

# Cardiopulmonary exercise testing and efficacy of percutaneous coronary intervention: a substudy of the ORBITA trial

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Received 14 September 2021; revised 10 March 2022; accepted 6 May 2022

## Abstract

### Aims

Oxygen-pulse morphology and gas exchange analysis measured during cardiopulmonary exercise testing (CPET) has been associated with myocardial ischaemia. The aim of this analysis was to examine the relationship between CPET parameters, myocardial ischaemia and anginal symptoms in patients with chronic coronary syndrome and to determine the ability of these parameters to predict the placebo-controlled response to percutaneous coronary intervention (PCI).

### Methods and results

Patients with severe single-vessel coronary artery disease (CAD) were randomized 1:1 to PCI or placebo in the ORBITA trial. Subjects underwent pre-randomization treadmill CPET, dobutamine stress echocardiography (DSE) and symptom assessment. These assessments were repeated at the end of a 6-week blinded follow-up period.

A total of 195 patients with CPET data were randomized (102 PCI, 93 placebo). Patients in whom an oxygen-pulse plateau was observed during CPET had higher (more ischaemic) DSE score [ $+0.82$  segments; 95% confidence interval (CI): 0.40 to 1.25,  $P = 0.0068$ ] and lower fractional flow reserve ( $-0.07$ ; 95% CI:  $-0.12$  to  $-0.02$ ,  $P = 0.011$ ) compared with those without. At lower (more abnormal) oxygen-pulse slopes, there was a larger improvement of the placebo-controlled effect of PCI on DSE score [oxygen-pulse plateau presence ( $P_{\text{interaction}} = 0.026$ ) and oxygen-pulse gradient ( $P_{\text{interaction}} = 0.023$ )] and Seattle angina physical-limitation score [oxygen-pulse plateau presence ( $P_{\text{interaction}} = 0.037$ )]. Impaired peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, peak oxygen-pulse, and oxygen uptake efficacy slope was significantly associated with higher symptom burden but did not relate to severity of ischaemia or predict response to PCI.

### Conclusion

Although selected CPET parameters relate to severity of angina symptoms and quality of life, only an oxygen-pulse plateau detects the severity of myocardial ischaemia and predicts the placebo-controlled efficacy of PCI in patients with single-vessel CAD.

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## Structured Graphical Abstract

### Key Question

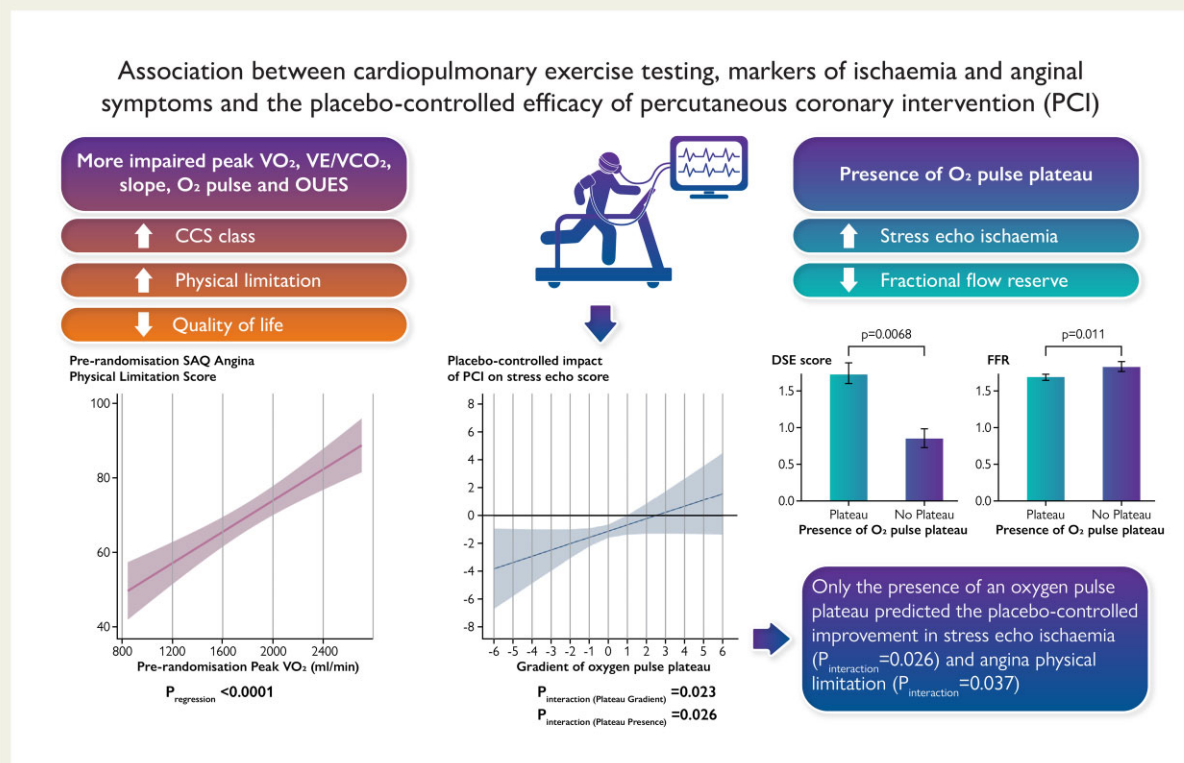
How does exercise physiology measured by cardiopulmonary exercise testing (CPET) relate to ischaemia and anginal symptoms? Following this, does O<sub>2</sub>-pulse morphology and exercise capacity predict the placebo-controlled efficacy of percutaneous coronary intervention?

### Key Finding

In 195 ORBITA patients, an O<sub>2</sub>-pulse plateau was associated with more ischaemia on stress-echo and fractional flow reserve (FFR) while other impaired CPET parameters were associated with greater symptom burden. However, only an O<sub>2</sub>-pulse plateau predicted improvement in stress-echo scores and angina physical-limitation.

### Take Home Message

Although selected CPET parameters relate to severity of angina symptoms and quality of life, only an O<sub>2</sub>-pulse plateau detects severity of myocardial ischaemia and predicts the placebo-controlled efficacy of percutaneous coronary intervention (PCI) in patients with single vessel coronary artery disease.



Only an oxygen pulse plateau relates to markers of ischaemia and predicts the placebo-controlled efficacy of percutaneous coronary intervention in patients with chronic coronary syndrome.

### Keywords

Cardiopulmonary exercise testing • Oxygen pulse • Stable coronary artery disease • Chronic coronary syndrome • Ischaemia • Angina • Peak oxygen uptake

## Introduction

Cardiopulmonary exercise testing (CPET) provides a non-invasive assessment of integrated exercise physiology through evaluation of ventilatory gas exchange (VGE). In chronic coronary syndrome, CPET permits reproducible quantification of cardio-respiratory fitness,<sup>1</sup> discriminates between exercise-limiting pathophysiological adaptations<sup>2</sup> and provides prognostic stratification.<sup>3,4</sup>

Several CPET parameters have been associated with inducible myocardial ischaemia in symptomatic patients with stable coronary artery disease (CAD).<sup>5,6</sup> Compared WITH exercise electrocardiography alone, assessments of work-rate trajectory (VO<sub>2</sub>/WR), oxygen-pulse (O<sub>2</sub>-pulse), and ventilatory efficiency during CPET have been shown to offer enhanced sensitivity and specificity for the detection of inducible myocardial ischaemia and perfusion defects.<sup>7-9</sup>

A linear increase of  $O_2$ -pulse has been described, which reflects the progressive stroke volume response during incremental exercise.<sup>10</sup> An  $O_2$ -pulse plateau may indicate the inability to augment stroke volume, a feature of exercise-induced cardiac dysfunction which precedes angina and has been reported as valuable in quantifying myocardial ischaemia.<sup>7,11</sup> Thus, this suggests that CPET, which provides an integrated assessment of cardiac function and exercise capacity, will be closely associated with indices of myocardial ischaemia and severity of anginal symptoms. However, the relationship between the  $O_2$ -pulse trajectory and other CPET parameters with gold-standard invasive and non-invasive measures of ischaemia (or even anginal symptoms), has never been assessed in patients with chronic coronary syndrome.

