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Coronary Microvascular Resistance as a Predictor of the Placebo-Controlled Response to Percutaneous Coronary Intervention

Microvascular-Stratified Analysis of ORBITA

Daniel J Taylor[1,2,3] MBChB MRes, Eron Yones[1,4] MRCP MD, Tom Newman[1,2,3,4] MRCP, Rebecca Gosling[1,2,3,4] MRCP PhD, Ian Halliday[1,2] PhD, Xu Xu[2,5] PhD, Harry Saxton[2,5] PhD, Krzysztof Czechowicz[1,2] PhD, Andrew Narracott[1,2] PhD, Alberto Biancardi[1,2] PhD, Rod Hose[1,2] PhD, Matthew J Shun-Shin[6,7] MRCP PhD, Julian P Gunn[1,2,3,4] MRCP PhD, Rasha Al-Lamee[6,7] MRCP PhD, Paul D Morris[1,2,3,4] MRCP PhD

[1]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK
[2]Insigneo Institute for in silico medicine, University of Sheffield, Sheffield, UK
[3]NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[4]Department of Cardiology and Cardiothoracic Surgery, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK
[5]School of Computer Science, University of Sheffield, Sheffield, United Kingdom
[6]Imperial College London, London, UK
[7]Imperial College Healthcare NHS Trust, London, UK

Correspondence: Dr Daniel J Taylor, The Medical School, University of Sheffield, Beech Hill Road, Sheffield, S102RX, United Kingdom. Telephone +44 (0) 114 2712863. Email: daniel.taylor@sheffield.ac.uk

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Abstract

Background: The first placebo-controlled trial of percutaneous coronary intervention (PCI), ORBITA (NCT02062593), found minimal symptom benefit with PCI. No placebo-controlled data describing the relationship between microvascular resistance (MVR) and PCI exist. We hypothesized patients with low MVR would derive the greatest benefit from PCI.

Objectives: Compute MVR in patients recruited to ORBITA and evaluate interaction with pre-specifed endpoints.

Methods: Hyperaemic MVR was calculated using computational fluid dynamics (MVR_{CFD}) and compared against placebo-controlled changes in treadmill exercise time, patient-reported symptoms, physician-assessed symptoms and dobutamine stress echocardiography scores at six weeks follow-up.

Results: MVR_{CFD} was computed for 131 patients (66 PCI and 65 placebo). Median MVR_{CFD} was 1.38 [0.89 – 2.09] mmHg.min/mL. Baseline exercise time correlated with MVR_{CFD} (ordinal correlation coefficient=0.20, 95% Credible Interval (CrI) 0.18 to 0.22). For patients with low (20^{th} centile) MVR_{CFD}, PCI increased exercise time by 48 seconds versus placebo (95% CrI 6 to 92 seconds, Pr=98.5%). Exercise time did not improve for patients with high (80^{th} centile) MVR_{CFD} (16 seconds, 95% CrI -29 to 61, Pr=75.2%), however, evidence for an interaction was modest ($Pr_{interaction}$=83.1%). A low MVR_{CFD} was also associated with a placebo-controlled benefit of PCI for likelihood of complete freedom from angina (Pr=98.8%) and improvements in angina frequency (Pr=97.8%) and stress echocardiography scores (Pr=99.9%).

Conclusions: The placebo-controlled benefit of PCI was greater in patients with a lower MVR_{CFD}, however, interactions with symptom-based endpoints were modest. For patients with severe single vessel disease, taking optimal medical therapy, microvascular dysfunction may attenuate functional and symptomatic benefits of PCI.

Keywords: Microvascular dysfunction, chronic coronary syndrome, ischaemia, percutaneous coronary intervention, computational fluid dynamics

Condensed abstract

In this sub-analysis of ORBITA, hyperaemic microvascular resistance (MVR) was retrospectively calculated in 131 patients and compared with trial outcomes. For patients with low (20^{th} centile) MVR, PCI increased exercise time by 48 seconds versus placebo (95% CrI 6 to 92 seconds, probability of significant difference (Pr)=98.5%). Low MVR was associated with a benefit of PCI for complete freedom from angina (Pr=98.8%), reduced angina frequency (Pr=97.8%) and improved stress echocardiography score (Pr=99.9%). In patients with elevated (80^{th} centile) MVR, PCI offered no benefit. This suggests microvascular physiology may modify symptomatic benefits of PCI in patients taking optimal medical therapy.

Abbreviations

PCI- Percutaneous coronary intervention

CAD- Coronary artery disease

FFR- Fractional flow reserve

DSE- Dobutamine stress echocardiography

CMD- Coronary microvascular dysfunction

MVR- Hyperaemic microvascular resistance

SAQ- Seattle angina questionnaire

EQ-5D-5L- Quality of life EuroQOL 5

CCS- Chronic coronary syndrome

CFD- Computational fluid dynamics

Introduction

Percutaneous coronary intervention (PCI) is a mainstay of treatment for anginal symptoms caused by flow-limiting epicardial coronary artery disease (CAD) (1) and this practice is supported by several previous, unblinded trials (2-4). The first placebo-controlled trial of PCI, ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina), challenged this belief. ORBITA recuited patients with severe single vessel epicardial disease already treated with maximal antianginal medication and showed that PCI did not lead to significant improvements in exercise capacity or symptoms compared with a placebo intervention (5). This was despite the inclusion of physiologically significant lesions (mean fractional flow reserve (FFR) 0.69) and objective evidence confirming myocardial ischaemia in almost all recruited patients. The lack of a significant benefit of PCI was independent of physiological lesion severity (6), or disease pattern (7), with no evidence of an interaction between FFR or instantaneous wave-free ratio with the placebo-controlled efficacy of PCI on exercise time and both patient-reported and physician-assessed symptoms. PCI in ORBITA did however improve dobutamine stress echocardiography (DSE) score. A subsequent sub-analysis showed this effect was predicted by invasive physiology, with greater improvements in DSE score with decreasing FFR and iFR (6).

The somewhat unexpected findings were suggested to have resulted from a complex pathway in the progression from luminal stenosis, to flow-limiting epicardial disease, stress myocardial ischaemia, and ultimately, patient symptoms (8). Limitations in diagnostic techniques may also have contributed; the pre-randomisation ischaemia testing did not include a focused assessment of coronary

microvascular dysfunction (CMD). This may have been important given the prevalence of CMD across the spectrum of chronic coronary syndromes (CCS) (1, 9) and remains a limitation of the original ORBITA study (5) and subsequent sub-analyses (8, 10). Established measures for quantifying microvascular resistance include Doppler-derived hyperaemic microvascular resistance and bolus thermodilution-derived index of microvascular resistance. However, these are indirect surrogates of flow and, even in expert hands, poorly correlate with each other (11). Invasive quantification of absolute hyperaemic microvascular resistance (MVR) is the emerging gold-standard assessment, but requires a dedicated continuous infusion thermodilution catheter (12) which was not used in the ORBITA trial. Recent developments in computational fluid dynamics (CFD) have allowed post-hoc computation of absolute coronary blood flow and MVR (MVR_{CFD}) from standard angiography and pressure wire data (13). In this retrospective analysis of the ORBITA dataset, we computed MVR_{CFD} and assessed its impact on the placebo-controlled effect of PCI on the primary and secondary endpoints of ORBITA.

Methods

ORBITA design and clinical data collection

ORBITA was a double-blind, randomised, controlled trial of PCI versus a placebo procedure in patients aged 18−85 years with stable angina and angiographically severe single-vessel coronary disease (≥70% stenosis). Patients were recruited across five study sites in the UK and randomised between Jan 6, 2014, and Aug 11, 2017. The full design has been previously reported (5). In brief, enrolled patients entered an initial six-week medical optimisation phase, where antianginal medications were uptitrated followed by pre-randomisation assessment including:

- Cardiopulmonary exercise testing with smoothed modified Bruce protocol (14)
- Patient-reported symptoms using the Seattle Angina Questionnaire (SAQ)
- Patient-reported symptoms using the Quality of life EuroQOL 5 (EQ-5D-5L) questionnaire
- Physician-assessed grading of angina severity (CCS class)
- DSE with each scan examined twice by six blinded imaging cardiology consultants. Wall motion was scored to represent the number of hypokinetic segments (6).

Enrolled patients then underwent blinded invasive coronary angiography, including blinded FFR and iFR assessment performed twice, according to standard techniques (15). After invasive physiologic assessment, patients were randomised 1:1 to either PCI or a placebo procedure. For patients allocated to intervention, the use of intravascular imaging was encouraged and post-PCI physiology was measured as part of the study protocol with a mandate to achieve complete revascularisation. Patients then entered a blinded six-week follow up period, at the end of which, all pre-randomisation assessments were repeated. The study was approved by a national ethics committee, compliant with the Declaration of Helsinki and all patients provided informed written consent. The ORBITA trial was registered with ClinicalTrials.gov, number NCT02062593.

Virtual physiologic assessment

Offline virtual physiologic quantification of MVR_{CFD} was performed at the University of Sheffield, UK, using virtuQ, an in-house developed CFD software package. This technique reconstructs a virtual 3D coronary artery, representative of

patient-specific coronary anatomy, and applies invasively measured pressures to derive MVR_{CFD} (Central illustration). A complete description of the virtuQ methodology, along with benchtop and *in-vivo* validation has been reported previously (13). Two angiographic projections of the vessel of interest, acquired at least 30° apart and during end-diastole, were manually selected and co-registered. The vessel centreline and luminal border were then traced semi-automatically in both images, with manual correction if required. The reconstructed vessel inlet and outlet corresponded to the location of proximal and distal pressure measurements during invasive FFR assessment. All reconstructions were performed by an operator blinded to invasive physiology and then checked for anatomical accuracy by a blinded interventional cardiologist with experience in computer modelling of coronary arteries.

Raw invasive physiology data from each reconstructed case were interrogated using a custom proprietary software (University of Sheffield) to compile transient pressure signals across several cardiac cycles. Transient pressure signals under hyperaemic conditions were compiled across a target ten and minimum five continuous cardiac cycles. This was performed for both FFR measurements and then averaged. The invasive pressure data defined inlet and outlet boundary conditions for CFD analysis. Simulations were performed using standard blood rheological parameters (density 1056 kg/m3; viscosity 0.0035 Pa s) and simulated regionalised side branch flow according to vessel taper, with a flow-diameter scaling exponent of 2.33 (16, 17). Absolute MVR_{CFD} was calculated by dividing distal pressure by distal flow and is reported as mmHg.min/mL. Thus, MVR_{CFD} was computed in the distal vessel, corresponding to the location of the pressure wire

transducer and is specific for microvascular physiology even in the context of epicardial stenoses. This contrasts with continuous thermodilution (12), which considers proximal resistance (corresponding to a higher subtended myocardial mass) and gives lower resistance values which are not microvascular-specific in the conext of epicardial stenoses. All research team members involved in processing data for the purpose of CFD simulations did so fully blinded to the clinical outcomes.

Statistical Analysis

This microvascular resistance-stratified sub-analysis of ORBITA considered patients with invasive physiological data taken at pre-randomisation under hyperaemic conditions. Summary statistics are presented as frequency (percentage), mean (standard deviation) and median [interquartile range] as appropriate. Correlation between pre-randomisation assessments with MVR_{CFD} was assessed using Somer's D (D_{xy}).

To assess the impact of MVR_{CFD} on the placebo-controlled response to PCI, ordinal (proportional odds) regression modelling was used. The follow-up value was conditioned on the pre-randomisation value, with non-linearity allowed using a restricted cubic spline with 3 knots (at the 10th, 50th and 90th centile), and randomisation arm and MVR_{CFD}. The randomisation arm was allowed to interact with MVR_{CFD}. For freedom of angina, a logistic regression model was used. All regression modelling was performed within a Bayesian framework. For the intercepts, priors were induced by a Dirichlet distribution on the cell probabilities where all covariates were set to their means. This enforced a strict ordering of the intercepts since they are defined by logits of cell probabilities accumulated over increasing values of the

response. For the treatment effect (log odds ratio (OR)), the prior was normal with mean zero and standard deviation chosen such that the prior probability that the OR < 0.25 equalled the prior probability OR > 4 with both equalling 0.05. Thus, the analysis was sceptical about the treatment effect being large in either direction. For covariates, a virtually flat prior was used, I.e., a distribution with mean 0 and standard deviation of 100 on a normalized covariate scale.

For all end points, the Markov chain Monte Carlo (MCMC) process used 4 chains with 20,000 samples (with 10,000 burn-in iterations). We calculated the relative explained variance of the interaction between the randomisation arm and MVR_{CFD} along with its probability value ($Pr_{interaction}$). To aid clinical interpretability, we also present a contrast derived from the model of a "typical" patient at the 20^{th} against the 80^{th} centile of MVR_{CFD}. This may be interpreted as the expected placebo-controlled benefit of PCI on outcome variables for patients with low and high MVR_{CFD} respectively. Results are therefore reported as the median placebo controlled effect of PCI, with associated 95% Credible Interval (CrI) and probability of significant benefit favouring PCI versus placebo (Pr) for low and high MVR_{CFD} patients, followed by quantification of the interactional effect ($Pr_{interaction}$) across the entire patient cohort. The regression model specifications, concentration parameters for Dirichlet priors, output, chain mixing plots, and density plots are included in the supplementary material. All analyses were performed in R, software version 4.4.1, using the rmsb package for Bayesian modelling and ggplot2 for graphs.

Results

From the 200 patients in ORBITA, 131 (66 from PCI, 65 from placebo) were included in this virtual physiology sub-analysis. Of the excluded patients, 39 did not have sufficient angiographic data, 18 had coronary anatomy unsuitable for vessel reconstruction, seven lacked hyperaemic pressure data and five successfully reconstructed vessels failed to reach CFD simulation convergence (supplementary).

Patient Demographics

The baseline data of the patients included in this sub-analysis are shown in table 1. Over 95% of patients had physician-assessed CCS class II or III angina severity at enrolment (n=82/131 (62.6%), n=46/131 (35.1%) respectively).

Medical Therapy

At pre-randomisation, 98.5% (129/131) of patients were taking dual antiplatelet therapy, with two patients intolerant to aspirin. Of the 131 included patients, 120 (91.6%) were taking a calcium channel antagonist, while 105 (80.2%) were taking a beta-blocker. After the medical optimisation phase, 28 (21.4%) of the 131 patients had CCS class 0 or I angina severity (supplementary tables 1 – 3).

Procedural Demographics

Of the 131 included patients, almost all (n=128, 97.7%) had at least one positive ischemia test at the time of randomisation, which included a pre-enrolment investigation, research DSE or physiologically significant trans-lesional pressure assessment (FFR ≤0.80 or iFR ≤0.89). All patients in the PCI arm received drug-eluting stents. Procedural demographics are shown in table 2. Most lesions were in the left anterior descending artery (n=103/131, 78.6%) and were frequently in the

proximal/ostial vessel (n=70/131, 53.4%). The mean FFR was 0.69 ±0.16 and 96 (n=96/131, 73.3%) patients had FFR ≤0.80. Mean FFR in the subgroup of patients with FFR significant disease (FFR ≤0.80) was 0.63±0.13; in the remainder this was 0.87±0.04. For computed virtual physiology, distributions of MVR_{CFD} and hyperaemic inlet and outlet flow are shown in the supplementary material. Median MVR_{CFD} was 1.38 [0.89 – 2.09] mmHg.min/mL. Patients were followed by for a median 6 [6 – 6] weeks after randomisation.

Study End Points

Exercise Time

At baseline there was mild evidence of a relationship between MVR_{CFD} and exercise time (ordinal correlation coefficient, 0.20; 95% Credible Interval (CrI) 0.18 to 0.22). Paired pre-randomisation and follow-up exercise time data were available for 129 patients (63 PCI, 66 placebo). Mean pre-randomisation exercise time was 495 ±188 seconds. For a patient with low MVR_{CFD} (0.77 mmHg.min/mL), PCI increased exercise time by a median 48 seconds versus placebo (95% CrI 6 to 92, Pr=98.5%). For a patient with high MVR_{CFD} (2.43 mmHg.min/mL), PCI increased exercise time by a median 16 seconds (95% CrI -29 to 61, Pr=75.2%) versus placebo (table 3). There was modest evidence for this interaction ($Pr_{interaction}$=83.1%, Central illustration, supplementary).

Dobutamine Stress Echocardiography

At baseline there was no evidence of a relationship between MVR_{CFD} and DSE score (ordinal correlation coefficient, 0.015; 95% CrI -0.038 to 0.047). Paired pre-randomisation and follow-up DSE data were available for 107 patients (48 PCI,

59 placebo). Mean pre-randomisation DSE score was 1.55 ±1.75. For a patient with low MVR_{CFD}, PCI decreased stress echocardiography score by a median 0.83 versus placebo (95% CrI -1.42 to -0.30, Pr=99.9%). For a patient with high MVR_{CFD}, PCI decreased stress echocardiography score by a median 0.10 units (95% CrI -0.63 to 0.42, Pr=65.9%) versus placebo (table 3). There was good evidence for this interaction ($Pr_{interaction}$=96.5%, Central illustration, supplementary).

Patient-Reported Symptoms and Quality of Life

At baseline there was no evidence of a relationship between MVR_{CFD} and freedom from angina (ordinal correlation coefficient, 0.17; 95% CrI -0.12 to 0.33). Paired pre-randomisation and follow-up data from the patient-reported SAQ were available in 127 patients (63 PCI 64 placebo). At pre-randomisation, 105 (82.7%) patients had angina. For a patient with low MVR_{CFD}, PCI increased log odds of complete freedom from angina by a median 1.24 versus placebo (95% CrI 0.16 to 2.38, Pr=98.8%). For a patient with high MVR_{CFD}, PCI increased log odds of complete freedom from angina by a median 0.10 (95% CrI -1.07 to 1.25, Pr=57.1%) versus placebo (table 3). There was modest evidence for this interaction ($Pr_{interaction}$=90.0%, figure 2A, supplementary).

At baseline, there was weak evidence of a relationship between MVR_{CFD} and SAQ angina frequency (ordinal correlation coefficient, 0.12; 95% CrI 0.01 to 0.15). Mean pre-randomisation SAQ angina frequency score was 71.7 ±23.4 points. For a patient with low MVR_{CFD}, PCI improved angina frequency score by a median 7.67 points versus placebo (95% CrI 0.25 to 15.6, Pr=97.8%). For a patient with high MVR_{CFD}, placebo improved angina frequency score by a median 0.25 points (95%

CrI -9.24 to 8.80, Pr=47.8%) versus PCI (table 3). There was modest evidence for this interaction ($Pr_{interaction}$=89.2%, Figure 2B, supplementary).

At baseline, there was mild evidence of a relationship between MVR_{CFD} and SAQ physical limitation score (ordinal correlation coefficient, 0.257; 95% CrI 0.250 to 0.258). Mean pre-randomisation SAQ physical limitation score was 67.7 ±24.7 points. For a patient with low MVR_{CFD}, PCI improved physical limitation score by a median 7.88 points versus placebo (95% CrI -0.01 to 15.5, Pr=97.9%). For a patient with high MVR_{CFD}, PCI improved physical limitation score by a median 8.96 points (95% CrI -0.92 to 17.8, Pr=96.6%) versus placebo (table 3). There was no evidence of an interaction between MVR_{CFD} with improvement in SAQ physical limitation score ($Pr_{interaction}$=43.6%, figure 2B, supplementary).

There was no strong evidence of interaction with MVR_{CFD}, or a difference in treatment outcome in low versus high MVR_{CFD} patients, for SAQ treatment satisfaction ($Pr_{interaction}$=80.2%), SAQ quality of life ($Pr_{interaction}$=61.2%), SAQ angina stability ($Pr_{interaction}$=29.6%), EQ-5D-5L quality of life ($Pr_{interaction}$=69.7%) or EQ-5D-5L visual analogue scale scores ($Pr_{interaction}$=34.7%)(table 3, supplementary).

Physician-Assessed Symptoms

At baseline, there was mild evidence of a relationship between MVR_{CFD} and physician-assessed CCS class (ordinal correlation coefficient, 0.26; 95% CrI 0.21 to 0.27). Paired pre-randomisation and follow-up physician-assessed CCS class data were available for 129 patients (63 PCI, 66 placebo). Median pre-randomisation CCS class was 2 [2 – 3]. For a patient with low MVR_{CFD}, PCI increased CCS class by a

median 0.10 versus placebo (95% CrI -0.41 to 0.64, Pr=35.8%). For a patient with high MVR_{CFD}, PCI decreased CCS class by median 0.05 (95% CrI -0.48 to 0.57, Pr=57.0%) versus placebo (table 3). There was no evidence of an interaction between MVR_{CFD} with improvement in physician-assessed CCS class ($Pr_{interaction}$=63.7%, supplementary).

Discussion

This study provides the first placebo-controlled data on the association between CMD with the benefits of PCI. The results suggest a relationship between microvascular physiology and response to PCI which is both biologically cogent and consistent across multiple outcome measures. Low MVR_{CFD} was associated with benefit of PCI versus placebo for exercise time, likelihood of complete freedom from angina, reduction in angina frequency and DSE score, however, the evidence for interactions with symptom-based endpoints were modest. For all these outcome variables, the presented results suggest patients with high MVR_{CFD} (80^{th} centile, indicating worse CMD) are unlikely to gain benefit of PCI versus placebo.

Ability of MVR_{CFD} to predict primary and secondary outcomes

ORBITA highlighted the need for placebo-controlled randomised trials in the treatment of stable angina. PCI was not associated with any significant improvement in exercise time, beyond the effect of the placebo (5), and stratification according the FFR and iFR did not help to select patients who might symptomatically benefit from PCI (6). The mechanism by which relief of occlusive epicardial stenoses translates to improvement in patient exercise capacity is complex (8). Despite randomisation and the presence of maximal antianginal medication, it is possible that concomitant CMD

may have attenuated the benefit of PCI for some patients in ORBITA (5). Results of the current sub-analysis suggest this may be true; in patients with low MVR_{CFD}, PCI offered an improvement in exercise time of around 50 seconds versus placebo, with a 97.1% chance of this representing benefit favouring PCI versus placebo. Despite this being the first evidence of an interactional effect on the placebo-controlled effect of PCI on exercise time in patients treated with anti-anginal medication, the expected incremental improvement in exercise time was lower than that attributed to balloon angioplasty in the unblinded Angioplasty Compared to Medicine (ACME) trial (4). It is therefore likely that the placebo effect of PCI remains significant even in those with no evidence of CMD.

Computed MVR was also associated with several patient-centred secondary endpoints. The strongest association was with complete freedom from angina, which is often the ultimate goal of treatment. Of those included in this sub-analysis, a patient with low (20^{th} centile) MVR_{CFD} might expect a 3.5-times greater likelihood of complete freedom from angina when treated with PCI versus placebo. Contrastingly, these benefits of PCI almost disappear in patients with high MVR_{CFD}. Even if symptoms did not resolve completely, our results suggest PCI may achieve a significant reduction in angina frequency for patients with low MVR_{CFD}. There was also significant improvement in the SAQ physical limitation score in patients with low MVR_{CFD}, but accounting for patients with high MVR_{CFD}, there was no evidence of an interactional effect.

An association was also observed between MVR_{CFD} and the placebo-controlled improvement in DSE score, with greater improvement in patients with low

MVR_{CFD}. Translesional indices FFR and iFR have previously been shown to predict DSE improvement in response to PCI (5, 8). However, these new results suggests a distinct mechanism relating stress-induced myocardial ischemia and regional wall abnormalities with CMD. This may be caused by structural microvascular remodelling, limiting myocardial flow, or chronic repeated ischemic injury uncoupling perfusion from contractility. As there was strong evidence for the interaction with DSE improvement, it is plausible that CMD may have been confined to a specific coronary territory in the current study. Given DSE improvements are also associated with epicardial lesion severity (6), patients with physiologically significant CAD *and* healthy microvasculature may expect the largest improvement in DSE score. This aligns well with current understanding of microvascular physiology, but the current data lack power to investigate for a secondary interactional effect. Furthermore, on a background of less intense medical therapy, the epicardial over microvascular contribution to angina provoking ischemia may be more significant, extending the benefits of PCI to patients with greater microvascular dysfunction.

Clinical implications

Over recent years, the significance of CMD for myocardial ischaemia has been drawn into sharp focus (9, 18). Current guidelines for the treatment of CCS place considerably more emphasis on angina with no obstructive coronary artery disease (ANOCA) than previous versions and recognise distinct CMD phenotypes (1, 19). However, diagnosis and management remain largely focused on the exclusion of significant CAD (20). The results of this study suggests an important, biologically plausible, relationship between MVR_{CFD} and response to PCI in those *wit*h significant epicardial stenoses. Whilst the clinical relevance of the relatively

small improvements in exercise time reported in this study (48s) are uncertain, those with low (20th centile) MVR_{CFD} also derived a 3.5-fold greater likelihood of complete freedom from angina when treated with PCI versus placebo. The ability to better identify those likely to derive benefit from PCI and those who may be better suited to medical therapy alone, is clearly beneficial but, requires prospective evaluation including MVR diagnostic threshold determination for dichotomising patients.

ORBITA included an intensive anti-anginal medication optimisation phase, with an average 2.8 antianginal agents per patient (1, 21). Levels of antianginals were comparable between both arms of the present sub-analysis, but this level of medical therapy may not reflect routine practice in many healthcare systems. This, combined with the inclusion of patients only with single vessel disease, may have introduced a ceiling effect for the potential benefit of PCI. Our results showed a large spread of MVR_{CFD} amongst included patients and indicate CMD attenuated the beneficial effect of PCI in several instances. We have shown that patients with low MVR_{CFD} may have gained an increase in treadmill time of approximately 50 seconds with PCI. This incremental improvement is close to the placebo-controlled PCI-mediated 60 second improvement in exercise time in patients taking no anti-anginal medication (22). Therefore, in patients with low MVR_{CFD}, who may be expected to gain maximum benefit of revascularisation, the beneficial effects of PCI on exercise time may only be partially attenuated by anti-anginal therapy. Patients with moderate or high MVR_{CFD} gained less improvement in exercise time from PCI compared to the average expected benefit of 48 to 55 seconds with anti-anginal monotherapy (23, 24).

