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Symptoms as a Predictor of the Placebo-Controlled Efficacy of PCI in Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND Placebo-controlled evidence from ORBITA-2 (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina-2) found that percutaneous coronary intervention (PCI) in stable coronary artery disease with little or no antianginal medication relieved angina, but residual symptoms persisted in many patients. The reason for this was unclear.

OBJECTIVES This ORBITA-2 secondary analysis investigates the relationship between presenting symptoms and disease severity (anatomic, noninvasive, and invasive ischemia) and the ability of symptoms to predict the placebo-controlled efficacy of PCI.

METHODS Prerandomization symptom severity and nature were assessed using the ORBITA smartphone application and symptom and quality of life questionnaires including the World Health Organization Rose angina questionnaire (Rose). Disease severity was assessed using quantitative coronary angiography, stress echocardiography, fractional flow reserve, and instantaneous wave-free ratio. Bayesian ordinal regression was used.

RESULTS At prerandomization, the median number of daily angina episodes was 0.8 (Q1-Q3: 0.4-1.6), 64% had Rose angina, quantitative coronary angiography diameter stenosis was 61% (Q1-Q3: 49%-74%), stress echocardiography score was 1.0 (Q1-Q3: 0.0-2.7), fractional flow reserve was 0.63 (Q1-Q3: 0.49-0.75), and instantaneous wave-free ratio was 0.78 (Q1-Q3: 0.55-0.87). There was little relationship between symptom severity and nature and disease severity: angina symptom score with quantitative coronary angiography ordinal correlation coefficient: 0.06 (95% credible interval [CrI]: 0.00-0.08); stress echocardiography: 0.09 (95% CrI: 0.02-0.10); fractional flow reserve: 0.04 (95% CrI: −0.03 to 0.07); and instantaneous wave-free ratio: 0.04 (95% CrI: −0.01 to 0.07). However, Rose angina and guideline-based typical angina were strong predictors of placebo-controlled PCI efficacy (angina symptom score: OR: 1.9; 95% CrI: 1.6-2.1; probability of interaction [$Pr_{Interaction}$] = 99.9%; and OR: 1.8; 95% CrI: 1.6-2.1; $Pr_{Interaction}$ = 99.9%, respectively).

CONCLUSIONS Although symptom severity and nature were poorly associated with disease severity, the nature of symptoms powerfully predicted the placebo-controlled efficacy of PCI. (J Am Coll Cardiol 2024;84:13-24)

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ABBREVIATIONS AND ACRONYMS

CCS = Canadian Cardiovascular Society

CrI = credible interval

EQ-5D-5L = EuroQol 5-Dimensions 5-Level

MacNew = MacNew Heart Disease Health-Related Quality of Life Instrument

MRC = Medical Research Council

PCI = percutaneous coronary intervention

$Pr_{Interaction}$ = probability of interaction

QCA = quantitative coronary angiography

Rose = World Health Organization Rose angina questionnaire

SAQ = Seattle Angina Questionnaire

Percutaneous coronary intervention (PCI) is currently recommended for patients with stable coronary artery disease with persistent angina despite antianginal medication.[1] The ORBITA-2 (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina-2) trial tested the efficacy of PCI as an antianginal monotherapy vs a placebo procedure.[2] Patients in the PCI group were three times more likely to become free from angina than those in the placebo group. However, despite complete revascularization with near resolution of ischemia in the PCI group, 60% of patients still reported symptoms during follow-up. The reason for the heterogeneity of treatment effect with PCI and how it is associated with the presenting symptoms remains unknown. This limits the ability of clinicians to target PCI to those who will benefit the most.

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Angina was first described 2 centuries ago as, "those who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes."[3] In recent decades, the focus of diagnosis, and subsequent revascularization decisions, have shifted away from symptom characterization toward diagnostic tests of coronary artery disease and myocardial ischemia. However, the link among symptoms, stenosis, and ischemia may be weak and nonlinear.[4] Now that PCI is a proven tool of angina relief, it is time to test whether the severity and nature of the presenting symptom can be used to identify the patients with the most to gain.

The symptom-stratified analysis of the ORBITA-2 trial assesses the association between the presenting symptom and subsequent findings of disease severity, assessed anatomically and with noninvasive and invasive ischemia tests, and the placebo-controlled angina relief from PCI.

METHODS

The London Central Research Ethics Committee approved the study. Written consent was obtained from all patients before enrollment. 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-2 trial has been reported previously.[2] In brief, patients were eligible for trial participation if they had stable angina, single or multivessel disease, and proven ischemia on noninvasive or invasive testing. A total of 301 patients from 14 UK centers were enrolled. At enrollment, all antianginal medications were stopped. Patients were instructed to use a dedicated smartphone application (ORBITA-app) to assess daily angina symptoms. Design, features, and validation of the ORBITA-app have been described previously.[5] Patients completed symptom and quality-of-life questionnaires (World Health Organization Rose angina questionnaire [Rose], Seattle Angina Questionnaire [SAQ], EuroQol 5-Dimensions 5-Level [EQ-5D-5L], MacNew Heart Disease Health-Related Quality of Life Instrument [MacNew], short-form McGill pain questionnaire, and Medical Research Council [MRC] Dyspnoea Scale), and Canadian Cardiovascular Society (CCS) class was physician-assessed.

Following a 2-week symptom assessment phase, patients returned for prerandomization assessment.

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Patient-reported and physician-assessed symptom and quality-of-life questionnaires, stress echocardiography, and treadmill exercise testing were performed. They then returned for the randomization procedure. Once a deep level of conscious sedation was achieved, patients were randomized to PCI or a placebo procedure. Both patients and the medical staff outside of the catheterization laboratory were blinded to the allocated treatment. Both treatment groups received dual antiplatelet therapy. The fidelity of blinding was assessed and reported.

The patients then underwent a 12-week blinded follow-up phase in which they and their medical and research teams had no knowledge of treatment allocation. During this phase they reported their angina daily using the ORBITA-app.

Patients then returned for a blinded follow-up assessment in which symptom and quality-of-life questionnaires, CCS class, stress echocardiography, and treadmill exercise test were repeated. The fidelity of blinding was reassessed. They were then unblinded and returned to routine clinical care.

