicated.

FOLLOW-UP

On the day of randomization, any antianginal medications that had been initiated during the prerandomization phase were stopped. Patients entered a 12-week blinded follow-up phase during which they continued daily symptom reporting with the use of the smartphone application. During this phase, initiation of antianginal medication and any subsequent dose increases of the medication were triggered by patient contact and were managed by trial personnel, who were unaware of the trial-group assignments, with the use of a treatment protocol that was identical to that used during the prerandomization phase.

At the end of the blinded follow-up phase, patients returned to complete the symptom and quality-of-life questionnaires, have an assessment of CCS class, and undergo a treadmill exercise test and dobutamine stress echocardiography. After these assessments were completed, the patients and research and medical teams were informed of the trial-group assignments. This marked the end of the trial. Patients returned to usual clinical care. Any subsequent actions that were taken or decisions that were made did not contribute to the trial end points.

END POINTS

The primary end point was the angina symptom score, an ordinal clinical outcome scale of health status associated with angina. The score was calculated on the basis of the number of angina episodes that a patient reported on a given day and the number of units of antianginal medication that were prescribed for a patient on that day (Tables S3 and S4). A higher number of episodes of angina and more antianginal medication use led to a higher score. A patient who had no episodes of angina and received no antianginal medications on a given day had a score of zero. This ordinal scale also incorporated the occurrence of unblinding owing to unacceptable angina requiring coronary angiography, the occurrence of acute coronary syndrome (defined as unstable angina or myocardial infarction meeting the Fourth Universal Definition of Myocar-

dial Infarction), and death (which would result in the maximum score of 79).[10]

Secondary end points were frequency of angina as reported by the patient (with the use of the smartphone application); initiation and any subsequent dose increase of antianginal medications; treadmill exercise time; physician-assessed severity of angina (according to the CCS class, which ranges from 0 to IV, with class 0 indicating no angina and class IV indicating angina at rest); frequency of angina, physical limitation, angina stability, and freedom from angina (all of which were assessed with the use of the SAQ); quality of life (assessed with the SAQ and the EQ-5D-5L); and stress echocardiography score (higher scores indicate a greater degree of ischemia).[14]

STATISTICAL ANALYSIS

The sample size was determined on the basis of an assumed standard deviation of 6 angina symptom score units; we estimated that a sample of 284 patients would provide the trial with 80% power to detect a difference of 2 angina symptom score units between the PCI and placebo groups, using a Student's t-test with an alpha level of 0.05. On the basis of previous experience, the enrollment of 396 patients was planned in order to achieve a trial population of 284 patients. The trial protocol specified that an analysis of covariance of the ordinal angina symptom score would be performed for the primary analysis. The statistical working group prepared a statistical analysis plan (available with the protocol) 2.2 years before the database lock. This analytical plan specified a Bayesian framework with a longitudinal analysis of the primary end point. However, the *Journal* required that we use a frequentist analysis of covariance to analyze the end points, as originally specified in the protocol. The statistical methods and results of the Bayesian analysis are provided in the Supplementary Appendix. All analyses were performed on an intention-to-treat basis.

For the primary end point, if daily symptom data were not available, the last entered value was used as the final follow-up value unless unblinding had occurred owing to unacceptable angina or unless acute coronary syndrome or death had occurred. During the coronavirus disease 2019 pandemic, hospital research visits for treadmill exercise tests and stress echocardiography were suspended while national restrictions were in place. This did not affect the primary end point, CCS class, or questionnaire-based end points. A complete case analysis is presented for the secondary end points. In a sensitivity analysis of the treadmill exercise time and stress echocardiography score end points, multiple imputation was used to account for missing data.

The primary end point was analyzed by means of an ordinal analysis of covariance, which uses a cumulative probability model (also referred to as a cumulative link model) that does not impose distributional assumptions on the outcome.[15] Individual components of the primary end point and the ordinal secondary end point, CCS class, were analyzed with the use of the same ordinal analysis-of-covariance technique. For the analysis of freedom from angina, a logistic-regression model was used. For the other secondary end points, an ordinary least-squares model was used. Restricted cubic splines were used to allow for nonlinear effects.