Accuracy of the CFD technique

The model of MVR_{CFD} has undergone benchtop (13) and, recently, multicentre *in-vivo* validation against the current invasive gold-standard of continuous infusion thermodilution (25). As this invasive comparator cannot quantify absolute resistance in the distal vessel, downstream of epicardial stenosis, the most appropriate microvascular-specific index for CFD validation is microvascular resistance reserve. This validation analysis included 116 vessels, in patients with epicardial disease, and found a moderate-strong relationship with continuous thermodilution for microvascular resistance reserve ($\rho = 0.58$, $p < 0.0001$). Furthermore, the AUC for diagnosing CMD at a predetermined threshold of 2.5 was 0.77 (95% CI 0.68 – 0.86). These data suggest a comparable relationship, and level of accuracy, to that observed between Doppler with bolus thermodilution ($r = 0.43$; $p < 0.0001$) (26) and bolus with continuous infusion thermodilution ($r = 0.26$; $p < 0.001$) (27), all of which are used in modern clinical practice. Nevertheless, uncertainties in geometric reconstruction accuracy and the method for implementation of side branch flow remain significant contributors to error in the current model (28, 29).

Limitations

This microvascular resistance-stratified analysis of ORBITA included only two thirds of trial patients. The statistical analysis plan was designed to maximise power with available data, but further work is required to confirm these findings. The CFD tool does not normalise for myocardial mass. Post-PCI iFR and FFR indicated some patients may have had residual ischaemia and the possibility this may have been due to potentially treatable focal lesions cannot be excluded (30). Further research will demonstrate whether the observed interactions are preserved in those taking

fewer antianginal agents. The absence of high MVR_{CFD} may not necessarily mean patient's chest pain was caused by epicardial disease. Evidence for guiding optimal management of CMD is relatively sparse (1) and is the subject of ongoing research (NCT04606459, NCT05102019).

Conclusion

In this microvascular resistance-stratified analysis of ORBITA, progressively lower MVR_{CFD} was associated with a larger benefit of PCI versus placebo for exercise time, likelihood of complete freedom from angina, frequency of anginal symptoms and improvement in DSE score. For patients with single vessel stenoses, already taking optimal anti-anginal medication, these results suggest that CMD may attenuate the response to PCI in terms of coronary blood flow, exercise capacity and patient-centred outcomes.

Perspectives

What Is Known?: Coronary microvascular dysfunction is an increasingly recognised cause of myocardial ischaemia.

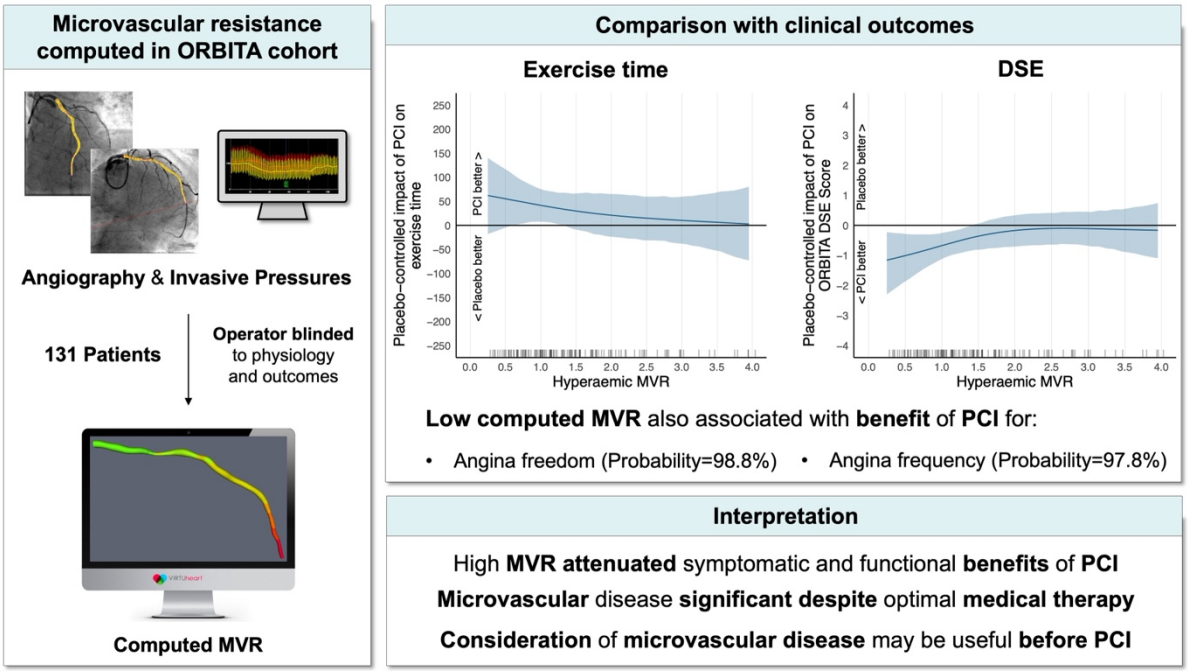
What Is New? In the presence of functionally significant epicardial stenoses, computed microvascular resistance was associated with the symptomatic and functional response to PCI in ORBITA.

What Is Next? The interaction between computed or measured microvascular resistance with PCI should be further evaluated, perhaps in the context of

revascularisation given as monotherapy or alongside less aggressive medical therapy regimens.

Data availability statement: All generated data are included in the manuscript and supplementary material.

Figures



Central Illustration. Study summary and main findings.

Pane 1 – Microvascular resistance computed in ORBITA cohort; summarises clinical data required to compute MVR, number of included patients and simulation protocol. Pane 2 – Comparison with clinical outcomes; shows regression plots demonstrating the relationship between change in pre-randomisation to follow-up total exercise time and DSE score against pre-randomisation MVR by randomisation arm. At progressively lower MVR values, there is a progressively larger difference between PCI and placebo on the end point of exercise time (Probability of interaction 83.1%). and DSE improvement (probability of interaction 96.5%). Pane 3 – Interpretation; summary of key findings. MVR, microvascular resistance; DSE, dobutamine stress echocardiography and PCI, percutaneous coronary intervention.

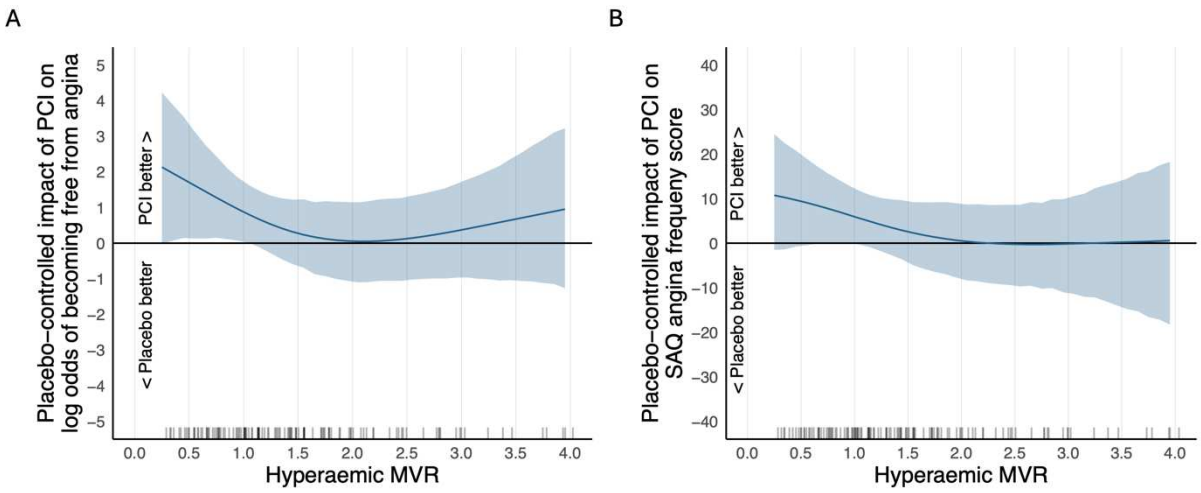


Figure 2. Relationship of change in pre-randomisation to follow-up SAQ scores against pre-randomisation MVR by randomisation arm. *Pane A, relationship of change in pre-randomisation to follow-up total log odds of complete freedom from angina and pre-randomisation MVR by randomisation arm (probability of interaction 90.0%). Pane B, relationship of change in pre-randomisation to follow-up total SAQ angina frequency score and pre-randomisation MVR by randomisation arm. At progressively lower MVR values, there is a progressively larger difference between PCI and placebo on the end point (probability of interaction 89.2%). At progressively lower MVR values, there is a progressively larger difference between PCI and placebo on the end point. MVR, microvascular resistance; SAQ, Seattle angina questionnaire and PCI, percutaneous coronary intervention.*

Tables

	Percutaneous coronary intervention (n= 66)	Placebo (n= 65)	Complete group (n= 131)
Age, y	64.7 ±9.3	67.9 ±7.6	66.3 ±8.6
Male	44 (66.7%)	47 (72.3%)	91 (69.5%)
Body Mass Index	28.5 ±5.0	29.0 ±4.9	28.7 ±5.0
Current or ex-smoker	31 (47.0%)	35 (53.8%)	66 (50.4%)
Comorbidities			
Hypertension	41 (62.1%)	50 (76.7%)	91 (69.5%)
Diabetes Mellitus	10 (15.2%)	16 (24.6%)	26 (19.8%)
Hypercholesterolaemia	54 (81.8%)	44 (67.7%)	98 (74.8%)
Previous myocardial infarction	2 (3.0%)	5 (7.7%)	7 (5.3%)
Previous percutaneous coronary intervention	5 (7.6%)	11 (16.9%)	16 (12.2%)
Canadian Cardiovascular Society Angina class			
I	2 (3.0%)	1 (1.5%)	3 (2.3%)
II	43 (65.2%)	39 (60%)	82 (62.6%)
III	21 (31.8%)	25 (38.5%)	46 (35.1%)
Angina duration, months	6 [3.5 – 10.5]	6 [3 – 9]	5 [4 – 12]
Positive functional test at enrolment			
Dobutamine stress echocardiography	13 (19.7%)	11 (16.9%)	24 (18.3%)
Magnetic resonance imaging perfusion	0	1 (1.5%)	1 (0.8%)
Exercise tolerance test	17 (25.8%)	12 (18.5%)	29 (22.1%)

Table 1. Patient Demographics at Enrolment. Values indicate n (%) or mean±SD.

	Percutaneous coronary intervention (n= 66)	Placebo (n= 65)	Complete group (n= 131)
Lesion characterisation			
Left anterior descending	53 (80.3%)	50 (76.9%)	103 (78.6%)
First diagonal branch	1 (1.5%)	1 (1.5%)	2 (1.5%)
Left circumflex	2 (3.0%)	7 (10.8%)	9 (6.9%)
Obtuse marginal branch	2 (3.0%)	0	2 (1.5%)
Intermediate branch	1 (1.5%)	1 (1.5%)	2 (1.5%)
Right coronary artery	7 (10.6%)	6 (9.2%)	13 (9.9%)
Ostial/proximal	44(66.7%)	26 (40.0%)	70 (53.4%)
Mid	20 (30.3%)	34 (52.3%)	54 (41.2%)
Distal	2 (3.0%)	5 (7.7%)	7 (5.3%)
Serial lesions	10 (15.2%)	8 (12.3%)	18 (13.7%)
Area stenosis by quantitative coronary angiography	85.3% ±12.5%	85.5% ±11.2	85.4% ±11.9%
Diameter stenosis by quantitative coronary angiography	65.3% ±16.1%	66.1% ±14.9%	65.3% ±15.5%
FFR Median [IQR]	0.69 ±0.15 0.71 [0.61 – 0.81]	0.69 ±0.16 0.72 [0.57 – 0.83]	0.69 ±0.16 0.71 [0.59 – 0.81]
iFR Median [IQR]	0.86 ±0.12 0.89 [0.84 – 0.93]	0.82 ±0.17 0.89 [0.81 – 0.92]	0.84 ±0.15 0.89 [0.83 – 0.92]
No. of patients with FFR ≤0.80	50 (75.8%)	46 (70.8%)	96 (73.3%)
No. of patients with iFR ≤0.89	33 (50.0%)	33 (50.8%)	66 (50.4%)
Procedural details			
Stent length, mm	23.0 [16.0 – 30.0]	-	-
Stent diameter, mm	3.00 [2.75 – 3.50]	-	-
FFR post-PCI (n=X) Median [IQR]	0.89 ±0.06 0.88 [0.86 – 0.93]	-	-
iFR post-PCI Median [IQR]	0.94 ±0.04 0.95 [0.92 – 0.96]	-	-
No. of patients with post-FFR>0.80	61 (92.4%)	-	-
No. of patients with post-iFR>0.89	60 (88.9%)	-	-

Table 2. Procedural Demographics. Values indicate n (%) or mean±SD. FFR indicates fractional flow reserve; iFR, instantaneous wave-free ratio; and IQR, interquartile range.

	Low microvascular resistance	High microvascular resistance
	Exercise time (seconds)	
n	129	
Baseline mean	495 ±188	
Correlation with hMVR	0.203 (95% CrI 0.184 to 0.218)	
Incremental effect of PCI over placebo	48 (6 to 92)	16 (-29 to 61)
Probability of significant benefit favouring PCI	98.5%	75.2%
Probability of interaction	83.1%	
	Dobutamine stress echocardiography score	
n	107	
Baseline mean	1.04 [0.42 – 2.02]	
Correlation with hMVR	0.015 (95% CrI -0.038 to 0.047)	
Incremental effect of PCI over placebo	-0.83 (-1.42 to -0.30)	-0.10 (-0.63 to 0.42)
Probability of significant benefit favouring PCI	99.9%	65.9%
Probability of interaction	96.5%	
	SAQ freedom from angina	
n	127	
Angina present	105 (82.7%)	
Correlation with hMVR	0.165 (95% CrI -0.117 to 0.327)	
Log odds of complete freedom from angina	1.24 (0.16 to 2.38)	0.10 (-1.07 to 1.25)
Probability of significant benefit favouring PCI	98.8%	57.1%
Difference in log odds ratios	1.14 (95% CrI -0.60 – 2.90)	
Probability of interaction	90.0%	
	SAQ angina frequency score	
n	127	
Baseline mean	71.7 ±23.4	
Correlation with hMVR	0.120 (95% CrI 0.097 to 0.148)	
Incremental effect of PCI over placebo	7.67 (0.25 to 15.6)	-0.25 (-9.24 to 8.80)
Probability of significant benefit favouring PCI	97.8%	47.8%
Probability of interaction	89.2%	
	SAQ physical limitation score	
n	114	
Baseline mean	67.7 ±24.7	
Correlation with hMVR	0.257 (95% CrI 0.250 to 0.258)	
Incremental effect of PCI over placebo	7.88 (-0.01 to 15.5)	8.96 (-0.92 to 17.8)
Probability of significant benefit favouring PCI	97.9%	96.6%
Probability of interaction	43.6%	
	SAQ treatment satisfaction score	
n	127	
Baseline mean	86.4 ±15.4	
Correlation with hMVR	0.043 (95% CrI -0.061 to 0.081)	
Incremental effect of PCI over placebo	0.92 (-3.84 to 5.59)	-2.46 (-8.44 to 2.91)
Probability of significant benefit favouring PCI	65.3%	19.0%
Probability of interaction	80.2%	

	SAQ quality of life score	
n	126	
Baseline mean	48.4 ±22.2	
Correlation with hMVR	0.115 (95% CrI 0.062 to 0.147)	
Incremental effect of PCI over placebo	2.51 (-7.50 to 12.6)	0.07 (-10.9 to 11.4)
Probability of significant benefit favouring PCI	68.7%	50.5%
Probability of interaction	61.2%	
	SAQ stability score	
n	126	
Baseline mean	64.5 ±25.8	
Correlation with hMVR	0.196 (95% CrI 0.150 to 0.213)	
Incremental effect of PCI over placebo	0.36 (-10.9 to 11.1)	-4.53 (-16.5 to 7.23)
Probability of significant benefit favouring PCI	52.7%	22.6%
Probability of interaction	29.6%	
	EQ-5D-5L quality of life score	
n	127	
Baseline mean	0.79 ±0.21	
Correlation with hMVR	0.210 (95% CrI 0.184 to 0.243)	
Incremental effect of PCI over placebo	0.00 (-0.05 to 0.06)	-0.02 (-0.08 to 0.04)
Probability of significant benefit favouring PCI	57.0%	27.8%
Probability of interaction	69.7%	
	EQ-5D-5L visual analogue score	
n	129	
Baseline mean	65.6 ±20.8	
Correlation with hMVR	0.139 (95% CrI 0.105 to 0.162)	
Incremental effect of PCI over placebo	0.79 (-6.10 to 7.99)	3.05 (-4.99 to 10.5)
Probability of significant benefit favouring PCI	58.8%	78.4%
Probability of interaction	34.7%	
	CCS angina classification	
n	129	
Baseline mean and median	1.94 ±0.93 2 [2 – 3]	
Correlation with hMVR	0.259 (95% CrI 0.208 to 0.266)	
Incremental effect of PCI over placebo	0.10 (-0.41 to 0.64)	-0.05 (-0.57 to 0.48)
Probability of significant benefit favouring PCI	35.8%	57.0%
Probability of interaction	63.7%	

Table 3: Bayesian analysis of primary and secondary end points.

SAQ indicates Seattle Angina Questionnaire; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; hMVR, hyperaemic microvascular resistance.

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Supplementary Material ORBITA virtu substudy

Supplementary table 1. CCS class at enrolment, pre-randomisation and post-randomisation

	Canadian Cardiovascular Society Angina class	Percutaneous coronary intervention (n= 66)	Placebo (n= 65)	Complete group (n= 131)
Enrolment	0	0	0	0
	I	2 (3.0%)	1 (1.5%)	3 (2.3%)
	II	43 (65.2%)	39 (60%)	82 (62.6%)
	III	21 (31.8%)	25 (38.5%)	46 (35.1%)
Pre-randomisation	0	8 (12.1%)	8 (12.3%)	16 (12.2%)
	I	7 (10.6%)	5 (7.7%)	12 (9.2%)
	II	35 (53.0%)	30 (46.2%)	65 (49.6%)
	III	16 (24.2%)	22 (33.8%)	38 (29.0%)
Post-randomisation	0	25 (37.9%)	18 (28.6%)	43 (33.3%)
	I	8 (12.1%)	13 (20.6%)	21 (16.3%)
	II	25 (37.9%)	21 (33.3%)	46 (35.7%)
	III	8 (12.1%)	11 (17.5%)	19 (14.7%)

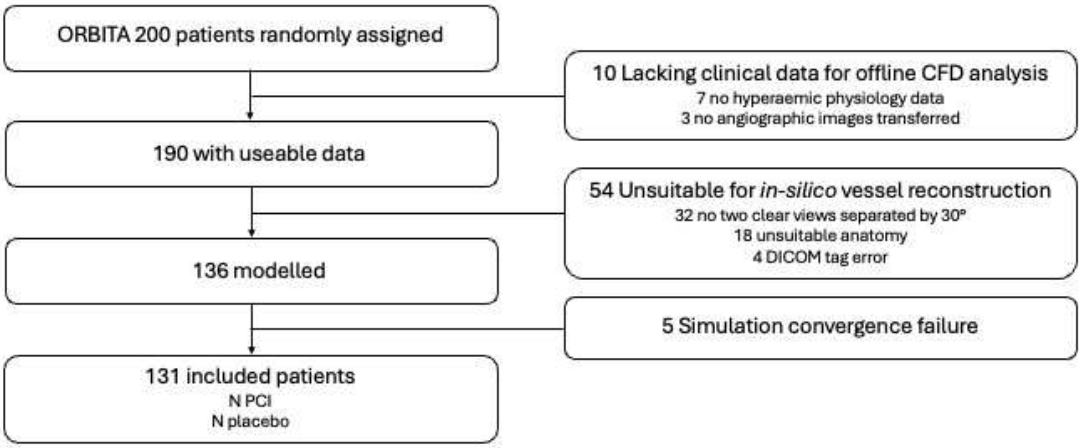
Supplementary Table 2. Angina frequency. Scores taken from SAQ questions 3 and 4. Lower scores denote worse health status.

Angina frequency score	Enrolment		Pre-randomisation		Post-randomisation	
	PCI	Placebo	PCI	Placebo	PCI	Placebo
0	2 (3.1%)	0	0	1 (1.5%)	0	0
10	1 (1.6%)	1 (1.6%)	1 (1.5%)	0	0	0
20	5 (7.8%)	3 (4.7%)	4 (6.2%)	1 (1.5%)	2 (3.8%)	1 (1.6%)
30	2 (3.1%)	3 (4.7%)	2 (3.1%)	1 (1.5%)	0	2 (3.1%)
40	5 (7.8%)	2 (3.1%)	8 (12.3%)	4 (6.1%)	3 (5.7%)	2 (3.1%)
50	6 (9.4%)	9 (14.1%)	3 (4.6%)	3 (4.5%)	7 (13.2%)	3 (4.7%)
60	8 (12.5%)	14 (21.9%)	5 (7.7%)	10 (15.2%)	5 (9.4%)	1 (1.6%)
70	11 (17.2%)	5 (7.8%)	8 (12.3%)	10 (15.2%)	8 (15.1%)	7 (10.9%)
80	4 (6.3%)	9 (14.1%)	13 (20.0%)	13 (19.7%)	8 (15.1%)	8 (12.5%)
90	10 (15.6%)	10 (15.6%)	10 (15.4%)	12 (18.2%)	12 (22.6%)	9 (14.1%)
100	10 (15.6%)	8 (12.5%)	11 (16.9%)	11 (16.7%)	8 (15.1%)	31 (48.4%)

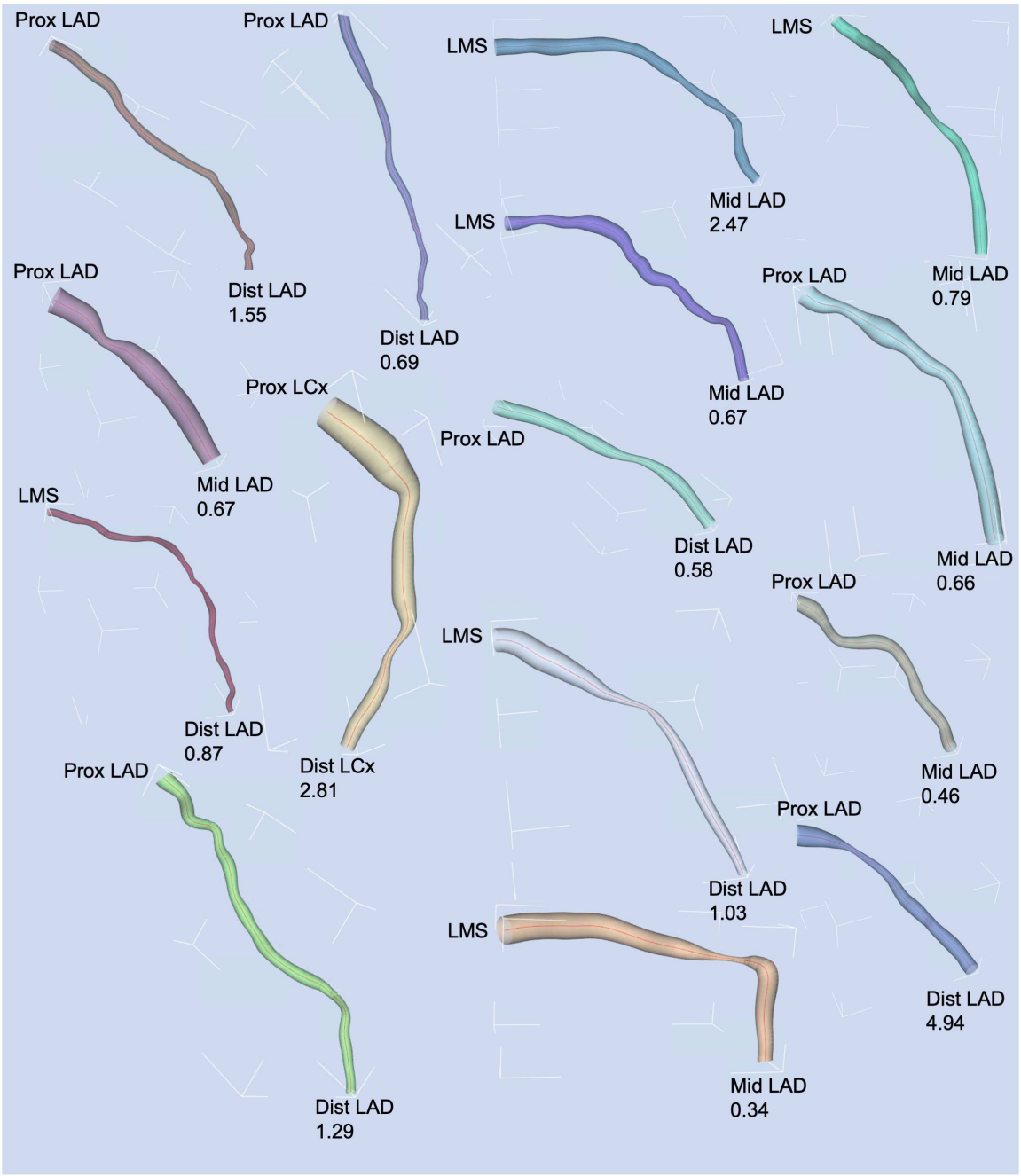
Supplementary Table 3. Pre-randomisation medical therapy