The primary endpoint of the ORBITA-2 trial was the angina symptom score, an ordinal clinical outcome scale, calculated daily based on angina frequency, use of antianginal medication, and relevant clinical events (intolerable angina leading to unblinding, myocardial infarction, and death).

Secondary endpoints were daily angina frequency; initiation and up-titration of antianginal medications; treadmill exercise time; physician-assessed severity of angina (CCS class); SAQ angina frequency, physical limitation, angina stability, and freedom from angina; quality of life (SAQ and the EQ-5D-5L); and stress echocardiography score.

SYMPTOM ASSESSMENT. Symptom severity. Patient-reported symptom severity was assessed using the ORBITA-app and symptom and quality-of-life questionnaires (SAQ, EQ-5D-5L, and MacNew).

ORBITA-app: The design, features, and validation of the smartphone application have been described previously.[5] In brief, the application systematically assessed angina burden from the preceding day through a series of sequential questions. The patients were asked whether they experienced angina, and they answered yes or no. If affirmative, the patients were asked how many episodes of angina they experienced (ranging from 1 to 6 or more), and the severity of the most intense episode (on a continuous scale with regions marked mild, moderate, and severe).

Additionally, at the time of enrollment, each patient chose 2 weekly activities, which they typically carried out each week, that had previously caused them angina. Patients were asked each week whether each of these activities had induced angina.

Seattle Angina Questionnaire: The SAQ comprises 19 items evaluating domains including angina frequency, physical limitation, angina stability, quality of life, and treatment satisfaction.[6]

EuroQol 5-Dimensions 5-Level: The EQ-5D-5L, established as a tool for evaluating a patient's health and quality-of-life status, encompasses 5 essential dimensions relating to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.[7]

MacNew Heart Disease Health-Related Quality of Life Instrument: The MacNew is designed to assess the implications of coronary artery disease on quality of life. It comprises a set of 27 questions to assess the impact of the condition on daily activities as well as physical, emotional, and social functioning.[8]

Symptom nature. The nature of symptoms was captured using the Rose angina questionnaire, the short-form McGill pain questionnaire, and the MRC Dyspnoea Scale.

World Health Organization Rose angina questionnaire: The Rose was developed as a research instrument for the identification of coronary artery disease. According to this framework, Rose angina is considered present if the person experiences chest pain induced either by walking on the level or walking uphill, resulting in the patient slowing down or coming to a complete stop, with the pain subsiding within 10 minutes. Moreover, the location of the pain must be either within the sternum, or within both the left chest and left arm, or can cover all these regions (Supplemental Table 1). If these criteria were reported, the patients were considered to have Rose angina and if not, they were designated Rose nonangina.[9]

Guideline-based angina: Typical angina is classically defined by meeting 3 key characteristics. First, it is described as chest discomfort; second, it is induced by physical exertion; third, it is relieved by rest or nitroglycerin within minutes. We defined typical angina if all 3 criteria were reported and nontypical angina if fewer than 3 were reported.[1] Typical and nontypical angina were derived from the Rose angina questionnaire (Supplemental Table 1).

Short-form McGill pain questionnaire: The McGill pain questionnaire aims to discern the nature of pain using 15 adjectives, and its severity as mild, moderate, or severe.[10]

Medical Research Council Dyspnoea Scale: The MRC Dyspnoea Scale is used to assess the degree of shortness of breath. The scale ranges from 1 to 5, with 1 indicating shortness of breath solely during

TABLE 1 Prerandomization Symptom and Procedural Characteristics

	PCI	Placebo	Overall
Symptom characteristics			
Angina episodes			
Baseline mean	1.1 ± 1.1	1.2 ± 1.0	1.2 ± 1.0
Baseline median	0.7 (0.3-1.6)	0.9 (0.4-1.7)	0.8 (0.4-1.6)
Angina symptom score			
Baseline mean	4.1 ± 6.5	5.0 ± 9.3	4.6 ± 8.0
Baseline median	1.4 (0.4-7.0)	1.3 (0.6-5.5)	1.4 (0.5-6.1)
CCS class			
Patients	147	146	293
Baseline median	2 (2-3)	2 (2-3)	2 (2-3)
SAQ angina frequency			
Patients	146	145	291
Baseline median	60 (50-80)	60 (40-70)	60 (40-70)
SAQ physical limitation			
Patients	139	144	283
Baseline median	67 (47-80)	67 (47-83)	67 (47-83)
SAQ angina stability			
Patients	145	145	290
Baseline median	50 (25-50)	50 (25-50)	50 (25-50)
SAQ quality of life			
Patients	145	145	290
Baseline median	42 (33-58)	42 (25-58)	42 (25-58)
EQ-5D-5L			
Patients	145	144	289
Baseline median	0.7 (0.6-0.8)	0.7 (0.6-0.7)	0.7 (0.7-0.8)
EQ-VAS			
Patients	146	143	289
Baseline median	70 (70-80)	70 (70-80)	70 (60-80)
MacNew			
Patients	96	95	191
Baseline median	5 (4-6)	5 (4-6)	5 (4-6)
MRC Dyspnoea Scale			
Patients	95	95	190
Baseline median	2 (2-3)	2 (2-4)	2 (2-3)
Disease severity characteristics			
QCA percentage of area stenosis			
Mean	80 ± 15	82 ± 15	81 ± 15
Median	83 (73-92)	85 (75-93)	84 (74-92)
QCA percentage of diameter stenosis			
Mean	61 ± 18	62 ± 17	61 ± 18
Median	60 (48-74)	63 (50-74)	61 (49-74)
Stress echocardiography score			
Mean	2.0 ± 2.3	1.7 ± 2.1	1.8 ± 2.2
Median	1.3 (0.2-2.7)	0.7 (0.0-2.7)	1.0 (0.0-2.7)
Fractional flow reserve			
Mean	0.60 ± 0.16	0.62 ± 0.16	0.61 ± 0.16
Median	0.61 (0.47-0.74)	0.65 (0.51-0.75)	0.63 (0.49-0.75)
Instantaneous wave-free ratio			
Mean	0.68 ± 0.22	0.71 ± 0.23	0.70 ± 0.22
Median	0.76 (0.50-0.86)	0.81 (0.58-0.89)	0.78 (0.55-0.87)

Values are mean ± SD, median (Q1-Q3), or n. Percentages may not total 100 because of rounding. The CCS class ranges from 0 to 4, 0 denoting no angina and class 4 denoting angina at rest. SAQ scores range from 0 to 100, with higher scores indicating a better health status. On the EQ-5D-5L descriptive system, values range from 0 to 1 and on the EQ-VAS from 0 to 100, with higher scores indicating better health status. The MacNew ranges from 1 to 7, with 1 indicating low heart disease health-related quality of life and 7 indicating a high health-related quality of life. MRC Dyspnoea Scale ranges from 1 to 5, with 1 denoting shortness of breath only on strenuous exercise and 5 denoting shortness of breath present with minimal exertion (eg, dressing).

