THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Foley MJ, Rajkumar CA, Ahmed-Jushuf F, et al. Coronary sinus reducer for the treatment of refractory angina (ORBITA-COSMIC): a randomised, placebo-controlled trial. *Lancet* 2024; published online April 8. https://doi.org/10.1016/S0140-6736(24)00256-3.

ORBITA-COSMIC Supplementary Appendix

Table of Contents

Trial Conduct

ORBITA-COSMIC investigators

Imperial College London
Michael Foley, Christopher Rajkumar, Fiyyaz Ahmed-Jushuf, Florentina Simader, Sashiananthan Ganesananthan, Danqi Wang, Muhammad Mohsin, Ahmed Salih, Prithvi Dixit, Rachel Pathimagaraj, Graham Cole, Ricardo Petraco, James Howard, Jamil Mayet, Darrel Francis, Matthew Shun-Shin, Rasha Al-Lamee

Imperial College London Healthcare NHS Trust
Ramzi Khamis, Rodney Foale, Jonathan Anderson, Ghada Mikhail, Henry Seligman, Sukhjinder Nijjer, Sayan Sen, Raffi Kaprielian, Iqbal Malik, Michael Bellamy

Mid and South Essex NHS Foundation Trust
Thomas Keeble, John Davies, Gerald Clesham,

St George's University Hospitals NHS Foundation Trust
James Spratt, Claudia Cosgrove

Royal Free London NHS Foundation Trust
Tushar Kotecha

University Hospitals Bristol NHS Foundation Trust
Tom Johnson

The Royal Brompton and Harefield Hospitals, Guys and St Thomas' NHS Foundation Trust
Ranil De Silva, Jonathan Hill, Kevin Cheng

University Hospitals of Dorset NHS Foundation Trust
Peter O'Kane

Trials sites

Supplementary table S1: trial sites

Centre	Principal Investigator	Coinvestigators	Support team	Patients enrolled
Hammersmith Hospital (Imperial College Healthcare NHS Trust)	Dr Rasha Al-Lamee	Professor Darrel Francis Dr Graham Cole Dr James Howard Dr Ghada Mikail Dr Iqbal Malik Dr Sayan Sen Dr Sukhjinder Nijjer Dr Raffi Kaprielian Dr Ramzi Khamis Dr Christopher Rajkumar Dr Michael Foley Mr Jonathan Anderson Dr Fiyyaz Ahmed-Jushuf Dr Henry Seligman Dr Michael Bellamy	Denise Rouse Hawa Amadu	34
Essex Cardiothoracic Centre (Mid and South Essex NHS Foundation Trust)	Dr John Davies	Dr Tom Keeble Dr Gerald Clesham	Raiji Koothoor Michael Galinato Craig Robertson Joanne Turton Ellie Gudde Joanne Hall Karen Lyons	10
Royal Bournemouth Hospital (University Hospitals of Dorset NHS Foundation Trust)	Dr Peter O'Kane		Stephanie Horler Annette Fraine Tanith Changuion	2
St George's Hospital (St George's University Hospitals NHS Foundation Trust)	Professor James Spratt and Dr Claudia Cosgrove		Giovanna Bonato	9
Royal Free Hospital (Royal Free London NHS Foundation Trust)	Dr Tushar Kotecha		Nina Arnold	2
Royal Brompton Hospital Guys and St Thomas's NHS Foundation Trust	Dr Jonathan Hill	Dr Ranil De Silva Dr Kevin Cheng	Patrik Pettersson	4

Trial steering committee

Dr Gerald Clesham (Chair)
Consultant Cardiologist; Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust

Dr Thomas Johnson (Co-Chair)
Consultant Cardiologist; University Hospitals Bristol NHS Foundation Trust

Dr Rasha Al-Lamee
Reader and BHF Intermediate Research Fellow; National Heart and Lung Institute, Imperial College London

Mr Kenneth Bowen
Patient Representative

Dr Graham Cole
Consultant Cardiologist; Imperial College Healthcare NHS Trust

Dr Claudia Cosgrove
Consultant Cardiologist; St George's Hospital NHS Foundation Trust

Dr John Davies
Consultant Cardiologist; Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust

Dr Michael Foley
Clinical Research Fellow; National Heart and Lung Institute, Imperial College London

Dr Jonathan Hill
Consultant Cardiologist; The Royal Brompton Hospital, Guys and St Thomas' NHS Foundation Trust

Dr Tushar Kotecha
Consultant Cardiologist; Royal Free London NHS Foundation Trust

Dr Peter O'Kane
Consultant Cardiologist; University Hospitals Dorset NHS Foundation Trust

Prof James Spratt
Consultant Cardiologist; University Hospitals Bristol NHS Foundation Trust