There were no prespecified plans to adjust for multiplicity. Therefore, the results are reported as point estimates and 95% confidence intervals, and the widths of the confidence intervals should not be used in place of a hypothesis test. The blinding index (reported on a scale from −1 to 1, with values between −0.2 and 0.2 indicating successful blinding) for the patients and staff at baseline and follow-up was calculated with the use of published methods described by Bang et al.[16] All the analyses were performed with the use of R software, version 4.3.0;[17] the rms package[18] was used for the frequentist analysis, the rmsb package[19] for Bayesian modeling, and the BI package[20] for the blinding index.

RESULTS

PATIENTS

Between November 12, 2018, and June 17, 2023, a total of 923 patients were assessed for eligibility. Of these patients, 439 were enrolled in the prerandomization symptom assessment phase, and 301 were subsequently randomly assigned to PCI (151 patients) or placebo (150 patients) (Fig. S2). The demographic and clinical characteristics of the 301 patients are presented in Table 1. The mean age of the patients was 64±9 years, and 79% were men. The trial population was representative of patients with stable coronary artery

disease in the United Kingdom (Table S5). At enrollment, 290 patients (96%) had angina of CCS severity class II or III. The results of cardiovascular risk factor assessment are provided in Table S6. The median number of antianginal agents that were prescribed for the patients at the time of enrollment (and before protocol-mandated cessation of these agents) was 1, which was equivalent to a median of 2 standardized antianginal units.

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	PCI (N=151)	Placebo (N=150)	Overall (N=301)
Age — yr	65±9	64±9	64±9
Male sex — no. (%)	120 (79)	118 (79)	238 (79)
Hypertension — no. (%)	97 (64)	92 (61)	189 (63)
Diabetes — no. (%)			
Non–insulin-dependent	40 (26)	24 (16)	64 (21)
Insulin-dependent	9 (6)	11 (7)	20 (7)
Hyperlipidemia — no. (%)	113 (75)	104 (69)	217 (72)
Smoking status — no. (%)			
Never smoked	65 (43)	50 (33)	115 (38)
Previous smoker	67 (44)	84 (56)	151 (50)
Current smoker	19 (13)	16 (11)	35 (12)
Left ventricular systolic function — no. (%)†			
Normal	144 (95)	146 (97)	290 (96)
Mild impairment	6 (4)	3 (2)	9 (3)
Moderate impairment	1 (1)	1 (1)	2 (1)
CCS class — no. (%)‡			
I	10 (7)	1 (1)	11 (4)
II	87 (58)	87 (58)	174 (58)
III	54 (36)	62 (41)	116 (39)
Median time since diagnosis of angina (IQR) — mo	8 (4–14)	8 (5–14)	8 (5–14)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. PCI denotes percutaneous coronary intervention, and IQR interquartile range.
† Normal was defined as 55% or higher, mild impairment as 45 to 54%, and moderate impairment as 35 to 44%.
‡ The Canadian Cardiovascular Society (CCS) angina severity class ranges from 0 to IV, with class 0 indicating no angina and class IV indicating angina at rest.

PROCEDURAL CHARACTERISTICS

Procedural characteristics are shown in Table 2. Radial-artery access was used in 288 patients (96%). Invasive physiological assessment was performed in a median of 1 vessel per patient. Cardiac territories with ischemia were identified with the use of prerandomization invasive physiological assessment and preenrollment noninvasive functional testing; 242 patients (80%) had ischemia in one territory, 52 (17%) in two territories, and 7 (2%) in three territories.

Images of the qualifying coronary lesions from the 301 patients who underwent randomization are provided in Figure S3. As assessed by quantitative coronary angiography, the mean (±SD) percent diameter stenosis was 61±18%. Fractional flow reserve was performed in 349 of 383 target vessels (91%) and instantaneous wave-free ratio in 352 of 383 target vessels (92%). In the target vessels, the median fractional flow reserve was 0.63 (interquartile range, 0.49 to 0.75), and the median instantaneous wave-free ratio was 0.78 (interquartile range, 0.55 to 0.87). Complete revascularization was achieved in all but 2 patients. In both patients, pressure-wire pullback analysis and intravascular imaging showed diffuse disease, which was managed conservatively. Results of the coronary physiological assessment that was performed after PCI are provided in Table S7.