CCS = Canadian Cardiovascular Society; EQ-5D-5L = EuroQol 5-Dimensions 5-Level questionnaire; EQ-VAS = EuroQOL Visual Analogue Scale; MacNew = MacNew Heart Disease Health-Related Quality of Life Instrument; MRC = Medical Research Council; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; SAQ = Seattle Angina Questionnaire.

strenuous exertion and 5 signifying severely limiting shortness of breath in daily activities (eg, dressing or undressing).[11]

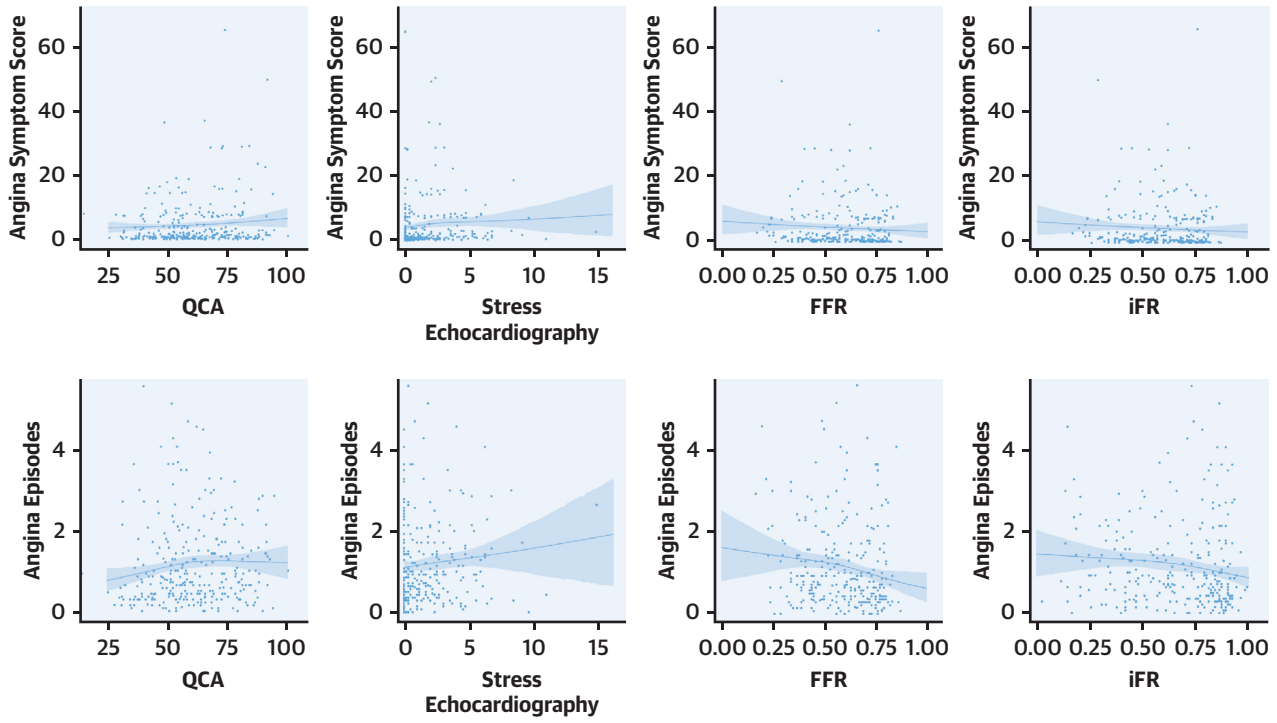
DISEASE SEVERITY ASSESSMENT. Disease severity was assessed anatomically using quantitative coronary angiography (QCA). The level of ischemia was measured noninvasively with stress echocardiography and invasively with fractional flow reserve and instantaneous wave-free ratio.

STATISTICAL ANALYSIS. Summary statistics were presented as appropriate for baseline characteristics.

The severity and nature of the prerandomization symptoms were assessed for their relationship with markers of disease severity (QCA, stress echocardiography, fractional flow reserve, and instantaneous wave-free ratio). In the case of multivessel disease, a mean value across all randomized vessels was used. Bayesian ordinal regression models were constructed for each combination of symptom and marker of disease severity. Nonlinearity was allowed through the use of a restricted cubic spline with 3 knots (at the package default 10th, 50th, and 90th centiles) placed on the predictor when continuous. The ordinal correlation coefficient Somers D and the associated 95% credible interval (CrI) was used to quantify the relationship.

The prerandomization symptom severity was assessed for its ability to predict symptoms after PCI controlled for placebo. Bayesian ordinal regression models were constructed for each of the symptom endpoints. The follow-up value was conditioned on the prerandomization value and allowed to interact with the treatment. Nonlinearity was allowed with the use of a restricted cubic spline with 3 knots on continuous predictors. The impact of the severity of the prerandomization symptom was assessed by contrasting the placebo-controlled outcome for a patient with a symptom severity at an upper quartile vs lower quartile derived from the model. Similarly, the impact of symptom nature at prerandomization (Rose angina, guideline-based typical angina, and shortness of breath, as assessed by the MRC Dyspnoea Scale and MacNew) on the placebo-controlled treatment effect of PCI was assessed using Bayesian ordinal modeling. The follow-up symptom severity was conditioned on the prerandomization symptom severity and the treatment effect that was allowed to interact with prerandomization symptom nature. The impact of the symptom nature was assessed by contrasting the placebo-controlled treatment effect, for example, in a patient with Rose angina against a patient with Rose nonangina. The results of these models are visualized by overlaying the raw data with the regression spline

FIGURE 1 Relationship Between Symptoms and Disease Severity



The relationships between mean prerandomization angina symptom score and mean prerandomization angina episodes and the anatomical and ischemic markers of disease severity. The quantitative coronary angiography (QCA) relates to the diameter stenosis. The stress echocardiography score counts the number of abnormal segments, with higher scores indicating a greater degree of ischemia. FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

of the relationship between the follow-up and baseline value, stratified by the treatment arm and the interacting term.