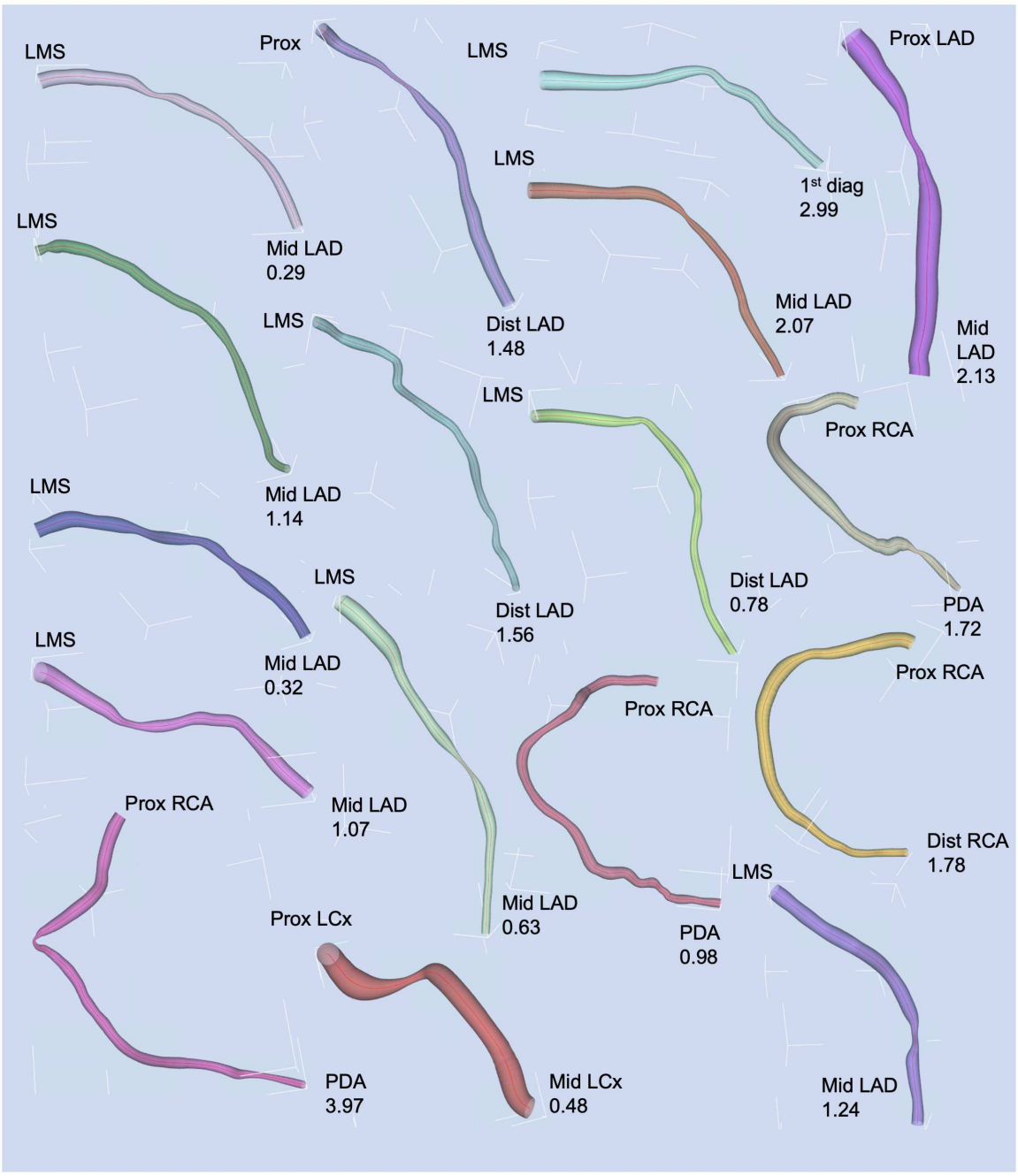
	Percutaneous coronary intervention (n= 66)	Placebo (n= 65)	Complete group (n= 131)
Lipid lowering therapy	62 (94.9%)	61 (93.9%)	123 (93.9%)
Dual Anti-platelet	65 (98.5%)	64 (98.5%)	129 (98.5%)
Calcium channel antagonist	62 (93.9%)	58 (89.2%)	120 (91.6%)
Beta blocker	53 (80.3%)	52 (80.0%)	105 (80.2%)

Supplementary S1 Consort diagram



Supplementary S2 All included vessel reconstructions
Labels indicate anatomical location of vessel inlet and outlet, values at vessel outlets denote computed hMVR in mmHg.min/mL.

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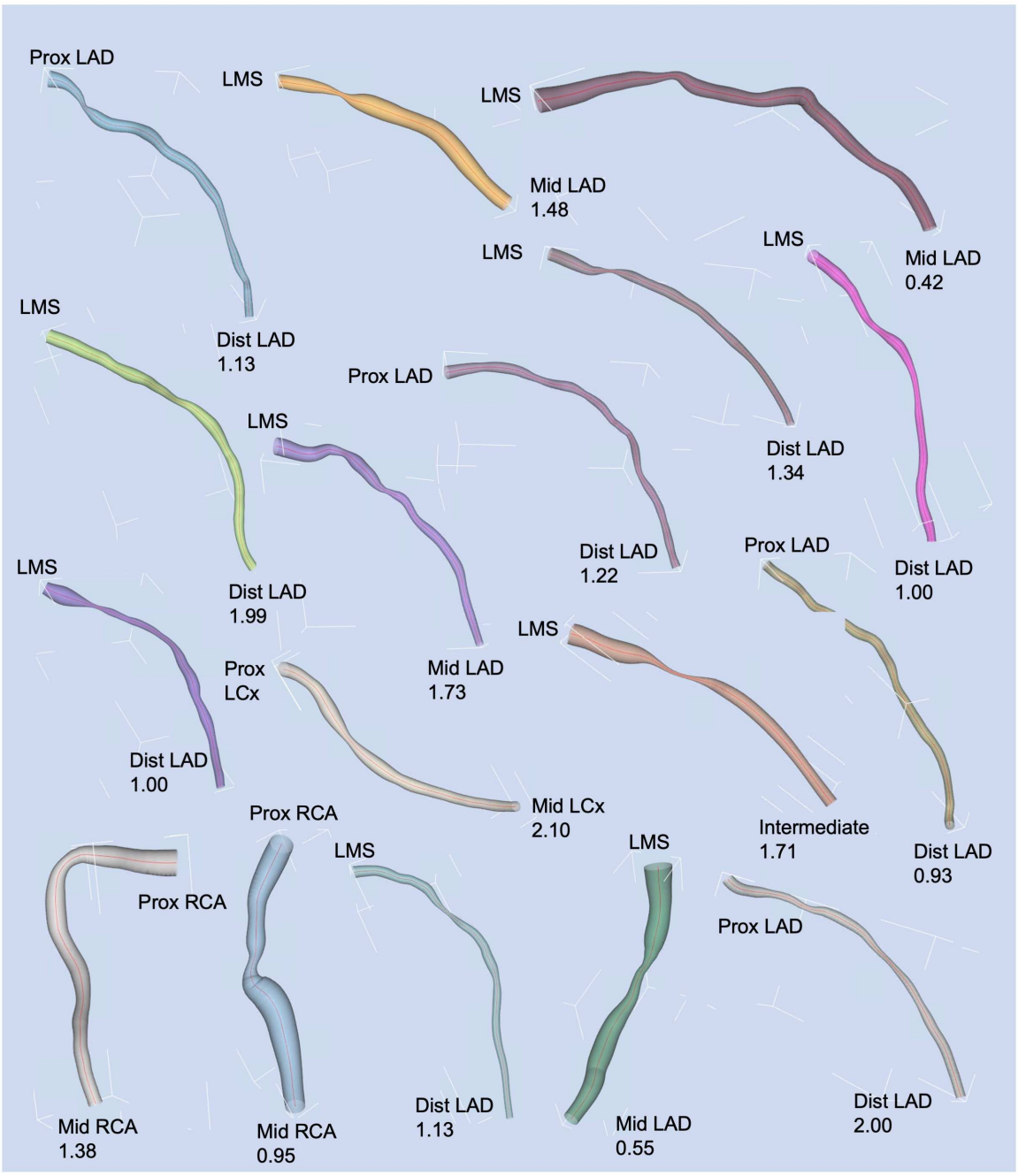
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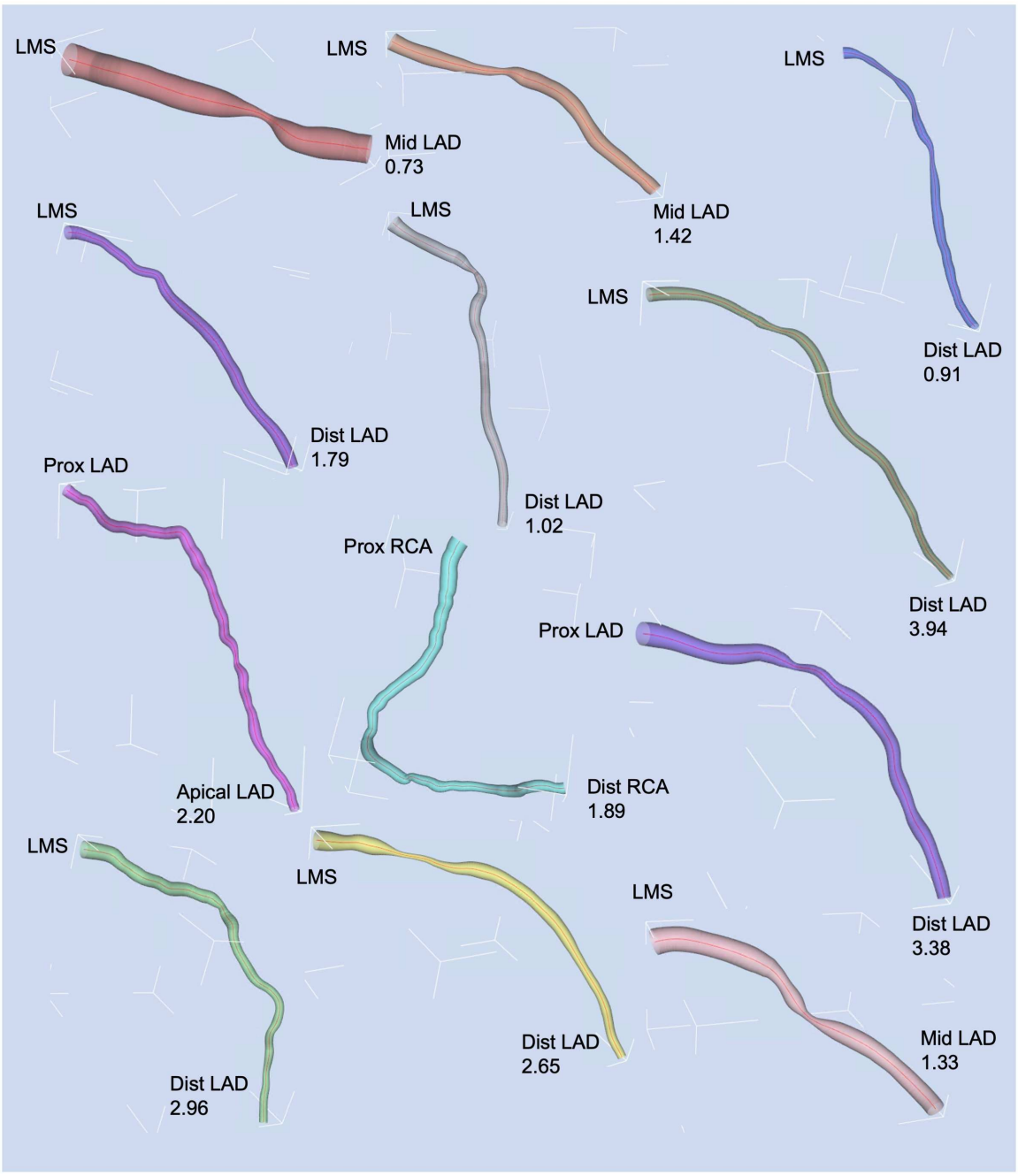
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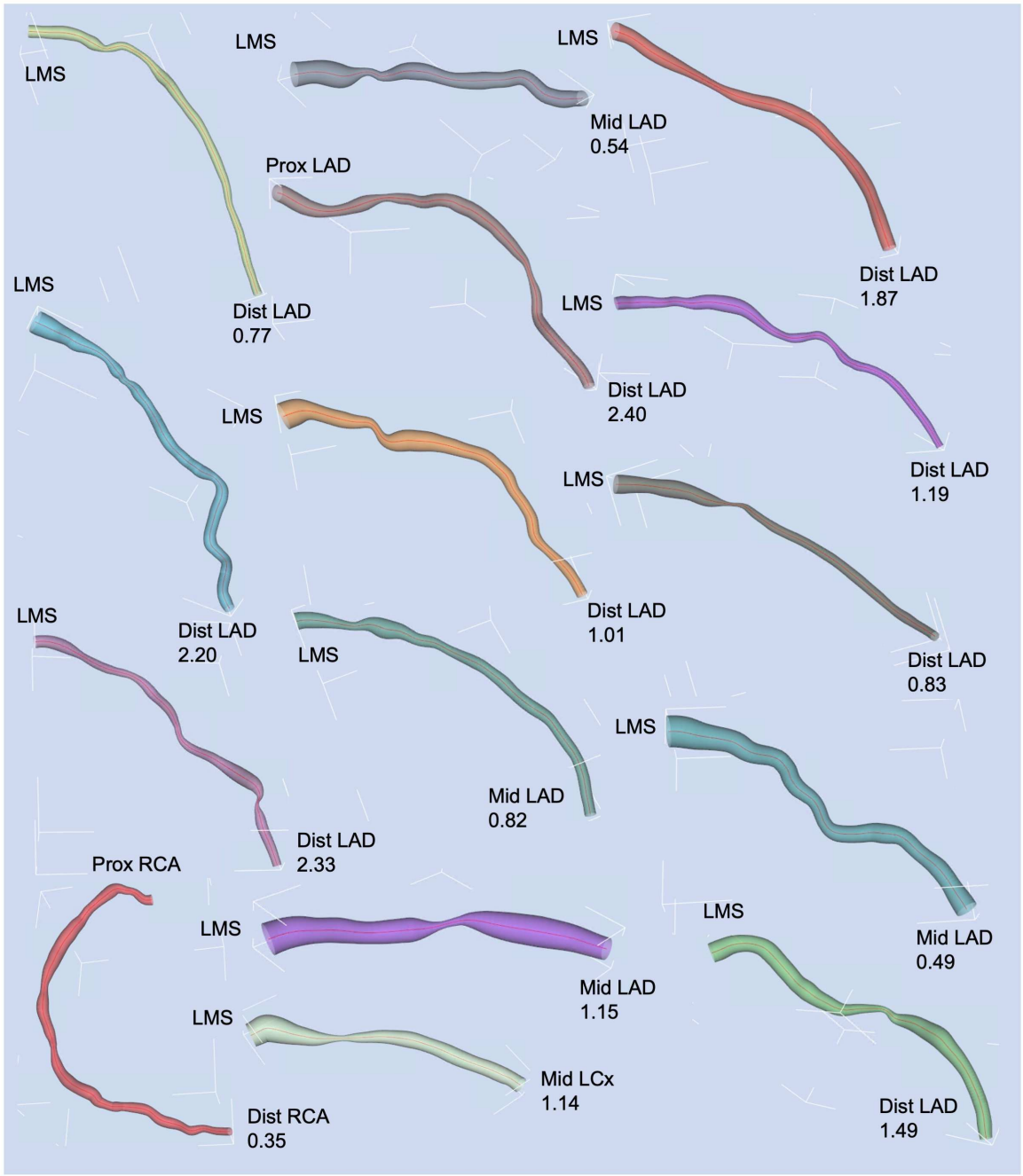
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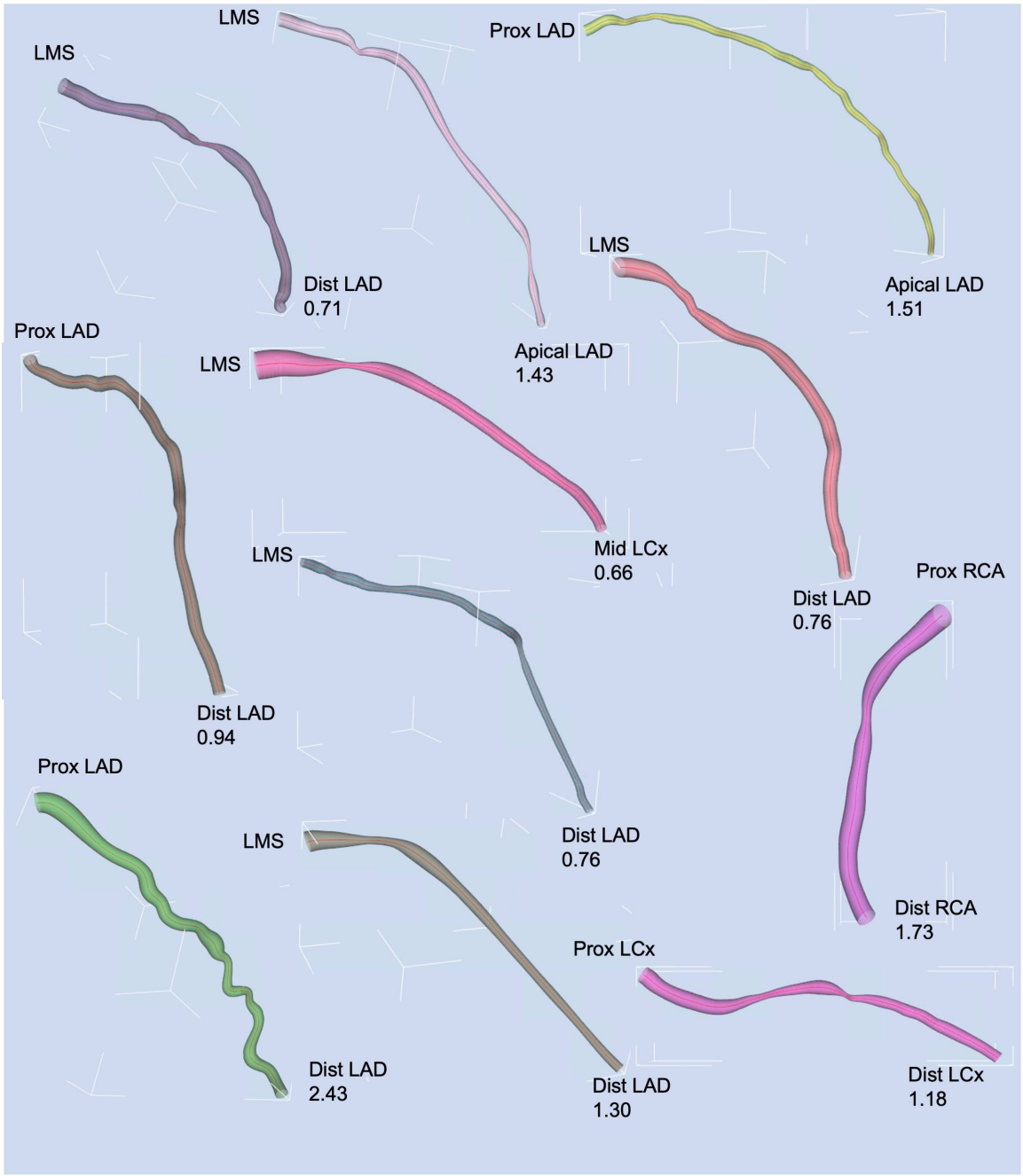
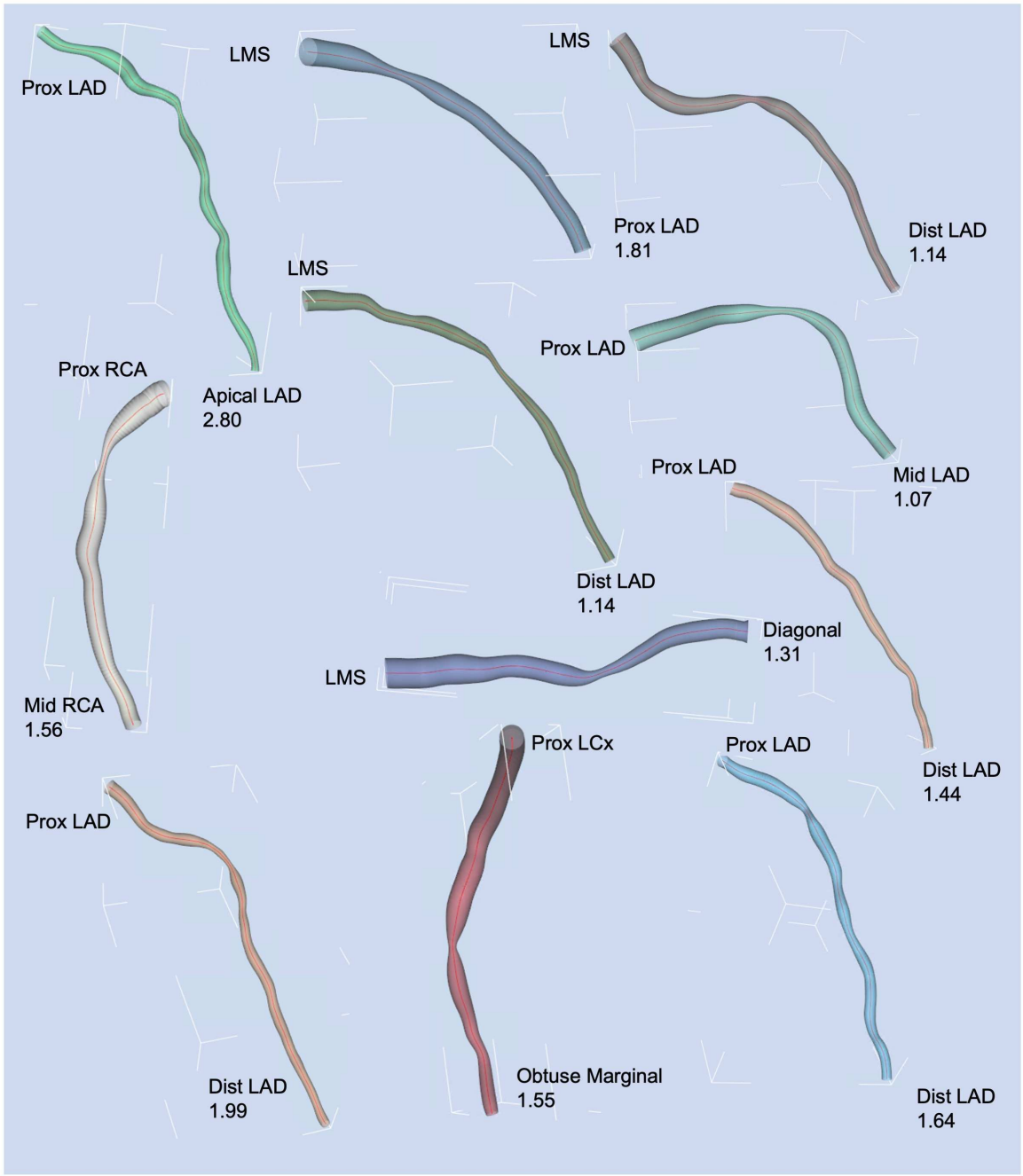
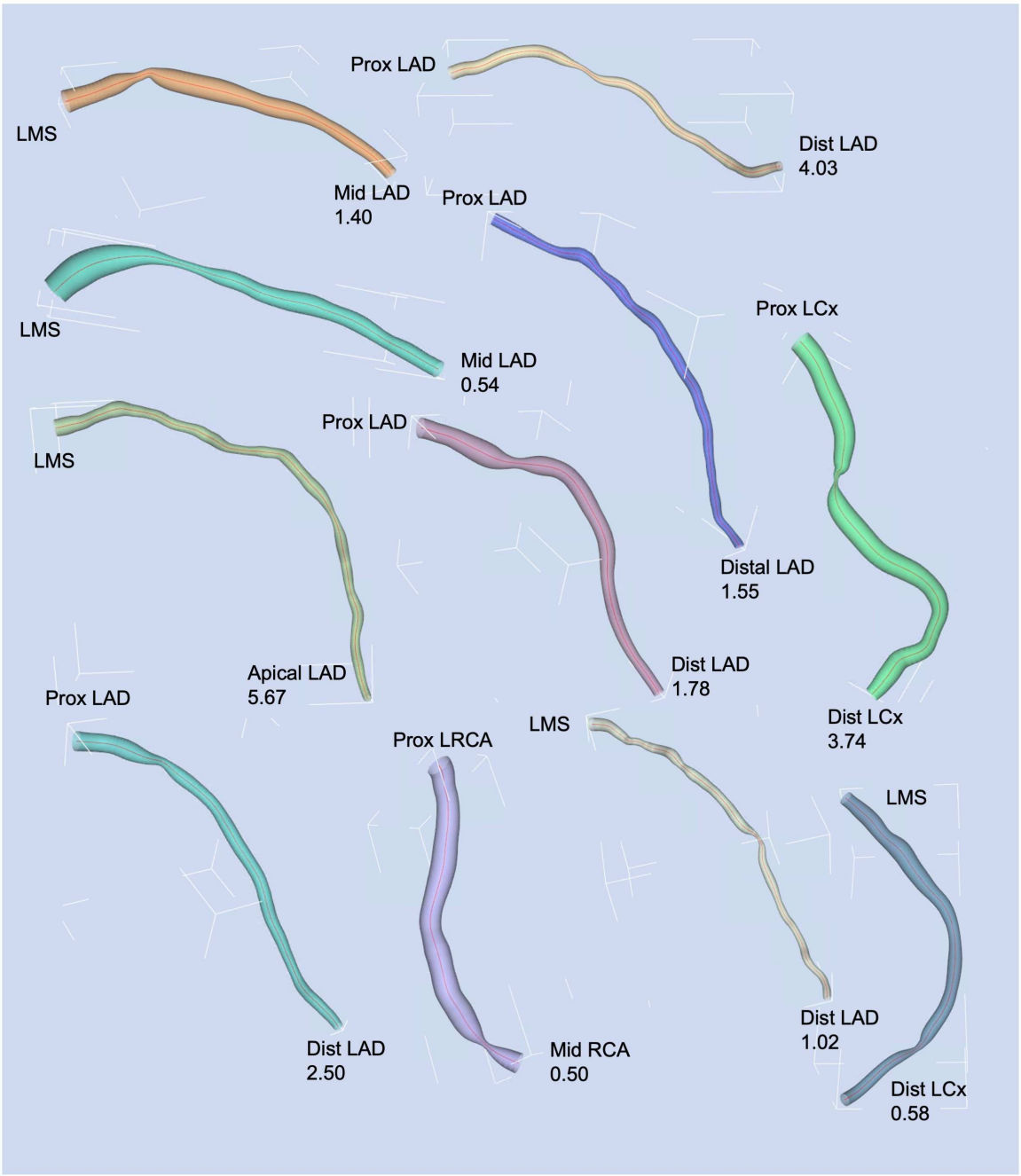
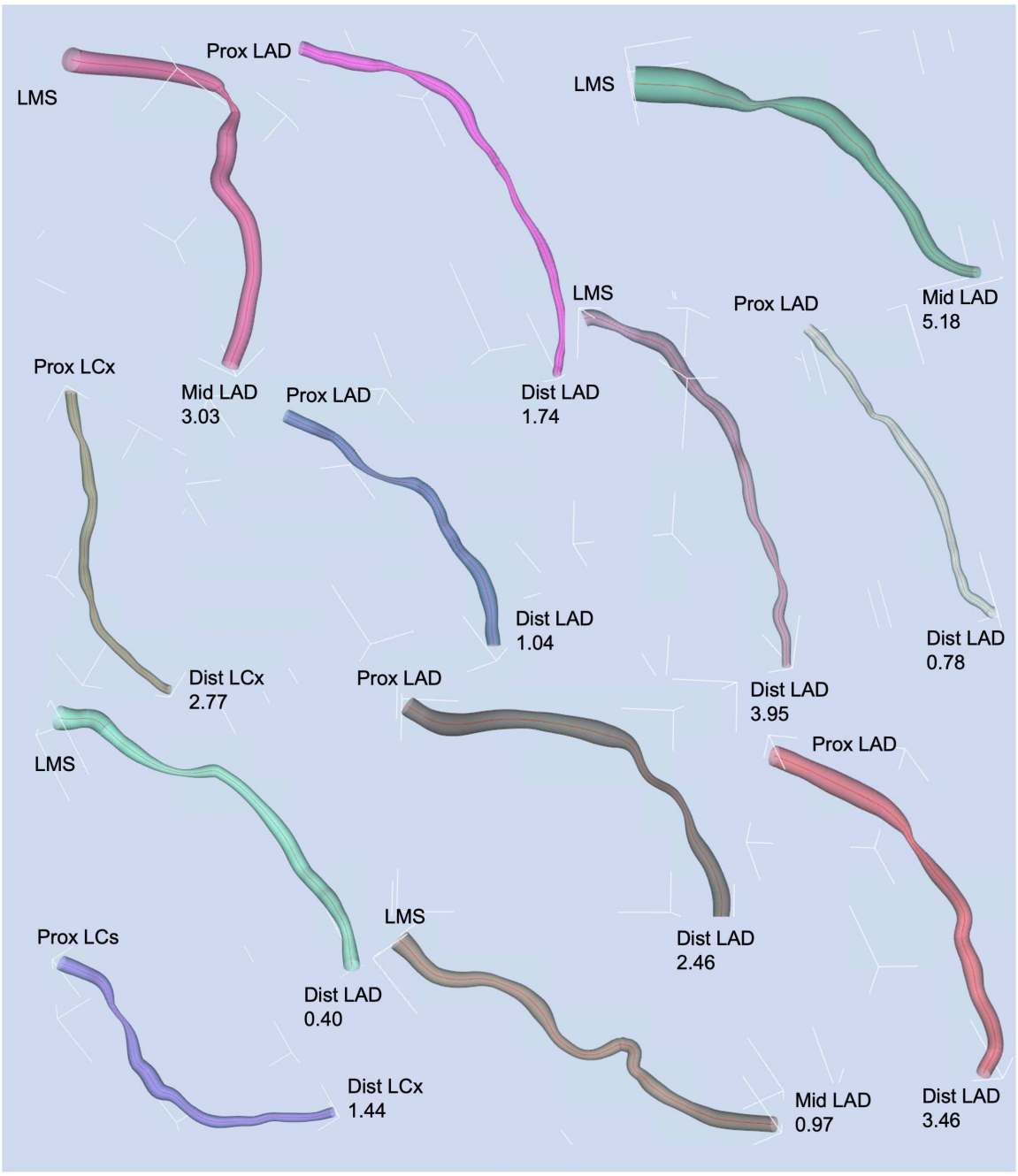
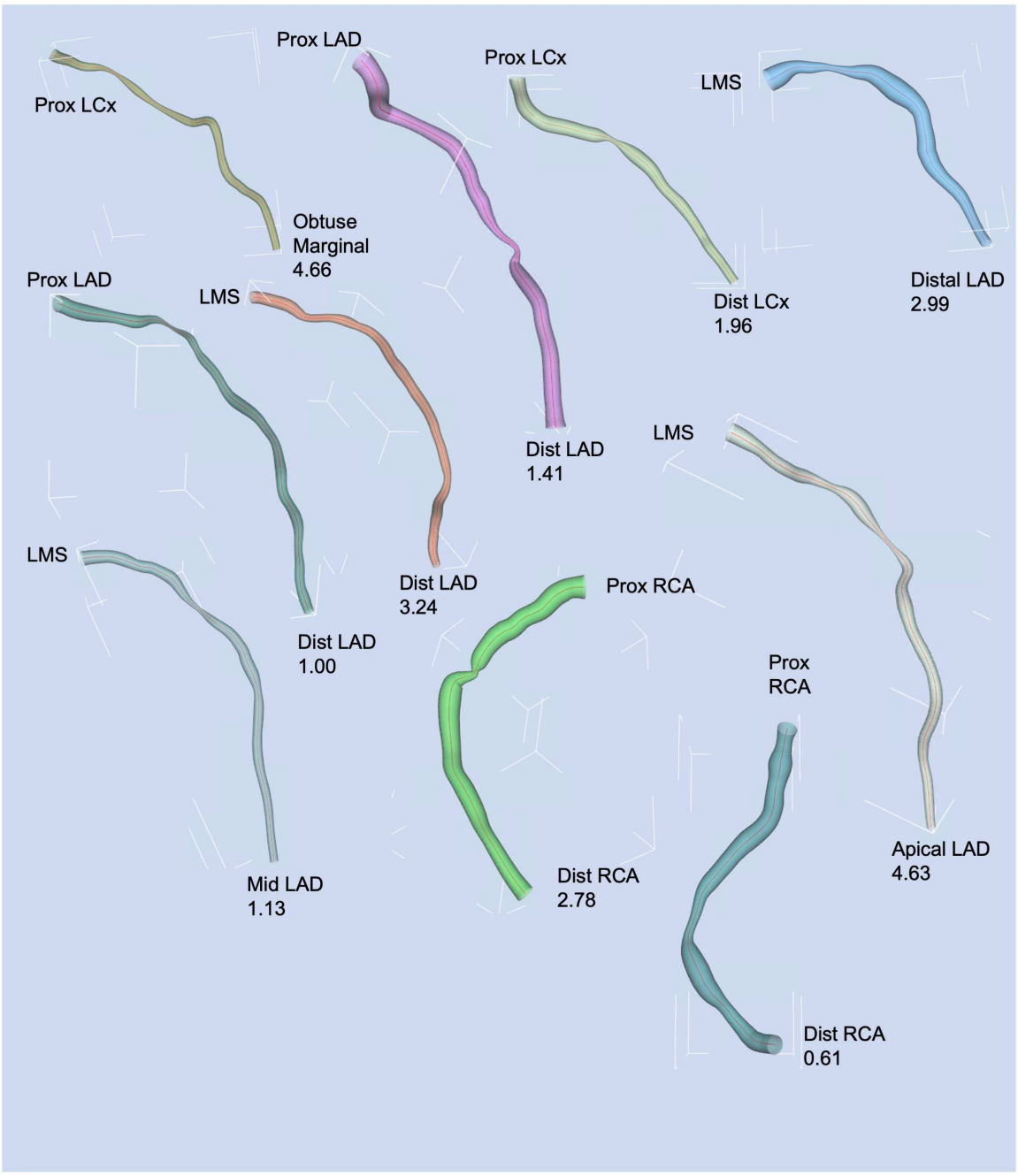
Dist LAD
1.49
Dist RCA
0.35