Previous unblinded studies have evaluated CPET as an effective technique to assess functional outcomes following revascularization. Significant improvements have been observed following percutaneous coronary intervention (PCI), in peak oxygen consumption ( $VO_2$ ), oxygen uptake kinetic responses, ventilatory anaerobic threshold and  $O_2$ -pulse response following PCI.<sup>12–17</sup> However, these observed beneficial effects of revascularization have never been tested against placebo control. Furthermore, it may be hypothesized that patients with more impaired functional capacity at baseline (i.e. those who were more symptomatic) or have features suggestive of ischaemia (such as an  $O_2$ -pulse plateau) on CPET may derive a greater placebo-controlled benefit from PCI.

Hence, in this analysis, we utilized data from the ORBITA (Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial to assess how the  $O_2$ -pulse morphology, measured through an automated quantitative analysis, and other CPET parameters, relate to severity of CAD scored by indices of myocardial ischaemia and symptom questionnaires. We assessed whether these parameters can predict the placebo-controlled efficacy of PCI. We also evaluated the effect of placebo-controlled PCI on CPET endpoints in patients with stable single-vessel CAD.

## Methods

This study was approved by the London Central Research Ethics Committee (reference 13/LO/1340) and all trial participants provided written consent before enrolment.

### Study design

The design of ORBITA has been reported previously.<sup>18</sup> ORBITA recruited patients with stable angina and angiographically severe single-vessel CAD ( $\geq 70\%$  stenosis), who were referred for elective PCI.

Following enrolment, patients underwent a 6-week medical optimization phase during which anti-anginal therapy was initiated and uptitrated. Patients then underwent pre-randomization assessments including CPET, dobutamine stress echocardiography (DSE) and symptom assessments including the physician-assessed Canadian Cardiovascular Society (CCS) class, patient-reported symptoms using the Seattle Angina Questionnaire (SAQ) and quality of life using the EuroQOL-5 (EQ-5D-5L) questionnaire. Invasive assessments of inducible myocardial ischaemia, including fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR), were made immediately prior to randomization.

Patient blinding was achieved with conscious sedation and auditory isolation using over-the-ear headphones playing music. Once sedated,

patients were randomly assigned 1:1 to PCI or a placebo procedure (randomization performed with SRUB Version 8.4.20). Patients and all subsequent caregivers remained blinded to treatment allocation for a 6-week follow-up period.

At the end of this period, all pre-randomization assessments including CPET, DSE, symptom, and quality of life questionnaires were repeated, prior to unblinding.

The full CPET assessment methodology and exercise testing protocol is described in the [Supplementary Appendix](#).

### Cardiopulmonary exercise testing reporting

CPET endpoints were reported twice by two cardiologists who were blinded to treatment allocation, time point of the test (pre- or post-randomization) and the other reporter's opinion.<sup>18</sup> Resting haemodynamics and VGE indices were measured as average values for 30 s prior to initiation of exercise. Anaerobic threshold (AT) time was estimated from breath-by-breath data using the V-slope method and validated with other plots, using the ventilatory-equivalent method and the respiratory exchange ratio (RER) method.<sup>19</sup>  $VO_2$  at AT was taken at this time point. The  $VE/VC_{O_2}$  slope was calculated from exercise onset to peak exercise by linear regression.<sup>20</sup> The oxygen uptake efficiency slope (OUES) was determined by the slope of the regression-line between the  $\log_{10}VE$  (x-axis) and  $VO_2$  (y-axis) during the whole exercise period ( $VO_2 = a \log_{10}VE + b$ , where  $a = OUES$ ,  $b = \text{intercept}$ ).<sup>21</sup>

At peak exercise,  $VO_2$  (ml/min/kg) was stated as the highest 30 s average within the last minute of exercise until the first 15 s of recovery.<sup>5</sup> Other peak values were calculated at identical timepoints. Peak  $O_2$ -pulse was calculated as the ratio of peak oxygen consumption and heart rate ( $VO_2/HR$ ). Breathing reserve (%) was calculated as:  $(MVV - VE_{\text{peak}})/MVV \times 100\%$ , where MVV is the maximum voluntary ventilation. Maximum voluntary ventilation was estimated as  $40 \times FEV_1$ .<sup>22</sup>

The analysis of the  $O_2$ -pulse morphology (presence of a plateau and gradient of slope) was determined by an automated quantitative technique, implemented using the Python Programming Language. Initially, two expert cardiologists identified the presence of an  $O_2$ -pulse plateau if there was a horizontal plateau of the  $O_2$ -pulse curve (an inflection in the slope) during exercise, where there was no increase in the  $VO_2/HR$  on visual assessment. A subset of these cases was then randomly selected to determine optimal cut-offs for the  $O_2$ -pulse morphology quantitative analysis to reproduce these expert opinions. We generated an automated algorithm from this subset of cases and applied it to the ORBITA data set. This began with applying a Savitzky–Golay filter with window length corresponding to 30 s of data using a second-order polynomial, to provide smoothed estimates of the  $VO_2$ , heart rate, stroke volume, and RER. Where subjects had reached a sufficient degree of exercise intensity on the treadmill (deemed as exercise times of at least 300 s), we compared the slope of the  $O_2$ -pulse in the last 2 min of exercise (considered as the late slope), to that of the remaining exercise slope until the last 2 min of exercise (considered as the early slope). These slopes were calculated using Huber regression, which is more resistant to outlier than simple linear regression. If the ratio of these two slopes (late slope over early slope) was lower than 0.4, this was deemed as a plateau in the  $O_2$ -pulse morphology. If the patient exercised for less than 5 min, we only analysed the morphology of the late slope (last 2 min of exercise), where a late slope of less than 0.3 ml/beat/min was deemed as a plateau. If there was less than 2 min of exercise data, this was considered inappropriate for  $O_2$ -pulse morphology analysis. In addition to the presence of an  $O_2$ -pulse plateau (dichotomous analysis), we also treated the  $O_2$ -pulse morphology as a continuous variable using either the ratio or late slope value based on the time

exerted on the treadmill. Example cases for morphology analysis are presented in the [Supplementary Appendix](#). We also provide the Python Programming Language code and example data sheet for data formatting and analysis purposes as [Supplementary Material](#).

## Ischaemia assessment and reporting

Invasive physiology assessment (FFR and iFR) was performed with the clinical operator blinded to the result. This enabled patients with a range of clinically representative FFR and iFR values to be randomized within single trial and allowed investigation of the ability of these parameters to predict the placebo-controlled efficacy of PCI.

Dobutamine stress echocardiography was performed according to a standardized protocol by a sonographer and a physician, blinded to other assessments and has been previously described.<sup>23</sup> Each scan was examined twice by six imaging cardiologists, blinded to time point, treatment allocation and their first opinion and reported as previously described.<sup>23</sup> This was conducted to reduce inter- and intra-observer variability of stress echocardiography assessment.

In our analysis, ischaemia was assessed using mean DSE scores, iFR and FFR; these parameters were treated as continuous variables.

## Statistical analysis

In this CPET-stratified analysis of ORBITA, data were obtained from all patients who underwent pre-randomization CPET. Summary statistics for baseline characteristics were presented with normality assessed using the Kolmogorov–Smirnov test.

The ORBITA primary analysis utilized two-sample *t*-tests to determine change scores of continuous variables, as had been prespecified in the statistical plan. In this and previous ORBITA stratified analysis,<sup>23,24</sup> regression modelling (a generalized form of analysis of covariance) was used, to assess the relationship between CPET parameters (e.g. O<sub>2</sub>-pulse plateau morphology, peak oxygen uptake, etc.) and DSE, invasive coronary physiology, patient-reported or physician-assessed symptoms and to determine the interaction between pre-randomization CPET parameters on the treatment effect of PCI on each endpoint. Regression modelling provides increased statistical power and allows incorporation of baseline values and clinical characteristics (such as age, weight, height, and sex) to determine treatment effect and associations.

Regression models were fitted for each endpoint. For continuous endpoints such as the VGE parameters, SAQ physical-limitation score, SAQ quality of life (QOL) score, EQ-5D-5L Visual Analogue Score (VAS) and exercise time, ordinary least squares models were used. For ordinal variables including the SAQ angina-frequency score, Duke treadmill score, freedom from angina (calculated from SAQ) and the CCS angina class, proportional odds logistics models were used.<sup>25</sup> For each component of the SAQ, EQ-5D-5L VAS and freedom from angina, a higher score indicates a better health status. Hence, an odds ratio (OR) of more than one (natural logarithm of OR = 0) indicates that PCI achieved a better health status than placebo.<sup>26</sup>

For both continuous and ordinal study endpoints, we modelled the follow-up (post-randomization) endpoint values conditioned on the pre-randomization endpoint values. Each covariate in the model was tested for linearity (where a *P*-value of >0.05 for non-linearity suggested that the covariate had a linear relationship with the endpoint).<sup>27</sup> A model was then fitted for each study endpoint with pre-randomization CPET variable interacting with the randomization arm. Age, weight, height, and sex were also adjusted in the model (and also tested for non-linearity) to account for the effects of these baseline characteristics on pre-randomization CPET parameter.<sup>28</sup> For

covariates that were non-linear, knots were positioned at the 25th, 50th, and 75th percentile of the covariate distribution. The graphs are shown of endpoints against pre-randomization CPET variables. The difference in study endpoint values between the two arms, conditioned on the pre-randomization value, was represented on the vertical axis. We report the interaction as the *P*-value (*P*<sub>interaction</sub>) from the combined main effect and interaction effect.

