

# Fractional Flow Reserve and Instantaneous Wave-Free Ratio as Predictors of the Placebo-Controlled Response to Percutaneous Coronary Intervention in Stable Coronary Artery Disease

**Running title:** *Foley et al.; Physiology-stratified analysis of ORBITA-2*

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## Abstract

**Background:** The Placebo-controlled Trial of Percutaneous Coronary Intervention for the Relief of Stable Angina (ORBITA-2) provided evidence for the role of percutaneous coronary intervention (PCI) for angina relief in stable coronary artery disease (CAD).

Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are often used to guide PCI, however their ability to predict placebo-controlled angina improvement is unknown.

**Methods:** Participants with angina, ischemia, and stable CAD were enrolled and antianginal medications were stopped. Participants reported angina episodes daily for 2 weeks using the ORBITA-app. At the research angiogram, FFR and iFR were measured. After sedation and auditory isolation, participants were randomized to PCI or placebo, before entering a 12-week blinded follow-up phase with daily angina reporting. The ability of FFR and iFR, analyzed as continuous variables, to predict the placebo-controlled effect of PCI, was tested using Bayesian proportional odds modelling.

**Results:** Invasive physiology data were available in 279 patients (140 PCI and 139 placebo). The median (IQR) age was 65 years (59.0 to 70.5) and 223 (79.9%) were male. Median FFR was 0.60 (0.46 to 0.73) and median iFR was 0.76 (0.50 to 0.86). The lower the FFR or iFR, the greater the placebo-controlled improvement with PCI across all endpoints. There was strong evidence that a patient with an FFR at the lower quartile would have a greater placebo-controlled improvement in angina symptom score with PCI than a patient at the upper quartile (FFR 0.46 vs. 0.73: OR 2.01, 95% CrI 1.79 to 2.26, Pr(Interaction)>99.9%).

Similarly, there was strong evidence that a patient with an iFR at the lower quartile would have a greater placebo controlled improvement in angina symptom score with PCI than a patient with an iFR at the upper quartile (iFR 0.50 vs. 0.86: OR 2.13, 95% CrI 1.87 to 2.45, Pr(Interaction) >99.9%). The relationship between benefit and physiology was seen in both Rose angina and Rose nonangina.

**Conclusion:** Physiological stenosis severity, as measured by FFR and iFR, predicts placebo-controlled angina relief from PCI. Invasive coronary physiology can be used to target PCI to those patients who are most likely to experience benefit.

Clinical Trial Registration:clinicaltrials.gov:NCT03742050

**Key Words:** Angina, ischemia, coronary artery disease, physiology, placebo-controlled trial

## Nonstandard Abbreviations and Acronyms

ORBITA-2 - The Placebo-controlled Trial of Percutaneous Coronary Intervention for the Relief of Stable Angina

PCI – percutaneous coronary intervention

CAD – coronary artery disease

FFR – fractional flow reserve

iFR – instantaneous wave-free ratio

DSE – dobutamine stress echocardiography

QCA – quantitative coronary angiography

CCS – Canadian Cardiovascular Society

EQ VAS – EQ-5D-5L visual analogue scale

Pr(Benefit) – probability of benefit

Pr(Interaction) – probability of interaction



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## Clinical Perspective

### What is new?

- On little or no antianginal medications in a Placebo-controlled Trial of Percutaneous Coronary Intervention for the Relief of Stable Angina (ORBITA-2), pre-randomization fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) predicted the symptom improvement with percutaneous coronary intervention (PCI) compared to placebo, as well as treadmill exercise time and stress echocardiography ischemia.
- The association between invasive physiology and outcome improvement was continuous. The lower the FFR and iFR, the greater the improvement in all outcomes with PCI.
- Patients with atypical symptoms required lower FFR and iFR values to benefit from PCI compared to patients with typical symptoms.



### What are the clinical implications?

- FFR and iFR predict the ability of PCI to improve angina symptoms under placebo-controlled conditions.
- These relationships are continuous and the interaction is affected by symptom characteristics.
- FFR and iFR can be used as an additional tool to identify patients with stable angina who are most likely to have symptom benefit with PCI.
- In patients with atypical symptoms, lower FFR and iFR values are needed to predict symptom benefit with PCI.

## Introduction

Percutaneous coronary intervention (PCI) relieves anatomical stenosis and ischemia in the setting of stable coronary artery disease (CAD). (1) It has been widely utilized and endorsed in international guidelines for angina relief, on the basis on unblinded trials and clinical experience. (2–4) The first placebo-controlled trial of PCI, Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA), was conducted in patients with single vessel and angiographically severe CAD, who were taking maximum-tolerated antianginal medication. (1) In ORBITA, one in five patients were more likely to be free from angina with PCI than placebo. (5) However, PCI did not improve exercise time or quality of life, despite near normalization of ischemia on dobutamine stress echocardiography (DSE). (6) While fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) predicted the improvement in stress echocardiography ischemia with PCI compared to placebo, they did not predict the placebo-controlled impact of PCI on angina. (5) This result was surprising and suggested that the link between stenosis, ischemia and symptoms is complex. It is possible that this link is modified by the presence of antianginal medications, which have placebo-controlled evidence of symptom benefit (7–9) and have been demonstrated to improve myocardial ischemia. (10)

The percutaneous coronary intervention for stable angina (ORBITA-2) trial demonstrated the placebo-controlled efficacy of PCI on symptoms, in patients with single and multivessel CAD, on little or no antianginal medication. (11) Whilst, on average, PCI was more effective than placebo, 59% of patients remained symptomatic at follow-up with significant heterogeneity of treatment effect. The ORBITA-2 data allow us to explore this variability, with the aim of identifying the best predictors of treatment response to PCI.

The first secondary analysis of ORBITA-2 investigated the association between symptom characteristics and placebo-controlled response to PCI. (12) It revealed that PCI

was most likely to improve symptoms in patients who presented with typical angina. In patients with atypical symptoms, PCI had limited efficacy as compared to placebo. Following symptom evaluation, the next step in the clinical pathway often involves assessment of anatomy or ischemia. (4,13) Abnormalities in these non-invasive tests often result in referral to the cardiac catheterization laboratory, where invasive physiological assessment is recommended for confirmation of ischemia prior to PCI. (13,14) This secondary analysis of ORBITA-2 investigates the predictive value of FFR and iFR on the placebo-controlled efficacy of PCI.

## Methods

The data, analytical methods, and study materials will not be made available to other researchers for the purposes of reproducing the results or replicating the procedure.



## Study design

ORBITA-2 was a randomized, double-blind, placebo-controlled trial of PCI, conducted at 14 sites in the United Kingdom. The design has been described previously. (15) Patients with angina and angiographically severe single and multi-vessel CAD on invasive coronary angiography or computed tomography coronary angiography were enrolled between November 12, 2018, and June 17, 2023. Antianginal medications were stopped and patients entered a 2-week symptom assessment phase with daily reporting of angina episodes using the ORBITA-app. (16) Only symptomatic patients progressed to randomization. Angina and quality of life questionnaires (Seattle Angina Questionnaire (SAQ) and EQ-5D-5L), Canadian Cardiovascular Society (CCS) class, treadmill exercise testing, and DSE were completed at pre-randomization and follow-up. The typicality of angina was assessed prior to randomization using the Rose questionnaire. The trial was approved by the London Central Research Ethics committee (reference 18/LO/1203). Written informed consent was obtained

from each patient. Patients who did not undergo complete invasive physiological assessment were excluded from this analysis.

### **Invasive physiological assessment**

Following the 2-week symptom assessment phase, patients attended for research angiography and the randomization procedure. Patients wore over the ear headphones playing music to establish auditory isolation. Coronary angiography was performed via the radial or femoral approach, followed by a systematic physiological investigation of every vessel that was  $\geq 2$ mm with an angiographic stenosis  $\geq 50\%$ . A guiding catheter was advanced to the coronary artery of interest. 100 units/kg heparin and 300mcg isosorbide dinitrate were administered. A pressure tipped intracoronary wire (*Verrata Wire, Philips, USA* or *Omniwire, Philips, USA*) was normalized, advanced until the pressure sensor was at least 3 vessel diameters distal to the most distal coronary stenosis, and FFR and iFR were measured. FFR measurement used peripherally administered intravenous adenosine at 140mcg/kg/min to establish hyperaemia. After completion of the measurements, the pressure wire was withdrawn and a drift check completed. If the ratio of distal to aortic pressure in the normalization position was  $1.00 \pm 0.02$ , the wire was renormalized, and the measurements were repeated. Participants who had no objective evidence of ischemia did not proceed to randomization. Patients with discordant invasive physiology values and no other evidence of ischemia could progress to randomization if either their FFR or iFR value was beneath the clinically utilised threshold. Unlike in ORBITA, the FFR and iFR values were made available to the operators. Prior to randomization, all stenoses which were suitable for PCI with evidence of ischemia were documented in the case report form.

### **Blinding and randomization**

Following physiological assessment, patients eligible for randomization received incremental doses of opiates and benzodiazepines to achieve a deep level of conscious sedation. Patients



were then randomized 1:1 to PCI or placebo using opensource software. (17) Auditory isolation was maintained throughout the procedure.

PCI was performed using standard techniques. Operators were instructed to aim for complete revascularization. Intracoronary imaging to guide and optimize the PCI was encouraged. Following PCI, FFR and iFR were remeasured. Operators were permitted to use these data to guide further stent optimization and, in these cases, FFR and iFR were remeasured.

The patient, clinical staff, and research team performing follow-up assessments, were all blinded to treatment allocation using the methodology previously described. (15)

## **Study endpoints**

### *Angina symptom score and daily angina episodes– ORBITA smartphone application*

On enrolment to the trial, patients were taught to use a dedicated smartphone application for daily angina reporting. The design and features of the ORBITA-app have been reported previously and are included in the supplementary appendix. (16) The angina symptom score was an ordinal clinical outcome score related to angina health status. It was calculated daily from the number of angina episodes reported by a patient on the ORBITA-app, the number of standardized units of antianginal medication prescribed on that day and high-level category over-ride events (death, myocardial infarction and unblinding due to intolerable angina).