LMS
LMS
Dist LAD
0.71
Prox LAD
Apical LAD
1.43
LMS
Apical LAD
1.51
Prox LAD
LMS
Mid LCx
0.66
LMS
Dist LAD
0.94
Dist LAD
0.76
Prox RCA
Prox LAD
LMS
Dist LAD
0.76
Dist RCA
1.73
Prox LCx
Dist LAD
2.43
Dist LAD
1.30
Dist LCx
1.18

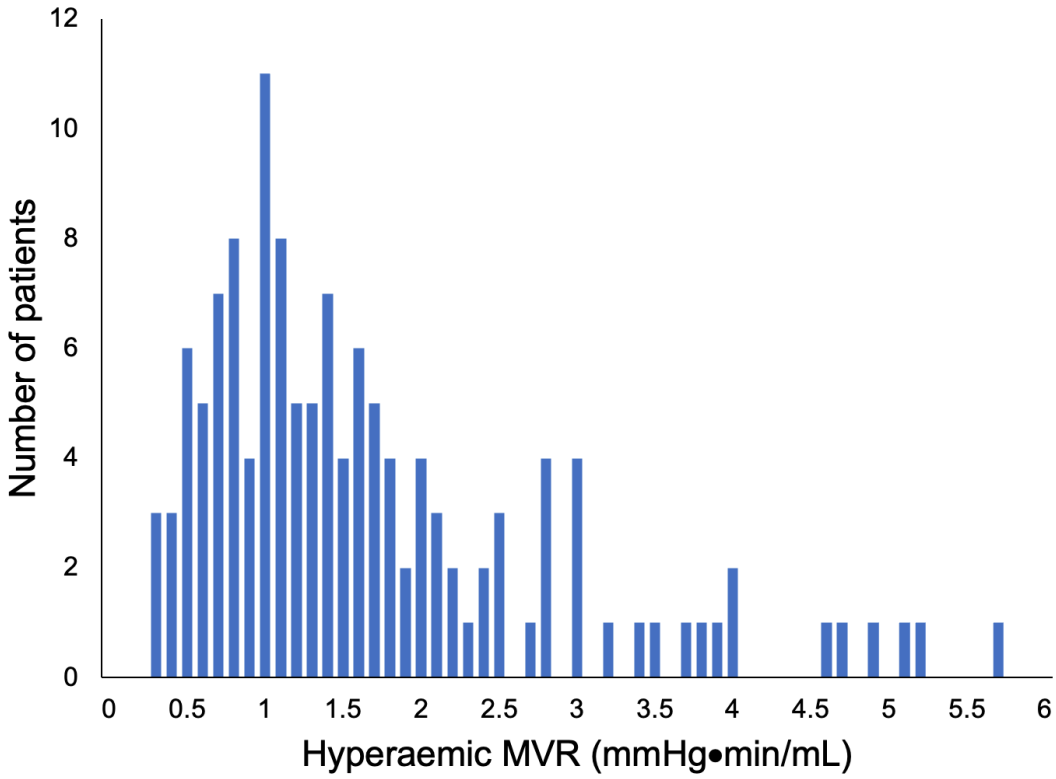

Prox LAD
LMS
LMS
Prox LAD
1.81
Dist LAD
1.14
LMS
Prox LAD
Prox RCA
Apical LAD
2.80
Mid LAD
1.07
Prox LAD
Dist LAD
1.14
Diagonal
1.31
LMS
Mid RCA
1.56
Prox LCx
Prox LAD
Dist LAD
1.44
Prox LAD
Dist LAD
1.99
Obtuse Marginal
1.55
Dist LAD
1.64

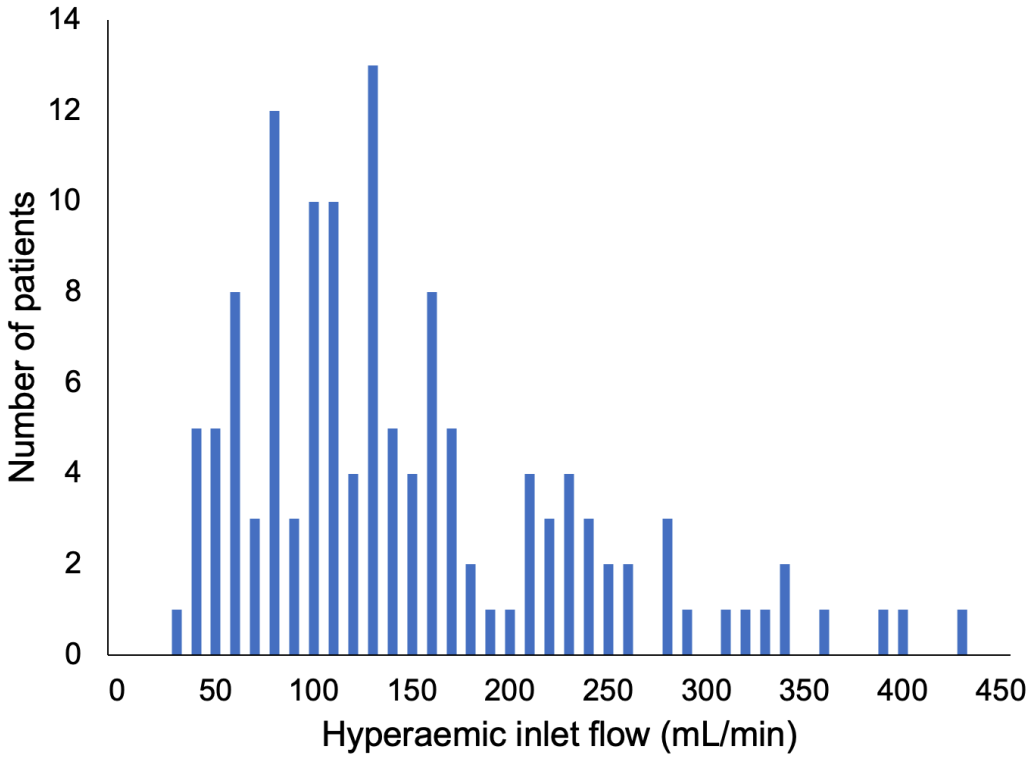

LMS
Mid LAD
1.40
Prox LAD
Dist LAD
4.03
LMS
Mid LAD
0.54
Prox LAD
Prox LCx
Distal LAD
1.55
LMS
Apical LAD
5.67
Prox LAD
Dist LAD
1.78
Dist LCx
3.74
Prox LAD
Dist LAD
2.50
Prox LRCA
Mid RCA
0.50
LMS
Dist LAD
1.02
LMS
Dist LCx
0.58

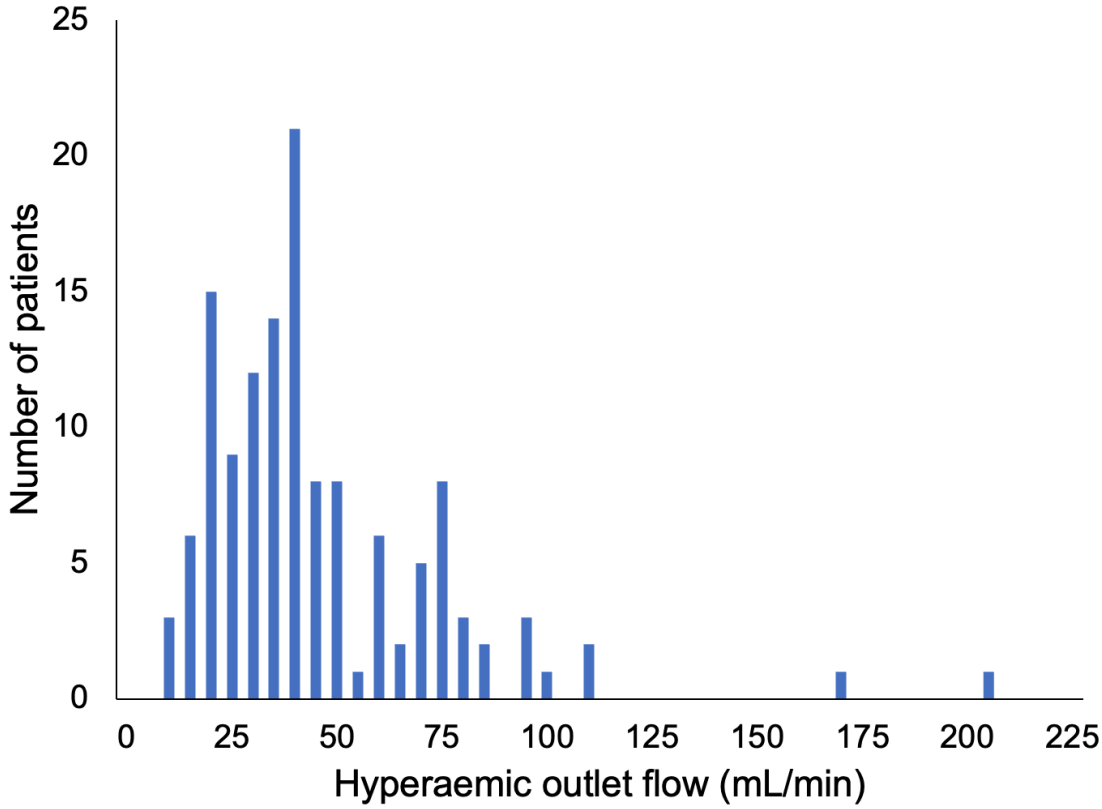

LMS
Prox LAD
Mid LAD
3.03
Prox LAD
Dist LAD
1.74
LMS
Mid LAD
5.18
LMS
Prox LAD
Prox LCx
Dist LCx
2.77
Prox LAD
Dist LAD
1.04
Dist LAD
0.78
Prox LAD
Dist LAD
3.95
LMS
Prox LAD
Dist LAD
2.46
LMS
Prox LCs
Dist LAD
0.40
Dist LCx
1.44
Mid LAD
0.97
Dist LAD
3.46


Prox LCx
Prox LAD
Prox LCx
LMS
Obtuse
Marginal
4.66
Dist LCx
1.96
Distal LAD
2.99
Prox LAD
LMS
Dist LAD
1.41
LMS
LMS
Dist LAD
3.24
Prox RCA
Dist LAD
1.00
Prox
RCA
Apical LAD
4.63
Mid LAD
1.13
Dist RCA
2.78
Dist RCA
0.61

Supplementary S3 Distribution of virtual physiology results
Hyperaemic MVR taken by dividing distal pressure by distal computed flow. The location where hMVR was measured in every case is recorded in supplementary S2




Number of patients
14
12
10
8
6
4
2
0
0
50
100
150
200
250
300
350
400
450
Hyperaemic inlet flow (mL/min)


Number of patients
25
20
15
10
5
0
0
25
50
75
100
125
150
175
200
225
Hyperaemic outlet flow (mL/min)

Supplementary S4 Exercise time x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.024 for Intercepts

```
blrm(formula = outcome_exercise_time_post ~
rcs(outcome_exercise_time_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 129 Draws 40000 Chains 4 Time 20.8s p 7	B 0.106 [0.098, 0.113]	g 4.465 [3.764, 5.211] gp 0.448 [0.433, 0.462] EV 0.631 [0.582, 0.684] v 15.754 [10.538, 20.724] vp 0.158 [0.145, 0.171]	C 0.855 [0.85, 0.859] Dxy 0.71 [0.699, 0.719]]

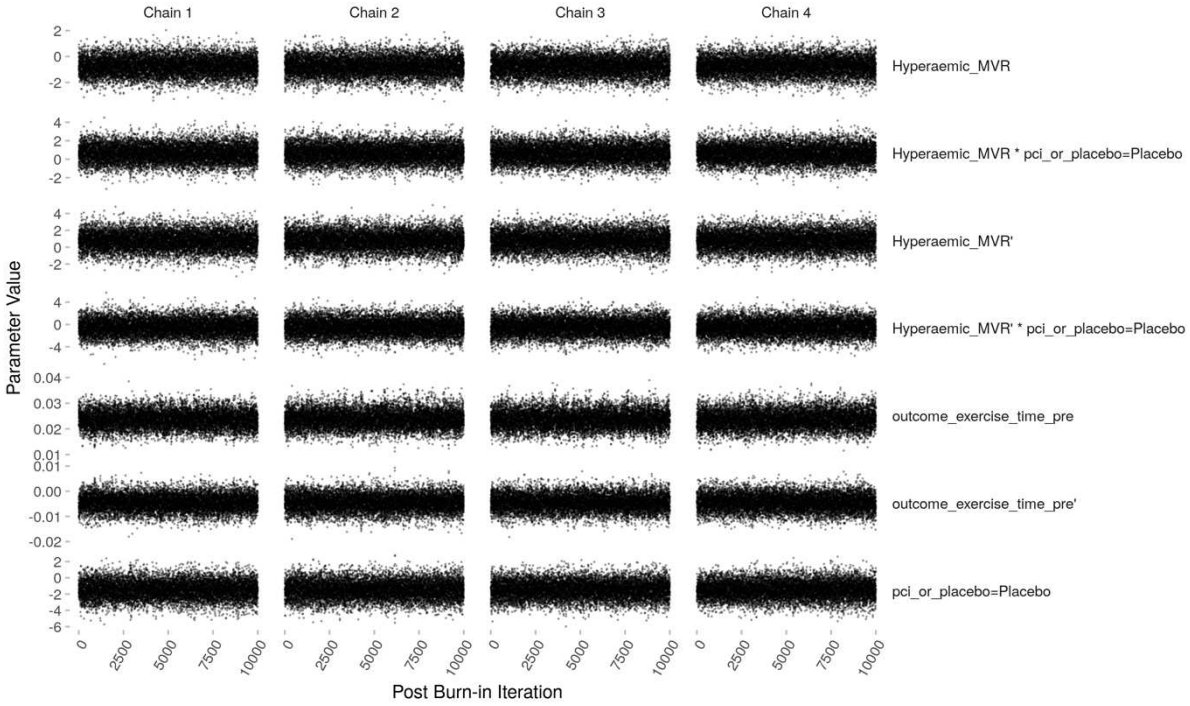
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_exercise_time_pre	0.0237	0.0236	0.0034	0.0170	0.0304	1.0000	1.07
outcome_exercise_time_pre'	-0.0045	-0.0045	0.0033	-0.0111	0.0017	0.0823	0.98
Hyperaemic_MVR	-0.7476	-0.7451	0.6900	-2.0670	0.6177	0.1386	0.99
Hyperaemic_MVR'	0.7644	0.7610	1.0520	-1.2626	2.8580	0.7662	1.00
pci_or_placebo = Placebo	-1.4774	-1.4712	1.0821	-3.5782	0.6517	0.0844	0.99
Hyperaemic_MVR * pci_or_placebo = Placebo	0.6116	0.6029	0.9313	-1.1780	2.4412	0.7420	1.01
Hyperaemic_MVR' * pci_or_placebo = Placebo	-0.4994	-0.4895	1.4407	-3.3245	2.2980	0.3694	1.00

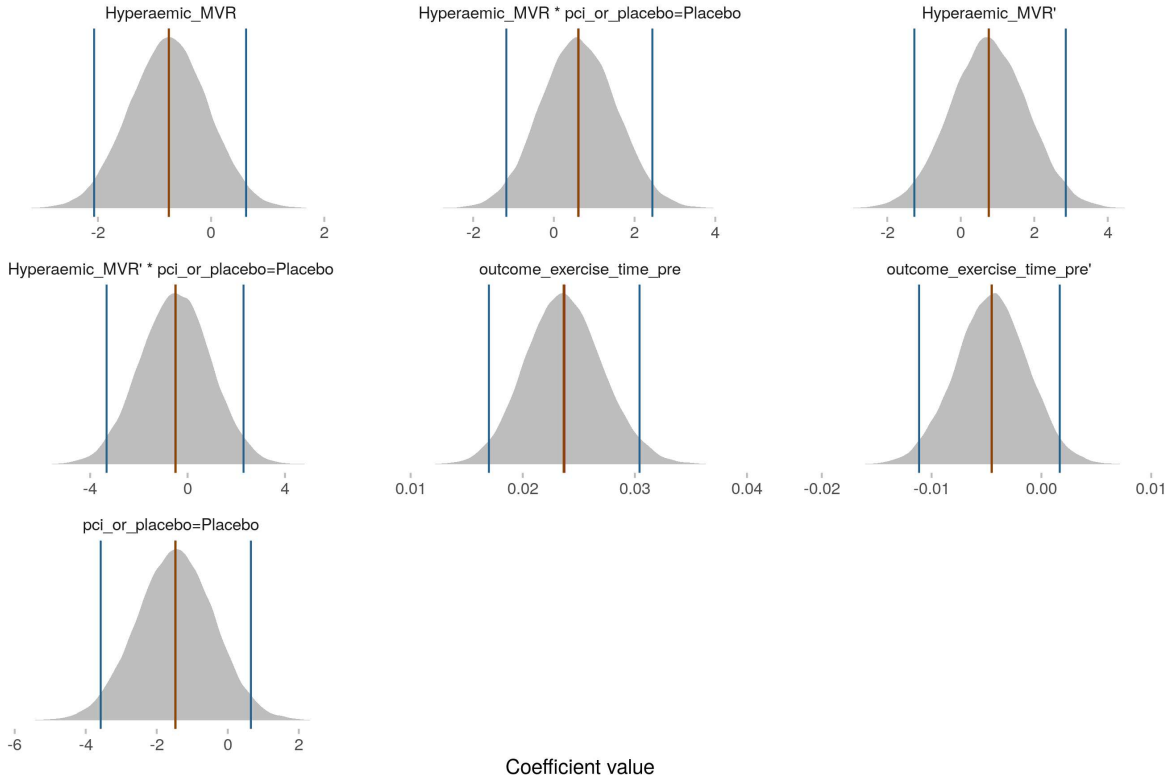
Contrasts Given Priors

[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_exercise_time_pre	0.938	0.821	0.990	2
Nonlinear	0.014	0.000	0.068	1
Hyperaemic_MVR (Factor + Higher-Order Factors)	0.016	0.001	0.098	4
All Interactions	0.009	0.000	0.064	2
Nonlinear (Factor + Higher-Order Factors)	0.004	0.000	0.055	2
pci_or_placebo (Factor + Higher-Order Factors)	0.043	0.004	0.139	3
All Interactions	0.009	0.000	0.064	2
Hyperaemic_MVR × pci_or_placebo (Factor + HO Factors)	0.009	0.000	0.064	2
Nonlinear	0.001	0.000	0.028	1
Nonlinear Interaction: f(A,B) vs. AB	0.001	0.000	0.028	1
TOTAL NONLINEAR	0.018	0.000	0.091	3
TOTAL NONLINEAR + INTERACTION	0.027	0.003	0.121	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
135.8 [98.5, 190.7]


Chain 1
Chain 2
Chain 3
Chain 4
Parameter Value
Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_exercise_time_pre
outcome_exercise_time_pre'
pci_or_placebo=Placebo
Post Burn-in Iteration


Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_exercise_time_pre
outcome_exercise_time_pre'
pci_or_placebo=Placebo
Coefficient value

Supplementary S5 DSE score x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.075 for Intercepts