PRIMARY END POINT

Data were available for 99.7% of the 22,823 patient-days in the trial. Two patients in the placebo group had missing data; for these patients, the last angina symptom score was carried forward in the analysis of the primary end point. At the 12-week follow-up, the mean angina symptom score was 2.9 in the PCI group and 5.6 in the placebo group (odds ratio, 2.21; 95% confidence interval [CI], 1.41 to 3.47; P<0.001) (Table 3 and Fig. 1A). The mean daily angina frequency was 0.3 episodes in the PCI group and 0.7 in the placebo group (odds ratio, 3.44; 95% CI, 2.00 to 5.91) (Table 3 and Fig. 1B). The mean daily use of antianginal medication was 0.2 and 0.3 units in the PCI and placebo groups, respectively (odds ratio, 1.21; 95% CI, 0.70 to 2.10) (Table 3 and Fig. 1C). The Bayesian longitudinal analysis of the primary end point is provided in Table S8 and Figures S4 through S18. The results of a sensitivity analysis in which priors on the effect of PCI as compared with placebo were used is provided in Table S9, and a summary of antianginal medication use is shown in Table S10.

Table 2. Procedural Characteristics.

Characteristic	PCI (N=151)	Placebo (N=150)	Overall (N=301)
No. of vessels with disease — no. (%)*			
1 vessel	122 (81)	120 (80)	242 (80)
2 vessels	25 (17)	27 (18)	52 (17)
3 vessels	4 (3)	3 (2)	7 (2)
Vessels leading to patient randomization†			
No. of vessels	193	190	383
Left anterior descending coronary artery — no. (%)	108 (56)	103 (54)	211 (55)
Circumflex coronary artery — no. (%)	16 (8)	17 (9)	33 (9)
Right coronary artery — no. (%)	42 (22)	43 (23)	85 (22)
Branch vessels — no. (%)	27 (14)	27 (14)	54 (14)
Serial stenoses — no. (%)	29 (19)	20 (13)	49 (16)
Percent diameter stenosis‡			
Mean	61±18	62±17	61±18
Median (IQR)	60 (48–74)	63 (50–74)	61 (49–74)
Area of stenosis‡			
Percentage	80±15	82±15	81±15
Median (IQR) — %	83 (73–92)	85 (75–93)	84 (74–92)
Fractional flow reserve			
Mean	0.60±0.16	0.62±0.16	0.61±0.16
Median (IQR)	0.61 (0.47–0.74)	0.65 (0.51–0.75)	0.63 (0.49–0.75)
No. of vessels assessed — no./total no. of target vessels	178/193	171/190	349/383
Instantaneous free-wave ratio§			
Mean	0.68±0.22	0.71±0.23	0.70±0.22
Median (IQR)	0.76 (0.50–0.86)	0.81 (0.58–0.89)	0.78 (0.55–0.87)
No. of vessels assessed — no./total no. of target vessels	178/193	174/190	352/383
Interventions			
Median no. of stents implanted (IQR)	2 (1–2)	—	—
Median total length of stent implanted (IQR) — mm	42 (23–64)	—	—
Median diameter of stent implanted (IQR) — mm	3.0 (2.5–3.5)	—	—
No. of stents in which postdilation was performed — no./total no. (%)	242/284 (85)	—	—
Intravascular imaging performed — no. (%)	104 (69)	—	—
Type of drug-eluting stent¶			
Everolimus-eluting — no. (%)	171 (60)	—	—
Zotarolimus-eluting — no. (%)	83 (29)	—	—
Other drug-eluting stent — no. (%)	29 (10)	—	—

* The number of vessels with disease was defined on the basis of evidence of ischemia from noninvasive imaging and invasive physiological assessment.
† This variable refers to the anatomical description of vessels with evidence of ischemia from noninvasive or invasive assessment.
‡ The measurements of stenosis were obtained on quantitative coronary angiography.
§ In cases in which instantaneous free-wave ratio was not available, an alternative nonhyperemic pressure ratio was used.
¶ The total number of drug-eluting stents was 283.