We additionally report the relationship between FFR and iFR on the number of angina episodes reported on the ORBITA-app in isolation, without contribution from other elements of the angina symptom score.

### *Treadmill exercise time*

Patients underwent treadmill exercise testing at pre-randomization and follow-up, utilizing the modified Bruce protocol. Details of the treadmill exercise protocol have been reported previously. (15)

***Patient reported and physician assessed symptoms and quality of life***

Angina and quality of life questionnaires, including SAQ and EQ-5D-5L were administered at pre-randomization and follow-up. The SAQ consists of multiple domains including physical limitation, angina frequency and quality of life. (18) The EQ-5D-5L questionnaire comprises 2 distinct quality of life measures: EQ-5D-5L descriptive system, which was combined with the UK value set producing an index value, and the EQ visual analogue scale (EQ VAS). (19) Physician assessment of angina using CCS class took place prior to pre-randomization and at follow-up.

***Dobutamine stress echocardiography***

DSE was performed at pre-randomization and follow-up. The patient, physician, and cardiac sonographer were all blinded to treatment allocation at follow-up (supplementary appendix). Interpretation of the DSE was performed in duplicate by 3 cardiac imaging consultants. They were blinded to scan time point, their own previous assessment, and treatment allocation, using a previously reported methodology, such that each scan received 6 independent assessments. (6)

***Contrasting the stratified effect using angina typicality***

The Rose angina questionnaire was designed as a tool to detect underlying coronary artery disease from a patient's description of their symptoms. (20) Patients who reported chest pain or discomfort, which comes on with exertion, causes them to stop, is relieved by rest within 10 minutes, located in the centre of the chest, or left chest and left arm, we designated "Rose angina". Patients with symptoms which were felt to represent angina by the referring physician, but which fell outside any of these parameters we designated "Rose nonangina". The treatment effect with PCI in patients with Rose angina, stratified by FFR and iFR, was compared to the same stratified PCI treatment effect in patients with Rose nonangina.

## Statistical analysis

In this manuscript, the analyses as specified in the primary publication and its associated statistical analysis plan are presented but in this physiology subset (i.e. those with both FFR and iFR). The statistical approach utilised Bayesian ordinal regression modelling. In brief, for the primary endpoint, the daily angina symptom score, and the number of daily episodes of angina, the daily odds ratio (OR) of transitioning to a better angina symptom score or fewer daily episodes of angina were calculated. ORs were constructed such that an OR higher than 1 reflected a reduction in the number of episodes of angina. The OR was derived by constructing a Bayesian Markov longitudinal ordinal model. This model included the value from the previous day (a first order Markov model), the mean score or daily angina episodes during the pre-randomization period, trial day number, and randomization allocation. Trial day number was allowed to interact with the randomization allocation to allow the model to detect variation in the treatment effect over time. The effects were allowed to be non-linear with restricted cubic splines, and partial proportional odds with constraints. Bayesian ordinal regression models were constructed for the secondary endpoints, measured at pre-randomization and follow-up. In these models, the follow-up value was conditioned on the pre-randomization value and allowed to interact with the randomization allocation. Nonlinearity was allowed with the use of a restricted cubic spline with 3 knots on continuous predictors.

To assess the impact of FFR and iFR on the placebo-controlled effect of PCI, these variables were included in these original models and allowed to interact with the randomization arm. Non-linearity was allowed with the use of a restricted cubic spline with 3 knots. For each patient, the single lowest FFR or iFR value was used.

To assess the impact of symptoms characteristics, a variable indicating if the patient had Rose angina or Rose nonangina was also introduced and allowed to interact with the randomization arm and baseline physiology.

To test if FFR or iFR impacted the response to PCI, a patient at the lower and upper quartiles of FFR and iFR values was compared, and the probability that more severe physiology derives greater benefit than less severe physiology was tested. A similar approach was used to compare the impact in patients with Rose angina and nonangina.

## Results

ORBITA-2 enrolled 439 patients, of whom 301 were randomized; 151 allocated to PCI and 150 to placebo. Eleven patients in the PCI group and 11 patients in the placebo group did not undergo invasive physiological assessment. Therefore, 279 patients were included in this analysis.

### Patient demographics

The baseline characteristics are described in Table 1. The median age was 65 years (IQR 59.0 to 70.5) and 223 (79.9%) were male. Over 96% of patients (n=268) were in CCS class II or III prior to randomization.

### Procedural demographics

The procedural demographics are shown in Table 2; 224 (80.3%) patients had an angiographically severe stenosis in 1 coronary territory, 49 (17.6%) in 2, and 6 (2.2%) in all 3 coronary territories. The 279 patients had a total of 355 affected coronary arteries deemed suitable for treatment with PCI. The most frequently affected was the left anterior descending (LAD) (197/355, 55.5%). The median FFR was 0.60 (IQR 0.46 to 0.73) and iFR was 0.76 (IQR 0.50 to 0.76). 269/279 (96.4%) patients had an FFR  $\leq$ 0.80 and 242/279 (86.7%) had an iFR  $\leq$ 0.89. The median length of stent per patient in the PCI group was 30mm (IQR 21mm to

49mm). Post-dilatation was performed in 217/252 stenoses (86.1%). In the PCI group, the median final FFR in the treated vessel was 0.88 (IQR 0.84 to 0.93) and iFR was 0.93 (IQR 0.91 to 0.97).

## **Study endpoints**

### ***Angina symptom score***

Angina symptom score data were available for 279 patients in the physiology-stratified analysis of ORBITA-2 (140 in the PCI group and 139 in the placebo group). There was strong evidence of benefit with PCI over placebo on angina symptom score in this group (OR 1.82, 95% CrI 1.51 to 2.21, Pr(Benefit)>99.9%). There was strong evidence of an interaction between both FFR and iFR, and the placebo-controlled impact of PCI on angina symptom score, with lower FFR and iFR values associated with greater treatment response (FFR OR 2.01, 95% CrI 1.79 to 2.26, Pr(Interaction)>99.9%; iFR OR 2.13, 95% CrI 1.87 to 2.45, Pr(Interaction)>99.9%); Tables 3 and 4, Figure 2). A visualization of the daily angina symptom score data dichotomized using the median FFR and iFR values is shown in Figure 1.

### ***Daily angina episodes***

Overall there was strong evidence of benefit with PCI over placebo on daily angina episodes (OR 1.84, 95% CrI 1.51 to 2.24, Pr(Benefit)>99.9%) in this physiology subgroup. There was strong evidence of an interaction between both FFR and iFR and the placebo-controlled effect of PCI on the number of daily angina episodes (FFR OR 2.02, 95% CrI 1.79 to 2.26, Pr(Interaction)>99.9%; iFR OR 2.24, 95% CrI 1.95 to 2.56, Pr(Interaction)>99.9%); Tables 3 and 4, Figure 2). The daily angina episodes dichotomized using median FFR and iFR values are shown in Figure 3.

### ***Patient reported and physician assessed symptoms and quality of life***

Questionnaire data were available from 270 patients in this analysis (136 in the PCI group and 134 in the placebo group) and CCS data were available in 272 patients (137 in the PCI group and 135 in the placebo group).

There was strong evidence of benefit with PCI over placebo on SAQ angina frequency (14.1, 95% CrI 9.1 to 19.4, Pr(Benefit)>99.9%). There was strong evidence of an interaction between both FFR and iFR and the placebo-controlled response to PCI on SAQ angina frequency (FFR 23.1, 95% CrI 13.5 to 32.6, Pr(Interaction)>99.9%; iFR 24.1, 95% CrI 13.5 to 35.1, Pr(Interaction)>99.9%; Tables 3 and 4, Figure 4). The interaction between FFR and iFR and the other components of the SAQ are in the supplementary appendix (figures S22, S30, S38, S46, S101, S109, S117 and S125).

There was evidence of benefit with PCI over placebo in the EQ-5D-5L descriptive system (0.07, 95% CrI 0.03 to 0.11, Pr(Benefit)>99.9%) and in the visual analogue scale (5.9, 95% CrI 2.0 to 9.7, Pr(Benefit)=99.9%). There was strong evidence of interaction between both FFR and iFR and the impact of PCI on the EQ-5D-5L descriptive system and EQ VAS, with lower values associated with a larger treatment response (Tables 3 and 4).

PCI improved CCS class compared with placebo (-0.69, 95% CrI -0.92 to -0.44, Pr(Benefit)>99.9%). There was strong evidence of interaction between FFR and iFR and placebo-controlled improvement in CCS class with PCI, with lower values associated with greater treatment response (FFR -1.1, 95% CrI -1.15 to -0.7, Pr(Interaction)>99.9%; iFR -1.1, 95% CrI -1.5 to -0.6, Pr(Interaction)>99.9%; Tables 3 and 4, Figure 4).

### ***Treadmill exercise time***

Treadmill exercise test data were available for 217 patients in the physiology-stratified analysis (114 in the PCI arm and 103 in the placebo arm). The effect of PCI over placebo on exercise time in these patients was 46.0s, 95% CrI 5.6 to 88.3, Pr(Benefit)=98.6%. There was

a strong evidence of an interaction between both FFR and iFR and the placebo-controlled impact of PCI on exercise time (FFR 147.0s, 95% CrI 71.3 to 221.0, Pr(Interaction)>99.9%; iFR 129.0s, 95% CrI 44.2 to 217.0, Pr(Interaction)=99.9%; Tables 3 and 4, Figure 4) with lower values associated with greater treatment response.

### ***Dobutamine stress echocardiography***

DSE data were available from 213 patients in this analysis (110 in the PCI group and 103 in the placebo group). PCI caused a reduction in stress echocardiography score, compared with placebo (-0.77, 95% CrI -1.15 to -0.41, Pr(Benefit)>99.9%). There was strong evidence of an association between FFR and iFR and stress echocardiography score (FFR -1.2, 95% CrI -1.8 to -0.6, Pr(Benefit)>99.9%; iFR -0.9, 95% CrI -1.5 to -0.3, Pr(Benefit)=99.8%; Tables 3 and 4, Figure 4) with lower values associated with greater treatment response.



