**Symptoms as a predictor of the placebo-controlled efficacy of PCI in stable coronary artery disease.**

**The symptom-stratified analysis of ORBITA-2**

Florentina A. Simader MD1,2, Christopher A. Rajkumar MBBS BSc1,2, Michael J. Foley MBBS BSc1,2, Fiyyaz Ahmed-Jushuf MBBS BSc1,2, Shayna Chotai MBBS BSc1,2, Nina Bual2 , Arif Khokhar BM BCh2, Aisha Gohar MB ChB PhD2, Ioannis Lampadakis MD3, Sashiananthan Ganesananthan MB BCh BSc1,2, Rachel H Pathimagaraj MB ChB BSc1,2, Alexandra Nowbar MBBS PhD4, John R. Davies MBBS PhD5,6, Tom R. Keeble MBBS MD5,6, Peter D. O’Kane MBBS PhD7, Peter Haworth MBBS BSc8, Helen Routledge MD9, Tushar Kotecha MBBS PhD10, James C Spratt MB ChB MD11,12, Rupert Williams MBBS PhD11, Sukhjinder S. Nijjer MB ChB PhD1,2, Sayan Sen MBBS PhD2, Nick Curzen BM PhD13, Manas Sinha MD14, James P. Howard MB BChir PhD1,2, Graham Cole MB BChir PhD1,2, Frank E. Harrell Jr. PhD15, Darrel P. Francis MB BChir MD1,2, Matthew J. Shun-Shin BM BCh PhD1,2, and Rasha K. Al-Lamee MBBS PhD1,2 for the ORBITA-2 Investigators

1. Imperial College London, London, UK

2. Imperial College Healthcare NHS Trust, London, UK

3. Athens Naval Hospital, Athens, Greece

4. Barking Havering and Redbridge University Hospitals NHS Trust, London, UK

5. Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust, Essex, UK

6. Anglia Ruskin University, Chelmsford, UK

7. University Hospitals of Dorset NHS Foundation Trust, Bournemouth, UK

8. Portsmouth Hospitals University NHS Trust, Portsmouth, UK

9. Worcestershire Acute Hospitals NHS Trust, Worcester, UK

10. Royal Free London NHS Foundation Trust, London, UK

11. St. George’s University Hospitals NHS Foundation Trust, London, UK

12. St George’s, University of London, London, UK

13. University Hospital Southampton NHS Foundation Trust, Southampton, UK

14. Salisbury NHS Foundation Trust, Salisbury, UK

15. Vanderbilt University School of Medicine, Nashville, Tennessee, USA

**Correspondence:**

Dr Rasha Al-Lamee

National Heart and Lung Institute

Imperial College London

Hammersmith Hospital, Du Cane Road

London W12 0HS

UK

Tel: +44 207 594 1093

Fax: +44 208 082 5109

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

Word count: 4065

**Declaration of interests:**

FS reports sponsorship from Servier pharmaceuticals. CAR reports speaker’s fees from Menarini and consultancy fees from Philips.MJF reports speaker’s fees from Menarini and Philips. SS reports speakers and consultancy fees from Philips, Medtronic, Recor and AstraZeneca. SSN reports speaker fees from Philips Volcano, Pfizer, Bayer, AstraZeneca, Boehringer Ingelheim and Amarin. JPH and GDC report shares in Mycardium AI**.** JPH reports a grant from the British Heart Foundation. JRD reports grants from Medtronic and Abbott, sponsorship from Vascular Perspectives, Boston Scientific, Medtronic and Abbott, and speaker’s honoraria from AstraZeneca, Pfizer, Bristol Myers Squibb and Novartis. TK reports honoraria from Bayer and Jansen. TRK reports advisory board for Abbott Vascular and SMT and institutional research funding from Terumo, Medtronic, Boston Scientific, Abbott Vascular, Philips Volcano and Cardionovum. PDO reports speaker’s fees from Abbott Vascular, Biosensors, Boston Scientific, Heartflow, Medtronic, Philips, Shockwave, Terumo. JS reports speaker’s fees from Boston Scientific Corporation and Shockwave Medical, Inc. NC reports grants from Beckman Coulter, Inc., Boston Scientific Corporation, Haemonetics Corporation and HeartFlow, Inc; speaker’s fees from Heartflow. AK reports speaker’s fees and travel support from Boston Scientific and Abbott. RAL reports advisory board: Janssen Pharmaceuticals, Abbott, Philips, and speaker’s honoraria: Abbott, Philips, Medtronic, Servier, Omniprex, Menarini. The other authors report no declarations of interest.