SECONDARY END POINTS

The treadmill exercise time and the physician-assessed CCS class in the two trial groups are shown in Figures 2A and 2B, respectively, and in Table 3. Table 3 also shows the scores for the frequency of angina, physical limitation, angina stability, quality of life, and freedom from angina, which were assessed with the use of the SAQ; quality of life, as assessed with the EQ-5D-5L descriptive system and visual analogue scale; and the stress echocardiography score. A sensitivity analysis of the treadmill exercise time and stress echocardiography score end points with multiple imputation for missing data is provided in Table S11. The Bayesian analyses of the secondary end points are provided in Table S8 and Figures S19 through S45.

SERIOUS ADVERSE EVENTS

Unblinding owing to unacceptable angina occurred in no patients in the PCI group and in 1 patient in the placebo group. Acute coronary syndromes occurred in 4 patients in the PCI group and in 6 patients in the placebo group. There were no deaths. Periprocedural myocardial infarction (type 4a) occurred in 4 patients in the PCI group and in no patients in the placebo group. Spontaneous myocardial infarction (type 1) occurred in no patients in the PCI group and in 6 patients in the placebo group. In the placebo group, there were two major periprocedural bleeding events and two spontaneous bleeding events in 4 patients who were receiving dual antiplatelet therapy. Stroke occurred in 2 patients in the PCI group and in no patients in the placebo group. Pressure-wire complications occurred in 1 patient in the PCI group and in 2 patients in the placebo group. All serious adverse events that occurred are listed in Tables S12 and S13. Cases in which patients did not undergo the procedure to which they were randomly assigned are listed in Table S14.

BLINDING INDEX

The principal assessment of blinding was performed after the patients had undergone PCI or the placebo procedure but before they were discharged. The blinding index for patients was 0.01 (95% CI, −0.05 to 0.06) in the PCI group and −0.09 (95% CI, −0.15 to −0.03) in the placebo group, results that indicated that the blinding strategy had been effective. The blinding index for staff was 0.01 (95% CI, −0.01 to 0.04) for the PCI group and 0 (95% CI, −0.03 to 0.03) for the placebo group, which also indicated an effective blinding strategy. At the end of the 12-week follow-up phase, the reassessment values for patients were 0.19 (95% CI, 0.05 to 0.34) in the PCI group and 0.24 (95% CI, 0.09 to 0.38) in the placebo group. For the staff, the values were 0.01 (95% CI, −0.01 to 0.02) for the PCI group and 0 (95% CI, −0.02 to 0.02) for the placebo group.

DISCUSSION

In this placebo-controlled trial involving patients with stable angina who were receiving little or no antianginal medication and who had coronary-artery stenoses that were causing ischemia, PCI resulted in a lower angina symptom score than the placebo procedure, indicating a better health status with respect to angina. The lower angina symptom score appeared to result from a lower daily number of angina episodes. Assignment to the PCI group was associated with an odds of becoming free from angina that was three times as high as the equivalent odds associated with assignment to the placebo group at the 12-week follow-up. The angina relief after PCI was observed immediately and persisted throughout the blinded follow-up phase.

The results of ORBITA-2 differed from those of ORBITA because the trials were designed to answer different questions. In ORBITA, patients adhered to guideline-directed treatment with antianginal medications, and PCI was used as add-on therapy.[21,22] The small effect size of PCI on treadmill exercise time in ORBITA was surprising in the context of the larger effects that were seen in clinical practice and in previous clinical trials. One plausible explanation is that the previous experience was unblinded and was therefore augmented by the placebo effect. Although guidelines recommend the use of escalating antianginal medications for recurrent symptoms, approximately half of patients undergoing elective cardiac catheterization are receiving only one antianginal medication or no such medication.[23] Achieving the high levels of antianginal medications that were used in ORBITA is challenging.[24] In fact, the patients in ORBITA-2 had been referred for PCI while they were taking a median of only one full-dose antianginal medication. Anal-