### **Invasive physiology and symptom characteristics**

There was evidence of an interaction between both FFR and iFR and the effect of PCI on angina symptom score in patients with Rose angina (FFR OR 2.05, 95% CrI 1.75 to 2.41, Pr(Interaction)>99.9%; iFR OR 2.11, 95% CrI 1.79 to 2.53, Pr(Interaction)>99.9%). In patients with Rose nonangina, there was strong evidence of greater benefit with PCI at lower FFR and iFR values, but this relationship was weaker than in patients with Rose angina (FFR OR 1.63, 95% CrI 1.27 to 2.09, Pr(Interaction)>99.9%; iFR OR 1.69, 95% CrI 1.32 to 2.17, Pr(Interaction)>99.9%) with no evidence of benefit around the clinically utilised cut points (Figure 2). A similar association between symptom characteristics and the physiology-stratified effect of PCI was seen with all other endpoints (supplementary figures S7, S8, S15, S23, S31, S39, S47, S54, S61, S69, S76, S94, S102, S110, S118, S126, S133, S141, S148, S155).

## Discussion

This physiology-stratified analysis of ORBITA-2 shows that FFR and iFR predict placebo-controlled angina reduction with PCI. For the first time, invasively measured vessel-specific indices have demonstrated an ability to predict the blinded symptom response to PCI. Furthermore, symptom characteristics influence the association between invasive coronary physiology and the efficacy of PCI. To see symptom benefit with PCI in patients with Rose nonangina, lesions needed to be more physiologically significant than in patients with Rose angina.

FFR and iFR are surrogate markers of myocardial ischemia and are frequently utilised to guide PCI in stable coronary artery disease, according to widely accepted binary clinical thresholds. (13,14) These cut points are often thought of as indicators that firstly, the stenosis is causing angina and secondly, treating the stenosis will relieve angina. However, whilst previous unblinded studies had suggested there may be an interaction between baseline FFR and angina response with PCI, (21) these assumptions were not previously supported by blinded data. (5)

Symptom characteristics have already been found to be important predictors of the placebo-controlled efficacy of PCI. (12) Patients with Rose angina are the most likely group to derive symptom benefit from PCI. This further analysis shows that in these patients, there is also a strong association between FFR and iFR, and angina relief. However, even in patients with typical symptoms, the effect of PCI was more marginal and less certain with higher FFR and iFR values, particularly around the binary clinical thresholds. Importantly, this relationship was also seen in patients with Rose nonangina, however much lower invasive physiology values were needed to detect symptom benefit with PCI, and the effect size was diminished.



In contrast to this analysis of ORBITA-2, in ORBITA no relationship was found between FFR and iFR and placebo-controlled angina improvement. (5) Possible explanations for this include the different endpoints used in the respective trials, the inclusion of multivessel disease, and the additional statistical power provided by a larger sample size. Perhaps the most likely reason is the difference in antianginal regimens in the respective trials and the relationship between antianginal medications, angina and ischemia. Patients were taking an average of 3 antianginals each in ORBITA while in ORBITA-2 antianginal medications were stopped. (11,22) Antianginal medications improve angina compared with placebo (7–9) and have been shown to reduce myocardial ischemia in experimental settings. (10) Perhaps the impact of a stenosis on angina and ischemia is attenuated by the presence of antianginal medication. Notably, the landmark association between FFR and non-invasive measures of ischemia was established in patients taking no antianginal medication. (23) It may be that the ability of FFR and iFR to predict the effect of treating a stenosis and relieving angina and ischemia is less powerful in the presence of antianginal medications.

For many decades, we have focused on finding and eliminating myocardial ischemia, on the assumption that this approach would lead to prognostic benefit. The use of anatomic and ischaemic tests remains widespread in patients with a broad range of symptoms, particularly in the presence of cardiovascular risk factors. Therefore, in contemporary clinical practice, many patients with symptoms which may not be cardiac are referred to the cardiac catheterization laboratory. The physiology-stratified secondary analysis of ORBITA-2 can inform our management of these patients, helping to target PCI to those most likely to benefit and minimise risk to those with the least to gain. Now that the primary role of PCI in stable coronary artery disease is as an antianginal procedure, the relationship between symptom characteristics, physiology and PCI treatment response should have a more prominent role in our clinical practice. Symptom assessment must take place prior to any anatomic or

ischaemic test. Patients with typical angina have the most to gain with PCI. In patients with atypical symptoms, the cause may be multifactorial and not solely attributable to the epicardial stenosis. Consequently, symptom improvement with PCI is only seen in those with the most physiologically severe stenoses (well below FFR of 0.80 and iFR of 0.89). This may be a setting where invasive coronary physiology adds greater additional value.

### **Limitations**

Every patient in ORBITA-2 had evidence of myocardial ischemia. In 88.5% of patients, this evidence was from pressure wire assessment during the randomization procedure. Patients with no other evidence of ischemia who had FFR and iFR measurements above the clinically utilised thresholds were not randomized. Therefore, the majority had FFR and iFR measurements below the clinically utilised thresholds and this secondary analysis does not represent the full physiological range.



After 12 weeks patients were unblinded and returned to routine care. Therefore, the longer-term effect of PCI, and the interaction between FFR and iFR on this effect, remains uncertain.

In ORBITA-2, patients were treated with the minimum tolerated antianginal medication. The relationship between invasive physiology and treatment response may vary on higher levels of antianginal medication.

### **Conclusion**

Invasive physiology can be used to predict symptom response with PCI. It is particularly useful in patients with little or no concomitant antianginal therapy. The strength of this relationship is in part dependent on the nature of symptoms. This physiology-stratified analysis of ORBITA-2 provides a framework to integrate symptoms and invasive physiological assessment in the contemporary use of PCI as an antianginal procedure.

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## Disclosures

Dr Foley has received speaker fees from Menarini and has received consulting and speaker fees from Shockwave Medical, Inc. and Philips. Dr Rajkumar has received speaker fees from Menarini, has received consulting fees from Philips and has received shared Mycardium AI. Dr Simader has received a sponsorship from Servier Pharmaceuticals. Dr Khokhar has received speaker fees and travel support from Boston Scientific and Abbott. Dr Davies has received grants from Medtronic and Abbott; has received sponsorship from Vascular Perspectives, Boston Scientific, Medtronic and Abbott; and has received speaker fees from AstraZeneca, Pfizer, Bristol Myers Squibb, and Novartis. Dr Keeble has served on advisory boards for Abbott Vascular and SMT; and has received institutional research funding from Terumo, Medtronic, Boston Scientific, Abbott Vascular, Philips Volcano, and Cardionovum. Dr O’Kane has received speaker fees from Abbott Vascular, Biosensors, Boston Scientific, Heartflow, Medtronic, Philips, Shockwave, and Terumo. Dr Kotecha has received honoraria from Bayer and Janssen. Dr Nijjer has received speaker fees from Philips Volcano, Pfizer, Bayer, AstraZeneca, Boehringer Ingelheim, and Amarin. Dr Spratt has received speaker fees from Boston Scientific Corporation and Shockwave Medical, Inc. Dr Sen has received speaker and consulting fees from Philips, Medtronic, Recor, and AstraZeneca. Dr Curzen has received grants from Beckman Coulter, Inc. Boston Scientific Corporation, Haemonetics Corporation, and HeartFlow Inc; and has received speaker fees from Heartflow. Dr Howard

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### **Supplemental Material**

ORBITA-2 supplementary appendix

Tables S1-7

Figures S1-162



# Circulation

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**Table 1. Baseline Characteristics**

	PCI (n=140)	Placebo (n=139)	Overall (n=279)
Age, y			
Median (IQR)	66 (59.8-71)	64 (58-70)	65 (59.0-70.5)
Male	112 (80.0)	111 (79.9)	223 (79.9)
Ethnicity			
White	104 (74.3)	114 (82.0)	218 (78.1)
Asian	35 (25.0)	23 (16.5)	58 (20.8)
Black	1 (0.7)	2 (1.4)	3 (1.1)
Hypertension	89 (63.6)	87 (62.6)	176 (63.1)
Hypercholesterolemia	103 (73.6)	96 (69.1)	199 (71.3)
Diabetes			
All	44 (31.4)	32 (23.0)	76 (27.2)
Non-insulin-dependent	37 (26.4)	22 (15.8)	59 (21.1)
Insulin-dependent	7 (5.0)	10 (7.2)	17 (6.1)
Previous PCI	15 (10.7)	18 (12.9)	33 (11.8)
Smoking status			
Never smoked	62 (44.3)	48 (34.5)	110 (39.4)
Ex-smoker	60 (42.9)	76 (54.7)	136 (48.7)
Current smoker	18 (12.9)	15 (10.8)	33 (11.8)
Canadian cardiovascular society class			
I	10 (7.1)	1 (0.7)	11 (4.0)
II	78 (55.7)	80 (57.6)	158 (56.6)
III	52 (37.1)	58 (41.7)	110 (39.4)
Angina duration (weeks)			
Median (IQR)	39.5 (19-65)	32 (19-63)	36 (19-64.5)
Ischaemia evidence			
Dobutamine stress echocardiography	7 (5.0)	4 (2.88)	11 (3.94)
Clinical pressure wire	4 (2.86)	7 (5.04)	11 (3.94)
Nuclear medicine myocardial perfusion scan	0 (0.0)	4 (2.88)	4 (1.43)
Magnetic resonance imaging perfusion	4 (2.86)	2 (1.44)	6 (2.15)
Randomisation pressure wire	125 (89.3)	122 (87.8)	247 (88.5)

Values are n (%) unless otherwise indicated. Percentages may not total 100 because of rounding. PCI = percutaneous coronary intervention, SD = standard deviation, IQR=interquartile range, CCS = Canadian cardiovascular society