```
blrm(formula = dse_highdose_post ~ rcs(dse_highdose_pre, 3) +
    rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

```
          0 0.0416666666666667 0.0833333333333333  0.166666666666667           0.25
0.291666666666667   16           1           7          13           9           1
 0.333333333333333  0.416666666666667           0.5  0.583333333333333  0.666666666666667
0.75         4           2           2           3           3           5
 0.833333333333333  0.916666666666667   1.08333333333333          1.25   1.33333333333333
1.41666666666667         5           3           1           5           1           1
  1.58333333333333   1.66666666666667   1.91666666666667   2.16666666666667          2.25
2.33333333333333          1           2           2           1           2           1
         2.5   2.66666666666667   2.91666666666667   3.08333333333333   3.16666666666667
3.41666666666667          1           1           2           3           1           1
  4.58333333333333   4.91666666666667           6   6.16666666666667   8.58333333333333          8.75
          1           2           1           1           1           1
```

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 107 Draws 40000 Chains 4 Time 8.4s p 7	B 0.185 [0.166 0.205]	g 1.883 [1.422 2.385] gp 0.319 [0.269 0.367] EV 0.31 [0.224 0.409] v 2.976 [1.545 4.693] vp 0.077 [0.054 0.101]	C 0.717 [0.704 0.728] Dxy 0.434 [0.407 0.455]

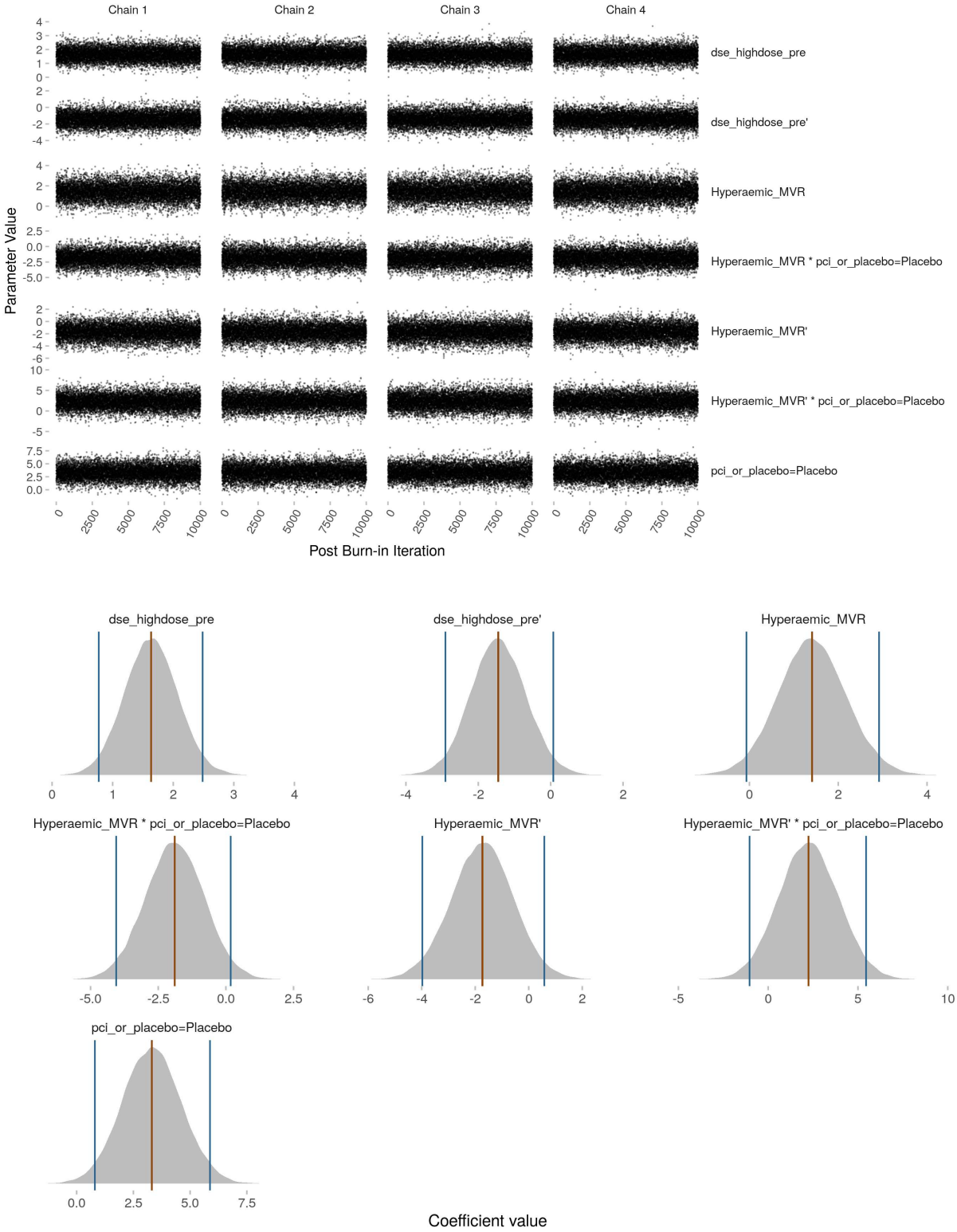
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
dse_highdose_pre	1.6352	1.6349	0.4379	0.7707	2.4850	0.9998	1.02
dse_highdose_pre'	-1.4447	-1.4519	0.7596	-2.9087	0.0731	0.0300	1.01
Hyperaemic_MVR	1.4126	1.4079	0.7602	-0.0676	2.9193	0.9689	1.02
Hyperaemic_MVR'	-1.7374	-1.7256	1.1558	-3.9778	0.5822	0.0648	0.98
pci_or_placebo=Placebo	3.3161	3.3104	1.2934	0.8026	5.8748	0.9951	1.02
Hyperaemic_MVR * pci_or_placebo=Placebo	-1.8925	-1.8895	1.0788	-4.0524	0.1771	0.0394	0.99
Hyperaemic_MVR' * pci_or_placebo=Placebo	2.2467	2.2420	1.6584	-1.0368	5.4505	0.9124	1.00

Contrasts Given Priors

```
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2]     contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Factor	REV	Lower	Upper	d.f.
dse_highdose_pre	0.836	0.579	0.958	2
Nonlinear	0.071	0.000	0.213	1
Hyperaemic_MVR (Factor+Higher Order Factors)	0.098	0.026	0.333	4
All Interactions	0.082	0.000	0.253	2
Nonlinear (Factor+Higher Order Factors)	0.048	0.001	0.195	2
pci_or_placebo (Factor+Higher Order Factors)	0.238	0.072	0.481	3
All Interactions	0.082	0.000	0.253	2
Hyperaemic_MVR * pci_or_placebo (Factor+Higher Order Factors)	0.082	0.000	0.253	2
Nonlinear	0.036	0.000	0.152	1
Nonlinear Interaction : f(A,B) vs. AB	0.036	0.000	0.152	1
TOTAL NONLINEAR	0.095	0.005	0.276	3
TOTAL NONLINEAR + INTERACTION	0.138	0.020	0.365	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
51.1 [30.8, 88.7]



Supplementary S6 Freedom from angina x Hyperaemic Microvascular Resistance

Bayesian Logistic Model Dirichlet Priors With Concentration Parameter 0.541 for Intercepts

```
blrm(formula = outcome_anginafree_post ~ outcome_anginafree_pre +
    rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

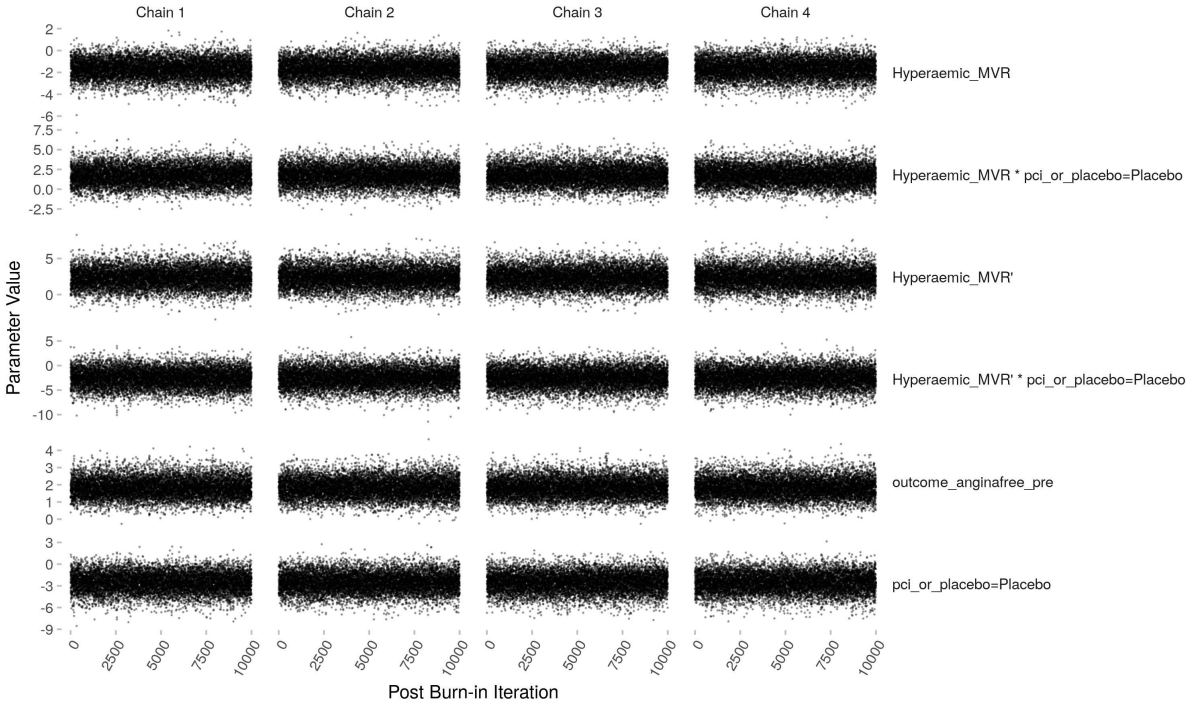
	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 127 FALSE 77 TRUE 50 Draws 40000 Chains 4 Time 3.6s p 6	B 0.213 [0.203 0.224]	g 1.151 [0.708 1.596] gp 0.233 [0.158 0.297] EV 0.2 [0.085 0.318] v 1.188 [0.401 2.184] vp 0.048 [0.024 0.078]	C 0.697 [0.656 0.732] Dxy 0.394 [0.313 0.464]

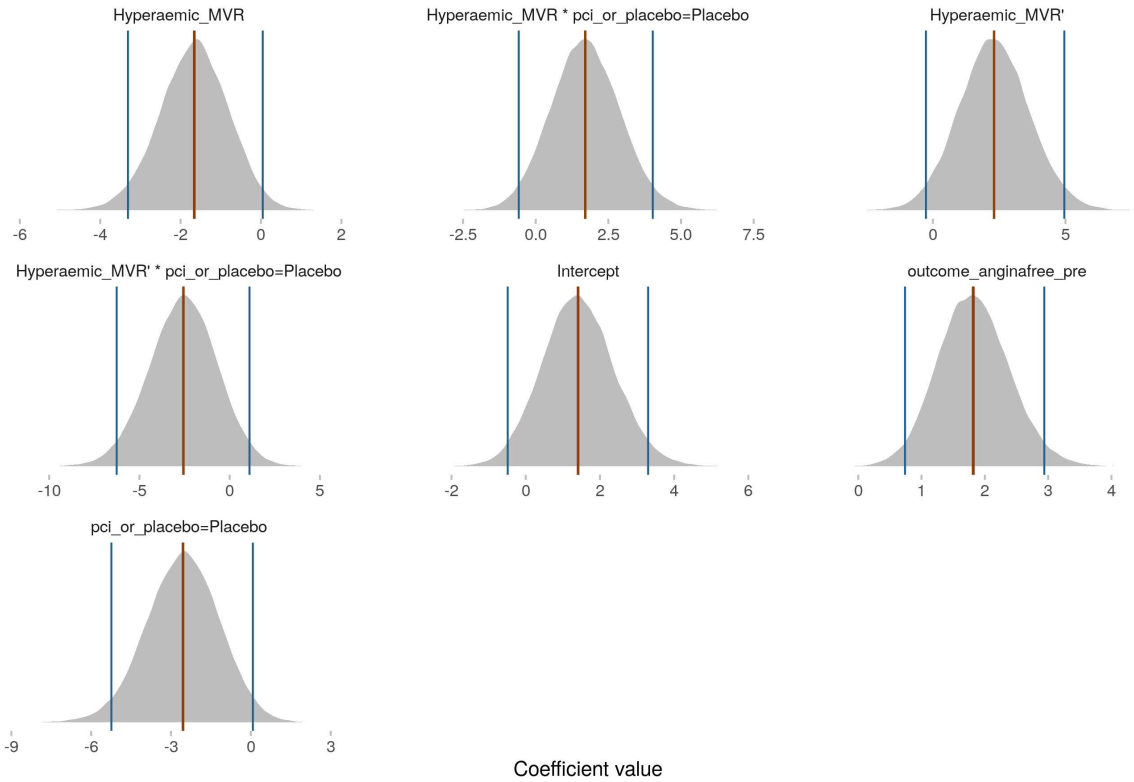
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
Intercept	1.4187	1.4012	0.9691	-0.4864	3.2983	0.9311	1.06
outcome_anginafree_pre	1.8244	1.8097	0.5616	0.7393	2.9395	0.9998	1.08
Hyperaemic_MVR	-1.6679	-1.6506	0.8553	-3.3088	0.0439	0.0226	0.94
Hyperaemic_MVR'	2.3144	2.2992	1.3300	-0.2623	4.9570	0.9610	1.04
pci_or_placebo=Placebo	-2.5613	-2.5390	1.3604	-5.2412	0.0748	0.0268	0.94
Hyperaemic_MVR * pci_or_placebo=Placebo	1.7130	1.6971	1.1814	-0.5823	4.0272	0.9283	1.04
Hyperaemic_MVR' * pci_or_placebo=Placebo	-2.5790	-2.5492	1.8765	-6.2615	1.0974	0.0815	0.96

Contrasts Given Priors
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_anginafree_pre	0.596	0.139	0.879	1
Hyperaemic_MVR (Factor+Higher Order Factors)	0.234	0.054	0.694	4
All Interactions	0.119	0.000	0.442	2
Nonlinear (Factor+Higher Order Factors)	0.175	0.010	0.493	2
pci_or_placebo (Factor+Higher Order Factors)	0.314	0.025	0.701	3
All Interactions	0.119	0.000	0.442	2
Hyperaemic_MVR * pci_or_placebo (Factor+Higher Order Factors)	0.119	0.000	0.442	2
Nonlinear	0.107	0.000	0.370	1
Nonlinear Interaction: f(A,B) vs. AB	0.107	0.000	0.370	1
TOTAL NONLINEAR	0.175	0.010	0.493	2
TOTAL NONLINEAR + INTERACTION	0.183	0.019	0.557	3
TOTAL	1.000	1.000	1.000	6

Approximate total model Wald total chi-square used in denominators of REV:
17.7 [6.5, 43.3]


Chain 1
Chain 2
Chain 3
Chain 4
Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_anginafree_pre
pci_or_placebo=Placebo
Parameter Value
Post Burn-in Iteration


Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
Intercept
outcome_anginafree_pre
pci_or_placebo=Placebo
Coefficient value

Supplementary S7 Angina Frequency x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.253 for Intercepts

```
blrm(formula = outcome_saq_angina_freq_post ~
rcs(outcome_saq_angina_freq_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

20	30	40	50	60	70	80	90	100
3	2	5	10	6	15	16	21	49

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 127 Draws 40000 Chains 4 Time 5s p 7	B 0.175 [0.162, 0.19]	g 1.555 [1.148, 2.083] gp 0.296 [0.244, 0.359] EV 0.273 [0.184, 0.383] v 1.944 [0.867, 3.15] vp 0.068 [0.045, 0.095]	C 0.736 [0.718, 0.751] Dxy 0.472 [0.436, 0.502]

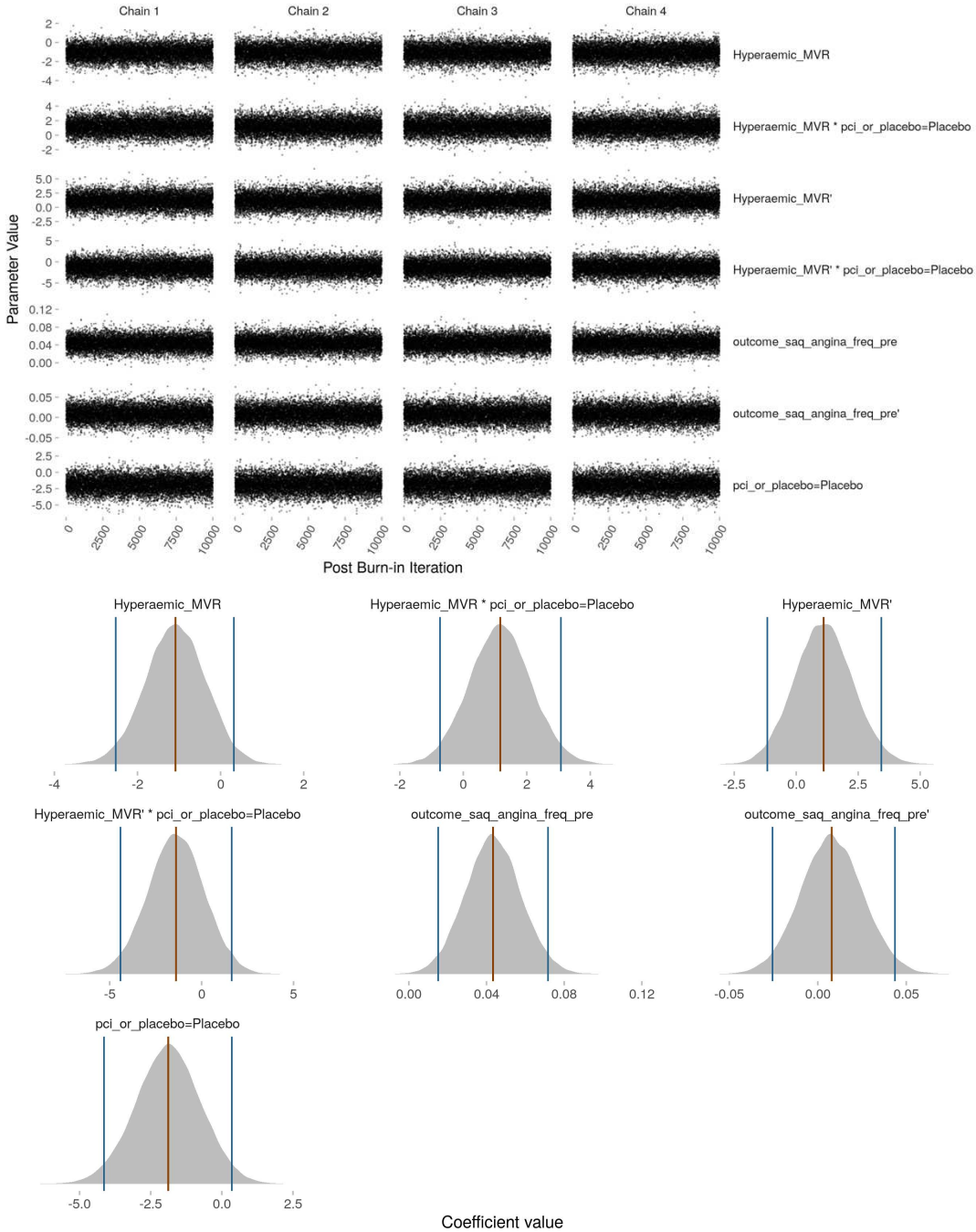
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
y ≥ 30	3.0240	3.0073	1.2907	0.5523	5.5960	0.9917	1.04
y ≥ 40	2.3478	2.3405	1.2361	-0.0793	4.7583	0.9726	1.02
y ≥ 50	1.4337	1.4315	1.2187	-0.9519	3.8166	0.8816	1.01
y ≥ 60	0.4827	0.4804	1.2281	-1.9440	2.8642	0.6537	1.01
y ≥ 70	0.0762	0.0758	1.2334	-2.3004	2.5195	0.5246	1.01
y ≥ 80	-0.7426	-0.7422	1.2467	-3.2480	1.6347	0.2717	1.00
y ≥ 90	-1.5009	-1.5022	1.2487	-3.9938	0.8920	0.1150	1.00
y ≥ 100	-2.4076	-2.4095	1.2421	-4.8274	0.0348	0.0261	1.00
outcome_saq_angina_freq_pre	0.0434	0.0433	0.0144	0.0151	0.0717	0.9989	1.02
outcome_saq_angina_freq_pre'	0.0079	0.0078	0.0177	-0.0256	0.0436	0.6724	1.01
Hyperaemic_MVR	-1.0879	-1.0829	0.7258	-2.5233	0.3201	0.0646	0.97
Hyperaemic_MVR'	1.1113	1.1011	1.1781	-1.1651	3.4341	0.8279	1.03
pci_or_placebo = Placebo	-1.8881	-1.8796	1.1444	-4.1416	0.3513	0.0488	0.97
Hyperaemic_MVR × pci_or_placebo = Placebo	1.1663	1.1622	0.9726	-0.7331	3.0755	0.8853	1.02
Hyperaemic_MVR' × pci_or_placebo = Placebo	-1.3963	-1.3891	1.5393	-4.4139	1.6367	0.1810	0.98

Contrasts Given Priors

```
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2]     contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Factor	REV	Lower	Upper	d.f.
outcome_saq_angina_freq_pre	0.778	0.475	0.928	2
Nonlinear	0.005	0.000	0.087	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.093	0.021	0.343	4
- All Interactions	0.042	0.001	0.205	2
- Nonlinear (Factor + Higher Order Factors)	0.022	0.000	0.176	2
pci_or_placebo (Factor + Higher Order Factors)	0.093	0.012	0.295	3
- All Interactions	0.042	0.001	0.205	2
Hyperaemic_MVR × pci_or_placebo (Factor + Higher Order Factors)	0.042	0.001	0.205	2
- Nonlinear Interaction (f(A,B) vs. AB)	0.019	0.000	0.126	1
TOTAL NONLINEAR	0.025	0.001	0.198	3
TOTAL NONLINEAR + INTERACTION	0.049	0.006	0.270	4
TOTAL	1.000	1.000	1.000	7
outcome_saq_angina_freq_pre	0.778	0.475	0.928	2

Approximate total model Wald total chi-square used in denominators of REV: 44.1 [24.9, 79.2]