**Acknowledgements**:

ORBITA-2 was an investigator-initiated trial sponsored by Imperial College London. The trial was funded by grants from NIHR Imperial Biomedical Research Centre, Medical Research Council, British Heart Foundation, NIHR and the Imperial Coronary Flow Trust. Philips Volcano supplied the coronary pressure wires. We acknowledge the support of the NIHR Clinical Research Network. We thank all patients and their families for their dedication and time, without which this research would not be possible. We thank the research and administrative teams at each of the 14 trial sites.

**ABSTRACT**

**Background**

Placebo–controlled evidence from ORBITA-2 found that percutaneous cutaneous intervention (PCI) in stable coronary artery disease with little or no antianginal medication relieved angina, but residual symptoms persisted in many. The reason for this was unclear.

**Objectives**

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

**Methods**

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

**Results**

At pre-randomization, the median number of daily angina episodes was 0.8 (0.4-1.6), 64% had Rose angina, QCA diameter stenosis 61 (49–74), stress echocardiography score 1.0 (0.0-2.7), FFR 0.63 (0.49–0.75), and iFR 0.78 (0.55–0.87). There was little relationship between symptom severity and nature and disease severity: angina symptom score with QCA ordinal correlation coefficient 0.06 (95% CrI 0.00 to 0.08); stress echocardiography 0.09 (95% CrI 0.02 to 0.10); FFR 0.04 (95% CrI -0.03 to 0.07); and iFR 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 to 2.1, Pr(Interaction)=99.9% and OR 1.8, 95% CrI 1.6 to 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.

**KEYWORDS: stable coronary artery disease, stable angina, percutaneous coronary intervention**

**Condensed Abstract:**

ORBITA-2 was the first randomized, placebo-controlled trial to show the efficacy of PCI on angina relief in patients with stable coronary artery disease.

In this symptom-stratified analysis, there was no discernible link between symptom severity and nature and disease severity. Importantly, however, Rose angina, as assessed by the Rose angina questionnaire, and guideline-based typical angina proved to be surprisingly powerful predictors of angina relief with PCI. The more typical the angina, the greater the angina reduction from PCI.

**ABBREVIATIONS AND ACRONYMS**

CCS=Canadian Cardiovascular Society

CrI=Credible interval

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

EQ-VAS=EuroQoL Visual Analogue Scale

FFR=Fractional flow reserve

iFR= instantaneous wave-Free Ratio

MRC=Medical Research Council

PCI=Percutaneous coronary intervention

QCA=Quantitative coronary angiography

SAQ=Seattle Angina Questionnaire

**INTRODUCTION**

Percutaneous coronary intervention (PCI) is currently recommended for patients with stable coronary artery disease with persistent angina despite anti-anginal medication1. ORBITA-2 (Objective Randomised Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina-2) tested the efficacy of PCI as an anti-anginal monotherapy versus a placebo procedure2. 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.

Angina was first described two 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 towards diagnostic tests of coronary artery disease (CAD) and myocardial ischemia. However, the link between symptoms, stenosis and ischemia may be weak and nonlinear4. 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 non-invasive 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 previously2. In brief, patients were eligible for trial participation if they had stable angina, single or multivessel disease, and proven ischemia on non-invasive or invasive testing. 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 previously5.​ Patients completed symptom and quality of life questionnaires (Rose angina questionnaire, Seattle Angina Questionnaire (SAQ), EuroQol 5-Dimensions 5-Level (EQ-5D-5L), MacNew Heart Disease Health-Related Quality of Life Instrument, short-form McGill pain questionnaire, and Medical Research Council (MRC) Dyspnoea Scale), Canadian Cardiovascular Society (CCS) class was physician-assessed.

Following a two-week symptom assessment phase, patients returned for pre-randomization assessment. 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 uptitration 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 patient was asked if they experienced angina, and answered yes or no. If affirmative, the patient was 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 two 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 satisfaction6.

#### 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 five essential dimensions relating to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression7.​

MacNew Heart Disease Health-Related Quality of Life Instrument**:** The MacNew is designed to assess the implications of coronary artery disease on daily activities. It comprises a set of 27 questions to assess the impact of the condition on daily activities as well as physical, emotional, and social functioning8.