**Table 2. Procedural Characteristics**

	PCI (n=140)	Placebo (n=139)	Overall (n=279)
<b>No. of vessels with disease*</b>			
1	114 (81.4)	110 (79.1)	224 (80.3)
2	23 (16.4)	26 (18.7)	49 (17.6)
3	3 (2.1)	3 (2.2)	6 (2.2)
Median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)
<b>Vessels leading to patient randomisation</b>			
Number of vessels	178	177	355
Number of lesions	210	196	406
Left anterior descending†	100 (56.2)	97 (54.8)	197 (55.5)
Ostial/proximal	51/121 (42.1)	54/108 (50.0)	105/229 (45.9)
Mid	64/121 (52.9)	48/108 (44.4)	112/229 (48.9)
Distal	6/121 (5.0)	4/108 (3.7)	10/229 (4.4)
N/A	0/121 (0.0)	2/108 (1.9)	2/229 (0.9)
Right coronary	38 (21.3)	38 (21.5)	76 (21.4)
Circumflex	15 (8.4)	16 (9.0)	31 (8.7)
First obtuse marginal	14 (7.9)	12 (6.8)	26 (7.3)
First diagonal	8 (4.5)	11 (6.2)	19 (5.4)
Intermediate	2 (1.1)	2 (1.1)	4 (1.1)
Posterior descending	1 (0.6)	0 (0.0)	1 (0.3)
Posterolateral	0 (0.0)	1 (0.6)	1 (0.3)
Serial lesions	27 (19.3)	18 (12.9)	45 (16.1)
Radial access	135 (96.4)	134 (96.4)	269 (96.4)
Number of patients with diameter stenosis $\geq 50\%$ by QCA	108 (77.1)	102 (73.4)	210 (75.3)
<b>Diameter stenosis by QCA</b>			
Median (IQR)	59.1 (51.0-72.8)	58.8 (49.2-72.3)	58.8 (50.2-72.6)
<b>Area stenosis by QCA</b>			
Median (IQR)	82.1 (74.7-90.0)	81.5 (73.3-89.9)	81.7 (73.7-90.0)
<b>Length stenosis by QCA</b>			
Median (IQR)	10.6 (8.6-13.8)	10.5 (8.2-13.9)	10.6 (8.4-13.9)
<b>FFR‡</b>			
Mean (SD)	0.58 (0.16)	0.60 (0.16)	0.59 (0.16)
Median (IQR)	0.59 (0.45-0.73)	0.63 (0.47-0.73)	0.60 (0.46-0.73)
<b>iFR‡</b>			
Mean (SD)	0.65 (0.22)	0.67 (0.23)	0.67 (0.23)
Median (IQR)	0.71 (0.47-0.85)	0.78 (0.55-0.87)	0.76 (0.50-0.86)
Number of patients with FFR $\leq 0.80$	135 (96.4)	134 (96.4)	269 (96.4)
Number of patients with iFR $\leq 0.89$	125 (89.3)	117 (84.2)	242 (86.7)
<b>Interventions</b>			
Number of stents implanted			
Median (IQR)	2 (1-2)	-	-
Total stent length, mm			
Median (IQR)	30 (21-49)	-	-
Stent diameter, mm			
Median (IQR)	3 (2.5-3.5)	-	-



Number of stents in which post-dilation was performed	217/252 (86.1)	-	-
Type of drug-eluting stent			
Everolimus-eluting	154 (61.1)	-	-
Zotarolimus-eluting	74 (29.4)	-	-
Other drug-eluting stent	24 (9.5)	-	-
<b>Post PCI physiology</b>			
FFR post-PCI (n=131)			
Mean (SD)	0.88 (0.07)	-	-
Median (IQR)	0.88 (0.84-0.93)	-	-
iFR post-PCI (n=133)			
Mean (SD)	0.94 (0.05)	-	-
Median (IQR)	0.93 (0.91-0.97)	-	-
No. of patients with post-FFR>0.80	118 (90.1)	-	-
No. of patients with post-iFR>0.89	114 (85.7)	-	-

Values are n (%) unless otherwise indicated. Percentages may not total 100 because of rounding. SD = standard deviation, IQR = interquartile range, QCA=quantitative coronary angiography, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio

\* The number of vessels with disease was defined on the basis of evidence of ischemia from non-invasive imaging and invasive physiological assessment.

† LAD breakdown totals > no. of LAD vessels due to serial lesions.

‡ FFR/iFR presented is the lowest FFR/iFR value per patient.



# Circulation

**Table 3. FFR Primary and Secondary Endpoints**

	<b>FFR at the 25<sup>th</sup> centile</b>	<b>FFR at the 75<sup>th</sup> centile</b>	<b>Probability of greater benefit in a patient with a lower FFR (Pr)</b>
<b>FFR</b>	<b>0.46</b>	<b>0.73</b>	
<b>Primary Endpoint: Angina symptom score at 12 weeks*</b>			
Odds of improvement	2.31 (1.90 to 2.82)	1.15 (0.95 to 1.40)	
Odds ratio	2.01 (1.79 to 2.26)		>99.9%
<b>Daily angina episodes</b>			
Odds of improvement	2.59 (2.09 to 3.17)	1.28 (1.04 to 1.58)	
Odds ratio	2.02 (1.79 to 2.26)		>99.9%
<b>Exercise time (s)</b>			
Baseline	667.0		
Change	114.0 (60.9 to 170.0)	-32.7 (-88.5 to 21.7)	
Difference	147.0 (71.3 to 221.0)		>99.9%
<b>SAQ angina frequency</b>			
Baseline	60.0		
Change	24.8 (17.9 to 31.5)	1.7 (-5.4 to 8.9)	
Difference	23.1 (13.5 to 32.6)		>99.9%
<b>SAQ physical limitation</b>			
Baseline	66.7		
Change	16.4 (10.8 to 21.9)	1.03 (-4.6 to 6.5)	
Difference	15.4 (7.7 to 22.9)		>99.9%
<b>SAQ angina stability</b>			

Baseline	50.0		
Change	7.7 (-0.3 to 15.7)	2.0 (-6.1 to 10.2)	
Difference	5.6 (-5.6 to 16.7)		83.9%
SAQ treatment satisfaction			
Baseline	93.8		
Change	8.1 (4.5 to 12.0)	0.8 (-3.2 to 4.8)	
Difference	7.4 (2.2 to 12.8)		99.7%
SAQ quality of life			
Baseline	41.7		
Change	20.0 (13.3 to 26.5)	-0.97 (-7.8 to 5.7)	
Difference	21.0 (11.9 to 30.1)		>99.9%
EQ-5D-5L			
Baseline	0.75		
Change	0.12 (0.07 to 0.17)	0.02 (-0.03 to 0.07)	
Difference	0.10 (0.02 to 0.17)		99.6%
EQ-VAS			
Baseline	70.0		
Change	10.9 (5.8 to 16.1)	0.50 (-4.9 to 5.7)	
Difference	10.5 (3.3 to 17.7)		99.8%
CCS Class			
Baseline	2.0		
Change	-1.2 (-1.52 to -0.91)	-0.0 (-0.41 to -0.23)	


Difference	-1.1 (-1.5 to -0.7)		>99.9%
Stress echocardiography score			
Baseline	1.80		
Change	-1.2 (-1.7 to -0.8)	-0.1 (-0.5 to 0.3)	
Difference	-1.2 (-1.8 to -0.6)		>99.9%


\*The angina symptom score is calculated daily, incorporating the number of angina episodes reported by a patient that day, the number of units of antianginal medication prescribed and the presence of high-level category over-ride events: death, myocardial infarction and unblinding due to intolerable angina. Data available from the following number of patients: angina symptom score = 279, daily angina episodes = 279, exercise time = 217, SAQ, EQ-5D-5L, EQ-VAS = 270, CCS = 272, stress echocardiography score = 213. FFR = Fractional Flow Reserve, PCI = percutaneous coronary intervention, SAQ = Seattle Angina Questionnaire, EQ-VAS denotes EQ-5D-5L visual analogue scale. CCS = Canadian Cardiovascular Society.



# Circulation

**Table 4. iFR Primary and Secondary Endpoints**

	<b>iFR at the 25<sup>th</sup> centile</b>	<b>iFR at the 75<sup>th</sup> centile</b>	<b>Probability of greater benefit in a patient with a lower iFR (Pr)</b>
<b>iFR</b>	<b>0.50</b>	<b>0.86</b>	
Primary endpoint: angina symptom score at 12 weeks*			
Odds of improvement	2.41 (1.96 to 2.93)	1.13 (0.93 to 1.36)	
Odds ratio	2.13 (1.87 to 2.45)		>99.9%
Daily angina episodes			
Odds of improvement	2.80 (2.26 to 3.45)	1.25 (1.02 to 1.54)	
Odds ratio	2.24 (1.95 to 2.56)		>99.9%
Exercise time (s)			
Baseline	667.0		
Follow up	110.0 (48.0 to 172.0)	-19.7 (-79.6 to 35.7)	
Difference	129.0 (44.2 to 217.0)		
SAQ angina frequency			
Baseline	60.0		
Follow up	26.4 (18.7 to 34.1)	2.3 (-5.1 to 9.5)	
Difference	24.1 (13.5 to 35.1)		>99.9%
SAQ physical limitation			
Baseline	66.7		
Follow up	18.2 (12.2 to 24.1)	-0.1 (-5.6 to 5.4)	
Difference	18.3 (10.3 to 26.6)		>99.9%
SAQ angina stability			