Table 3. Primary and Secondary End Points.*

End Point	PCI (N=151)		Placebo (N=150)		Odds Ratio or Difference (95% CI)†
	value	*no. of patients with data*	*value*	*no. of patients with data*	
Primary end point: angina symptom score — mean score‡	2.9	151	5.6	150	2.21 (1.41 to 3.47)§
Mean daily angina episodes — no.	0.3	151	0.7	150	3.44 (2.00 to 5.91)
Mean daily antianginal medication use — units¶	0.2	151	0.3	150	1.21 (0.70 to 2.10)
Secondary end points					
Mean treadmill exercise time — sec	700.9	123	641.4	112	59.5 (16.0 to 103.0)
CCS class — mean	0.9	147	1.7	146	3.76 (2.43 to 5.82)
End points assessed with the use of the SAQ‖					
Frequency of angina	80.6	146	66.2	145	14.4 (9.5 to 19.4)
Physical limitation	82.7	139	73.9	144	8.8 (4.7 to 12.9)
Angina stability	61.8	145	55.3	145	6.5 (0.5 to 12.5)
Quality of life	62.8	145	51.6	145	11.2 (6.2 to 16.1)
Freedom from angina	40	146	15	145	3.69 (2.10 to 6.46)
EQ-5D-5L descriptive system — mean score**	0.82	145	0.73	144	0.09 (0.05 to 0.13)
EQ-VAS — mean score**	73.1	146	66.9	143	6.2 (2.4 to 10.0)
Stress echocardiography score — mean score††	0.79	119	1.95	111	–1.17 (–1.56 to –0.78)

* For all the end points, the mean follow-up values were predicted from their respective models for a typical patient. A typical patient was considered to be the mean patient at the prerandomization time point for treadmill exercise time and stress echocardiography score and the median patient for all other end points. A complete case analysis was performed in all the patients for whom complete data were available for the secondary end points.

† Odds ratios are shown for the primary end point, CCS class, and freedom from angina; differences are shown for all other end points. The widths of the confidence intervals have not been adjusted for multiplicity; therefore, they should not be used to make definitive conclusions regarding the effects of PCI.

‡ The range of possible scores is 0 to 79, with lower scores indicating a better health status with respect to angina.

§ P<0.001.

¶ Daily antianginal medication use refers to the mean standardized units of antianginal medications that were taken by patients on each day of follow-up.

‖ All end points assessed with the use of the Seattle Angina Questionnaire (SAQ) are reported as mean scores, with the exception of freedom from angina, which is reported as the percentage of patients. SAQ scores range from 0 to 100, with higher scores indicating better health status. Freedom from angina is defined as an SAQ angina frequency score of 100.

** The EuroQol Group 5-Dimensions 5-Level questionnaire (EQ-5D-5L) includes both the descriptive system, which assesses five dimensions of quality of life (range, 0 to 1, with higher scores indicating better quality of life), and the visual analogue scale (EQ-VAS) component of overall health perception (range, 0 to 100, with higher scores indicating better health status).

†† The derivation of the stress echocardiography score has been previously published.[14] Higher scores indicate a greater degree of ischemia.

ogous to renal denervation trials,[25,26] measurement of the efficacy of PCI in patients with angina in a setting that is controlled for both placebo and the attenuating effect of background antianginal medication required a trial with the design of ORBITA-2.

ORBITA-2 introduced a new end point, informed by patient and public engagement and