For the endpoints of angina symptom score and angina episodes, and presence of angina during the weekly tester activities, similar models were used as previously described,[2] with the addition of the appropriate interactions as described herein. The priors, iterations, and chains are provided in the Supplemental Appendix.

All analyses were performed using the statistical environment R, using the package "rsmb" for Bayesian modeling.[12]

RESULTS

A total of 301 patients were randomized. The baseline characteristics have been described previously (Supplemental Tables 2 and 3).[2] Symptom characteristics before randomization and disease severity markers are presented in **Table 1**. The median daily number of angina episodes prerandomization was 0.8 (Q1-Q3: 0.4-1.6). The median angina symptom score was 1.4 (Q1-Q3: 0.5-6.1). The median stress echocardiography score was 1.0 (Q1-Q3: 0.0-2.7). The median percentage of diameter stenosis was 61% (Q1-Q3: 49%-74%). The median fractional flow reserve was 0.63 (Q1-Q3: 0.49-0.75), and instantaneous wave-free ratio was 0.78 (Q1-Q3: 0.55-0.87) (**Table 1**).

RELATIONSHIP BETWEEN SYMPTOMS AND DISEASE SEVERITY. There was little relationship between symptom severity and nature (daily ORBITA-app data and symptom and quality-of-life questionnaires) and anatomic and ischemic markers of disease severity (**Figure 1**, **Table 2**, Supplemental Table 4).

SYMPTOM SEVERITY AS A PREDICTOR OF THE PLACEBO-CONTROLLED EFFECT OF PCI. There was an interaction between prerandomization SAQ angina frequency and angina stability and the placebo-controlled effect of PCI in these domains. Patients with a lower SAQ angina frequency and stability score, indicating a worse health state, were more likely to achieve a better placebo-controlled health state with PCI than patients with a higher score (OR: 4.3; 95% CrI: 2.1-8.7; probability of interaction

TABLE 2 Relationship Between Symptoms and Disease Severity

	Ordinal Correlation Coefficient (Somers D) (95% CrI)			
	QCA Diameter Stenosis	Stress Echocardiography Score	FFR	iFR
Angina symptom score[a]	0.06 (0.00-0.08)	0.09 (0.02-0.10)	0.04 (−0.03 to 0.07)	0.04 (−0.01 to 0.07)
Angina episodes[a]	0.07 (0.05-0.08)	0.06 (0.01-0.09)	0.12 (0.10-0.12)	0.10 (0.07-0.11)
SAQ physical limitation	0.01 (−0.03 to 0.04)	0.00 (−0.04 to 0.04)	0.04 (−0.02 to 0.06)	0.01 (−0.02 to 0.05)
Rose angina questionnaire	0.22 (0.18-0.26)	0.14 (0.06-0.20)	0.30 (0.29-0.35)	0.04 (−0.06 to 0.08)

The association between selected symptom parameters and disease severity. Full data on all endpoints is shown in Supplemental Table 4. [a]Mean averaged across the 2-week prerandomization phase.

CrI = credible interval; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; Rose = World Health Organization Rose angina questionnaire; other abbreviations as in Table 1.

[$Pr_{Interaction}$] = 99.9%; and OR: 2.1; 95% CrI: 1.1-4.1; $Pr_{Interaction}$ = 98.6%, respectively).

There was no strong interaction between the prerandomization symptom severity and the placebo-controlled benefit of PCI for any of the other symptom domains (Supplemental Tables 5 and 6).

SYMPTOM NATURE AS A PREDICTOR OF THE PLACEBO-CONTROLLED EFFECT OF PCI. Data from the Rose angina questionnaire was available for 89% (267 of 301) of patients. Of those, 64% (171 of 267) of patients met the criteria for Rose angina (Supplemental Table 7). There was little relationship between sex and diabetes and the presence of Rose angina (Pr = 24.7% and Pr = 67.9%, respectively). Patients with Rose angina were more likely to have a placebo-controlled benefit with PCI on the angina symptom score (OR: 1.9; 95% CrI: 1.6-2.1, $Pr_{Interaction}$ = 99.9%) (**Figure 2**) and angina episodes (OR: 2.1; 95% CrI: 1.8-2.4; $Pr_{Interaction}$ = 99.9%) compared to those with Rose nonangina (**Figure 3**, **Table 3**).

Patients with Rose angina were also more likely to have a placebo-controlled benefit of PCI on exercise treadmill time (OR: 3.0; 95% CrI: 1.2-7.6; $Pr_{Interaction}$ = 98.9%), CCS class (OR: 4.1; 95% CrI: 1.7-10.2; $Pr_{Interaction}$ = 99.9%), and domains of the symptom and quality-of-life questionnaires (**Figure 4**, **Table 4**, Supplemental Table 8). However, there was little evidence that patients with Rose angina were more likely to have a placebo-controlled benefit of PCI on the stress echocardiography score (OR: 2.0; 95% CrI: 0.8-5.4; $Pr_{Interaction}$ = 91.8%) (**Table 4**, Supplemental Table 8).

There was no strong evidence that symptom descriptors, as assessed by the McGill questionnaire, predicted the placebo-controlled efficacy of PCI on the angina symptom score or daily angina episodes (Supplemental Table 9).

There was no clear evidence that shortness of breath on MRC Dyspnoea Scale predicted the placebo-controlled efficacy of PCI on the angina symptom score (OR: 0.5; 95% CrI: 0.2-1.3; $Pr_{Interaction}$ = 21.9%) (Supplemental Table 10).

Guideline-based criteria for typical angina was met in 66% (176 of 267) of patients and in 34% (91 of 267) for nontypical angina (Supplemental Table 7). There was strong evidence that patients with typical angina were more likely to achieve a better angina symptom score (OR: 1.8; 95% CrI: 1.6-2.1; $Pr_{Interaction}$ = 99.9%) and fewer angina episodes (OR: 2.0; 95% CrI: 1.7-2.3; $Pr_{Interaction}$ = 99.9%) with PCI than patients with nontypical angina (Supplemental Table 11).