### **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 non-angina9​.

#### 

Guideline-based angina: Typical angina is classically defined by meeting three 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 three criteria were reported and non-typical angina if any fewer than three were reported1. Typical and non-typical 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 either mild, moderate, or severe10.

#### 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 strenuous exertion and 5 signifying severely limiting shortness of breath in daily activities (e.g. dressing or undressing)11. A score of ≥3 was considered limiting shortness of breath.

## **Disease severity assessment**

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

## **Statistical analysis**

Summary statistics were presented as appropriate for baseline characteristics.

The severity and nature of the pre-randomization symptoms was assessed for their relationship with markers of disease severity (QCA, DSE, FFR, and iFR). 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. Non-linearity was allowed through the use of a restricted cubic spline with three 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 was used to quantify the relationship.

The pre-randomization 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 pre-randomization value and allowed to interact with the treatment. Non-linearity was allowed with the use of a restricted cubic spline with three knots on continuous predictors. The impact of the severity of the pre-randomization 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 pre-randomization (Rose angina, 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 modelling. The follow-up symptom severity was conditioned on the pre-randomization symptom severity and the treatment effect which was allowed to interact with pre-randomization 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 non-angina. The results of these models are visualized by overlaying the raw data with the regression spline 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 described2, with the addition of the appropriate interactions as described above. The priors, iterations and chains are provided in the supplementary appendix.

All analyses were performed using the statistical environment R, utilizing the package “rsmb” for Bayesian modelling12.

# **RESULTS**

301 patients were randomized. The baseline characteristics have been described previously2 (Supplemental Table 2 and 3). Symptom characteristics before randomization and disease severity markers are presented in Table 1. The median daily number of angina episodes pre-randomization was 0.8 (0.4-1.6). The median angina symptom score was 1.4 (0.5-6.1). The median stress echocardiography score was 1.0 (0.0-2.7). The median percent diameter stenosis was 61 (49–74). The median FFR was 0.63 (0.49–0.75), and iFR was 0.78 (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, and Supplemental Table 4).

**Symptom severity as a predictor of the placebo-controlled effect of PCI**

There was an interaction between pre-randomization 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 to 8.7, Pr(Interaction)=99.9% and OR 2.1, 95% CrI 1.1 to 4.1, Pr(Interaction)=98.6%, respectively).

There was no strong interaction between the pre-randomization 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% (n=267/301) of patients. 64% (n=171/267) of patients met the criteria for Rose angina (Supplemental Table 7). 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 to 2.1, Pr(Interaction)=99.9%) (Figure 2) and angina episodes (OR 2.1, 95% CrI 1.8 to 2.4, Pr(Interaction)=99.9%) compared to those with Rose non-angina (Figure 3 and 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 to 7.6, Pr(Interaction)=98.9%), CCS class (OR 4.1, 95% CrI 1.7 to 10.2, Pr(Interaction)=99.9%), and domains of the symptom and quality of life questionnaires (Figure 4, Table 4, and 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 to 5.4, Pr(Interaction)=91.8%) (Table 4 and 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 to 1.3, Pr(Interaction)=21.9%) (Supplemental Table 10).

Guideline-based criteria for typical angina was met in 66% (n=176/267) of patients and in 34% (n=91/267) for non-typical 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 to 2.1, Pr(Interaction)=99.9%) and fewer angina episodes (OR 2.0, 95% CrI 1.7 to 2.3, Pr(Interaction)=99.9%) with PCI than patients with non-typical angina (Supplemental Table 11).

**Weekly testers**

Every week, patients were questioned if 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 to 4.1, Pr(Benefit)=99.9%; high-grade activity, OR 4.2, 95% CrI 2.5 to 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 to 4.8, Pr(Interaction)=99.9%; high-grade activity, 3.4, 95% CrI 2.4 to 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 backwards from the anatomical finding of coronary artery disease to a re-interpretation of the patient’s symptoms through the lens of the stenosis. In this context any symptom, including shortness of breath, can be labelled 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.

It is striking that despite centuries of discovery, the key to predicting treatment response with PCI comes from the 1962 standardization9 based on William Heberden’s initial description of angina in 17723.