All statistical analyses were performed using open-source statistical environment R.<sup>29</sup> Regression models were built using the rms package<sup>27</sup> and graphs were created with the tidyverse package.<sup>30</sup>

## Results

Of the 200 patients randomized in ORBITA, pre-randomization CPET data were available for 195 patients (102 PCI and 93 placebo). CPET data were unreliable in three patients due to persistent mask leaks, and in two patients, who declined to wear the mask required for CPET.

### Patient and procedural characteristics

Patient demographic data are shown in [Table 1](#). Most patients had physician-assessed CCS Class II or III angina severity at enrolment (98% in the PCI arm and 96.8% in the placebo arm). A total of 187 (95.9%) patients had at least one positive ischaemia test prior to randomization. This included any pre-enrolment clinical positive functional test ([Table 1](#)), pre-randomization stress echocardiography score ≥1, FFR ≤0.80 and iFR ≤0.89 (see [Supplementary material online, Table S1](#)).

### Pre-randomization lung function and cardiopulmonary exercise testing assessment

Pre-randomization resting lung function and CPET data are shown in [Supplementary material online, Table S2](#). These CPET parameters were well balanced between groups. A total of 152 patients (77.9%) were on beta-blockers and 6 patients (3.1%) were in non-sinus rhythm during exercise testing. Most patients (76.9%) attained a RER of ≥1.00 (a marker of acceptable exercise effort).

### The association between cardiopulmonary exercise testing parameters and markers of ischaemia

DSE, FFR, and iFR data were available in 178 (91.3%), 189 (96.9%), and 191 (97.9%) patients, respectively. A plateau of the O<sub>2</sub>-pulse was detected in 142/192 (74%) patients using the automated analysis (see [Supplementary material online, Table S2](#)). There were no clinical (risk factors for cardiovascular disease, [Table 1](#)) or demographic factors (age, gender) associated with a greater probability of attaining an O<sub>2</sub>-pulse plateau.

Patients with an O<sub>2</sub>-pulse plateau (detected via automated analysis) had significantly higher DSE scores [+0.82 segments; 95% confidence interval (CI) 0.40 to 1.25, *P* = 0.0068; [Figure 1A](#)] and lower FFR values (−0.07; 95% CI: −0.12 to −0.02, *P* = 0.011; [Figure 1B](#)) compared with those without. Although there was a trend towards patients with an O<sub>2</sub>-pulse plateau having a lower iFR, this

**Table 1** Patient demographics at enrolment

Demographics	PCI (n = 102)	Placebo (n = 93)	Total (n = 195)
Age, years	65.9 ± 9.6	66.2 ± 8.5	66.1 ± 9.1
Male sex	71 (69.6)	72 (77.4)	143 (73.3)
Height, cm	168.5 ± 9.9	169.2 ± 8.6	168.9 ± 9.3
Weight, kg	79.6 ± 15.0	83.3 ± 16.0	81.4 ± 15.6
Smoking status			
Current	11 (10.8)	14 (15.1)	25 (12.8)
Previous	38 (37.3)	36 (38.7)	74 (38.0)
Never	53 (51.9)	43 (46.2)	96 (49.2)
Hypertension	70 (68.6)	65 (69.9)	135 (69.2)
Hypercholesterolaemia	80 (78.4)	61 (65.6)	141 (72.3)
Diabetes mellitus	15 (14.7)	20 (21.5)	35 (17.9)
Previous MI	5 (4.9)	5 (5.4)	10 (5.1)
Previous PCI	10 (9.8)	13 (14.0)	23 (11.8)
CCS Class			
I	2 (2.0)	3 (3.2)	5 (2.6)
II	64 (62.7)	53 (57.0)	117 (60.0)
III	36 (35.3)	37 (39.8)	73 (37.4)
Left ventricular systolic function			
Normal	95 (93.1)	84 (90.3)	179 (91.8)
Mild impairment	3 (2.9)	7 (7.5)	10 (5.1)
Moderate impairment	4 (4.0)	2 (2.2)	6 (3.1)
Severe impairment	0 (0)	0 (0)	0 (0)
Angina duration, months	5 (4–10)	6 (4–9)	6 (4–9)
Pre-enrolment clinical positive functional test	54 (52.9)	42 (45.2)	96 (49.2)
ETT	26 (25.5)	17 (18.3)	43 (22.1)
MIBI	9 (8.8)	11 (11.8)	20 (10.3)
DSE	19 (18.6)	13 (14.0)	32 (16.3)

Values are given as mean ± standard deviation, n (%), or median (interquartile range).

CCS, Canadian Cardiovascular Society angina class; DSE, dobutamine stress echocardiography; ETT, exercise tolerance test; MI, myocardial infarction; MIBI, nuclear medicine myocardial perfusion scan; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention.

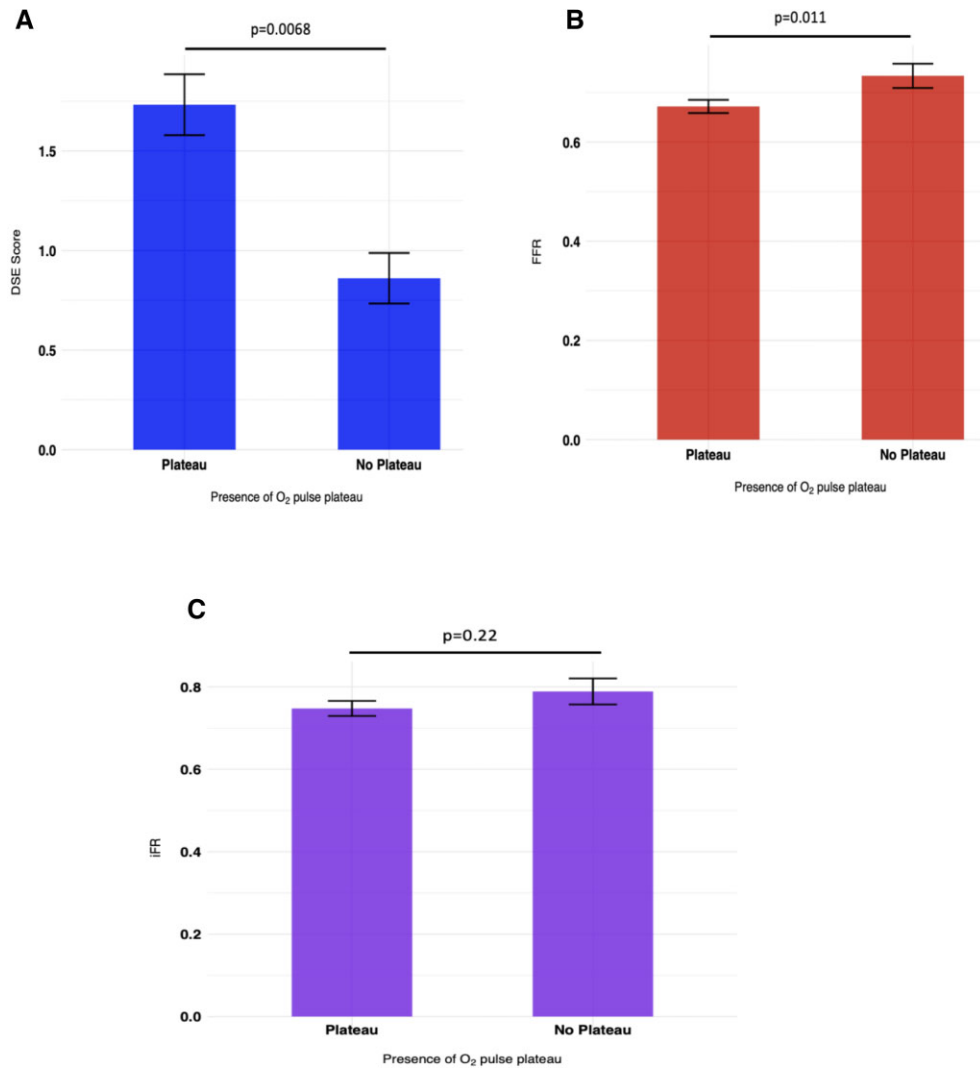
difference was not statistically significant ( $-0.04$ ; 95% CI:  $-0.11$  to  $0.02$ ,  $P=0.22$ ; [Figure 1C](#)). Incorporation of peak RER attained by each participant in the regression model also showed similar results; [DSE scores:  $+0.98$  segments (95% CI:  $0.30$  to  $1.66$ ,  $P=0.0047$ ), FFR:  $-0.06$  (95% CI:  $-0.12$  to  $-0.003$ ,  $P=0.041$ ) and iFR:  $-0.05$  (95% CI:  $-0.13$  to  $0.03$ ,  $P=0.22$ )]. Analysis of the  $O_2$ -pulse morphology as a continuous variable however did not suggest a significant relationship between these parameters (see [Supplementary material online, Figure S1](#)).