WEEKLY TESTERS. Every week, patients were questioned whether they experienced symptoms during their personally defined low-grade and high-grade activity. There was strong evidence that patients in the PCI group were more likely to report freedom of symptoms during these activities at week 12 (low-grade activity: OR: 2.5; 95% CrI: 1.5-4.1; $Pr_{Benefit}$ = 99.9%; high-grade activity: OR: 4.2; 95% CrI: 2.5-7.1; $Pr_{Benefit}$ = 99.9%) (Supplemental Figure 1).

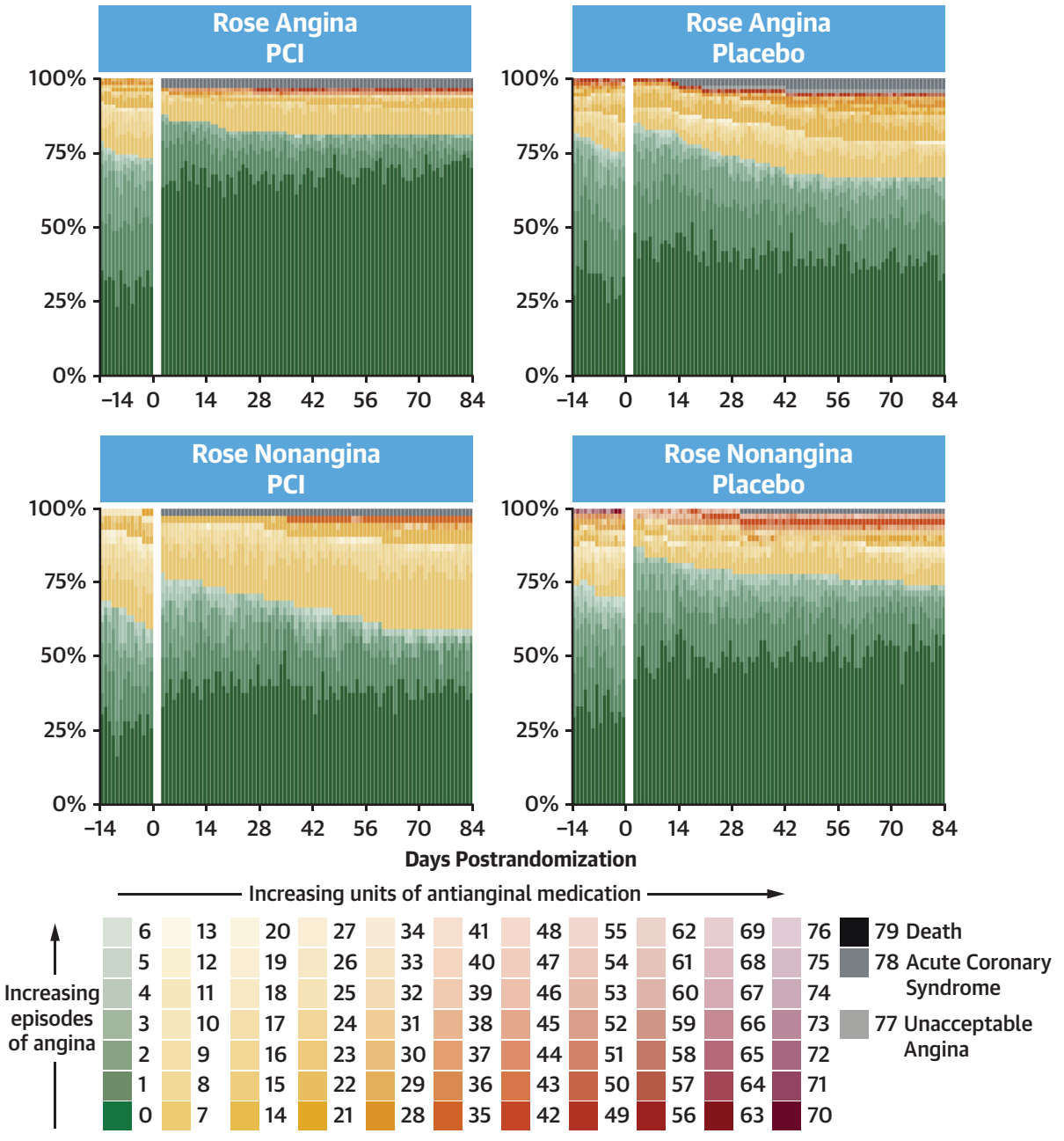
Patients with Rose angina were more likely to benefit from PCI on these activities (low-grade activity: OR: 3.4; 95% CrI: 2.5-4.8; $Pr_{Interaction}$ = 99.9%; high-grade activity: OR: 3.4; 95% CrI: 2.4-4.7; $Pr_{Interaction}$ = 99.9%) (Supplemental Figure 2).

DISCUSSION

This symptom-stratified analysis of the ORBITA-2 trial shows that, surprisingly, there was little relationship between the severity or nature of symptoms and the anatomical severity of coronary disease and physiological severity of ischemia. However, this is not because the presenting symptom is not meaningful. On the contrary, it is the nature of the symptom, rather than its severity, that powerfully predicts the treatment response to PCI (**Central Illustration**).