Baseline	50.0		
Follow up	10.4 (1.3 to 19.4)	-0.2 (-8.2 to 7.8)	
Difference	10.6 (-1.9 to 22.9)		95.4%
SAQ treatment satisfaction			
Baseline	93.8		
Follow up	7.8 (3.5 to 12.0)	1.3 (-2.6 to 5.2)	
Difference	6.4 (0.9 to 12.4)		98.6%
SAQ quality of life			
Baseline	41.7		
Follow up	23.1 (15.5 to 30.2)	-2.0 (-8.9 to 4.6)	
Difference	25.1 (14.5 to 34.8)		>99.9% 
EQ-5D-5L			
Baseline	0.74		
Follow up	0.14 (0.09 to 0.20)	0.01 (-0.04 to 0.06)	
Difference	0.13 (0.05 to 0.21)		>99.9%
EQ-VAS			
Baseline	70.0		
Follow up	11.4 (5.7 to 17.2)	0.7 (-4.85 to 6.2)	
Difference	10.7 (2.8 to 19.0)		99.5%
CCS Class			
Baseline	2.0		
Follow up	-1.2 (-1.5 to -0.9)	-0.1 (-0.5 to 0.2)	
Difference	-1.1 (-1.5 to -0.6)		>99.9%

Stress echocardiography score		
Baseline	1.80	
Follow up	-1.1 (-1.6 to -0.6)	-0.2 (-0.6 to 0.2)
Difference	-0.9 (-1.5 to -0.3)	99.8%

\*The angina symptom score is calculated daily, incorporating the number of angina episodes reported by a patient that day, the number of units of antianginal medication prescribed and the presence of high-level category over-ride events: death, myocardial infarction and unblinding due to intolerable angina. Data available from the following number of patients: angina symptom score = 279, daily angina episodes = 279, exercise time = 217, SAQ, EQ-5D-5L, EQ-VAS = 270, CCS = 272, stress echocardiography score = 213. iFR = instantaneous wave-free ratio, PCI = percutaneous coronary intervention, SAQ = Seattle Angina Questionnaire, EQ-VAS denotes EQ-5D-5L visual analogue scale, CCS = Canadian Cardiovascular Society.



# Circulation

## Figure Legends

### **Figure 1. The placebo- controlled effect of PCI on angina symptom score dichotomized by median FFR and iFR**

The angina symptom score ranges from 0 to 79, with lower scores indicating a better angina health status. It is calculated using the number of daily angina episodes, the number of units of antianginal medication prescribed that day, and high-level category override events (severe angina leading to unblinding, myocardial infarction, and death). PCI = percutaneous coronary intervention, FFR = fractional flow reserve, iFR= instantaneous wave-free ratio

### **Figure 2. Daily angina episodes stratified by FFR and iFR**

Vertical lines on the X axis represent the distribution of individual FFR and iFR values. Rose is a symptom characteristics questionnaire from which patients can be designated Rose angina or Rose nonangina. PCI = percutaneous coronary intervention, FFR = fractional flow reserve, iFR= instantaneous wave-free ratio, Pr(Interaction) = probability of interaction

### **Figure 3. The placebo-controlled effect of PCI on daily angina episodes dichotomized by median FFR and iFR.**

PCI = percutaneous coronary intervention, FFR = fractional flow reserve, iFR= instantaneous wave-free ratio

### **Figure 4. Physiology-stratified placebo-controlled PCI treatment effect**

The placebo-controlled effect of PCI on SAQ angina frequency, CCS class, treadmill exercise time and dobutamine stress echocardiography score stratified by FFR and iFR. Vertical lines on the X axis represent the distribution of individual FFR and iFR values. PCI =



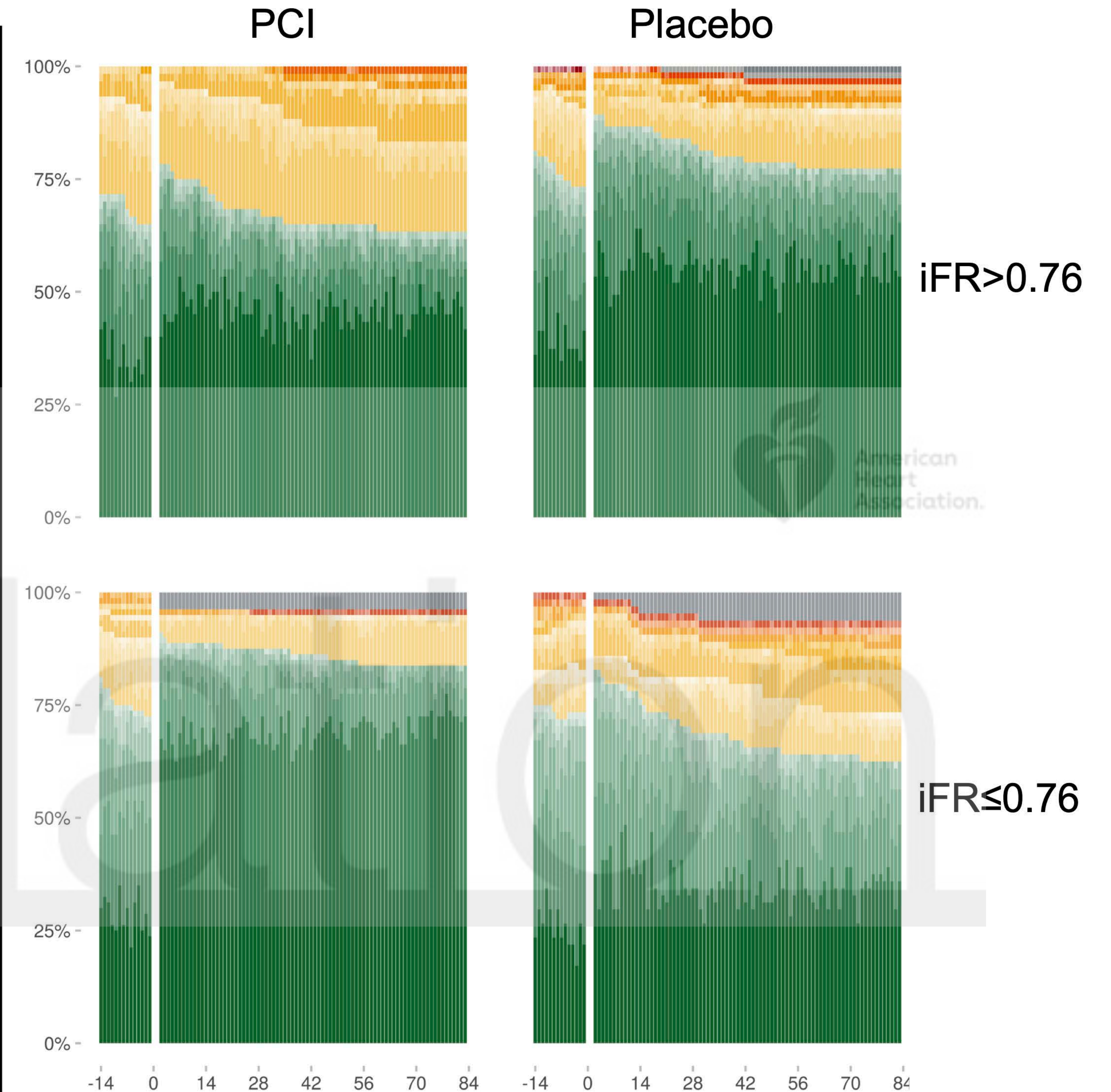
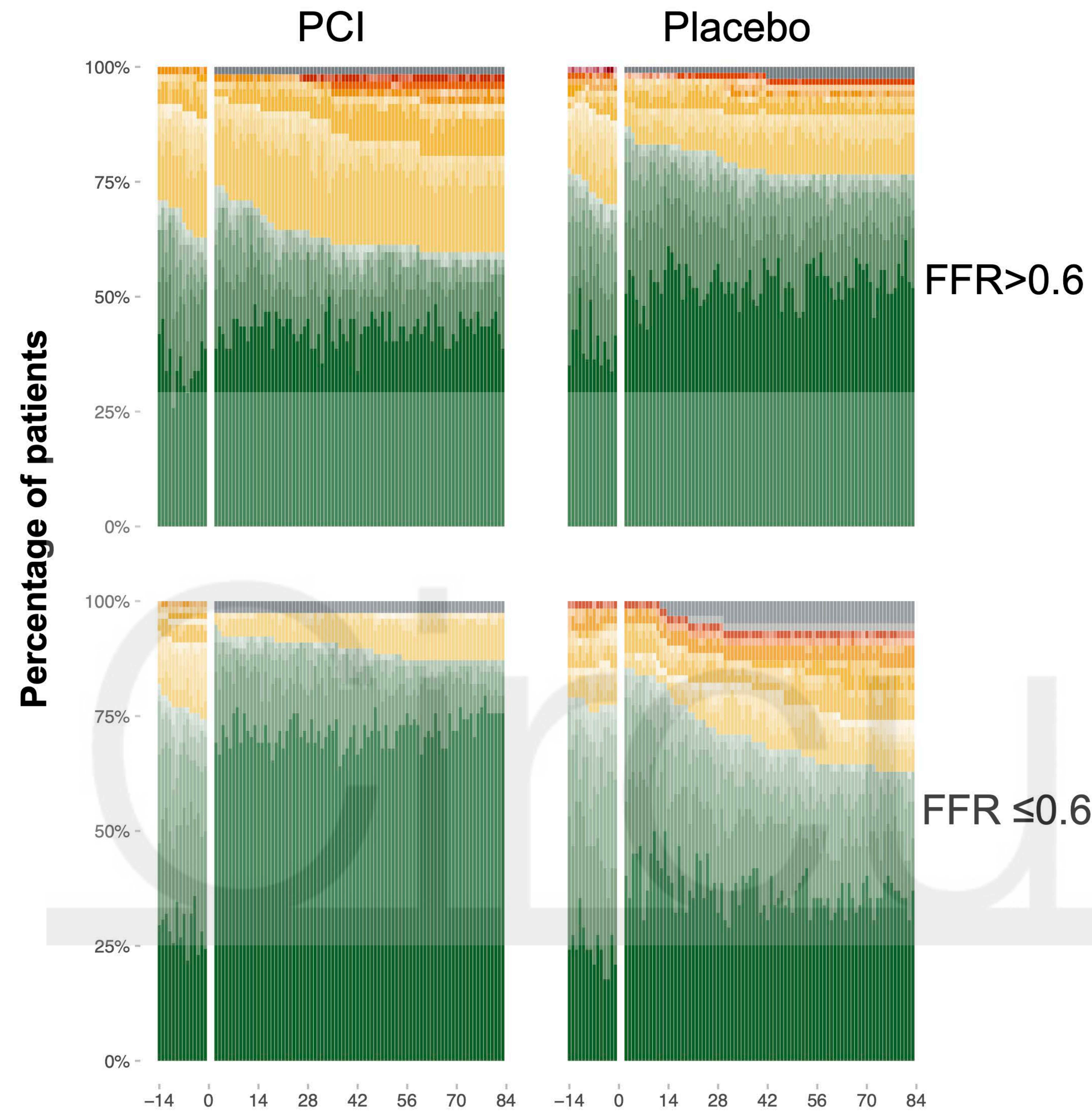
percutaneous coronary intervention, FFR = fractional flow reserve, iFR= instantaneous wave-free ratio, SAQ = Seattle angina questionnaire, CCS= Canadian cardiovascular society class, Pr(Interaction) = probability of interaction