Similarly, greater impairment of other CPET parameters at pre-randomization (peak  $VO_2$ ,  $VE/VCO_2$  slope, peak  $O_2$ -pulse, and OUES) did not suggest more ischaemia as assessed by FFR, iFR and DSE ([Figure 2](#) for peak  $VO_2$  and see [Supplementary material](#)

[online, Figure S2](#) for  $VE/VCO_2$ , peak  $O_2$ -pulse, and OUES). Patients with more impaired peak  $VO_2$ , peak  $O_2$ -pulse, and OUES had significantly higher FFR.

### Relationship between cardiopulmonary exercise testing parameters and symptom severity

Across the cohort, a significantly positive association was observed between the total duration of treadmill exercise and the peak  $VO_2$  achieved ( $P<0.0001$ ; [Figure 3A](#)). Patients with higher peak  $VO_2$  also had higher EQ-5D-5L VAS ( $P=0.0002$ ; [Figure 3B](#)), higher SAQ domain scores including angina-frequency ( $P=0.0015$ ; [Figure 3C](#)), physical-limitation ( $P<0.0001$ ; [Figure 3D](#)), and QOL



**Figure 1** Relationship between the presence of an O<sub>2</sub>-pulse plateau and severity of ischaemia. Relationship between the presence of an oxygen-pulse plateau and (A) DSE score, (B) FFR, and (C) iFR. Data are presented as mean with error bars indicating standard error values. DSE, Dobutamine stress echocardiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; and O<sub>2</sub>, oxygen. *P* values were calculated from the regression model which was adjusted for age, weight, height, and sex.

( $P=0.0005$ ; [Figure 3E](#)) and lower (milder) physician-assessed CCS score ( $P<0.0001$ ; [Figure 3F](#)).

Patients with a lower VE/VCO<sub>2</sub> (less impaired) slope had significantly better patient-reported and physician-assessed symptoms (see [Supplementary material online, Figure S3](#)). Similarly, higher peak O<sub>2</sub>-pulse and OUES were mostly associated with better physician-assessed CCS and patient-reported symptoms (see [Supplementary material online, Figures S4 and S5](#)).

### Placebo-controlled effect of percutaneous coronary intervention on Duke treadmill score, ventilatory gas exchange, and exercise haemodynamics

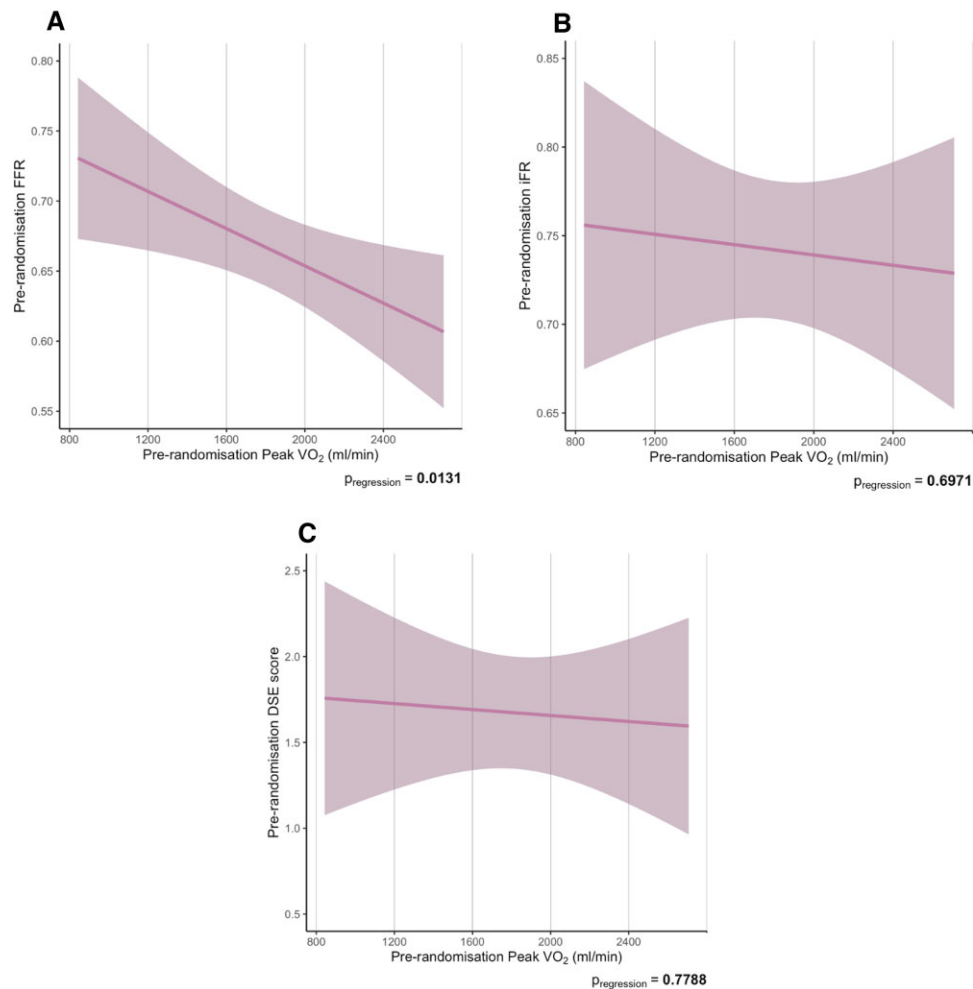
At 6-week follow-up, there was no significant effect of PCI compared with placebo on peak VO<sub>2</sub> ( $-8.03$  ml/min, 95% CI:  $-80.07$  to  $64.00$ ,

$P=0.826$ ), presence of O<sub>2</sub>-pulse plateau (OR: 1.13, 95% CI: 0.56–2.26,  $P=0.735$ ), or any CPET parameters during exercise ([Table 2](#)). However, PCI was more likely to result in improvement in Duke treadmill score compared with placebo (OR: 1.73, 95% CI: 1.05–2.85,  $P=0.032$ , [Table 2](#)).

### Cardiopulmonary exercise testing as a predictor of the placebo-controlled effect of percutaneous coronary intervention on study endpoints

#### O<sub>2</sub>-pulse morphology

Paired (pre- and post-) DSE scores were available for 155 patients (88 in the PCI arm and 67 in the placebo arm). PCI significantly reduced the DSE score compared with placebo ( $-1.083$ , 95% CI:  $-1.46$  to  $-0.71$ ,  $P<0.0001$ , see [Supplementary material online,](#)



**Figure 2** Relationship between pre-randomization peak  $\text{VO}_2$  and pre-randomization FFR (A), iFR (B) and DSE score (C). Data are presented as mean with error bars indicating standard error values. DSE, dobutamine stress echocardiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio;  $\text{O}_2$ , oxygen; OUES, oxygen uptake efficiency slope;  $\text{VE}/\text{VCO}_2$ : Minute ventilation to carbon dioxide  $\text{VO}_2$ : oxygen uptake  $P$  values were calculated from the regression model which was adjusted for age, weight, height, and sex.

Table S3). The presence of an  $\text{O}_2$ -pulse plateau ( $P_{\text{interaction}} = 0.026$ , Figure 4A) and the  $\text{O}_2$ -pulse gradient ( $P_{\text{interaction}} = 0.023$ , Figure 4A) predicted progressively larger improvement of DSE scores at lower (more abnormal)  $\text{O}_2$ -pulse slopes.