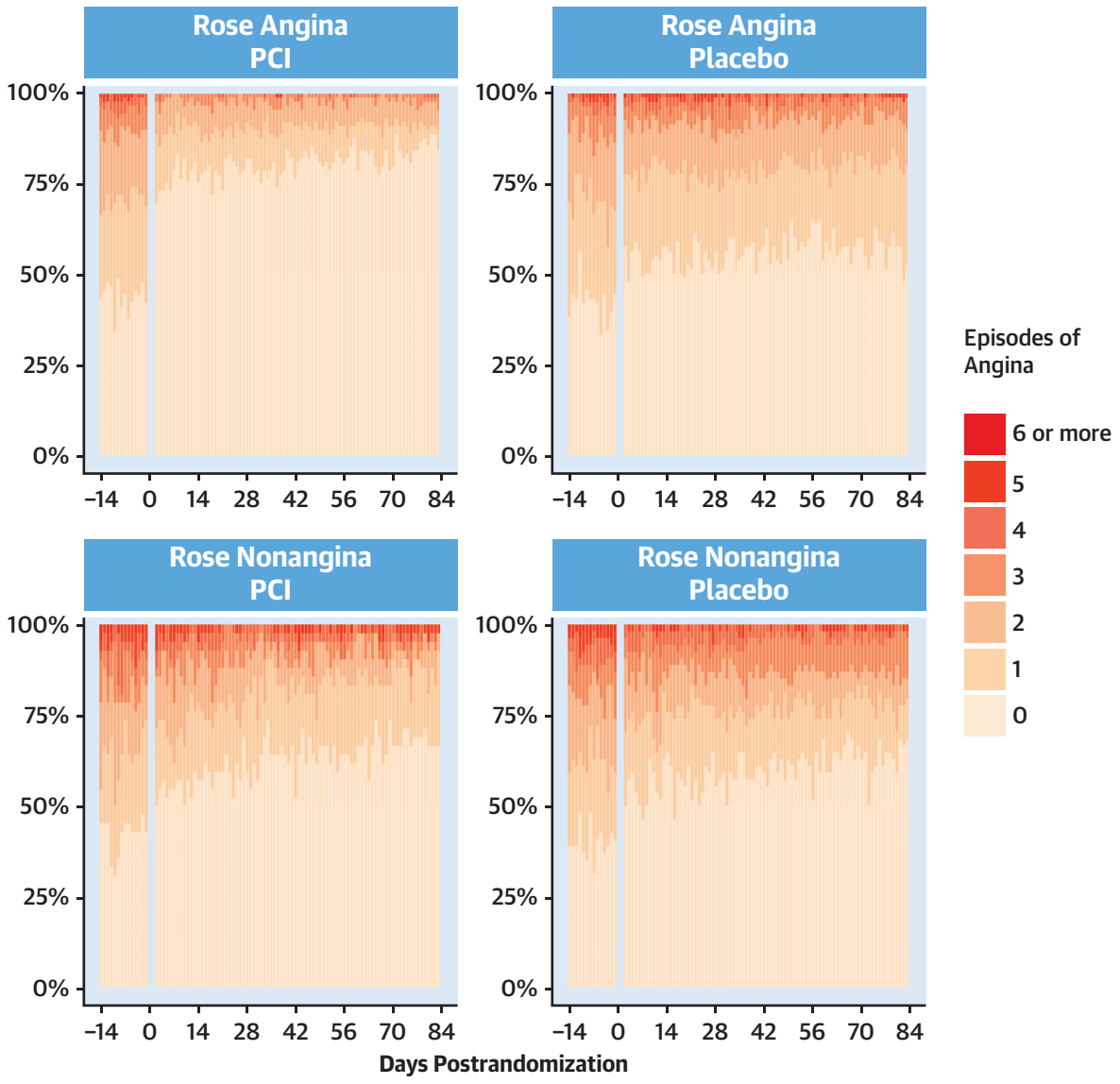
In clinical practice we frequently work backward from the anatomical finding of coronary artery disease to a reinterpretation of the patient's symptoms

FIGURE 2 **Rose Angina as a Predictor of the Angina Symptom Score**



Rose angina as a predictor of the placebo-controlled efficacy of percutaneous coronary intervention (PCI) on the angina symptom score. Daily individual patient data composition of the angina symptom score according to trial group and Rose angina status. The angina symptom score ranges from 0 to 79, with lower scores indicating a better health status with respect to angina. It is calculated based on the daily number of angina episodes, the number of units of antianginal medication prescribed that day, and relevant clinical events (unacceptable angina leading to unblinding, myocardial infarction, and death). Rose = World Health Organization Rose angina questionnaire.

FIGURE 3 Rose Angina as a Predictor of Angina Episodes



Rose angina as a predictor of the placebo-controlled efficacy of PCI on angina episodes. Daily individual patient data of daily angina episodes by treatment and presence of Rose angina. Abbreviations as in Figure 2.

TABLE 3 Rose Angina as a Predictor of the Placebo-Controlled Efficacy of PCI on the Primary Endpoint