Supplementary S8 SAQ Physical Limitation Score x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.075 for Intercepts

```
blrm(formula = outcome_saq_pl_post ~ rcs(outcome_saq_pl_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

8.33 11.11 16.67 22.22 25 27.78 30.56 31.94 33.33 36.11 38.89 44.44 50 52.78 55.56 58.33 61.11 63.89 66.67 69.44 70.83

1 1 1 1 1 1 2 1 1 6 1 1 5 1 3 2 3 4 2 6 1

72.22 75 77.78 79.17 80.56 83.33 84.72 86.11 88.89 91.67 93.06 94.44 95.83 97.22 100

5 3 3 1 2 1 1 2 10 6 1 6 2 4 22

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 114 Draws 40000 Chains 4 Time 8.9s p 7	B 0.004 [0.001, 0.008]	g 2.778 [2.2, 3.347] gp 0.021 [0, 0.048] EV 0.31 [0.018, 0.55] v 6.455 [3.807, 9.229] vp 0.004 [0, 0.012]	C 0.798 [0.788, 0.805] Dxy 0.595 [0.575, 0.609]

Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_saq_pl_pre	0.1115	0.1112	0.0209	0.0708	0.1527	1.0000	1.04
outcome_saq_pl_pre'	-0.0380	-0.0379	0.0244	-0.0865	0.0089	0.0590	0.98
Hyperaemic_MVR	-0.6858	-0.6744	0.7413	-2.1076	0.7960	0.1758	0.97
Hyperaemic_MVR'	0.8138	0.8014	1.1119	-1.3420	2.9923	0.7672	1.02
pci_or_placebo=Placebo	-1.6262	-1.6147	1.1508	-4.0285	0.5095	0.0776	0.98
Hyperaemic_MVR × pci_or_placebo=Placebo	0.8595	0.8531	1.0039	-1.1013	2.8334	0.8044	1.02
Hyperaemic_MVR' × pci_or_placebo=Placebo	-2.1745	-2.1600	1.5427	-5.2046	0.8598	0.0789	0.98

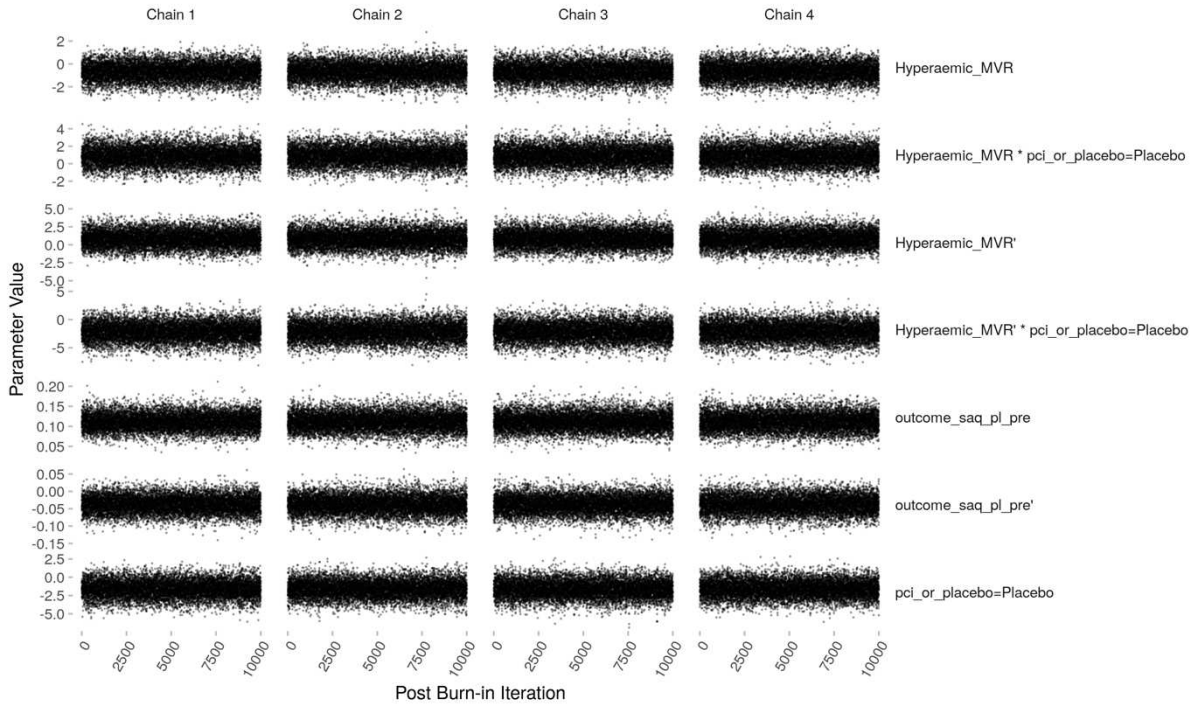
Contrasts Given Priors

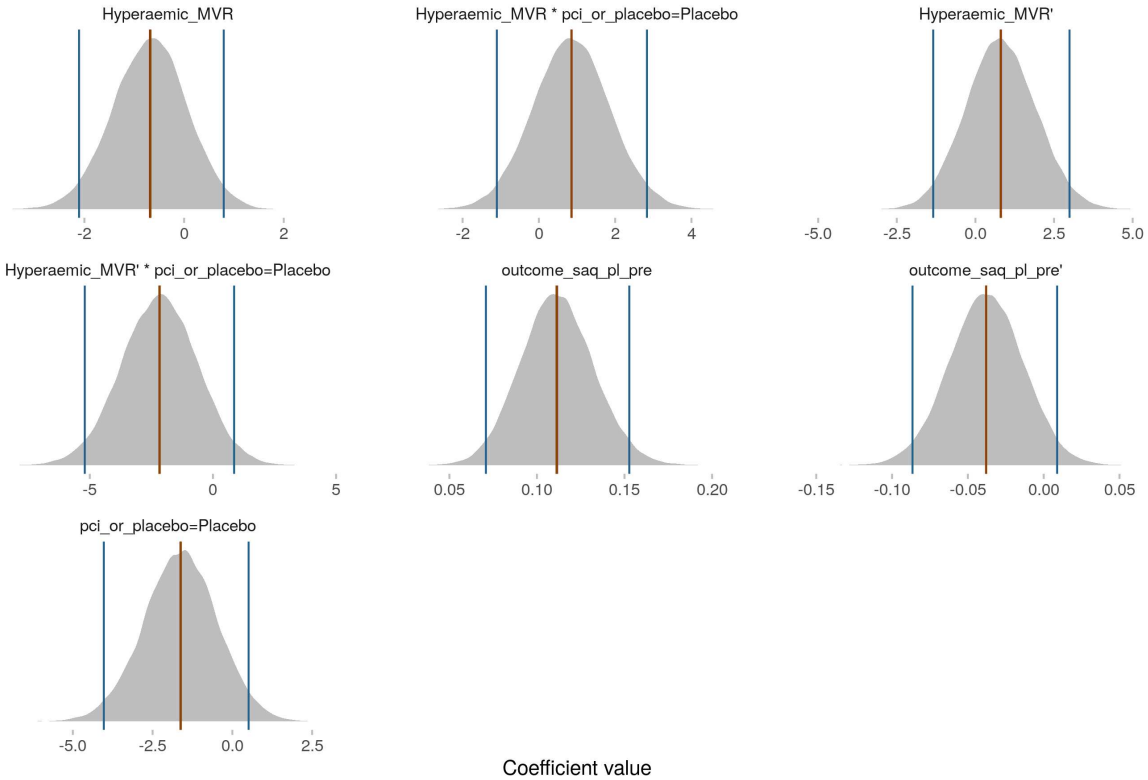
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),

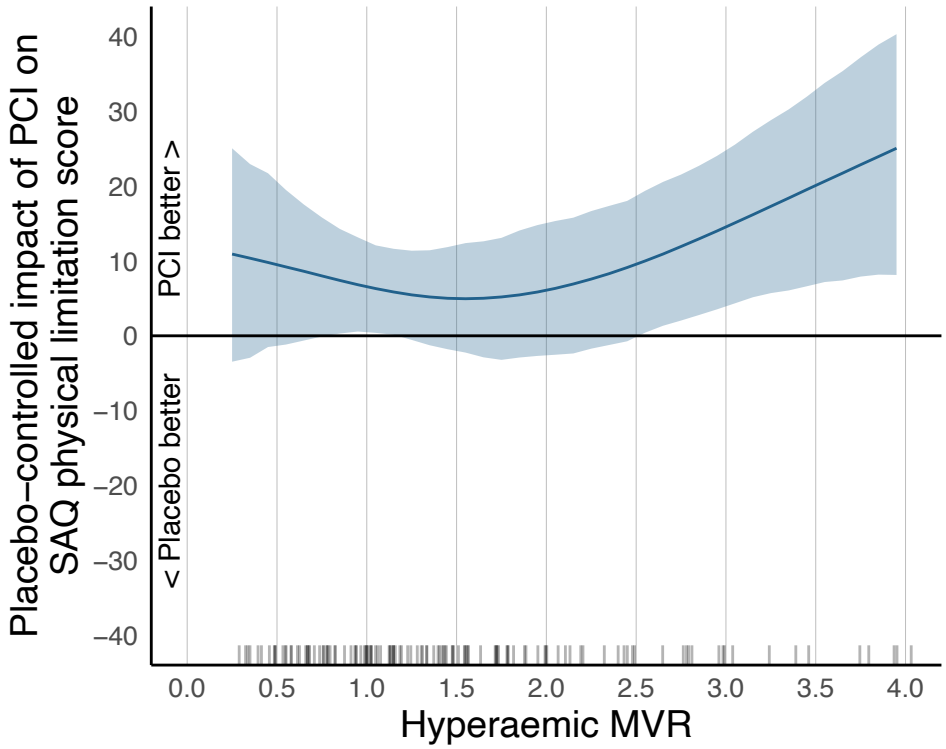
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_saq_pl_pre	0.813	0.607	0.924	2
Nonlinear	0.030	0.000	0.116	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.138	0.045	0.313	4
All Interactions	0.052	0.000	0.183	2
Nonlinear (Factor + Higher Order Factors)	0.026	0.000	0.140	2
pci_or_placebo (Factor + Higher Order Factors)	0.162	0.038	0.343	3
All Interactions	0.052	0.000	0.183	2
Hyperaemic_MVR × pci_or_placebo (Factor + Higher Order Factors)	0.052	0.000	0.183	2
Nonlinear	0.025	0.000	0.127	1
Nonlinear Interaction : f(A,B) vs. AB	0.025	0.000	0.127	1
TOTAL NONLINEAR	0.058	0.006	0.190	3
TOTAL NONLINEAR + INTERACTION	0.078	0.009	0.239	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
79.6 [52, 121.4]







Supplementary Figure S9. Relationship of change in pre-randomisation to follow-up SAQ physical limitation score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 43.6%). SAQ, Seattle Angina Questionnaire and PCI, percutaneous coronary intervention.*

Supplementary S10 SAQ Treatment Satisfaction x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.175 for Intercepts

```
blrm(formula = outcome_saq_ts_post ~ rcs(outcome_saq_ts_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

37.5	41.6666666666667	43.75	50	56.25	62.5	66.6666666666667
2	1	2	1	2	7	2
68.75	75	81.25	83.3333333333333	87.5	93.75	100
2	11	16	1	12	19	49

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 127 Draws 40000 Chains 4 Time 5.6s p 7	B 0.174 [0.167, 0.182]	g 1.701 [1.246, 2.136] gp 0.314 [0.261, 0.365] EV 0.308 [0.209, 0.407] v 2.38 [1.24, 3.62] vp 0.077 [0.052, 0.101]	C 0.746 [0.732, 0.755] Dxy 0.491 [0.464, 0.51]

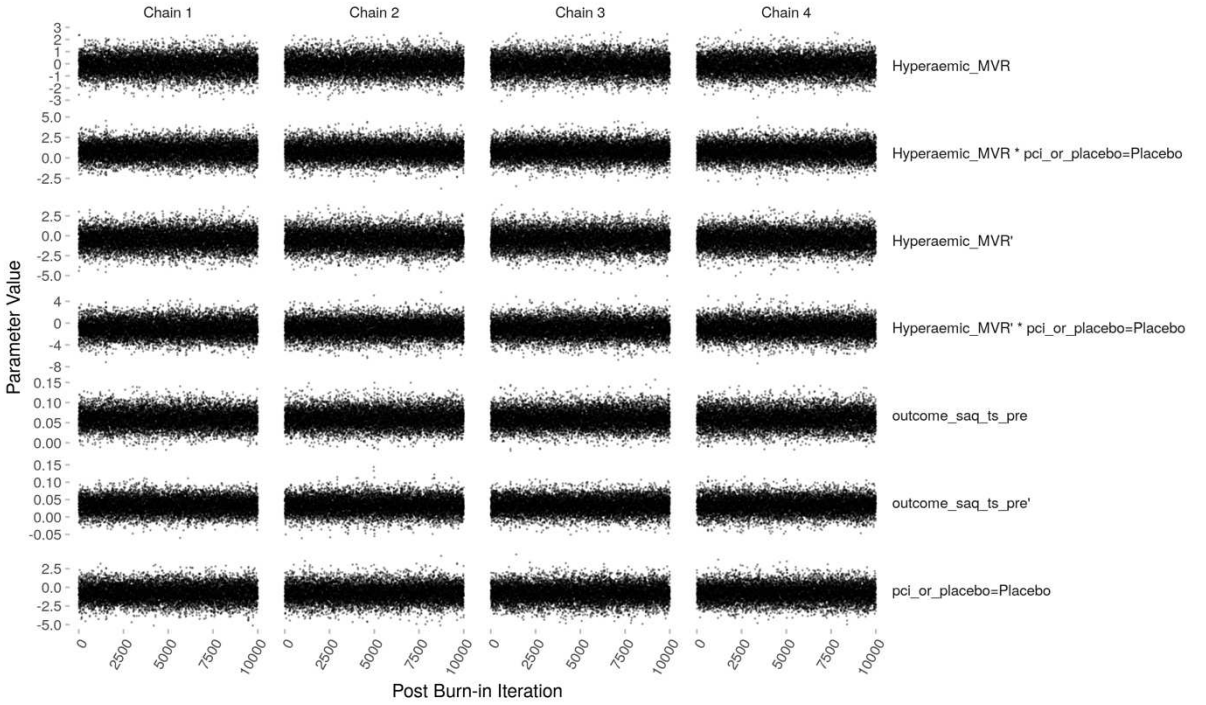
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_saq_ts_pre	0.0597	0.0593	0.0221	0.0169	0.1036	0.9974	1.06
outcome_saq_ts_pre'	0.0330	0.0331	0.0227	-0.0112	0.0776	0.9273	0.99
Hyperaemic_MVR	-0.1366	-0.1393	0.7381	-1.6026	1.2755	0.4264	0.99
Hyperaemic_MVR'	-0.4691	-0.4651	1.1285	-2.7425	1.6705	0.3408	1.00
pci_or_placebo = Placebo	-0.7795	-0.7803	1.1175	-2.9551	1.4403	0.2414	0.99
Hyperaemic_MVR * pci_or_placebo = Placebo	0.7788	0.7775	0.9827	-1.1520	2.7152	0.7864	1.01
Hyperaemic_MVR' * pci_or_placebo = Placebo	-1.0092	-1.0142	1.5205	-4.0086	1.9534	0.2534	1.00

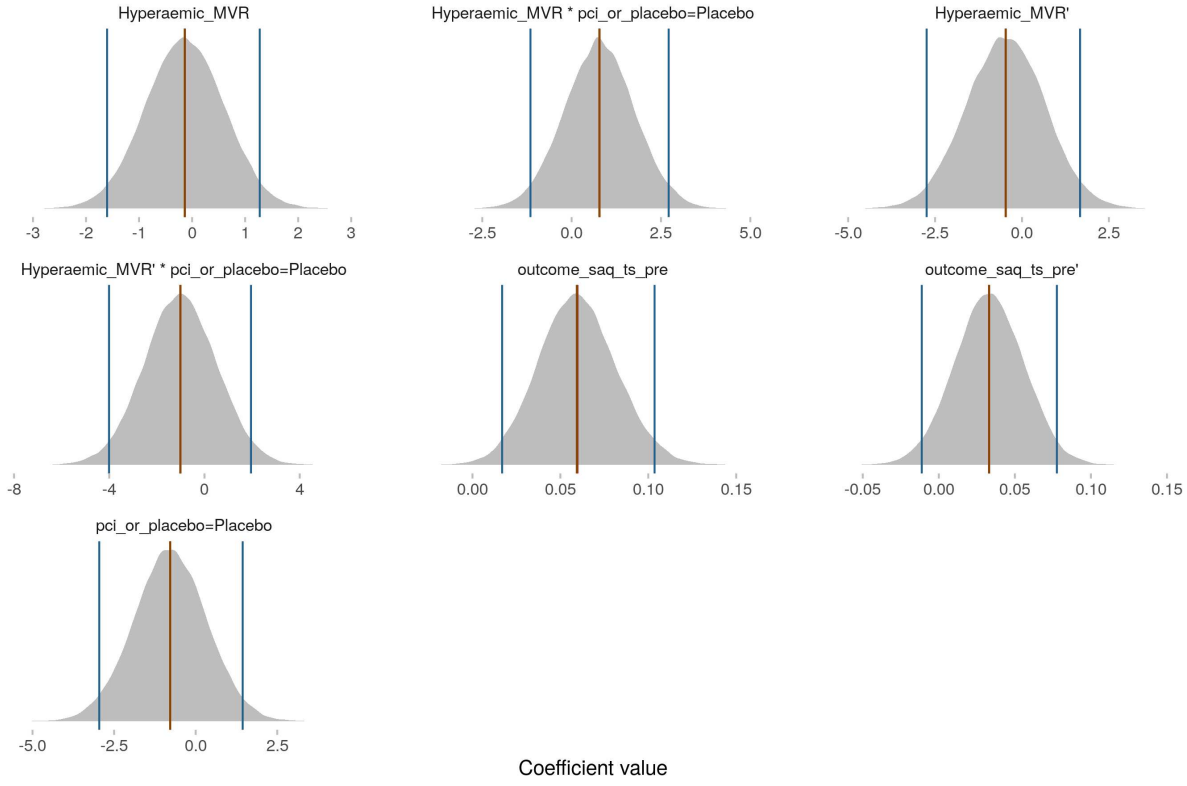
Contrasts Given Priors

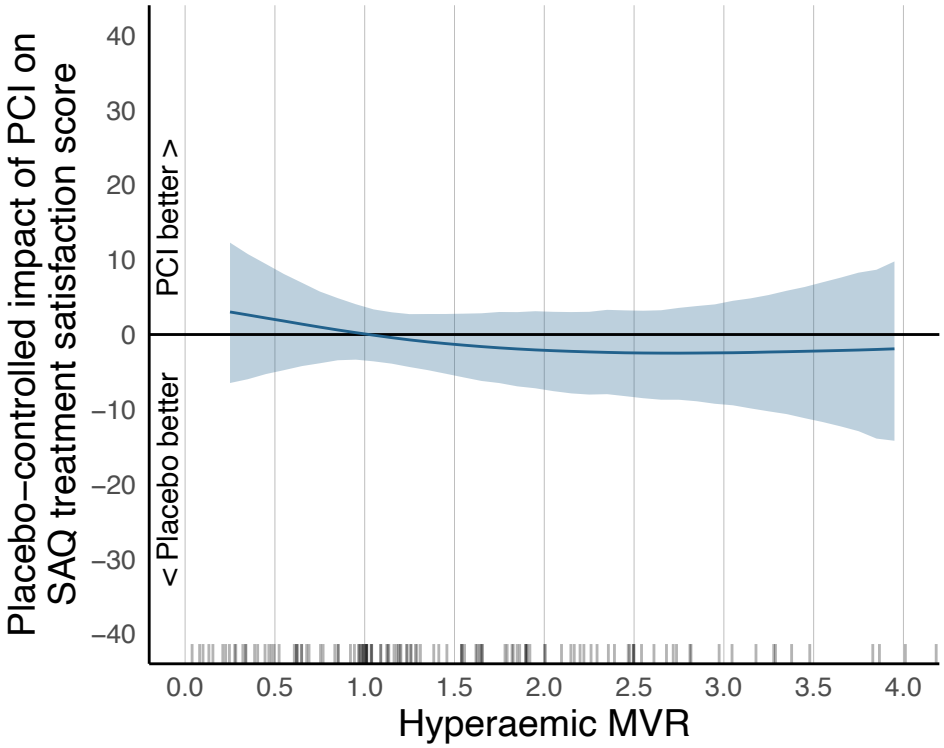
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_saq_ts_pre	0.906	0.674	0.979	2
Nonlinear	0.040	0.000	0.149	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.126	0.026	0.348	4
All Interactions	0.013	0.000	0.134	2
Nonlinear (Factor + Higher Order Factors)	0.039	0.000	0.177	2
pci_or_placebo (Factor + Higher Order Factors)	0.016	0.000	0.166	3
All Interactions (pci_or_placebo)	0.013	0.000	0.134	2
Hyperaemic_MVR * pci_or_placebo (Factor + Higher Order Factors)	0.013	0.000	0.134	2
Nonlinear (Hyperaemic_MVR * pci_or_placebo interaction)	0.008	0.000	0.088	1
Nonlinear Interaction: f(A,B) vs. AB	0.008	0.000	0.088	1
TOTAL NONLINEAR	0.079	0.010	0.265	3
TOTAL NONLINEAR + INTERACTION	0.084	0.018	0.292	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
53 [32.8, 89.1]







Supplementary Figure S11. Relationship of change in pre-randomisation to follow-up SAQ treatment satisfaction score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 80.2%). SAQ, Seattle Angina Questionnaire and PCI, percutaneous coronary intervention.*