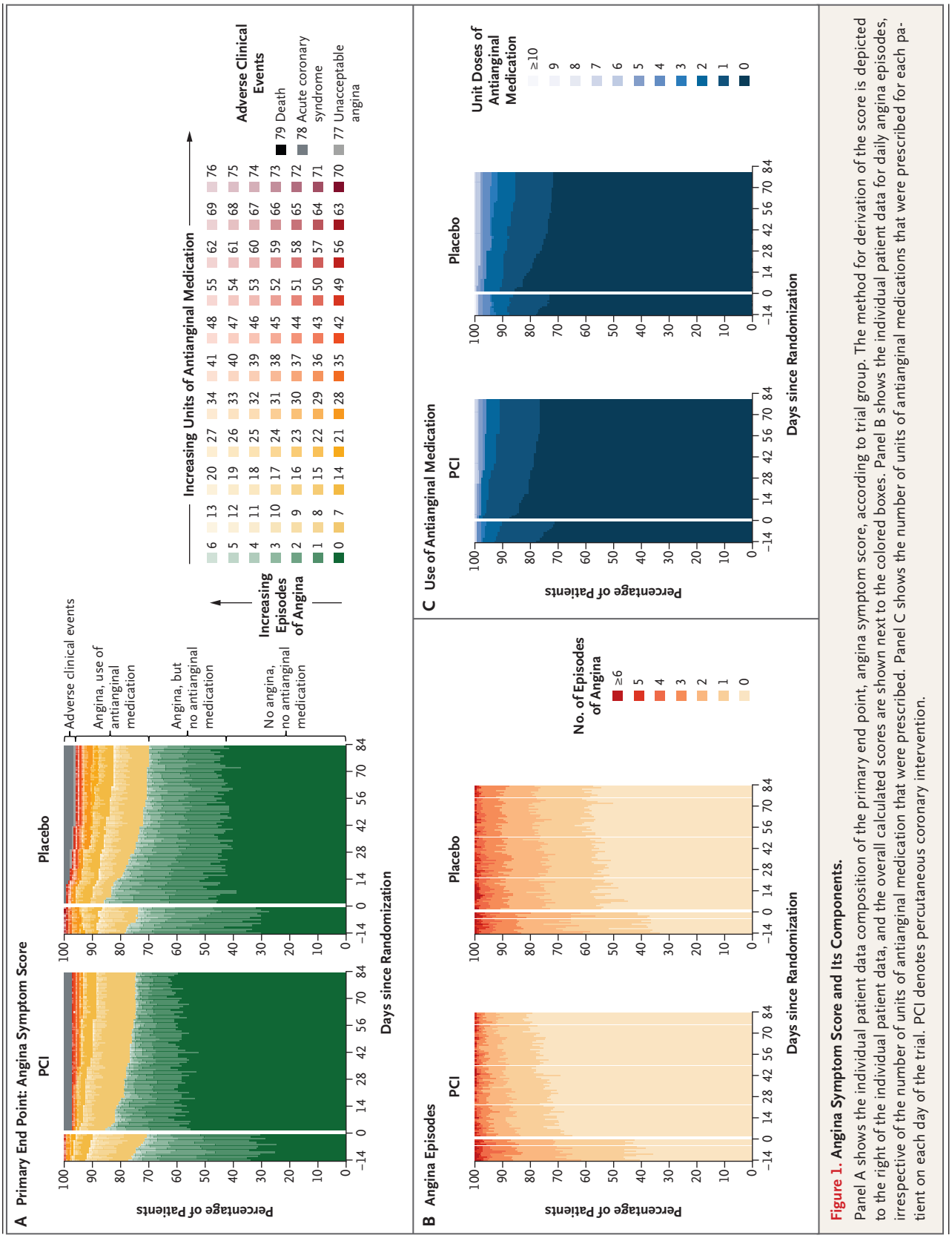

Figure 1. Angina Symptom Score and Its Components.

Panel A shows the individual patient data composition of the primary end point, angina symptom score, according to trial group. The method for derivation of the score is depicted to the right of the individual patient data, and the overall calculated scores are shown next to the colored boxes. Panel B shows the individual patient data for daily angina episodes, irrespective of the number of units of antianginal medication that were prescribed. Panel C shows the number of units of antianginal medications that were prescribed for each patient on each day of the trial. PCI denotes percutaneous coronary intervention.