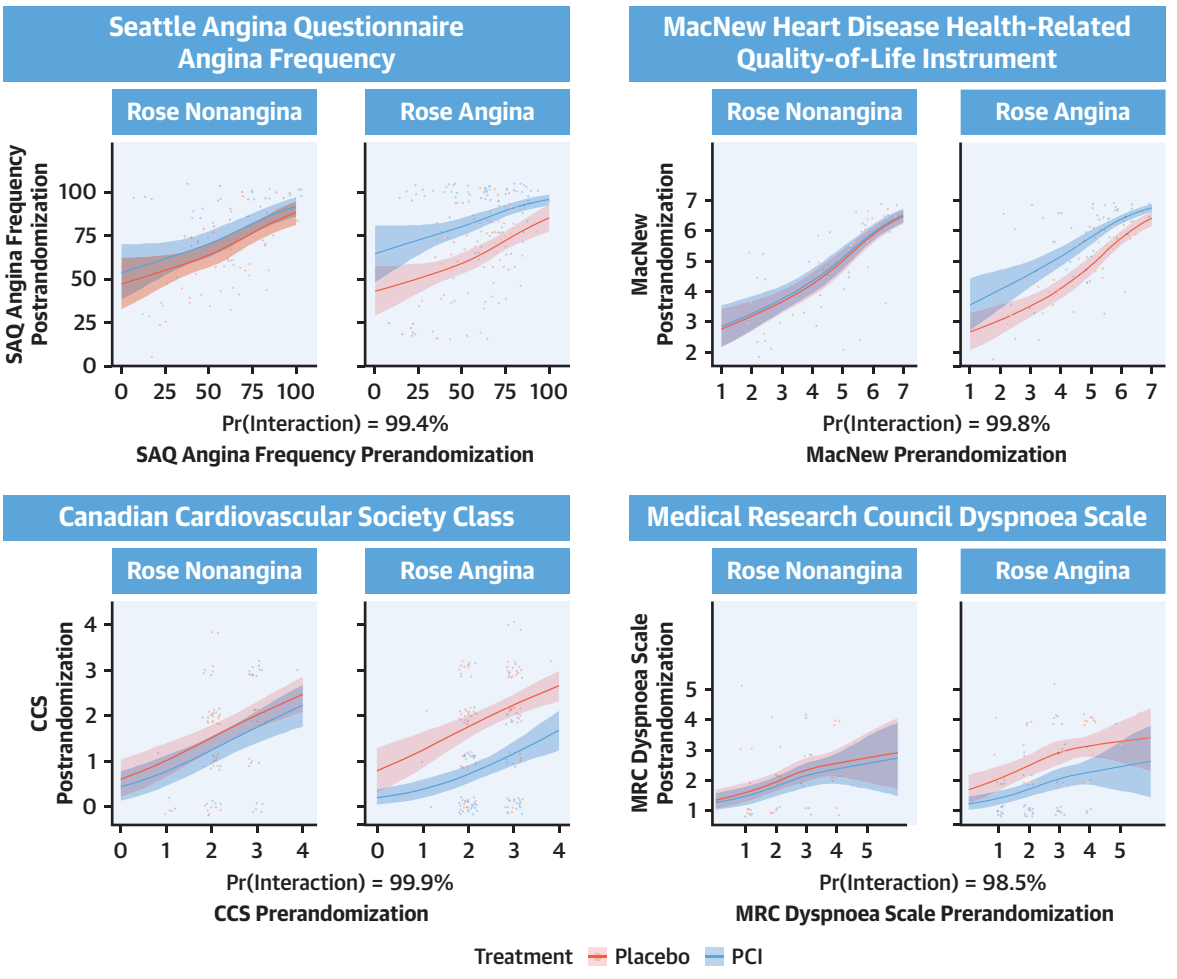
Angina	OR (95% CrI) for Benefit for PCI vs Placebo	OR (95% CrI) for Benefit for Rose Angina vs Rose Nonangina	$Pr_{interaction}$ (%)
Primary endpoint: angina symptom score			
Rose angina	2.3 (2.0-2.7)	1.9 (1.6-2.1)	99.9
Rose nonangina	1.2 (1.1-1.4)		
Angina episodes			
Rose angina	2.6 (2.1-3.2)	2.1 (1.8-2.4)	99.9
Rose nonangina	1.3 (1.0-1.6)		

Rose angina as a predictor of the placebo-controlled efficacy of PCI on the angina symptom score and angina episodes.

$Pr_{interaction}$ = probability of interaction; other abbreviations as in Tables 1 and 2.

through the lens of the stenosis. In this context any symptom, including shortness of breath, can be labeled as some variant of "angina" or "angina-equivalent" to make the case for revascularization. Even in the absence of cardiac symptoms, "silent ischemia" can be used to justify revascularization. This is not unexpected, because physicians are trained to have an inherent desire to resolve a clinical problem. However, the present study shows that if the nature of the symptoms does not fit Rose angina, and therefore may not be cardiac in origin, relief of a stenosis is unlikely to relieve symptoms beyond placebo.

FIGURE 4 Rose Angina as a Predictor of Selected Secondary Endpoints



Rose angina as a predictor of the placebo-controlled efficacy of PCI on Seattle Angina Questionnaire (SAQ) angina frequency, Canadian Cardiovascular Society (CCS) class, MacNew Heart Disease Health-Related Quality of Life Instrument (MacNew), and Medical Research Council (MRC) Dyspnoea Scale. Abbreviations as in Figure 2.

It is striking that despite centuries of discovery, the key to predicting treatment response with PCI comes from the 1962 standardization[9] based on William Heberden's initial description of angina in 1772.[3]

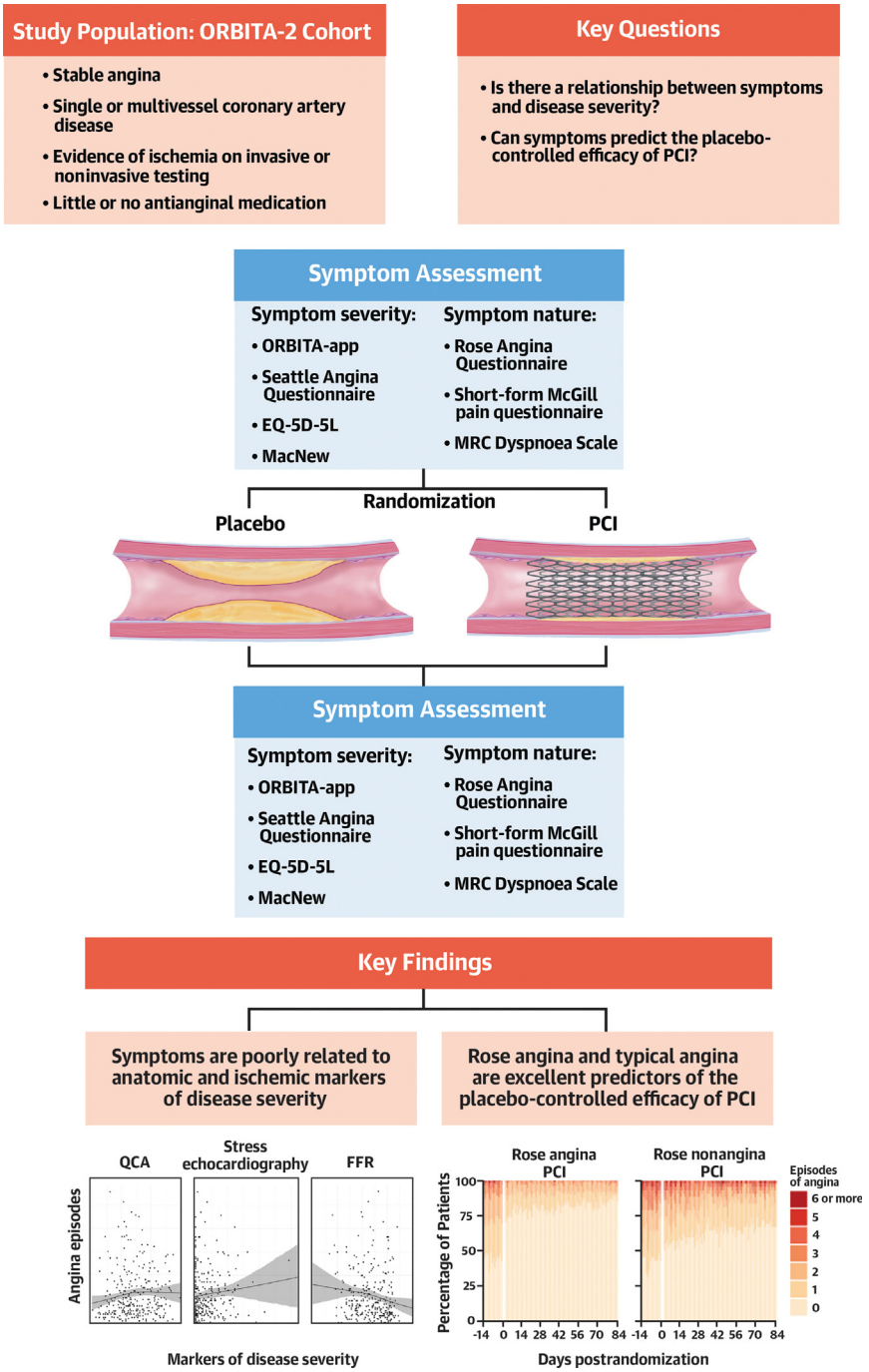
The Rose angina questionnaire[9] consists of 6 mainly dichotomous questions and 1 diagram used to localize the pain. Through simple rules, it categorizes the pain into "angina" vs "nonangina." In the ORBITA-2 trial it emerged as an excellent predictor of the placebo-controlled efficacy of PCI on the angina symptom score, angina episodes, CCS class, exercise treadmill time, and domains of the symptom and quality-of-life questionnaires. An essential feature of the success of the Rose in this prediction is the integration of all its elements.