Trial management group

Dr Michael Foley
Clinical Research Fellow; Imperial College London

Dr Fiyyaz Ahmed-Jushuf
Clinical Research Fellow; Imperial College London

Dr Rasha Al-Lamee
Reader and BHF Intermediate Research Fellow; National Heart and Lung Institute, Imperial College London

Dr Christopher Rajkumar
Clinical Research Fellow; Imperial College London

Dr Florentina Simader
Clinical Research Fellow; Imperial College London

COSMIC interventional multi-disciplinary team

Dr Rasha Al-Lamee
Reader and BHF Intermediate Research Fellow; National Heart and Lung Institute, Imperial College London

Dr Claudia Cosgrove
Consultant Cardiologist; St George's Hospital NHS Foundation Trust

Dr John Davies
Consultant Cardiologist; Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust

Dr Ranil De Silva
Consultant Cardiologist; The Royal Brompton Hospital, Guys and St Thomas' NHS Foundation Trust

Dr Jonathan Hill
Consultant Cardiologist; The Royal Brompton Hospital, Guys and St Thomas' NHS Foundation Trust

Dr Thomas Keeble
Consultant Cardiologist; Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust

Dr Tushar Kotecha
Consultant Cardiologist; Royal Free London NHS Foundation Trust

Dr Peter O'Kane
Consultant Cardiologist; University Hospitals Dorset NHS Foundation Trust

Prof James Spratt
Consultant Cardiologist; University Hospitals Bristol NHS Foundation Trust

Cardiac magnetic resonance imaging core laboratory

Dr Graham Cole
Consultant Cardiologist; Imperial College Healthcare NHS Trust

Dr James Howard
Consultant Cardiologist; Imperial College Healthcare NHS Trust

Dr Tushar Kotecha
Consultant Cardiologist; Royal Free London NHS Foundation Trust

Data and safety monitoring board

The data and safety monitoring board reviewed all serious adverse events in the trial. The board convened every 3 months or every 5 randomisation procedures, whichever came soonest.

Dr Denise Braganza
Consultant Cardiologist; Royal Papworth Hospital NHS Foundation Trust

Dr Jason Dungu
Consultant Cardiologist; Essex Cardiothoracic Centre, Mid and South Essex NHS Foundation Trust

Statistical working group

Dr Rasha Al-Lamee
Reader and BHF Intermediate Research Fellow; National Heart and Lung Institute, Imperial College London

Professor Frank E Harrell, Jr.
Professor of Biostatistics; Vanderbilt University School of Medicine

Dr Matthew Shun-Shin
Clinical Senior Lecturer and Consultant Cardiologist; Imperial College London

Writing committee

Dr Rasha Al-Lamee
Reader and BHF Intermediate Research Fellow; National Heart and Lung Institute, Imperial College LondonDr Michael Foley
Clinical Research Fellow; Imperial College London

Dr Michael Foley
Clinical Research Fellow; National Heart and Lung Institute, Imperial College London

Professor Darrel Francis
Professor of Cardiology; Imperial College London

Dr Matthew Shun-Shin
Clinical Senior Lecturer and Consultant Cardiologist; Imperial College London

Supplementary methods

Inclusion and exclusion criteria

Supplementary table S2: inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Established epicardial CAD • Angina on maximally tolerated anti-anginal therapy • Ischaemia on quantitative stress perfusion CMR, beyond the inferior wall • No further options for PCI or CABG	• Age<18 years • Pregnancy • Inability to consent • Recent acute coronary syndrome (3 months) • Recent revascularisation (6 weeks) • Permanent pacemaker or defibrillator leads in the right heart • Severe left ventricular impairment (<25%) • Indication for CRT • Right atrial pressure ≥15mmHg • Life expectancy <1 year • Severe renal impairment (eGFR<15) • Contraindication to CMR • Contraindication to adenosine • Ischaemia isolated to inferior wall • Ongoing participation in a separate interventional study

COSMIC-MDT

Local hospital Heart Teams at the 6 ORBITA-COSMIC trial sites, or their affiliated hospitals, were able to refer patients to the trial. After referral by the local hospital Heart Team (composed of general cardiologists, interventional cardiologists, and cardiac surgeons), each patient was reviewed again by a group of interventional cardiologists from each of the trial sites, with expertise in the management of complex coronary artery disease (COSMIC-MDT). Any patients who were felt to have options for antianginal procedures (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) did not proceed to randomisation.