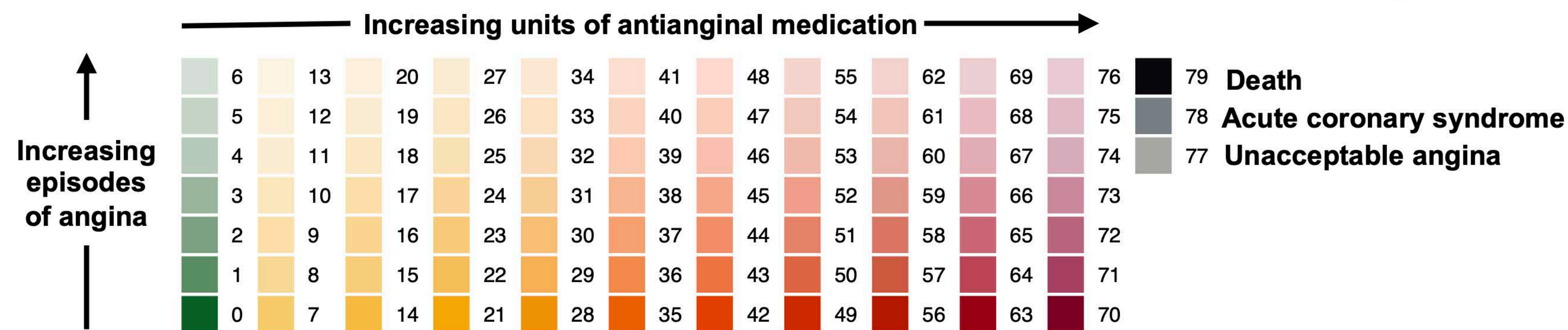
# Circulation

# FFR

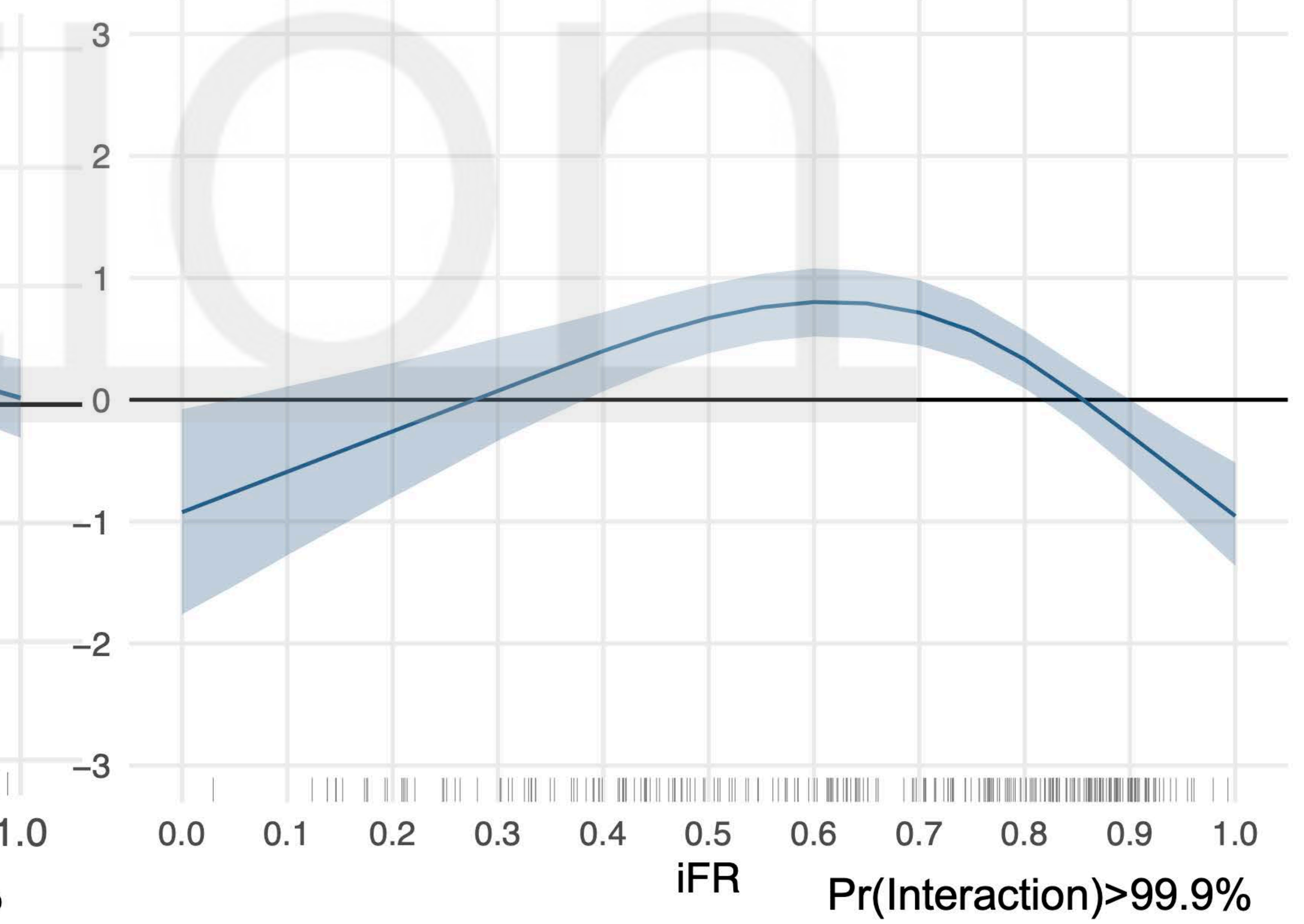
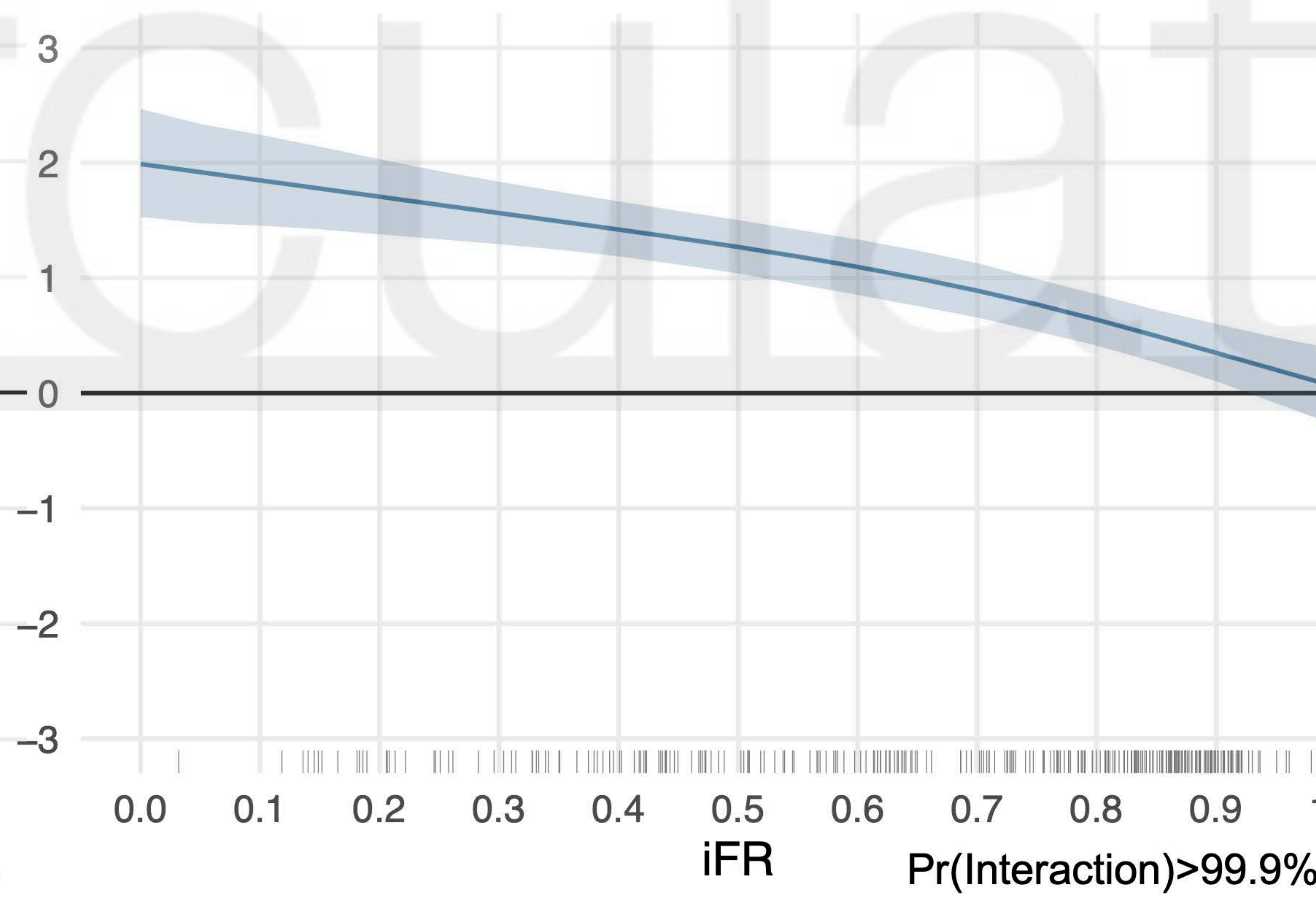