The Rose angina questionnaire9, developed in 1962, consists of six mainly dichotomous questions and one diagram used to localize the pain. Through simple rules, it dichotomously categorizes the pain into “angina” vs. “non-angina”. In ORBITA-2 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. For the purpose of this clinical study, with detailed patient phenotyping, the pre-specified 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, 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 upon 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 two days of experiencing pain5. 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 angina13. 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 decline14. This might be because of ischemic preconditioning15, collateral vessel formation16, 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 stenosis17. 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 non-diabetic. 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 while it is likely to have been heterogeneous, the combination of randomization, placebo-control and blinding should have equally distributed this effect between the groups.

**CONCLUSION**

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.

**CLINICAL PERSPECTIVE  
What is known:**

ORBITA-2 was the first randomized trial to show the placebo-controlled effect of PCI on symptom relief in patients with angina and stable coronary artery disease.

**What is new:**

The severity and nature of symptoms were surprisingly poorly related to disease severity. However, the nature of symptoms strongly predicted the placebo-controlled efficacy of PCI. Clinicians should not use measures of disease severity to predict treatment response when there is a more patient-centered approach that starts at the beginning of the clinical pathway.

**What is next:**

When evaluating a patient with angina, physicians should incorporate the Rose angina questions into their assessment. This will ensure that PCI is targeted to those in whom it will provide symptom relief beyond placebo.

# **REFERENCES**

1. Neumann FJ, Sechtem U, Banning AP, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477. doi:10.1093/eurheartj/ehz425

2. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, et al. A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina. *New England Journal of Medicine*. Published online December 21, 2023. doi:10.1056/nejmoa2310610

3. Heberden W. Some account of a disorder of the breast. *Medical Transactions, The Royal College of Physicians of London,*. Published online 1772:59-67.

4. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *The Lancet*. 2018;391(10115):31-40. doi:10.1016/S0140-6736(17)32714-9

5. Nowbar AN, Howard JP, Shun-Shin MJ, et al. Daily angina documentation versus subsequent recall: Development of a symptom smartphone app. *European Heart Journal - Digital Health*. 2022;3(2):276-283. doi:10.1093/ehjdh/ztac015

6. Garratt AM, Hutchinson A, Russell I. *The UK Version of the Seattle Angina Questionnaire (SAQ-UK): Reliability, Validity and Responsiveness*. Vol 54.; 2001.

7. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Economics (United Kingdom)*. 2018;27(1):7-22. doi:10.1002/hec.3564

8. Höfer S, Lim L, Guyatt G, Oldridge N. *Health and Quality of Life Outcomes The MacNew Heart Disease Health-Related Quality of Life Instrument: A Summary*.; 2004. http://www.hqlo.com/content/2/1/3

9. Rose GA. *The Diagnosis of Ischaemic Heart Pain and Intermittent Claudication in Field Surveys\**. Vol 27.; 1962.

10. Melzack R. The short-form McGill pain questionnaire. *Pain*. 1987;30(2). https://journals.lww.com/pain/fulltext/1987/08000/the\_short\_form\_mcgill\_pain\_questionnaire.5.aspx

11. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586. doi:10.1136/thx.54.7.581

12. Harrell F. *Rmsb: Bayesian Regression Modeling Strategies, R Package, Version 1.0-0. R Foundation, 2022*.; 2023. Accessed March 13, 2024. https://CRAN .R-project.org/package=rmsb

13. Ganesananthan S, Rajkumar CA, Foley M, Francis D, Al-Lamee R. Remote digital smart device follow-up in prospective clinical trials: early insights from ORBITA-2, ORBITA-COSMIC, and ORBITA-STAR. *European Heart Journal, Supplement*. 2022;24(Sh):H32-H42. doi:10.1093/eurheartjsupp/suac058

14. Mesnier J, Ducrocq G, Danchin N, et al. International Observational Analysis of Evolution and Outcomes of Chronic Stable Angina: The Multinational CLARIFY Study. *Circulation*. 2021;144(7):512-523. doi:10.1161/CIRCULATIONAHA.121.054567

15. Lambiase PD, Edwards RJ, Cusack MR, Bucknall CA, Redwood SR, Marber MS. Exercise-induced ischemia initiates the second window of protection in humans independent of collateral recruitment. *J Am Coll Cardiol*. 2003;41(7):1174-1182. doi:10.1016/S0735-1097(03)00055-X

16. Traupe T, Gloekler S, De Marchi SF, Werner GS, Seiler C. Assessment of the human coronary collateral circulation. *Circulation*. 2010;122(12):1210-1220. doi:10.1161/CIRCULATIONAHA.109.930651

17. Biswas MP, Capell WH, McDermott MM, et al. Exercise Training and Revascularization in the Management of Symptomatic Peripheral Artery Disease. *JACC Basic Transl Sci*. 2021;6(2):174-188. doi:10.1016/j.jacbts.2020.08.012

**FIGURES**

**Figure 1. Relationship between symptoms and disease severity**

**The relationship between mean pre-randomization angina symptom score and mean pre-randomization 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.