Cardiac magnetic resonance protocol

Patients underwent CMR at 1.5T (Aera, Siemens Healthineers, Erlangen, Germany) using our standard clinical protocol including cine imaging, stress and rest perfusion and late gadolinium enhancement. A dual sequence steady-state free precession pulse sequence was used. For stress, adenosine was infused at 140mcg/kg/min for four minutes (increased to 175mcg/kg/min and then 210mcg/kg/min for a further two minutes if the heart rate increased by <10% or there were no symptoms). At the end of the infusion a gadolinium-based contrast agent (Gadovist, Bayer, Leverkusen, Germany) was injected peripherally at 4.5mls/s at a dose of 0.05mmol/kg and 70 images were acquired for three short-axis left ventricular slices. Rest perfusion images were acquired at least 5 minutes after the end of adenosine infusion. Images were analysed in CVI42 *(Circle Cardiovascular Imaging, Calgary, Canada)*. The quantitative perfusion sequence generates maps representing myocardial blood flow on a pixel-by-pixel basis with automated inline readouts of segmental blood flow including on an endocardial and epicardial basis.[1] The same CMR protocol was used at pre-randomisation and follow-up. Patients abstained from caffeine and nicotine for 12 hours, and dipyridamole and long-acting nitrates for 24 hours, prior to the scan. The antianginal medication taken before the follow-up scan was matched to the pre-randomisation scan, where possible.

The CSR is not known to cause significant device related artefact on CMR. Our clinical experience of CMR in patients with a CSR had shown no artefact and we found no evidence of CSR related artefact in this trial.

Cardiac magnetic resonance analysis protocol

CMR analysis was conducted by 3 experts who analysed each scan independently, twice, blinded to randomisation arm, scan order and their own previous assessment. For each segment of each scan, they determined (1) ischaemic or non-ischaemic and (2) the percentage thickness of infarction (0, 1-24, 25-49, 50-74, 75-99 or 100) using their experience and judgement. They had access to conventional first pass perfusion cine imaging at stress and rest, late gadolinium enhancement and dark blood sequences. A segment was defined as ischaemic if ≥50% of opinions (≥3/6) were ischaemia, scarred if ≥50% of opinions were the presence of infarction (of any thickness) or transmurally scarred if ≥50% of opinions were 100% thickness infarction.

For the scar outcome, from the reporters percentage of scar (e.g. 1-24%) the midpoint (in this case 12.5%) was used as the numerical value for analysis. For each segment, the percentage scar was averaged across the 6 reports and then averaged across the 17 segments of the heart (including the apical cap which is not included for perfusion).

The left ventricle was segmented for perfusion analysis inline using the Gagetron software into the American Heart Association 16 segment model. The artificial intelligence generated segmentation was reviewed and errors in segmentation or arterial input function led to the removal of the scan from the analysis.

Treadmill exercise protocol – modified bruce

The test was terminated upon the development of symptoms (angina, dyspnoea or fatigue), heart rhythm or blood pressure abnormalities or significant ST segment deviation (>0.2mV associated with angina or in the first phase of exercise). This

outcome was assessed by two blinded assessors who were unaware of the timing of the test (pre-randomisation or follow-up) or the randomisation arm (CSR or placebo).

Symptom application concept and design

The ORBITA-COSMIC smartphone application is similar in concept and design to the ORBITA-2 application (ORBITA-app).[2] In consultation with patients with lived experience of severe, refractory angina, two key changes were made. The first was that the upper limit of recordable daily angina episodes was increased from 6 to 10, after feedback from patients that more than 6 episodes per day was not uncommon. Secondly, an additional question was utilised regarding “avoiding” angina. This is because patients with long term, refractory angina reported that they had adapted to avoid angina provoking activities and may therefore experience no angina due to behaviour modification.

At initiation of the application, participants were asked to define their angina symptom in their own words (i.e. “pressure in the chest”, “tightness in the chest and throat”, “heaviness in the chest and left arm”). They additionally selected two activities which currently reliably bring on their angina symptoms from a pre-specified list (i.e. walking up a flight of stairs without stopping, walking briskly for 10 minutes). Participants were encouraged to undertake these activities at least once a week.

Throughout the trial, from enrolment to trial exit, participants were asked to record daily:

- Did you have angina? (Yes or no)
- How many episodes did you have? (1-10)

- How severe was the worst episode of angina? (Visual analogue scale of mild, moderate, or severe, generating a score of 0-600)
- Did you avoid any activity to avoid getting angina? (Yes or no)

On a weekly basis, participants were asked if they experienced angina with the two pre-specified angina triggering activities.

At trial enrolment, participants completed a short training module with the ORBITA-app, to ensure they were comfortable with its use. Throughout the trial they had 24/7 access to a blinded member of the trial team for technical support as required. If data was not entered for more than 3 days, a blinded member of the team sent a text reminder. If necessary, a follow up telephone call was also performed.

The daily angina episodes reported on the smartphone application were used to calculate angina status on a 233-point angina ordinal outcomes scale. This is shown in supplementary table 1. The calculation of antianginal "units" for use in the ordinal outcomes scale is shown in supplementary table 2.