Supplementary S12 SAQ Quality of Life x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.2 for Intercepts

```
blrm(formula = outcome_saq_qol_post ~ rcs(outcome_saq_qol_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

8.3333333333333	16.6666666666667	25	33.3333333333333	41.6666666666667	50	58.3333333333333
1	7	3	12	11	13	9
66.6666666666667	75	83.3333333333333	91.6666666666667	100		
16	12	21	12	9		

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 126 Draws 40000 Chains 4 Time 5.5s p 7	B 0.2 [0.19, 0.211]	g 1.422 [1.008, 1.84] gp 0.276 [0.221, 0.332] EV 0.238 [0.156, 0.334] v 1.669 [0.789, 2.608] vp 0.059 [0.039, 0.083	C 0.689 [0.669, 0.703] Dxy 0.379 [0.338, 0.406]

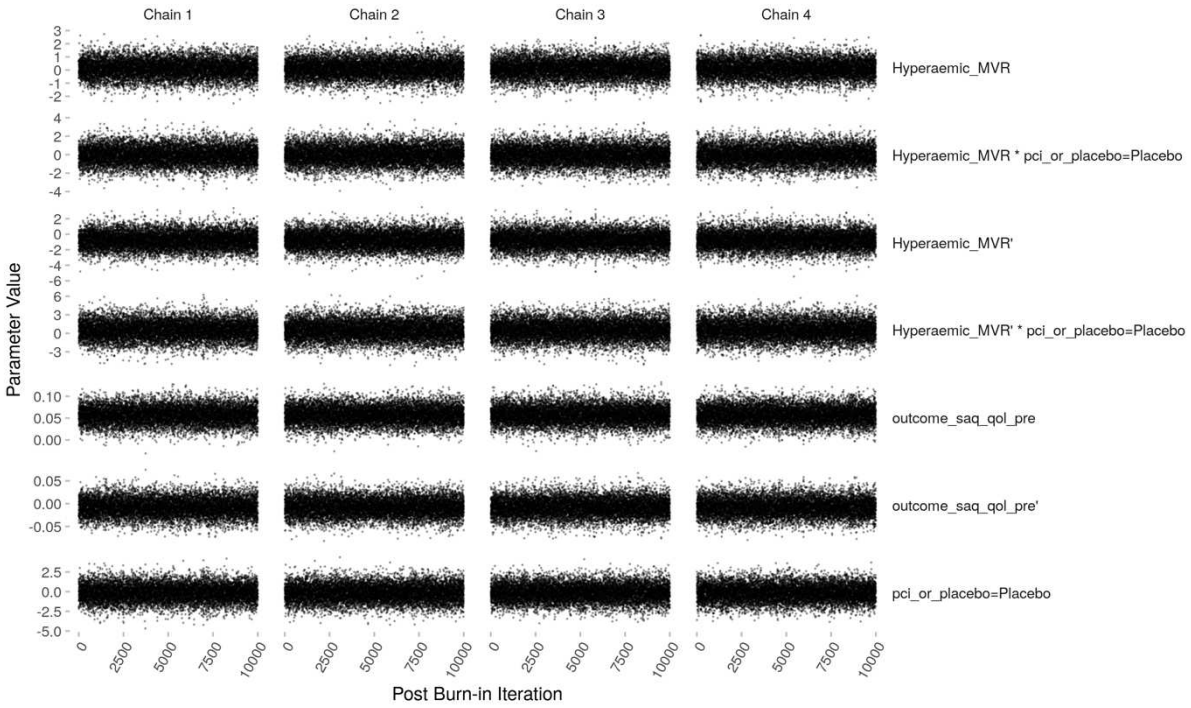
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_saq_qol_pre	0.0570	0.0570	0.0196	0.0190	0.0960	0.9979	1.00
outcome_saq_qol_pre'	-0.0079	-0.0080	0.0193	-0.0455	0.0302	0.3361	1.00
Hyperaemic_MVR	0.0971	0.0984	0.6619	-1.1822	1.4225	0.5598	0.99
Hyperaemic_MVR'	-0.7753	-0.7665	1.0477	-2.8721	1.2457	0.2270	0.99
pci_or_placebo = Placebo	-0.1629	-0.1675	1.0792	-2.2927	1.9295	0.4400	0.99
Hyperaemic_MVR * pci_or_placebo = Placebo	-0.0703	-0.0729	0.9473	-1.9226	1.7829	0.4690	1.00
Hyperaemic_MVR' * pci_or_placebo = Placebo	0.4933	0.4917	1.4656	-2.4102	3.3400	0.6347	1.01

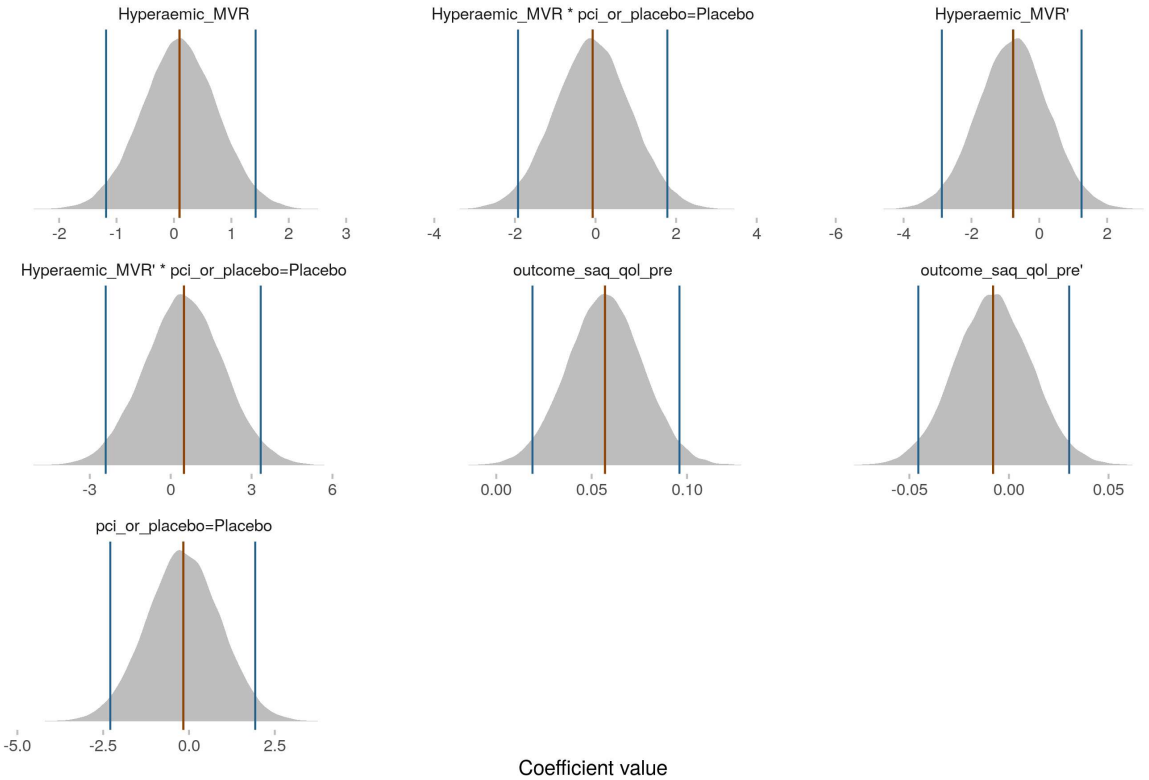
Contrasts Given Priors

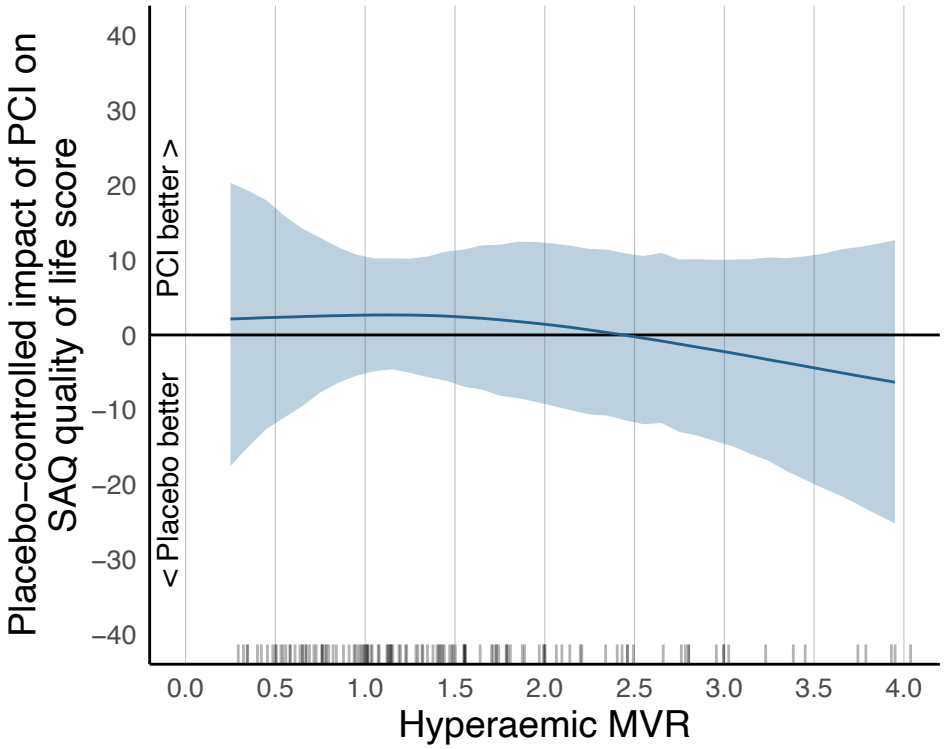
```
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2]     contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Factor	REV	Lower	Upper	d.f.
outcome_saq_qol_pre	0.830	0.544	0.948	2
Nonlinear	0.004	0.000	0.093	1
Hyperaemic_MVR (Factor+Higher Order Factors)	0.081	0.018	0.330	4
All Interactions	0.017	0.000	0.183	2
Nonlinear (Factor+Higher Order Factors)	0.014	0.000	0.163	2
pci_or_placebo (Factor+Higher Order Factors)	0.021	0.001	0.214	3
All Interactions	0.017	0.000	0.183	2
Hyperaemic_MVR * pci_or_placebo (Factor+Higher Order Factors)	0.017	0.000	0.183	2
Nonlinear	0.003	0.000	0.102	1
Nonlinear Interaction: f(A,B) vs. AB	0.003	0.000	0.102	1
TOTAL NONLINEAR	0.020	0.001	0.201	3
TOTAL NONLINEAR + INTERACTION	0.033	0.009	0.261	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV: 41.8 [22, 72.5]







Supplementary Figure S13. Relationship of change in pre-randomisation to follow-up SAQ quality of life score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 61.2%). SAQ, Seattle Angina Questionnaire and PCI, percutaneous coronary intervention.*

Supplementary S14 SAQ Stability Score x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.392 for Intercepts

```
blrm(formula = outcome_saq_stab_post ~ rcs(outcome_saq_stab_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

0 25 50 75 100
4 2 74 19 27

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 126 Draws 40000 Chains 4 Time 4.8s p 7	B 0.048 [0.045, 0.054]	g 0.736 [0.4, 1.113] gp 0.037 [0.011, 0.069] EV 0.036 [0.003, 0.096] v 0.469 [0.064, 0.873] vp 0.002 [0, 0.006]	C 0.602 [0.56, 0.633] Dxy 0.205 [0.119, 0.265]

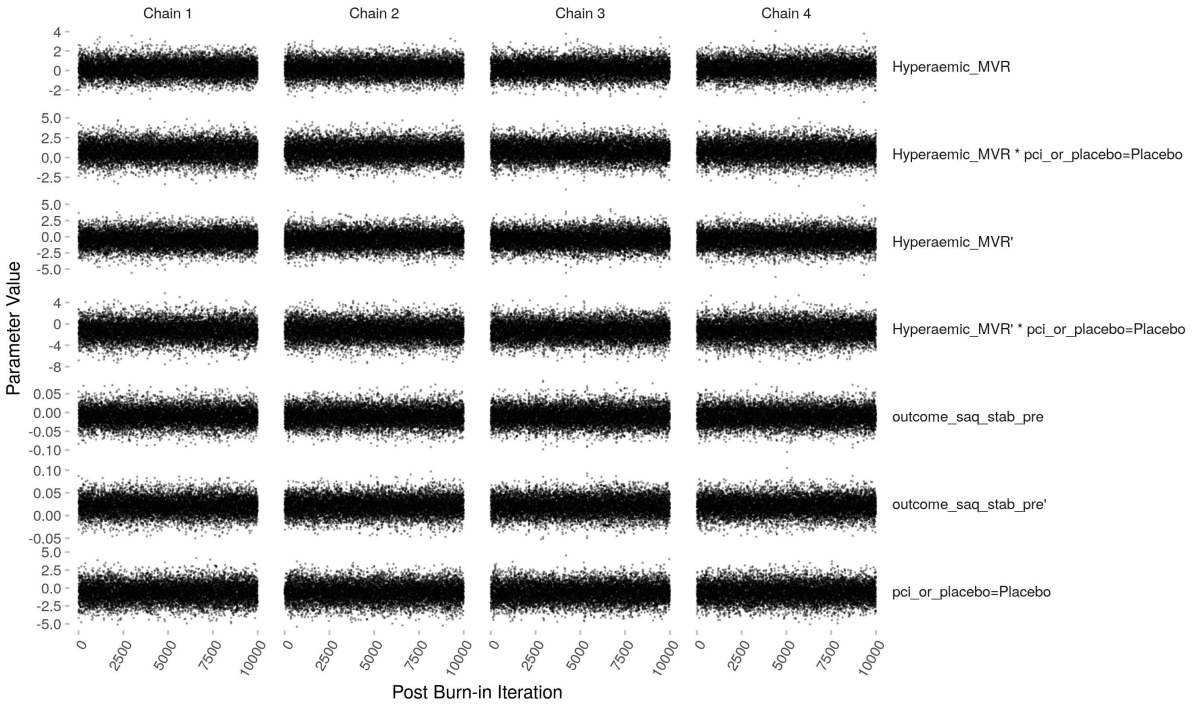
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
y ≥ 25	3.5121	3.5123	1.5183	0.5710	6.5324	0.9898	1.01
y ≥ 50	3.0188	3.0173	1.4916	0.0397	5.8954	0.9786	1.00
y ≥ 75	-0.7356	-0.7231	1.4509	-3.6160	2.0718	0.3055	0.98
y ≥ 100	-1.5415	-1.5268	1.4561	-4.3826	1.3281	0.1437	0.98
outcome_saq_stab_pre	-0.0104	-0.0105	0.0223	-0.0547	0.0327	0.3174	1.01
outcome_saq_stab_pre'	0.0210	0.0209	0.0192	-0.0162	0.0593	0.8636	1.00
Hyperaemic_MVR	0.1796	0.1721	0.7998	-1.3830	1.7700	0.5848	1.02
Hyperaemic_MVR'	-0.4374	-0.4261	1.2153	-2.8540	1.9232	0.3622	0.99
pci_or_placebo = Placebo	-0.6376	-0.6381	1.2460	-3.0389	1.8439	0.3028	1.00
Hyperaemic_MVR * pci_or_placebo = Placebo	0.7855	0.7841	1.0741	-1.3400	2.8714	0.7687	0.99
Hyperaemic_MVR' * pci_or_placebo = Placebo	-1.3122	-1.3099	1.6488	-4.4937	1.9646	0.2118	1.00

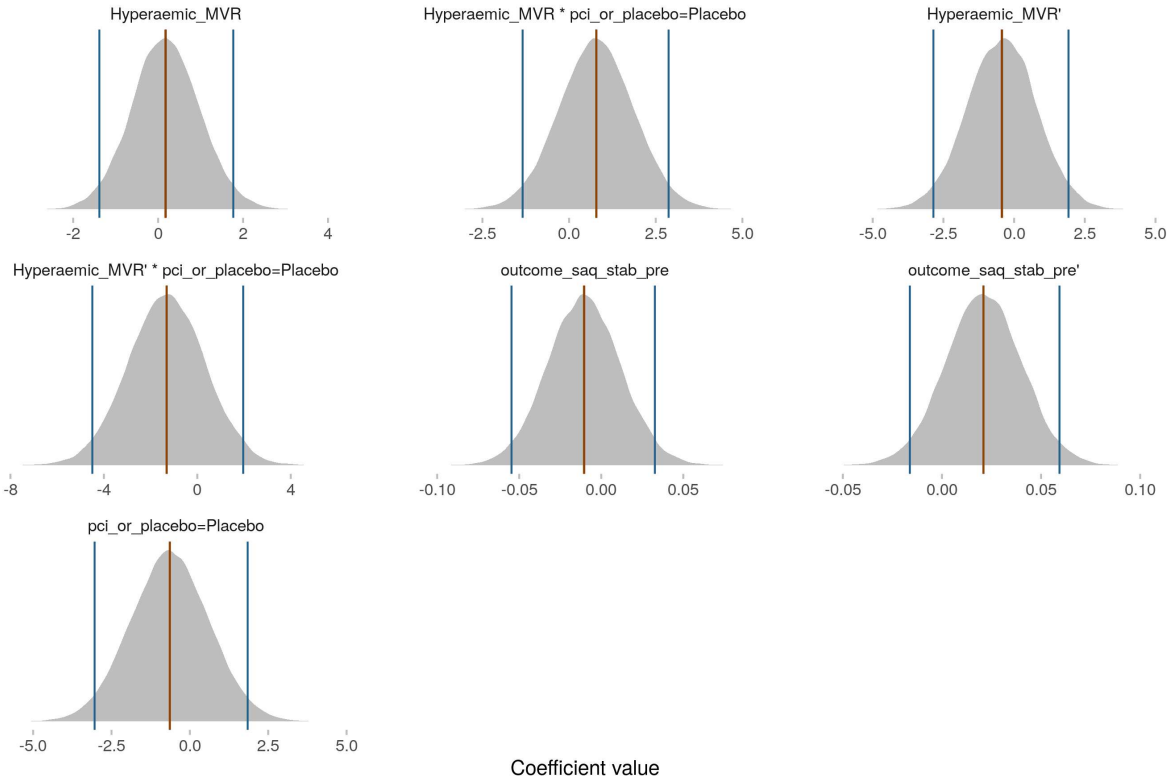
Contrasts Given Priors

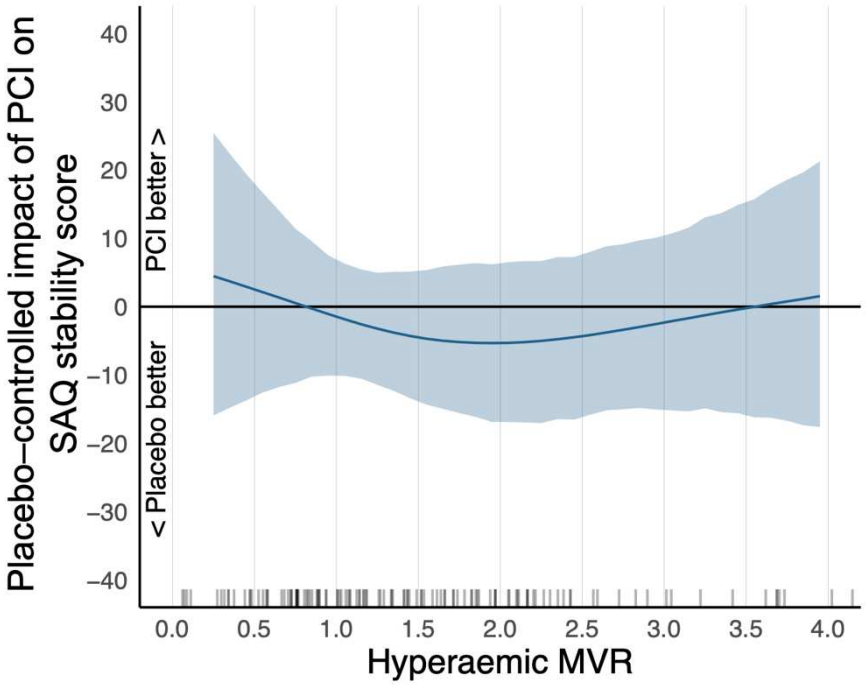
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_saq_stab_pre	0.504	0.003	0.765	2
Nonlinear	0.149	0.000	0.457	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.317	0.068	0.850	4
All Interactions	0.080	0.000	0.514	2
Nonlinear (Factor + Higher Order Factors)	0.286	0.003	0.653	2
pci_or_placebo (Factor + Higher Order Factors)	0.117	0.002	0.683	3
All Interactions	0.080	0.000	0.514	2
Hyperaemic_MVR * pci_or_placebo (Factor + Higher Order Factors)	0.080	0.000	0.514	2
Nonlinear	0.079	0.000	0.393	1
Nonlinear Interaction: f(A,B) vs. AB	0.079	0.000	0.393	1
TOTAL NONLINEAR	0.505	0.059	0.863	3
TOTAL NONLINEAR + INTERACTION	0.511	0.121	0.942	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
8 [2.6, 27.8]







Supplementary Figure S15. Relationship of change in pre-randomisation to follow-up SAQ stability score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 29.6%). SAQ, Seattle Angina Questionnaire and PCI, percutaneous coronary intervention.*

Supplementary S16 EQ5D Quality Of Life x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.05 for Intercepts

```
blrm(formula = outcome_eq5d_qol_post ~ rcs(outcome_eq5d_qol_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

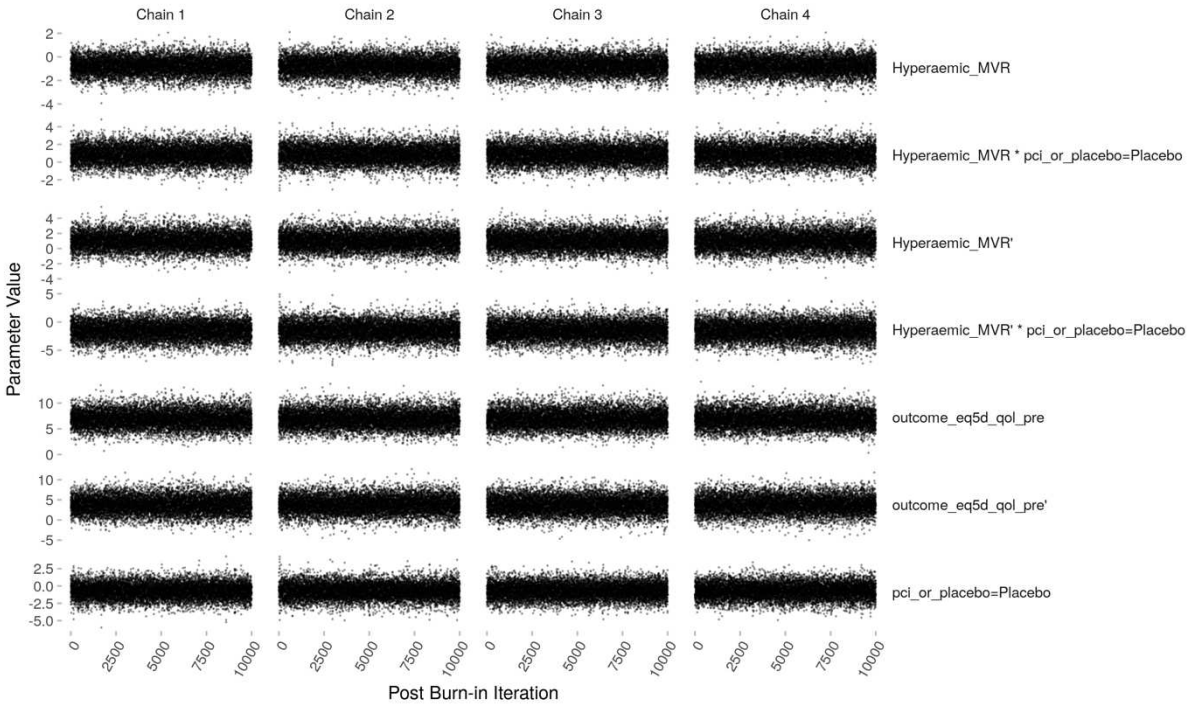
	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 127 Draws 40000 Chains 4 Time 11.7s p 7	B 0.151 [0.139, 0.163]	g 2.242 [1.769, 2.668] gp 0.343 [0.294, 0.375] EV 0.358 [0.276, 0.429] v 4.345 [2.587, 6.061] vp 0.089 [0.07, 0.108]	C 0.768 [0.757, 0.777] Dxy 0.537 [0.514, 0.555]

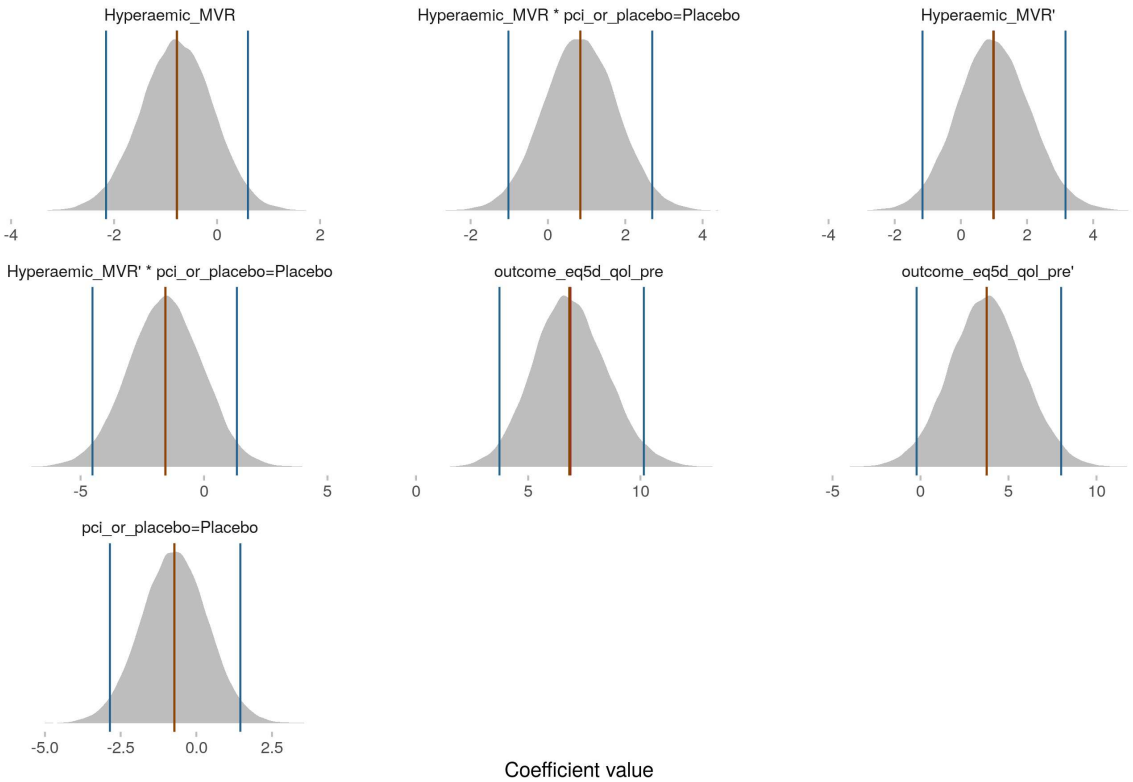
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_eq5d_qol_pre	6.8715	6.8352	1.6256	3.6526	9.9908	1.0000	1.06
outcome_eq5d_qol_pre'	3.7778	3.7561	2.0910	-0.2645	7.9393	0.9653	1.02
Hyperaemic_MVR	-0.7899	-0.7838	0.6993	-2.1583	0.5789	0.1287	0.97
Hyperaemic_MVR'	1.0059	0.9959	1.0914	-1.1399	3.1332	0.8222	1.04
pci_or_placebo=Placebo	-0.7326	-0.7351	1.1056	-2.8592	1.4971	0.2518	1.00
Hyperaemic_MVR * pci_or_placebo=Placebo	0.8457	0.8439	0.9540	-1.0187	2.7276	0.8144	0.99
Hyperaemic_MVR' * pci_or_placebo=Placebo	-1.5796	-1.5730	1.4904	-4.4542	1.3666	0.1433	0.99

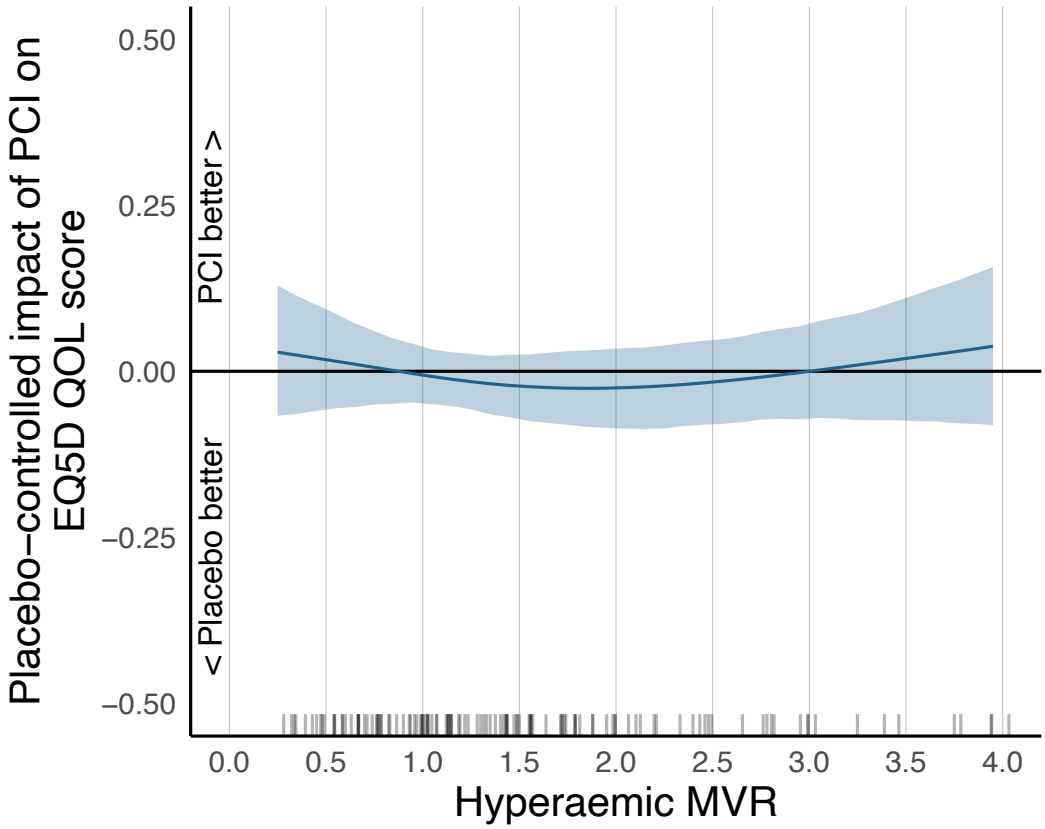
Contrasts Given Priors
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_eq5d_qol_pre	0.879	0.669	0.966	2
Nonlinear	0.042	0.000	0.135	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.050	0.008	0.209	4
All Interactions	0.016	0.000	0.119	2
Nonlinear (Factor + Higher Order Factors)	0.015	0.000	0.105	2
pci_or_placebo (Factor + Higher Order Factors)	0.017	0.000	0.143	3
All Interactions	0.016	0.000	0.119	2
Hyperaemic_MVR * pci_or_placebo (Factor + Higher Order Factors)	0.016	0.000	0.119	2
Nonlinear	0.014	0.000	0.084	1
Nonlinear Interaction : f(A,B) vs. AB	0.014	0.000	0.084	1
TOTAL NONLINEAR	0.053	0.002	0.186	3
TOTAL NONLINEAR + INTERACTION	0.055	0.003	0.211	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
76.6 [49.2, 123.3]