Although PCI did not improve SAQ physical-limitation score (4.14, 95% CI:  $-1.33$  to  $9.62$ ,  $P = 0.137$ , see Supplementary material online, Table S3), the presence of an  $\text{O}_2$ -pulse plateau significantly modified this effect ( $P_{\text{interaction}} = 0.037$ , Figure 4B) with greater benefit of PCI seen in patients with an  $\text{O}_2$ -pulse plateau compared to those without. This was despite there being no interaction between the gradient of the  $\text{O}_2$ -pulse morphology and physical-limitation at baseline ( $P_{\text{interaction}} = 0.44$ , Figure 4B).

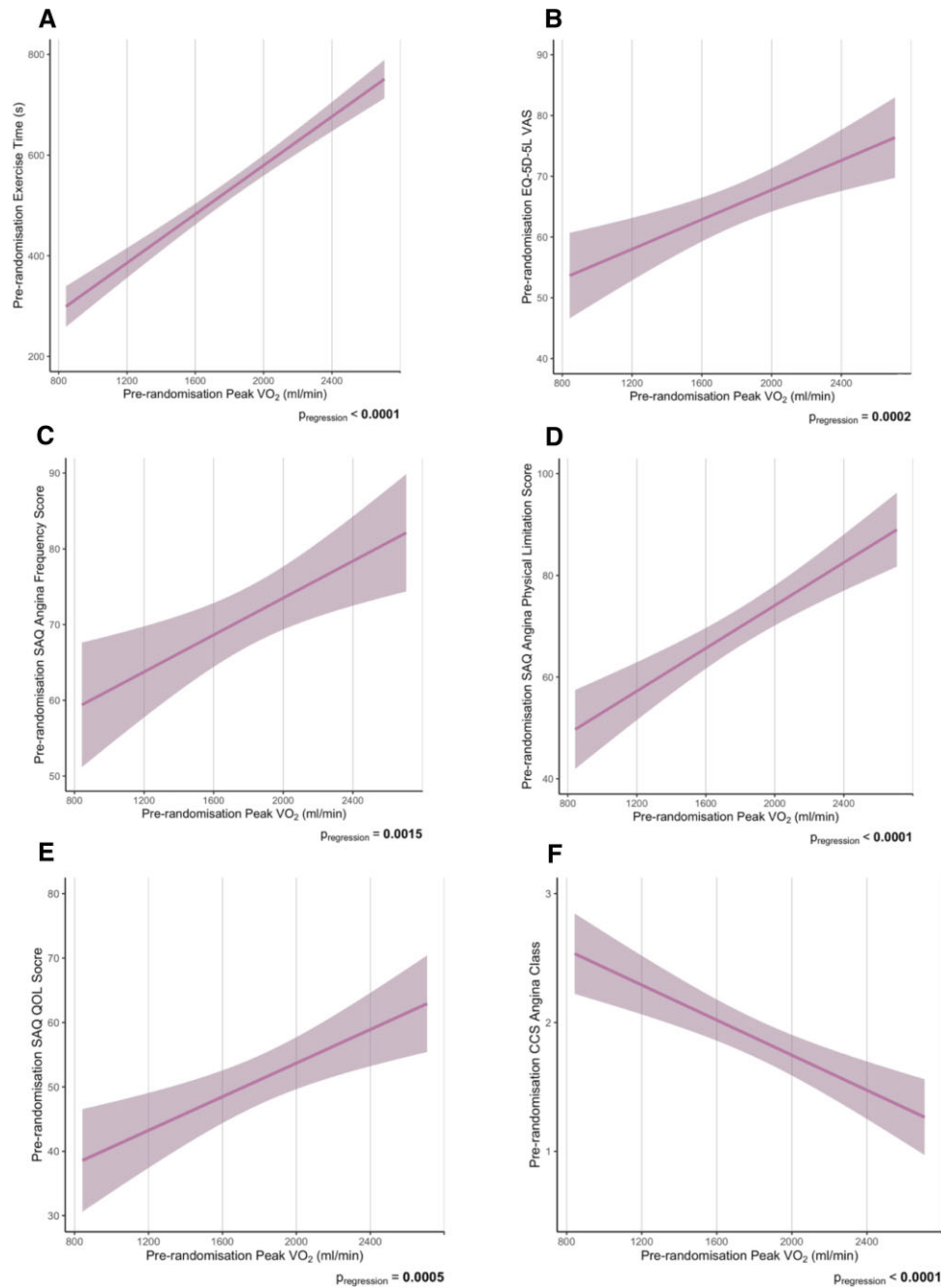
Percutaneous coronary intervention was more likely to result in improvement of SAQ angina-frequency score (OR: 1.73, 95% CI: 1.02–2.96,  $P = 0.0432$ , see Supplementary material online, Table S3) and lead to freedom from angina (OR 2.58, 95% CI: 1.35–4.92,  $P = 0.004$ , see Supplementary material online, Table S3) vs. placebo. However,

there was no detectable interaction between  $\text{O}_2$ -pulse morphology ( $\text{O}_2$ -pulse plateau presence  $P_{\text{interaction}} = 0.22$ ;  $P_{\text{interaction}} = 0.28$  and  $\text{O}_2$ -pulse gradient  $P_{\text{interaction}} = 0.76$ ,  $P_{\text{interaction}} = 0.99$ , Figure 4C–4D, respectively) and the effect of PCI on these study endpoints.

Similarly, there was no interaction between the pre-randomization  $\text{O}_2$ -pulse morphology and the placebo-controlled efficacy of PCI on SAQ QOL (Figure 4E), EQ-5D-5L VAS (Figure 4F), CCS class (Figure 4G), and exercise time (Figure 4H).

### Exercise capacity and other cardiopulmonary exercise testing parameters

There was no interaction between pre-randomization exercise capacity as assessed by exercise time or peak  $\text{VO}_2$  and the placebo-controlled efficacy of PCI on any of the study endpoints in this stratified analysis. Furthermore, there were no convincing interactions



**Figure 3** Relationship between pre-randomization peak  $\text{VO}_2$  and pre-randomization patient-reported and physician-assessed anginal symptoms including exercise time (A), EQ-5D-5L VAS (B), SAQ angina frequency score (C), SAQ angina physical limitation score (D), SAQ quality of life score (E) and CCS angina class (F). The shaded area represents the 95% CI for the estimate of this mean effect. Higher scores on the questionnaires indicate a better angina health status and quality of life. CCS indicates Canadian Cardiovascular Society; EQ-5D-5L indicates five level version of EuroQol 5 dimensions; QOL, quality of life; SAQ, Seattle Angina Questionnaire; VAS, visual analogue score;  $\text{VO}_2$ , oxygen uptake.  $P$  values were calculated from the regression model which was adjusted for age, weight, height, and sex.

between other CPET parameters such as  $\text{VE}/\text{VCO}_2$  slope, peak  $\text{O}_2$ -pulse, and OUES with the PCI study endpoints (see [Supplementary material online, Figures S6–S9](#)). These results were consistent, despite the finding that patients who had more impaired peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$ ,  $\text{O}_2$ -pulse, and OUES were more symptomatic and exercised for lesser times at baseline ([Figure 3](#)).

## Discussion

This is the first placebo-controlled analysis of the effect of revascularization with PCI in chronic coronary syndrome on VGE parameters during exercise. Principally, through an automated quantitative analysis of  $\text{O}_2$ -pulse morphology, we found that the



**Table 2** Placebo-controlled effect of PCI on CPET parameters, exercise haemodynamics and Duke treadmill score

CPET endpoint	ANCOVA estimate with the covariate modelled as a restricted cubic spline (PCI over placebo)	ANCOVA P-value
<b>CPET variable during exercise</b>		
Peak VO <sub>2</sub> (mL/min)	−8.03 (95% CI: −80.07 to 64.00)	0.826
Peak O <sub>2</sub> -pulse (ml/beat)	0.04 (95% CI: −0.65 to 0.73)	0.903
O <sub>2</sub> -pulse plateau presence	OR: 1.13 (95% CI: 0.56–2.26)	0.735
O <sub>2</sub> -pulse plateau gradient	−0.26 (95% CI: −0.60 to 0.087)	0.142
OUES	−40.72 (95% CI: −131.29 to 49.86)	0.376
VE/VCO <sub>2</sub> slope	0.22 (95% CI: −9.57 to 22.33)	0.431
Peak VE (L)	−1.35 (95% CI: −5.24 to 2.54)	0.495
Peak RER	0.0076 (95% CI: −0.020 to 0.035)	0.585
VO <sub>2</sub> at AT (mL/min)	2.22 (95% CI: −57.78 to 62.22)	0.942
<b>Exercise haemodynamics</b>		
Peak SBP (mmHg)	4.52 (95% CI: −2.56 to 11.59)	0.210
Peak HR (bpm)	−0.34 (95% CI: −3.86 to 3.18)	0.847
RPP (mmHg • bpm)	740.89 (95% CI: −432.65 to 1914.40)	0.215
<b>Duke treadmill score</b>		
Maximal ST-segment depression (mm)	−0.55 (95% CI: −1.10 to −0.02)	0.041
Treadmill angina index	OR: 1.07 (95% CI: 0.49–2.34)	0.869

Treatment effect estimates were generated using regression modelling. The follow-up values were modelled conditioned to pre-randomization value and treatment.