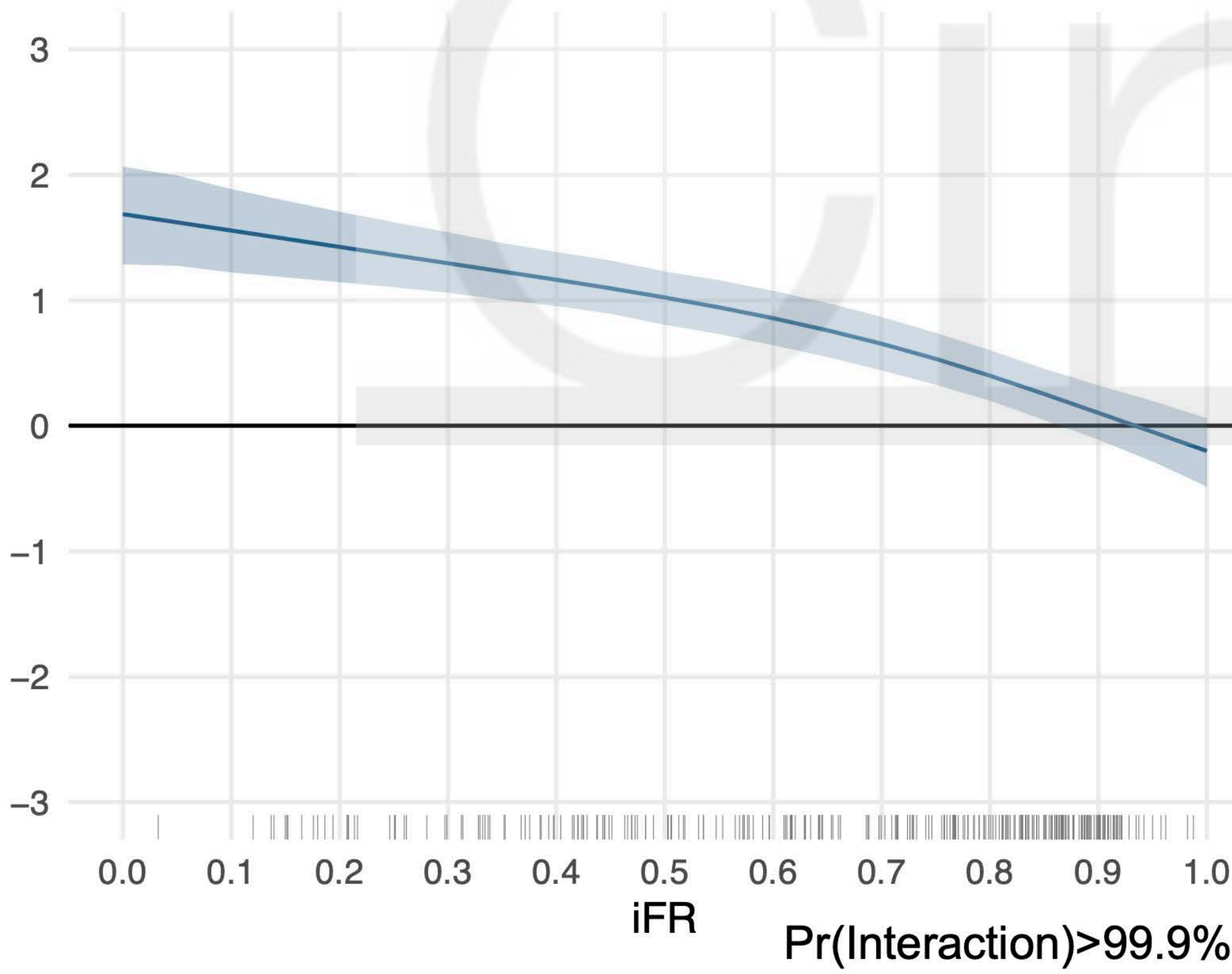
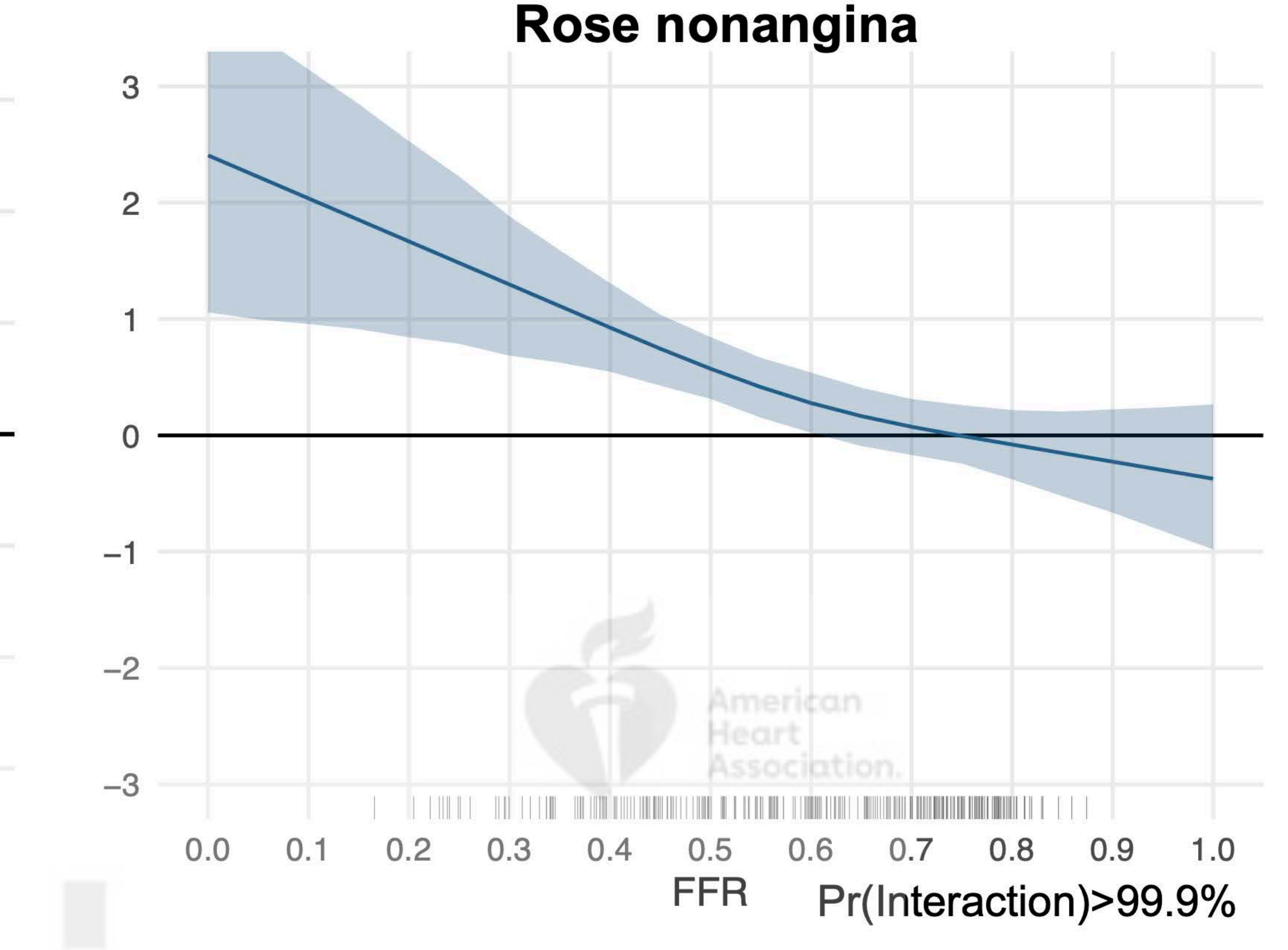
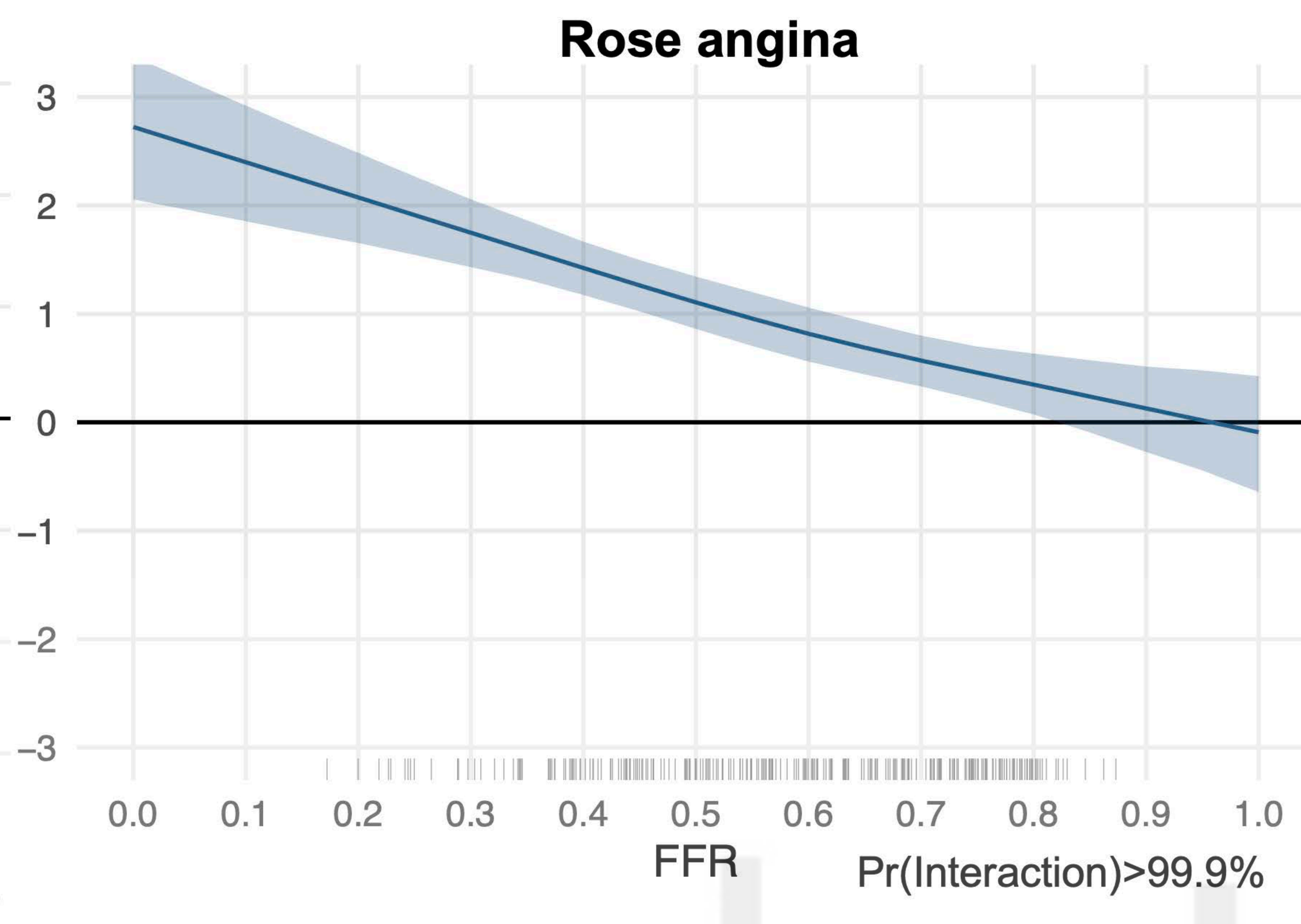
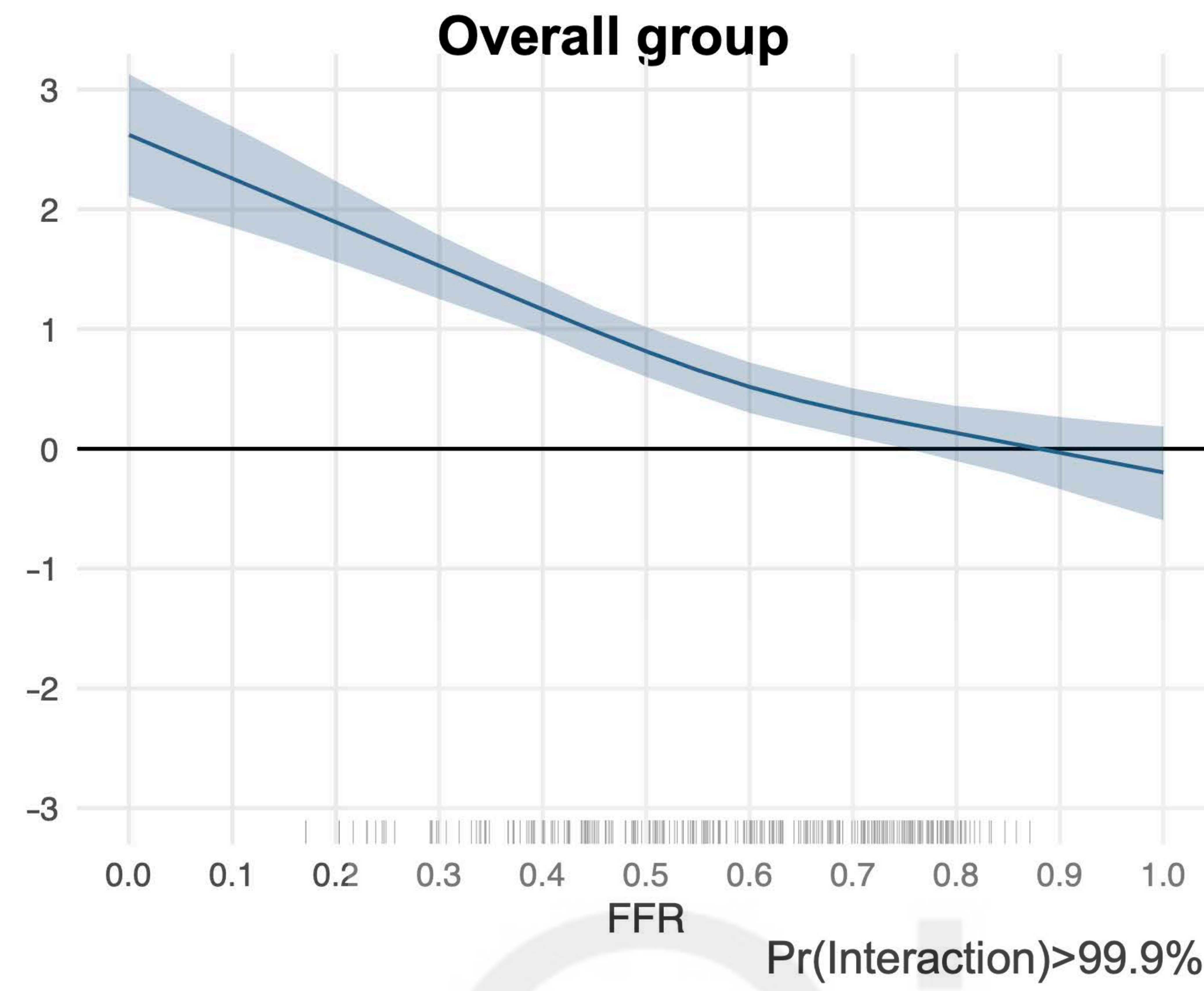
# iFR