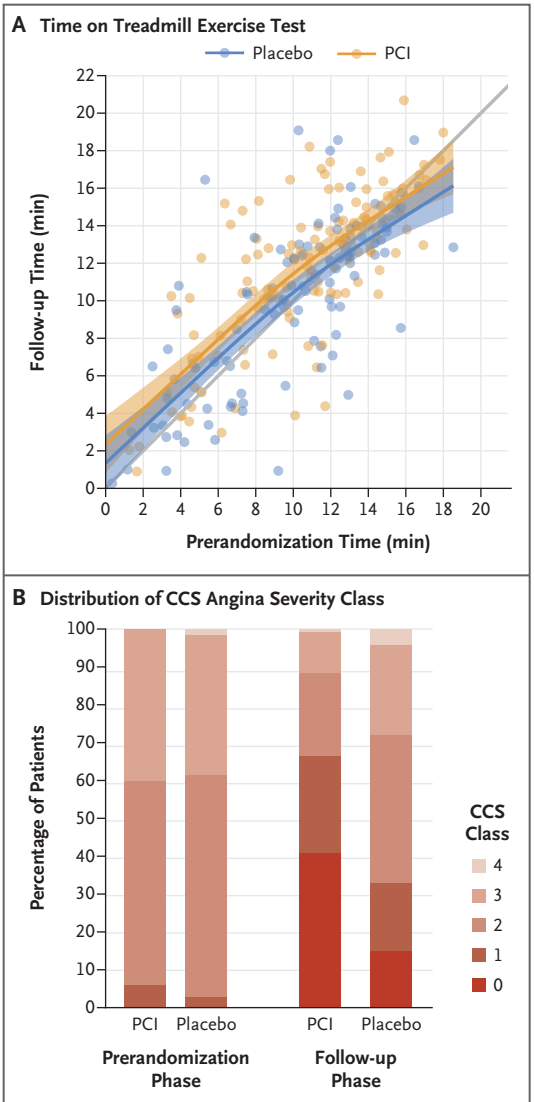

Figure 2. Secondary End Points.

Panel A shows the treadmill exercise time at the 12-week follow-up according to the prerandomization exercise time. The shaded areas indicate 95% confidence intervals. Panel B shows the distribution of the physician-assessed Canadian Cardiovascular Society (CCS) angina severity class during the prerandomization and follow-up phases. The CCS class ranges from 0 to IV, with class 0 indicating no angina and class IV indicating angina at rest. The widths of the confidence intervals have not been adjusted for multiplicity; therefore, they should not be used to make definitive conclusions regarding the effects of PCI.

involvement, that was centered on contemporaneous documentation of daily angina on a smartphone application. This approach has several advantages: high temporal fidelity of data, minimization of recall bias, and maximization of data completeness. This tool is being used in several clinical trials (ClinicalTrials.gov numbers, NCT05459051, NCT04280575, and NCT04892537). The ordinal angina symptom score expanded on these daily symptom data by incorporating daily antianginal medication use and relevant clinical events.

ORBITA provided evidence of the ethical basis, feasibility, and necessity of placebo-controlled trials for evaluating PCI.[8,13,27] ORBITA-2 built on this approach by illustrating the ethical basis, feasibility, and necessity of testing a coronary interventional procedure without the use of background therapy that may attenuate its effect. Only by not mandating guideline-directed antianginal medication as a precondition for PCI[28] could the unattenuated efficacy of PCI on angina be tested. Together, the two trials indicate that the recommendation to restrict PCI to patients with inadequate response to antianginal medications may be inadvertently selecting the cohort with the least to gain.

However, despite decades of technical advances in PCI, including the introduction of stents, the effect of PCI on treadmill exercise time in the blinded ORBITA-2 trial was still 37 seconds less than the 96-second effect attributed to balloon angioplasty in the unblinded Angioplasty Compared to Medicine (ACME) trial that was conducted three decades ago.[4] The effect of PCI as monotherapy was a 59.5-second difference in the treadmill exercise time as compared with placebo, which was similar to the 48 to 55 seconds achieved with a full-dose single antianginal medication.[29,30]

With the use of background antianginal medications and PCI, 61% of the patients in ORBITA had residual symptoms. In ORBITA-2, with PCI and the use of antianginal medications only if necessary, 59% of the patients still had residual symptoms. In both trials, the PCI group had near-normalization of ischemia, as detected by stress echocardiography. These trials did not ascertain the cause of the residual symptoms. Perhaps for angina relief, the first therapy administered — either antianginal medication or an antianginal procedure, such as PCI — has the greatest chance of efficacy.

Our trial had limitations. First, the duration of the follow-up phase was only 12 weeks. However, the daily data showed that the effect of PCI

was immediate and sustained. Second, the trial required the stopping of antianginal medications, which was against guideline recommendations. However, the use of this design allowed PCI to be tested as antianginal monotherapy. Third, the withdrawal of antianginal medication may have led to unmeasured behavioral changes. Fourth, the use of nitroglycerin spray was recorded as part of the SAQ but was not included in the calculation of the angina symptom score. Fifth, although patients with single-vessel and multivessel disease were enrolled, 80% of the patients had ischemia in a single territory, similar to what has been observed among patients in routine clinical practice, when ischemia was tested systematically.[31] Finally, the smartphone application was available in English only; translation was provided as necessary.

In this trial, among patients with stable angina who were receiving little or no antianginal medication and who had objective evidence of ischemia, PCI resulted in a lower angina symptom score than a placebo procedure, indicating a better health status with respect to angina.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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