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

**Figure 2. Rose angina as a predictor of the angina symptom score**

**Rose angina as a predictor of the placebo-controlled efficacy of 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 (intolerable angina leading to unblinding, myocardial infarction, and death).

PCI=Percutaneous coronary intervention

**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.

PCI = Percutaneous coronary intervention

**Figure 4. Rose angina as a predictor of selected secondary endpoints**

**Rose angina as a predictor of the placebo-controlled efficacy of PCI on SAQ angina frequency, CCS, MacNew, and MRC Dyspnoea Scale.**

CCS= Canadian Cardiovascular Class, PCI=Percutaneous coronary intervention, SAQ=Seattle Angina Questionnaire

**CENTRAL ILLUSTRATION:** The symptom-stratified analysis of ORBITA-2

Key findings of the symptom-stratified analysis of the ORBITA-2 trial.

EQ-5D-5L=EuroQol 5-Dimensions 5-Level questionnaire, MRC= Medical Research Council, SAQ=Seattle Angina Questionnaire

**TABLES**

**Table 1. Pre-randomization 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) |
| **Canadian Cardiovascular Society class** | | | |
| **n** | 147 | 146 | 293 |
| **Baseline median (IQR)** | 2 (2-3) | 2 (2-3) | 2 (2-3) |
| **SAQ angina frequency** | | | |
| **n** | 146 | 145 | 291 |
| **Baseline median (IQR)** | 60 (50-80) | 60 (40-70) | 60 (40-70) |
| **SAQ physical limitation** | | | |
| **n** | 139 | 144 | 283 |
| **Baseline median (IQR)** | 67 (47-80) | 67 (47-83) | 67 (47-83) |
| **SAQ angina stability** | | | |
| **n** | 145 | 145 | 290 |
| **Baseline median (IQR)** | 50 (25-50) | 50 (25-50) | 50 (25-50) |
| **SAQ quality of life** | | | |
| **n** | 145 | 145 | 290 |
| **Baseline median (IQR)** | 42 (33-58) | 42 (25-58) | 42 (25-58) |
| **EQ-5D-5L** | | | |
| **n** | 145 | 144 | 289 |
| **Baseline median (IQR)** | 0.7 (0.6-0.8) | 0.7 (0.6-0.7) | 0.7 (0.7-0.8) |
| **EQ-VAS** | | | |
| **n** | 146 | 143 | 289 |
| **Baseline median (IQR)** | 70 (70-80) | 70 (70-80) | 70 (60-80) |
| **MacNew** | | | |
| **n** | 96 | 95 | 191 |
| **Baseline median (IQR)** | 5 (4-6) | 5 (4-6) | 5 (4-6) |
| **MRC Dyspnoea Scale** | | | |
| **n** | 95 | 95 | 190 |
| **Baseline median (IQR)** | 2 (2-3) | 2 (2-4) | 2 (2-3) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease severity characteristics** | | | |
| **QCA percent area stenosis** | | | |
| **Mean** | 80±15 | 82±15 | 81±15 |
| **Median** | 83 (73-92) | 85 (75–93) | 84 (74–92) |
| **QCA percent 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) |

Plus–minus values are mean and standard deviations (SD). Medians are displayed with their interquartile range (IQR). Percentages may not total 100 because of rounding.

The Canadian Cardiovascular Society 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 EuroQol 5-Dimensions 5-Level (EQ-5D-5L) descriptive system values range from 0-1, and on the EQ-VAS from 0 to 100, with higher scores indicating better health status.

The MacNew ranges from 1 to 7, 1 indicating low heart disease health-related quality of life (HRQL) and 7 indicating a high HRQL.