ANCOVA, analysis of covariance; AT, anaerobic threshold; bpm, beats per minute; CI, confidence interval; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; HR, heart rate; OUES, oxygen uptake efficiency slope; OR, odds ratio; RER, respiratory exchange ratio; RPP, rate pressure product; SBP, systolic blood pressure; VE, minute ventilation; VO<sub>2</sub>, oxygen uptake.

Estimates are either expressed as absolute values for continuous variables or odds ratios for discrete variables. Duke treadmill score was calculated as follows: Duration of exercise in minutes = (5 × the maximal net ST-segment deviation during or after exercise, in millimetres) − (4 × the treadmill angina index). The angina index has a value of 0 if the patient had no angina during exercise, 1 if the patient had non-limiting angina, and 2 if angina was the reason the patient stopped exercising.

presence of an O<sub>2</sub>-pulse plateau during CPET was associated with more ischaemia as assessed by DSE or invasive coronary physiology (FFR). The presence of an O<sub>2</sub>-pulse plateau also predicted greater reduction of DSE ischaemia and greater improvement in angina physical-limitation score at 6 weeks following placebo-controlled PCI. Secondly, we found that although a greater impairment of peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, peak O<sub>2</sub>-pulse and OUES was associated with more severe symptoms and worse QOL, these did not predict the placebo-controlled efficacy of PCI. Finally, we found that in comparison to a placebo procedure, PCI with drug-eluting stents had no significant effect on any conventionally reported measure of VGE during exercise (Graphical abstract).

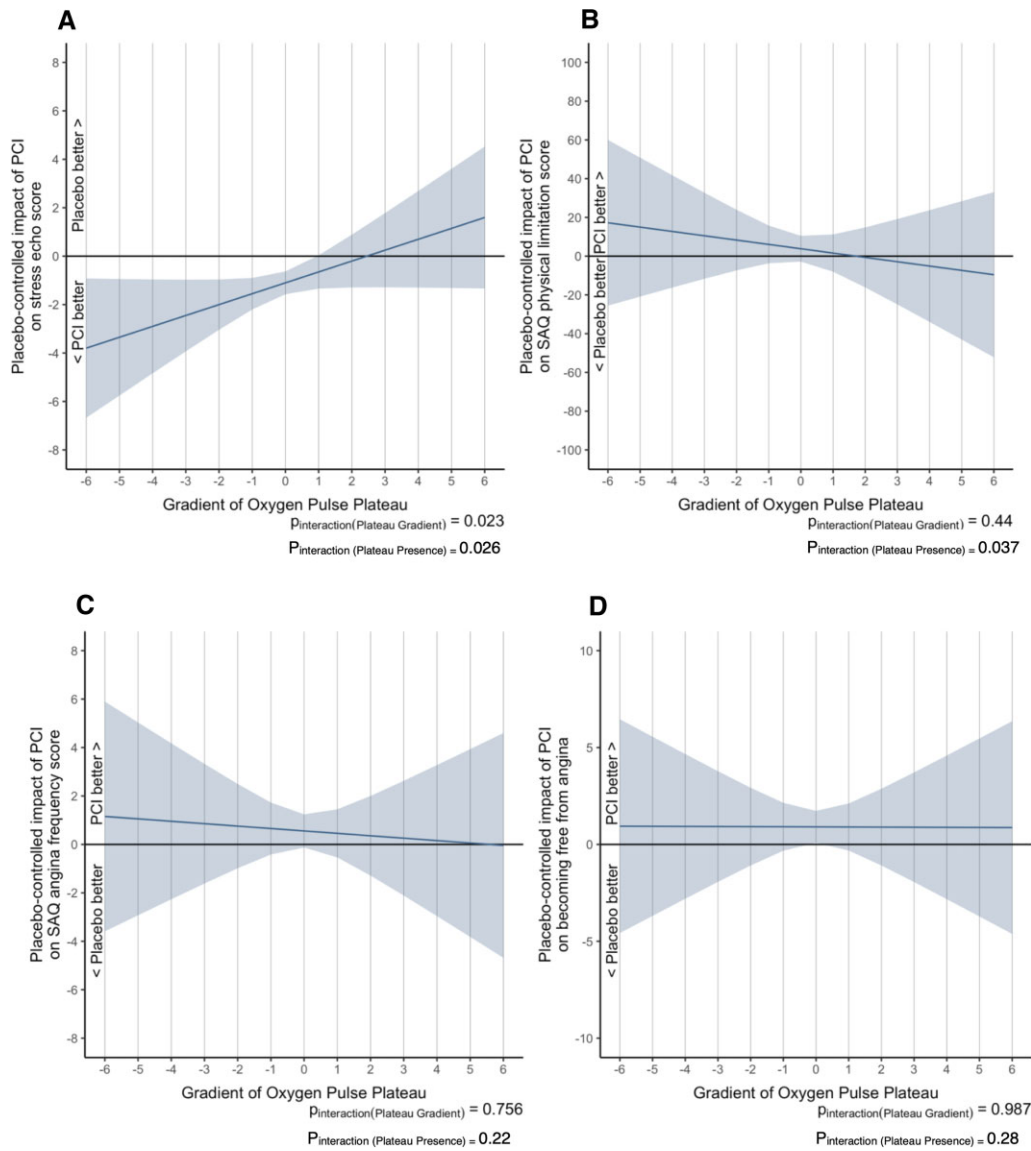
### Association between assessments at pre-randomization

We found that the presence of an O<sub>2</sub>-pulse plateau selected individuals with more ischaemia as evidenced by more wall motion abnormalities on DSE and lower FFR. This finding supports the theory that an O<sub>2</sub>-pulse plateau occurs when there is an inability to adequately increase the stroke volume response during exercise. While previous

studies solely utilized visual assessment and applied scoring scales to grade individual O<sub>2</sub>-pulse curves in relation to the normal appearance of the slope,<sup>12,15,31</sup> we provide a reproducible method which reduces bias from highly subjective categorization. Our sensitivity analysis for varying cut-offs of ratio and late slope gradient (shown in [Supplementary Appendix](#)) further emphasizes O<sub>2</sub>-pulse morphology as a physiological manifestation of ischaemia.

However, greater impairment of other CPET parameters (including peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, peak O<sub>2</sub>-pulse, and OUES) was not associated with more ischaemia. This finding contrasts with previously reported smaller, unblinded studies.<sup>32–34</sup> Although these selected parameters are not necessarily specific for cause of exercise limitation, the OUES, which was found to discriminate between circulatory and respiratory limitation, was equally not related to ischaemia severity.<sup>2</sup> Our blinded analysis is hence robust to these conclusions.

Despite this lack of association with severity of ischaemia, these CPET parameters did correlate with severity of symptoms and QOL in patients with single-vessel CAD, suggesting that a patient's exercise capacity is linked to the symptoms they report. Patients with the lowest exercise capacity (and consequently lowest peak



**Figure 4** Interaction between pre-randomization O<sub>2</sub>-pulse plateau gradient and the efficacy of placebo-controlled PCI on ORBITA endpoints. The shaded area represents the 95% CI for the estimate of this mean effect. In panels 4A, 4B, 4E, 4F, and 4H, the vertical axis shows the absolute improvement or worsening with PCI over placebo where an unweighted linear regression model was used to calculate the improvement or worsening in dobutamine stress echocardiography (DSE) scores, SAQ physical-limitation score, SAQ quality of life (QOL) score, EQ-5D-5L visual analogue score (VAS) and exercise time. In panels 4C, 4D, and 4G, the vertical axis shows the natural logarithm of the odds ratio for improvement or worsening with PCI over placebo where an ordinal cumulative probability model was used to calculate the improvement or worsening in SAQ angina frequency, becoming free from angina and CCS angina class. CCS, Canadian Cardiovascular Society; EQ-5D-5L indicates 5 level version of EuroQol 5 dimensions; PCI, percutaneous coronary intervention; SAQ; SAQ, Seattle Angina Questionnaire; VAS, Visual Analogue Score; VO<sub>2</sub>, oxygen uptake.