Chain 1
Chain 2
Chain 3
Chain 4
Parameter Value
Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_eq5d_qol_pre
outcome_eq5d_qol_pre'
pci_or_placebo=Placebo
Post Burn-in Iteration


Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_eq5d_qol_pre
outcome_eq5d_qol_pre'
pci_or_placebo=Placebo
Coefficient value



Supplementary Figure S17. Relationship of change in pre-randomisation to follow-up EQ5D quality of life score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 69.7%). PCI, percutaneous coronary intervention.*

Supplementary S18 EQ5D Visual Analogue Score x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.109 for Intercepts

```
blrm(formula = outcome_eq5d_vas_post ~ rcs(outcome_eq5d_vas_pre,
    3) + rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses

0	20	30	35	40	45	50	55	60	65	68	70	75	77	78	80	85	87	88	90	95	97	98	100
1	2	5	2	8	1	3	4	9	8	1	19	8	1	2	12	16	1	1	14	4	1	1	5

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 129 Draws 40000 Chains 4 Time 8.2s p 7	B 0.169 [0.158, 0.179]	g 1.8 [1.296, 2.227] gp 0.328 [0.273, 0.377] EV 0.328 [0.213, 0.417] v 2.553 [1.378, 3.894] vp 0.082 [0.053, 0.104]	C 0.741 [0.724, 0.756] Dxy 0.482 [0.448, 0.511]

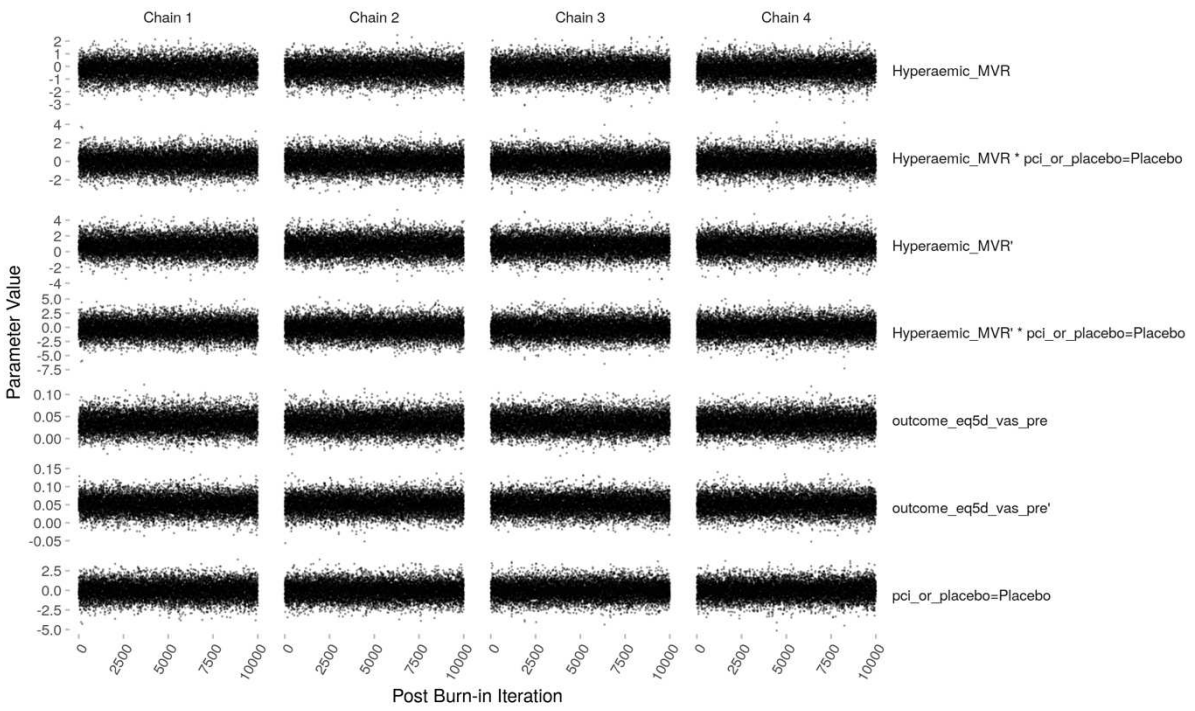
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
outcome_eq5d_vas_pre	0.0359	0.0355	0.0198	-0.0027	0.0748	0.9688	1.05
outcome_eq5d_vas_pre'	0.0501	0.0502	0.0230	0.0050	0.0949	0.9847	0.98
Hyperaemic_MVR	-0.2500	-0.2443	0.6721	-1.6036	1.0362	0.3552	0.98
Hyperaemic_MVR'	0.7153	0.7081	1.0595	-1.3146	2.8399	0.7510	1.02
pci_or_placebo = Placebo	-0.0468	-0.0427	1.0266	-2.0598	1.9480	0.4841	0.99
Hyperaemic_MVR * pci_or_placebo = Placebo	-0.0660	-0.0719	0.8972	-1.8209	1.6951	0.4672	0.99
Hyperaemic_MVR' * pci_or_placebo = Placebo	-0.2365	-0.2321	1.4150	-2.9523	2.5984	0.4339	1.01

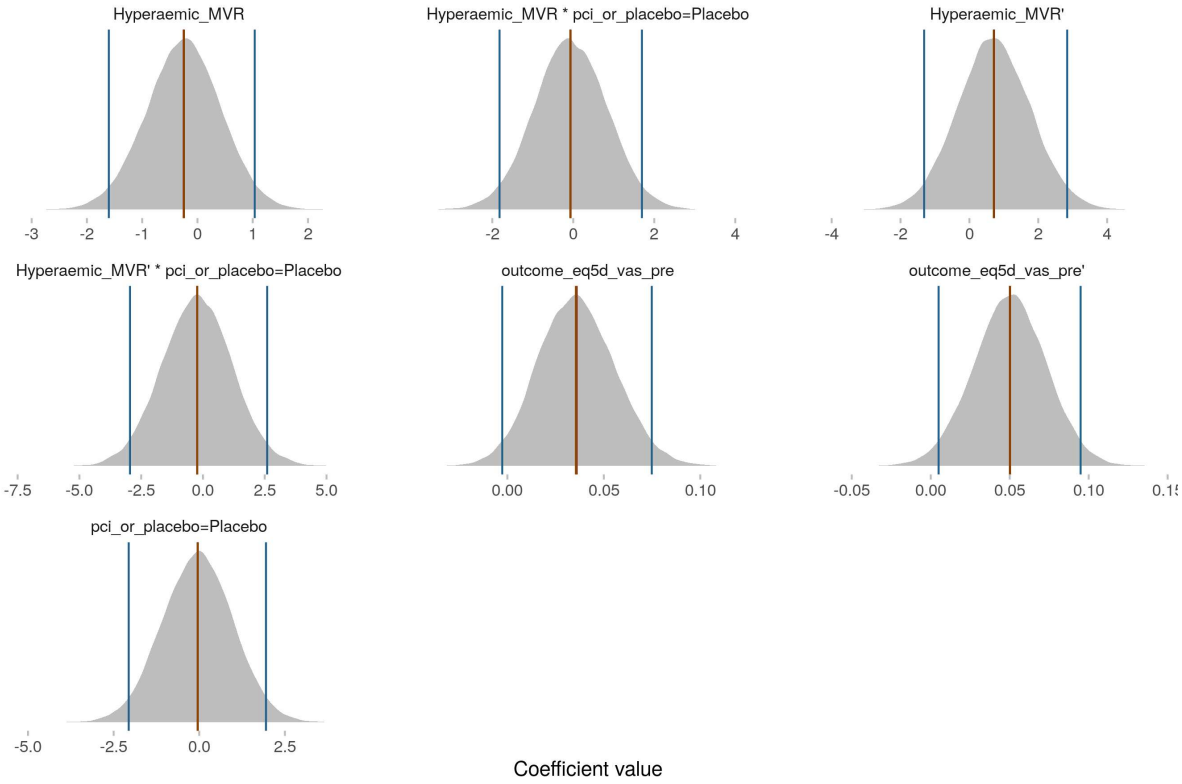
Contrasts Given Priors

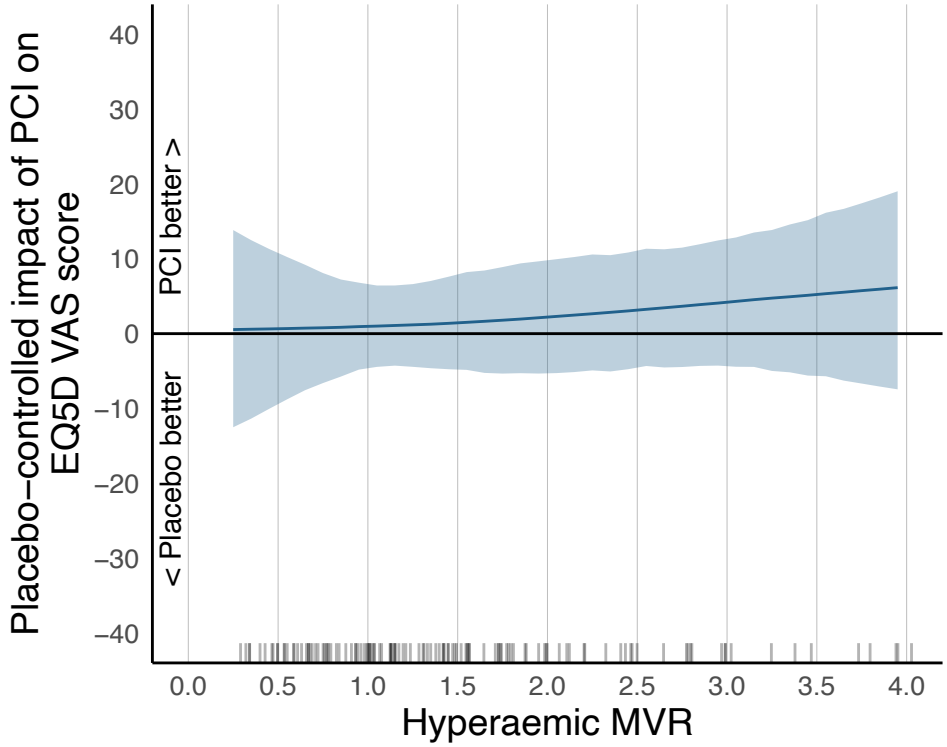
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_eq5d_vas_pre	0.955	0.730	0.992	2
Nonlinear	0.085	0.000	0.238	1
Hyperaemic_MVR (Factor + Higher Order Factors)	0.022	0.002	0.203	4
All Interactions	0.009	0.000	0.113	2
Nonlinear (Factor + Higher Order Factors)	0.012	0.000	0.130	2
pci_or_placebo (Factor + Higher Order Factors)	0.019	0.000	0.162	3
All Interactions	0.009	0.000	0.113	2
Hyperaemic_MVR * pci_or_placebo (Factor + Higher Order Factors)	0.009	0.000	0.113	2
Nonlinear	0.001	0.000	0.068	1
Nonlinear Interaction : f(A,B) vs. AB	0.001	0.000	0.068	1
TOTAL NONLINEAR	0.092	0.003	0.281	3
TOTAL NONLINEAR + INTERACTION	0.103	0.026	0.319	4
TOTAL	1.000	1.000	1.000	7

Approximate total model Wald total chi-square used in denominators of REV:
55.7 [36.5, 93.1]


Chain 1
Chain 2
Chain 3
Chain 4
Parameter Value
Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_eq5d_vas_pre
outcome_eq5d_vas_pre'
pci_or_placebo=Placebo
Post Burn-in Iteration


Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_eq5d_vas_pre
outcome_eq5d_vas_pre'
pci_or_placebo=Placebo
Coefficient value



Supplementary Figure S19. Relationship of change in pre-randomisation to follow-up EQ5D visual analogue score against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 34.7%). PCI, percutaneous coronary intervention.*

Supplementary S20 CCS x Hyperaemic Microvascular Resistance

Bayesian Proportional Odds Ordinal Logistic Model Dirichlet Priors With Concentration Parameter 0.455 for Intercepts

```
blrm(formula = outcome_ccsangina_post ~ outcome_ccsangina_pre +
    rcs(Hyperaemic_MVR, 3) * pci_or_placebo, data = d_final_virtq,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "interact_res1.progress.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file =
file.path(output_dir,
        "interact_res1.blrm.rds"))
```

Frequencies of Responses
0 1 2 3
43 21 46 19

	Mixed Calibration/Discrimination Indexes	Discrimination Indexes	Rank Discrimination Indexes
Obs 129 Draws 40000 Chains 4 Time 4.6s p 6	B 0.21 [0.197, 0.226]	g 1.393 [0.885, 1.789] gp 0.268 [0.21, 0.325] EV 0.226 [0.136, 0.318] v 1.645 [0.697, 2.703] vp 0.056 [0.033, 0.078]	C 0.727 [0.708, 0.743] Dxy 0.455 [0.416, 0.487]

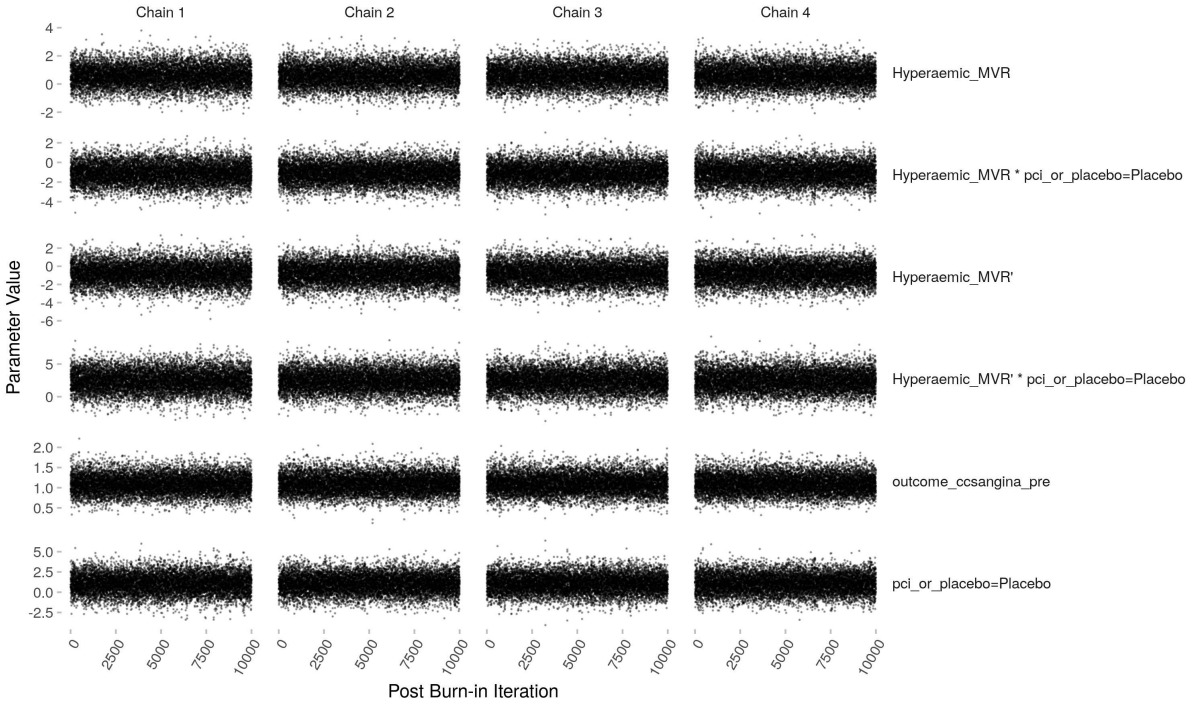
Variable	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
y >= 1	-1.9877	-1.9737	0.8411	-3.6260	-0.3365	0.0073	0.95
y >= 2	-2.8521	-2.8335	0.8580	-4.5498	-1.1979	0.0002	0.95
y >= 3	-5.0196	-4.9992	0.9314	-6.8773	-3.2381	0.0000	0.93
outcome_ccsangina_pre	1.0926	1.0891	0.2337	0.6357	1.5518	1.0000	1.06
Hyperaemic_MVR	0.5814	0.5789	0.7176	-0.8068	1.9889	0.7922	1.01
Hyperaemic_MVR'	-0.7919	-0.7885	1.1012	-2.9131	1.3925	0.2363	0.99
pci_or_placebo = Placebo	1.0392	1.0442	1.1661	-1.2343	3.3248	0.8128	1.00
Hyperaemic_MVR * pci_or_placebo = Placebo	-1.1190	-1.1117	1.0094	-3.0560	0.8830	0.1340	1.01
Hyperaemic_MVR' * pci_or_placebo = Placebo	2.4079	2.3895	1.5883	-0.6790	5.5163	0.9364	1.02

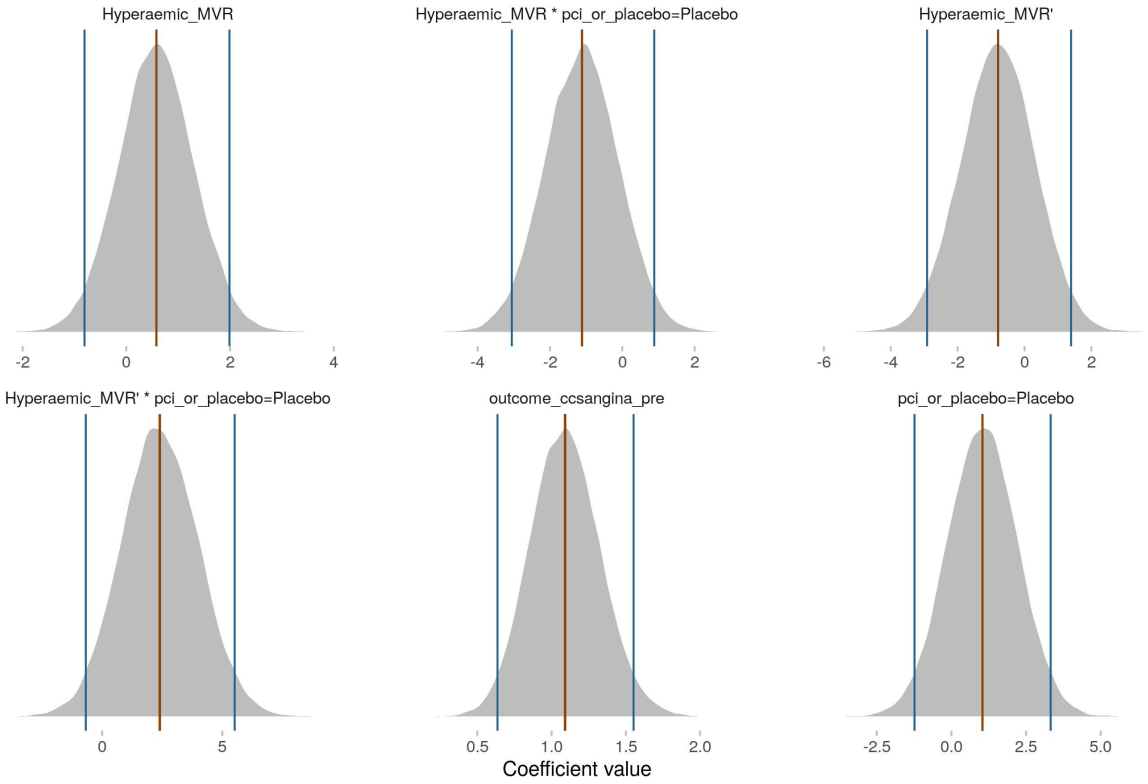
Contrasts Given Priors

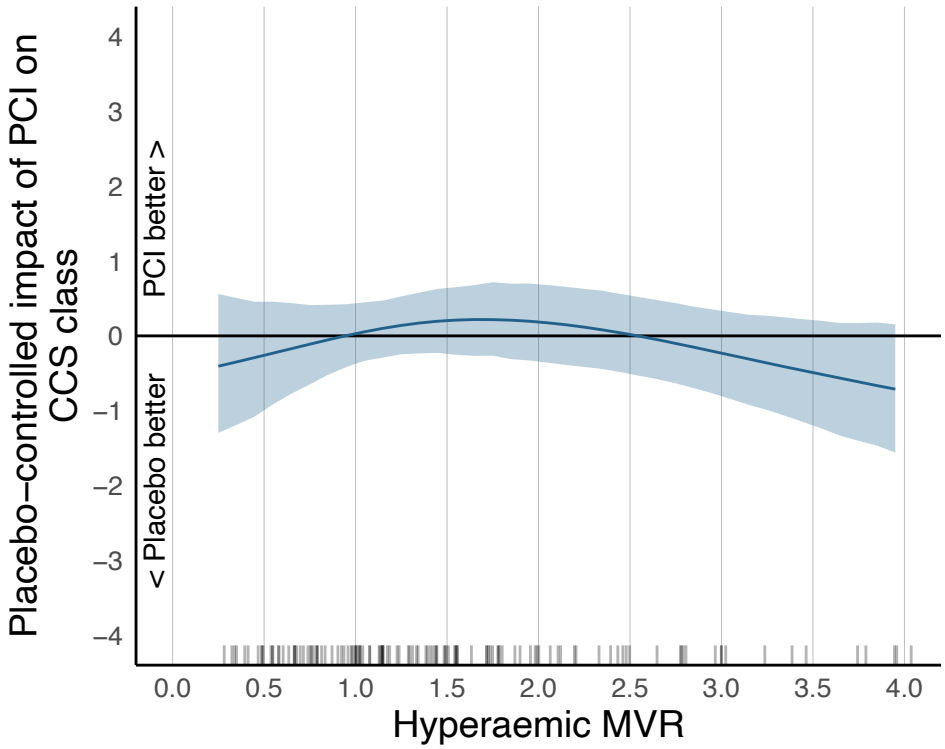
[1] list(c1 = list(pci_or_placebo = "PCI"), c2 = list(pci_or_placebo = "Placebo"),
[2] contrast = expression(c1 - c2), sd = 0.842807127883599)

Factor	REV	Lower	Upper	d.f.
outcome_ccsangina_pre	0.693	0.345	0.892	1
Hyperaemic_MVR (Factor+Higher Order Factors)	0.188	0.026	0.509	4
All Interactions	0.106	0.001	0.355	2
Nonlinear (Factor+Higher Order Factors)	0.079	0.000	0.319	2
pci_or_placebo (Factor+Higher Order Factors)	0.108	0.006	0.394	3
All Interactions	0.106	0.001	0.355	2
Hyperaemic_MVR * pci_or_placebo (Factor+Higher Order Factors)	0.106	0.001	0.355	2
Nonlinear	0.073	0.000	0.257	1
Nonlinear Interaction : f(A,B) vs. AB	0.073	0.000	0.257	1
TOTAL NONLINEAR	0.079	0.000	0.319	2
TOTAL NONLINEAR + INTERACTION	0.111	0.002	0.392	3
TOTAL	1.000	1.000	1.000	6

Approximate total model Wald total chi-square used in denominators of REV:
31.5 [13.5, 62]


Chain 1
Chain 2
Chain 3
Chain 4
Parameter Value
Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_ccsangina_pre
pci_or_placebo=Placebo
Post Burn-in Iteration


Hyperaemic_MVR
Hyperaemic_MVR * pci_or_placebo=Placebo
Hyperaemic_MVR'
Hyperaemic_MVR' * pci_or_placebo=Placebo
outcome_ccsangina_pre
pci_or_placebo=Placebo
Coefficient value



Supplementary Figure S21. Relationship of change in pre-randomisation to follow-up physician-assessed CCS class against pre-randomisation hMVR by randomisation arm. *There is no discernible dependence on pre-randomisation hMVR (probability of interaction 63.7%). CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention.*

Supplementary S22 Distribution of hyperaemic *inlet* resistance values
These values represent total distal resistance at the position of the vessel inlet which is most comparable with those taken with a Rayflow continuous infusion thermodilution catheter. Note these values are representative of a much larger subtended myocardial mass versus the values used to evaluate interaction with ORBITA outcomes and combine resistance of the epicardial stenosis *and* microvasculature.