TABLE 4 Rose Angina as a Predictor of the Placebo-Controlled Efficacy of PCI on Selected Secondary Endpoints

	OR (95% CrI) for Benefit for Rose Angina vs Rose Nonangina	$Pr_{interaction}$ (%)
Treadmill exercise time	3.0 (1.2-7.6)	98.9
CCS class	4.1 (1.7-10.2)	99.9
SAQ angina frequency	3.2 (1.4-7.8)	99.4
SAQ physical limitation	3.2 (1.3-7.7)	99.4
SAQ quality of life	3.3 (1.4-8.2)	99.6
MacNew	5.3 (1.8-15.7)	99.8
MRC Dyspnoea Scale	3.3 (1.1-10.4)	98.5
Stress echocardiography score	2.0 (0.8-5.4)	91.8

The full data on all endpoints is shown in Supplemental Table 8.
Abbreviations as in Tables 1 to 3.

CENTRAL ILLUSTRATION Symptom-Stratified Analysis of ORBITA-2



Simader FA, et al. J Am Coll Cardiol. 2024;84(1):13-24.

Key findings of the symptom-stratified analysis of the ORBITA-2 (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina-2) trial. EQ-5D-5L = EuroQol 5-Dimensions 5-Level questionnaire; MRC = Medical Research Council; SAQ = Seattle Angina Questionnaire.

For the purpose of this clinical study, with detailed patient phenotyping, the prespecified Rose questionnaire was used. However, the criteria used in guidelines are similar to the Rose and indeed guideline-based typical angina similarly predicted the placebo-controlled efficacy of PCI. The McGill questionnaire, which addressed multiple aspects of the nature of the pain (eg, heavy vs stabbing), showed that no specific descriptors of pain predicted the placebo-controlled effect of PCI on angina.

The design of ORBITA-2 allowed us to improve on physician assessment of angina with CCS and patient-reported symptom questionnaires. It has been shown that patients' recollection of the number of angina episodes is poor, particularly declining after the first 2 days of experiencing pain.[5] Moreover, some patients avoid activities that may trigger angina, and this behavioral adaption is not visible in simple angina episode counts. The ORBITA-app allowed daily reporting of symptoms, individualized to the patient. It also introduced weekly tester questions addressing symptom responses to standardized activities that had previously caused angina.[13] This prevented artificially low scores from patients intentionally limiting their activity to avoid angina. The presence of Rose angina strongly predicted the placebo-controlled efficacy of PCI on these weekly tester questions.

There was no association between the severity or nature of symptoms and disease severity. A possible explanation is that, over time, angina severity tends to decline.[14] This might be because of ischemic preconditioning,[15] collateral vessel formation,[16] reduced patient activities, or altered interpretations of symptoms with time. In peripheral arterial disease, the phenomenon of "walk through pain" is well described, and exercise therapy is known to improve symptoms of claudication without procedural treatment of the arterial stenosis.[17] Perhaps we should not use coronary anatomy, stress-induced wall motion abnormalities, and measures of hemodynamic pressure-gradients as indicators of symptom severity.

STUDY LIMITATIONS. The follow-up period was only 12 weeks. However, the difference in reduction of angina between the PCI and placebo groups was seen immediately and remained constant. Information on the nature of symptoms was obtained using standardized symptom questionnaires. The responses to the Rose angina questionnaire were used to extrapolate typical angina based on the guidelines. The MacNew and MRC Dyspnoea Scale were introduced at an interim stage of the study and were therefore only available for a subset of patients. ORBITA-2 assessed the placebo-controlled efficacy of PCI in patients with obstructive coronary artery disease, evidence of ischemia, and angina. The majority of participants were male and nondiabetic. Application of the data to wider populations should be conducted with this in mind. No data were systematically collected on the activity levels of the patients, and although it is likely to have been heterogeneous, the combination of randomization, placebo-control, and blinding should have equally distributed this effect between the groups.

CONCLUSIONS

This analysis suggests that selecting the right patients for PCI should start at the beginning of the clinical pathway. Patients can provide the information on whether angioplasty will improve their symptoms purely by describing the nature of their pain. Patients with Rose angina are the most likely to benefit from PCI. Unfortunately, for those patients whose symptoms do not fit this pattern, PCI is unlikely to make them feel better beyond placebo. This knowledge may help to target PCI to maximize its efficacy and minimize the number of patients who have residual symptoms despite anatomically and physiologically successful revascularization.

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KEY WORDS percutaneous coronary intervention, stable angina, stable coronary artery disease

APPENDIX For supplemental methods, results, figures, tables, and list of investigators, please see the online version of this paper.