MRC Dyspnoea scale ranges from 1 to 5, 1 denoting shortness of breath only on strenuous exercise and 5 denoting shortness of breath present with minimal exertion (e.g. dressing)

IQR=Interquartile range, EQ-5D-5L= EuroQol 5-Dimensions 5-Level questionnaire, EQ-VAS=EuroQOL visual analogue scale, MRC=Medical Research Council, n=number PCI=Percutaneous coronary intervention, SAQ=Seattle Angina Questionnaire, SD=Standard deviation, QCA=quantitative coronary angiography

**Table 2. Relationship between symptoms and disease severity**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Ordinal correlation coefficient (Somers’ D)** | | | |
|  | **QCA diameter stenosis** | **Stress**  **echocardiography score** | **Fractional flow reserve** | **Instantaneous**  **wave-free ratio** |
| **Angina**  **symptom**  **score\*** | 0.06  (95% CrI  0.00 to 0.08) | 0.09  (95% CrI  0.02 to 0.10) | 0.04  (95% CrI  -0.03 to 0.07) | 0.04  (95% CrI  -0.01 to 0.07) |
| **Angina episodes\*** | 0.07  (95% CrI  0.05 to 0.08) | 0.06  (95% CrI  0.01 to 0.09) | 0.12  (95% CrI  0.10 to 0.12) | 0.10  (95% CrI  0.07 to 0.11) |
| **SAQ**  **physical limitation** | 0.01  (95% CrI  -0.03 to 0.04) | 0.00  (95% CrI  -0.04 to 0.04) | 0.04  (95% CrI  -0.02 to 0.06) | 0.01  (95% CrI  -0.02 to 0.05) |
| **Rose angina questionnaire** | 0.22  (95% CrI  0.18 to 0.26) | 0.14  (95% CrI  0.06 to 0.20) | 0.30  (95% CrI  0.29 to 0.35) | 0.04  (95% CrI  -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.

\*mean averaged across the two-week pre-randomization phase

QCA= Quantitative coronary angiography, CrI=Credible interval, SAQ=Seattle Angina Questionnaire

### **Table 3. Rose angina as a predictor of the placebo-controlled efficacy of PCI on the primary endpoint**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Angina** | **Odds ratio for benefit for PCI vs placebo** | **Odds ratio for benefit for Rose angina vs Rose non-angina** | | **Probability of interaction** |
| **Primary endpoint: Angina symptom score** | | | | |
| **Rose angina** | 2.3  (95% CrI 2.0 to 2.7) | | 1.9  (95% CrI 1.6 to 2.1) | 99.9% |
| **Rose**  **non-angina** | 1.2  (95% CrI 1.1 to 1.4) | |
| **Angina episodes** | | | | |
| **Rose angina** | 2.6  (95% CrI 2.1 to 3.2) | | 2.1  (95% CrI 1.8 to 2.4) | 99.9% |
| **Rose**  **non-angina** | 1.3  (95% CrI 1.0 to 1.6) | |

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

CrI=Credible interval

**Table 4. Rose angina as a predictor of the placebo-controlled efficacy of PCI on selected secondary endpoints**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Odds ratio for benefit for Rose angina vs Rose non-angina** | **Probability of interaction** |
| **Treadmill exercise time** | 3.0  (95% CrI 1.2 to 7.6) | 98.9% |
|
| **Canadian Cardiovascular Society class** | 4.1  (95% CrI 1.7 to 10.2) | 99.9% |
|
| **SAQ**  **angina frequency** | 3.2  (95% CrI 1.4 to 7.8) | 99.4% |
|
| **SAQ**  **physical limitation** | 3.2  (95% CrI 1.3 to 7.7) | 99.4% |
|
| **SAQ**  **quality of life** | 3.3  (95% CrI 1.4 to 8.2) | 99.6% |
|
| **MacNew** | 5.3  (95% CrI 1.8 to 15.7) | 99.8% |
|
| **MRC**  **Dyspnoea scale** | 3.3  (95% CrI 1.1 to 10.4) | 98.5% |
|
| **Stress echocardiography score** | 2.0  (95% CrI 0.8 to 5.4) | 91.8% |

Rose angina as a predictor of the placebo-controlled efficacy of PCI on selected secondary endpoints. The full data on all endpoints is shown in Supplemental Table 8.

CrI=Credible interval, EQ-5D-5L=EuroQol 5-Dimensions 5-Level questionnaire, MRC= Medical Research Council, SAQ=Seattle Angina Questionnaire