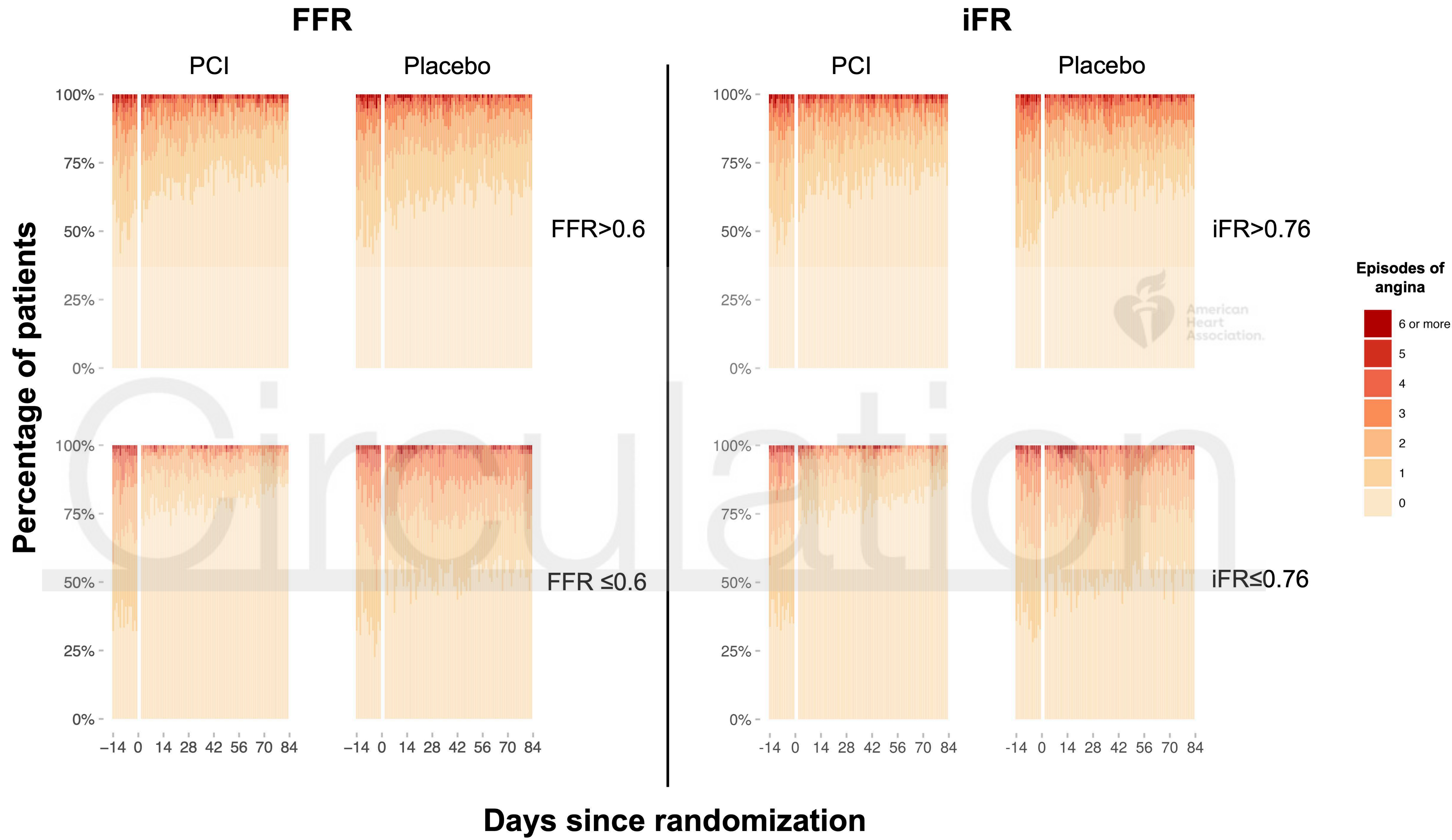


Days since randomization



Placebo-controlled impact of PCI on log(odds) of a reduction in episodes of angina





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