VO<sub>2</sub>), consistently reported the greatest angina symptom burden. The same relationship was observed for physician-assessed and patient-reported symptoms despite previous reported discrepancies between these metrics.<sup>35,36</sup> Similar associations were also observed with our VE/VCO<sub>2</sub> slope and the OUES, other indicators of functional capacity which incorporate volitional effort. Much like patients with chronic heart failure, potential mechanisms implicated in these exercise ventilatory efficiency abnormalities in patients with CAD include early lactic acidosis and greater sympathetic

and neurohormonal activation.<sup>37–39</sup> The symptom of angina may draw parallels with these impairments, leading to elevation of the VE/VCO<sub>2</sub> slope or decrease in OUES.

### Effect of percutaneous coronary intervention on ventilatory gas exchange

In ORBITA, PCI was found to be highly effective in normalizing the anatomical and physiological features of a coronary stenosis, and in

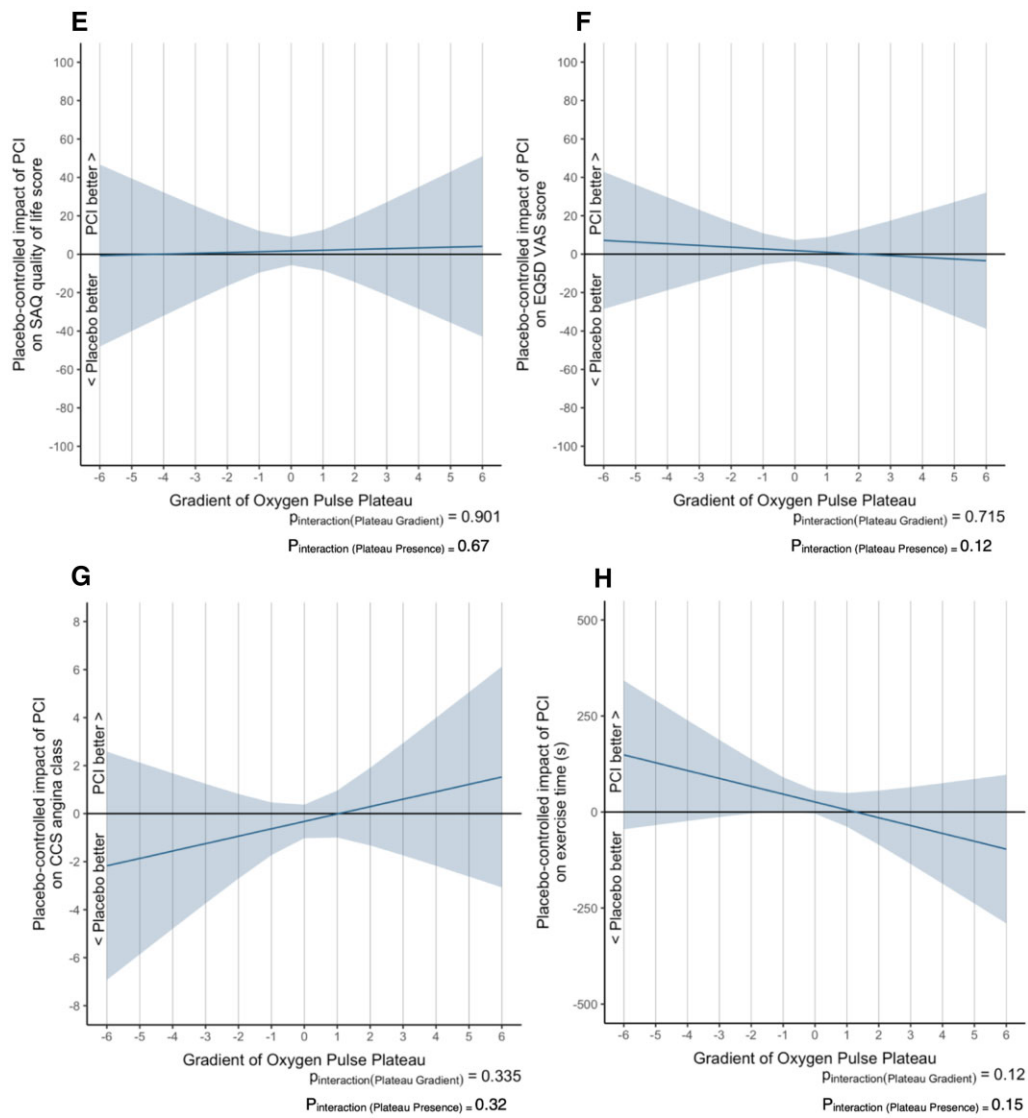


Figure 4 Continued

doing so, ischaemia was essentially eradicated in the active treatment arm. However, we found no effect of ischaemia eradication on exercise physiology (VGE and haemodynamics), contrasting with previous unblinded CPET and exercise haemodynamic studies.<sup>33,40</sup> Importantly, the lack of placebo control in unblinded studies increases the likelihood of misinterpretation of the placebo effect as a treatment effect.

Peak exercise measures are strongly influenced by volition and are limited by symptoms. Hence, they are endpoints highly vulnerable to bias in an unblinded trial. Indeed, patients who are aware of their treatment arm are more likely to be influenced by a therapy that is believed to improve symptoms, especially during the anticipation of these symptoms during exertion. Submaximal VGE measures such as the  $O_2$  uptake efficiency slope and anaerobic/ventilatory threshold aim to reduce the influence of subject motivation by consideration of a range of data points or by identification of frequently attained thresholds.<sup>41</sup> However, these parameters are determined by the operator

using methods which are subject to considerable interobserver variability. The subjective decisions of the physician to terminate CPET based on symptoms,<sup>42,43</sup> further emphasizes a point in the assessment chain that is, again, vulnerable to bias with an unblinded design.

Interestingly, we did not find a change in the  $O_2$ -pulse morphology following placebo-controlled PCI, again contrasting with previous studies.<sup>12,15</sup> Since this morphology incorporates volitional effort (also adjusted into our algorithm based on their total exercise time) and hence limited by symptom perception, there is considerable bias in the attainment of a plateau/slope of the morphology in unblinded trials. Furthermore,  $O_2$ -pulse morphology is based on other factors such as peripheral  $O_2$  extraction, a training effect and deconditioning.<sup>44,45</sup> It is therefore a global functional assessment as opposed to a simple measure of ischaemia. A follow-up of more than 6 weeks may have possibly been required to manifest a change in this metabolic endpoint of exercise along with other CPET parameters.

We found an improvement in the Duke treadmill score, driven by a decrease in ST-segment deviations in the PCI group compared with the placebo group. This improvement in an ischaemic endpoint is concordant with our analysis of placebo-controlled improvement in DSE scores,<sup>23</sup> suggesting a further point on the ischaemic cascade amenable to PCI. Whether this translates into improvement in long-term prognosis among our patients with single-vessel CAD remains uncertain.

## Baseline cardiopulmonary exercise testing as a predictor of placebo-controlled percutaneous coronary intervention

In patients enrolled in ORBITA, the average pre-randomization peak  $\text{VO}_2$  was 76% of the predicted value, whereas using anthropometric and resting  $\text{VO}_2$  measurements in our patient cohort, the average metabolic equivalent of task was between 4.85 and 6.10. These values are well below age predicted normal ranges.<sup>46</sup> This suggests that the disparity of our results with previous studies and the unexpected primary result of ORBITA on exercise time, was not due to enrolment of patients with a 'well-preserved' exercise capacity at baseline and hence less likely to benefit from PCI.

However, for the prediction of patients most able to benefit symptomatically from PCI, it has previously been reported that patients with a lower baseline peak  $\text{VO}_2$  ( $\leq 15$  ml/kg/min) derived more benefit following revascularization, with greater improvements in exercise capacity compared with patients who were less impaired at baseline.<sup>13,47</sup> In direct contrast, however, we found no association between pre-randomization exercise capacity assessed by peak  $\text{VO}_2$  or exercise time (or other CPET parameters) and the placebo-controlled effect of PCI on nearly all symptom endpoints. We treated exercise capacity as a continuum using high quality VGE data, rather than estimates solely from treadmill time and speed, hence permitting a more sensitive interpretation. However, despite this, baseline CPET parameters (peak  $\text{VO}_2$ ,  $\text{VE}/\text{CO}_2$  slope, peak  $\text{O}_2$ -pulse, and OUES) which significantly relate to symptoms burden, QOL, and exercise capacity, were also not able to predict which patients would likely benefit from PCI on most endpoints.

Only the  $\text{O}_2$ -pulse morphology at baseline predicted the placebo-controlled efficacy of PCI on DSE scores (both gradient and presence of plateau) and angina physical limitation (only presence of plateau). The  $\text{O}_2$ -pulse morphology was associated with greater ischaemia on DSE and FFR (ischaemic potential) at pre-randomization. Hence, this finding establishes the  $\text{O}_2$ -pulse morphology as an important physiological parameter. Although the  $\text{O}_2$ -pulse morphology is not linearly related to the severity of ischaemia,<sup>11</sup> its presence indicates more severe ischaemia which is amenable to intervention. This finding also suggests that eradication of ischaemia on DSE is related to patient-reported angina, concordant with our previous DSE stratified analysis.<sup>23</sup>

## Clinical implications

Primary analysis of the ISCHAEMIA trial<sup>48</sup> and previously from COURAGE<sup>49</sup> have suggested that coronary revascularization, in addition to medical therapy, does not lead to reduction in all-cause mortality or risk of ischaemic cardiovascular events. Subsequent

hypothesis-generating secondary analyses of ISCHAEMIA have suggested that the results may be more nuanced than at first considered. For example, greater ischaemia burden at baseline or presence of lesions such as proximal left anterior descending artery stenosis of  $\geq 70\%$ , were not associated with greater risk<sup>50</sup>; Type 1 myocardial infarction rates were more frequent with the conservative strategy<sup>51</sup> and that the invasive strategy lowered cardiovascular death and myocardial infarction rates in those with the most extensive anatomic disease.<sup>50</sup> More data are required to understand which patients are most likely to benefit from PCI but it does seem that in the majority, the primary remit of PCI is symptom relief.

Given that ORBITA demonstrated a smaller than expected effect size of PCI vs. placebo for angina relief in patients with single-vessel disease, it is key to determine which patients would benefit symptomatically from this invasive procedure.<sup>18</sup> Intracoronary pressures measured invasively (FFR/iFR) did not show a detectable ability to predict symptom relief from PCI.<sup>24</sup> However, non-invasive ischaemia testing using DSE<sup>23</sup> and in this analysis,  $\text{O}_2$ -pulse morphology from CPET, suggested that the presence of a greater burden of ischaemia at pre-randomization predicted a greater placebo-controlled effect of PCI.

Although our results, and those of previous studies, suggest that CPET may provide improved granularity in the evaluation of patients with chronic coronary syndrome compared with standard exercise testing, there may be multiple reasons that have meant that CPET has not been integrated into routine clinical practice in this condition. Expert staff are required for calibration, administration, and interpretation of test results, and facial masks or mouthpiece use may cause discomfort for some patients. Furthermore, exercise testing may not be suitable in all patient groups.<sup>5</sup>

However, once these challenges are met, incorporation of CPET in clinical practice is relevant, practical and potentially cost-effective. In patients presenting with symptoms attributed to stable CAD and ischaemia manifested as an  $\text{O}_2$ -pulse plateau, CPET may select patients who are most likely to derive symptomatic benefit from PCI thereby allowing intervention to be targeted to those patients who are most likely to benefit from the procedure.

## Limitations

This CPET-stratified analysis of ORBITA incorporated 195 patients (97.5%) of the original cohort and is therefore the largest analysis to date examining the relationship between baseline exercise capacity and symptomatic improvement following PCI. Despite this, the sample size may limit the power of this analysis since the effect of PCI on the primary endpoint of exercise times (and symptoms) was smaller than expected. Matched pre-post data for study endpoints were also not available for all patient in this stratified analysis (see [Supplementary material online, Table S3](#)); 79.4% of participants (155/195) had paired (pre- and post-) DSE scores: 86.3% in the PCI arm (88/102) and 72.0% in the placebo arm (67/93). There is a potential for selection bias if the remaining patients differed in some way. Furthermore, only 30% of participants in this analysis were women and it has been shown that women have more frequent angina and less severe ischaemia than men.<sup>52</sup>

Our assessments of VGE, exercise capacity and symptom severity are vulnerable to the presence of possible alternative confounding diagnoses, which may be an explanation for the absence of

association with myocardial ischaemia in most CPET parameters. However, the patients enrolled into ORBITA were deemed to be symptomatic from their epicardial coronary stenosis and were candidates listed for PCI.<sup>18</sup> Indeed, cardiac dysfunction detected by CPET also identifies a global ischaemic burden, including ischaemia from non-obstructive coronary arteries. In ORBITA, we did not quantify coronary flow reserve or microvascular resistance. Similarly, antianginals such beta-blockers (despite a blunted heart rate response) and ranolazine have shown to improve peak  $\text{VO}_2$  through enhanced microcirculatory and endothelial function.<sup>53–55</sup> Hence, the effect of intensive guideline-directed medical therapy at pre-randomization may have also reduced the incremental effect size from PCI. Cardiopulmonary exercise testing was not performed at enrolment, therefore we do not know the effect size of medical therapy alone on VGE in patients with stable CAD.<sup>56</sup>

Although we used treadmill testing, studies identifying exercise-induced myocardial ischaemia with CPET have previously utilized cycle ergometry.<sup>7</sup> Cycle ergometry permits assessment of the HR/WR slope and the  $\text{O}_2$  uptake work rate ( $\Delta\text{VO}_2/\Delta\text{WR}$ ) slope, which allows estimation of the exercise load at which myocardial ischaemia develops.<sup>57</sup> Treadmill CPET does not allow for these measurements as work rate is not expressed as Watts and does not increase linearly. However, treadmill testing confers a more physiological and familiar form of daily exercise that reduces localized fatigue and works larger muscle groups. Hence, treadmill testing typically produces a greater peak  $\text{VO}_2$  and haemodynamic response within an individual compared with cycle ergometry. These are potential reasons why treadmill testing has recently appeared more reliable than cycle ergometry in CAD quantification.<sup>9</sup>

Finally, ORBITA recruited patients with single-vessel CAD. All patients were taking optimal medical therapy with a mean number of three anti-anginal agents at the time of the pre-randomization tests. ORBITA-2 (NCT03742050) is recruiting patients with single and multi-vessel disease taking real-world anti-anginal therapy and will therefore test the placebo-controlled efficacy of PCI in wider range of patients.

## Conclusion

Although CPET parameters relate to severity of angina symptoms and quality of life, only the presence of an  $\text{O}_2$ -pulse plateau detects the severity of myocardial ischaemia and predicts the placebo-controlled efficacy of PCI in patients with stable single-vessel CAD.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Acknowledgements

The authors are grateful for infrastructural support from the NIHR Imperial Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

## Funding

C.A.R. (MR/S021108/1) and M.F. (MR/V001620/1) are supported by the Medical Research Council (United Kingdom). A.N.N. was supported by

the NIHR Academy. R.P. (FS/11/46/28861), D.F. (FS 04/079), and M.S.-S. (FS/14/27/30752) were supported by the British Heart Foundation. J.H. was supported by the Wellcome Trust (212183/Z/18/Z).

**Conflict of interest:** S.G., C.A.R., M.F., D.T., R.W., D.F., and R.P. have nothing to disclose. A.N.N. reports receiving support for a Doctoral Fellowship by the NIHR Academy which was paid to her institution. H.S. reports research funding from the Imperial College COVID research fund and the Foundation for Circulatory Support. S.S. reports individual grants from Medtronic and Phillips and speaker's honoraria from Medtronic, Phillips and Pfizer. S.N. reports consulting and speaking fees from Phillips Volcano. S.A.T. reports an unpaid leadership role with the UK National Institute for Health Research cardiovascular advisory panel. J.D. reports receipt of consulting fees (from Boston Scientific, Abbott and Medtronic), speaker's honoraria (from Pfizer, Bayer and Novartis), and equipment support (from Abbott and Terumo). M.S.-S. reports speaker's honoraria from Pfizer. J.H. reports a small cardiac MRI project grant from the Academy of Medical Sciences. R.A.-L. reports speaker's honoraria from Philips Volcano, Abbott Vascular, and Menarini Pharmaceuticals.

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