Supplementary table S3: derivation of the angina ordinal outcome scale

Grade	Number of angina episodes in a day	Units of antianginal medication	Unblinding due to intolerable angina	Acute coronary syndrome	Death
0	0	0	No	No	No
1	1	0	No	No	No
2	2	0	No	No	No
3	3	0	No	No	No
4	4	0	No	No	No

5	5	0	No	No	No
6	6	0	No	No	No
7	7	0	No	No	No
8	8	0	No	No	No
9	9	0	No	No	No
10	10 or more	0	No	No	No
11	0	1	No	No	No
12	1	1	No	No	No
13	2	1	No	No	No
14	3	1	No	No	No
15	4	1	No	No	No
16	5	1	No	No	No
17	6	1	No	No	No
18	7	1	No	No	No
19	8	1	No	No	No
20	9	1	No	No	No
21	10 or more	1	No	No	No
22	0	2	No	No	No
23	1	2	No	No	No
24	2	2	No	No	No
25	3	2	No	No	No
26	4	2	No	No	No
27	5	2	No	No	No
28	6	2	No	No	No
29	7	2	No	No	No

30	8	2	No	No	No
31	9	2	No	No	No
32	10 or more	2	No	No	No
33	0	3	No	No	No
34	1	3	No	No	No
35	2	3	No	No	No
36	3	3	No	No	No
37	4	3	No	No	No
38	5	3	No	No	No
39	6	3	No	No	No
40	7	3	No	No	No
41	8	3	No	No	No
42	9	3	No	No	No
43	10 or more	3	No	No	No
44	0	4	No	No	No
45	1	4	No	No	No
46	2	4	No	No	No
47	3	4	No	No	No
48	4	4	No	No	No
49	5	4	No	No	No
50	6	4	No	No	No
51	7	4	No	No	No
52	8	4	No	No	No
53	9	4	No	No	No
54	10 or more	4	No	No	No

55	0	5	No	No	No
56	1	5	No	No	No
57	2	5	No	No	No
58	3	5	No	No	No
59	4	5	No	No	No
60	5	5	No	No	No
61	6	5	No	No	No
62	7	5	No	No	No
63	8	5	No	No	No
64	9	5	No	No	No
65	10 or more	5	No	No	No
66	0	6	No	No	No
67	1	6	No	No	No
68	2	6	No	No	No
69	3	6	No	No	No
70	4	6	No	No	No
71	5	6	No	No	No
72	6	6	No	No	No
73	7	6	No	No	No
74	8	6	No	No	No
75	9	6	No	No	No
76	10 or more	6	No	No	No
77	0	7	No	No	No
78	1	7	No	No	No
79	2	7	No	No	No

80	3	7	No	No	No
81	4	7	No	No	No
82	5	7	No	No	No
83	6	7	No	No	No
84	7	7	No	No	No
85	8	7	No	No	No
86	9	7	No	No	No
87	10 or more	7	No	No	No
88	0	8	No	No	No
89	1	8	No	No	No
90	2	8	No	No	No
91	3	8	No	No	No
92	4	8	No	No	No
93	5	8	No	No	No
94	6	8	No	No	No
95	7	8	No	No	No
96	8	8	No	No	No
97	9	8	No	No	No
98	10 or more	8	No	No	No
99	0	9	No	No	No
100	1	9	No	No	No
101	2	9	No	No	No
102	3	9	No	No	No
103	4	9	No	No	No
104	5	9	No	No	No

105	6	9	No	No	No
106	7	9	No	No	No
107	8	9	No	No	No
108	9	9	No	No	No
109	10 or more	9	No	No	No
110	0	10	No	No	No
111	1	10	No	No	No
112	2	10	No	No	No
113	3	10	No	No	No
114	4	10	No	No	No
115	5	10	No	No	No
116	6	10	No	No	No
117	7	10	No	No	No
118	8	10	No	No	No
119	9	10	No	No	No
120	10 or more	10	No	No	No
121	0	11	No	No	No
122	1	11	No	No	No
123	2	11	No	No	No
124	3	11	No	No	No
125	4	11	No	No	No
126	5	11	No	No	No
127	6	11	No	No	No
128	7	11	No	No	No
129	8	11	No	No	No

130	9	11	No	No	No
131	10 or more	11	No	No	No
132	0	12	No	No	No
133	1	12	No	No	No
134	2	12	No	No	No
135	3	12	No	No	No
136	4	12	No	No	No
137	5	12	No	No	No
138	6	12	No	No	No
139	7	12	No	No	No
140	8	12	No	No	No
141	9	12	No	No	No
142	10 or more	12	No	No	No
143	0	13	No	No	No
144	1	13	No	No	No
145	2	13	No	No	No
146	3	13	No	No	No
147	4	13	No	No	No
148	5	13	No	No	No
149	6	13	No	No	No
150	7	13	No	No	No
151	8	13	No	No	No
152	9	13	No	No	No
153	10 or more	13	No	No	No
154	0	14	No	No	No

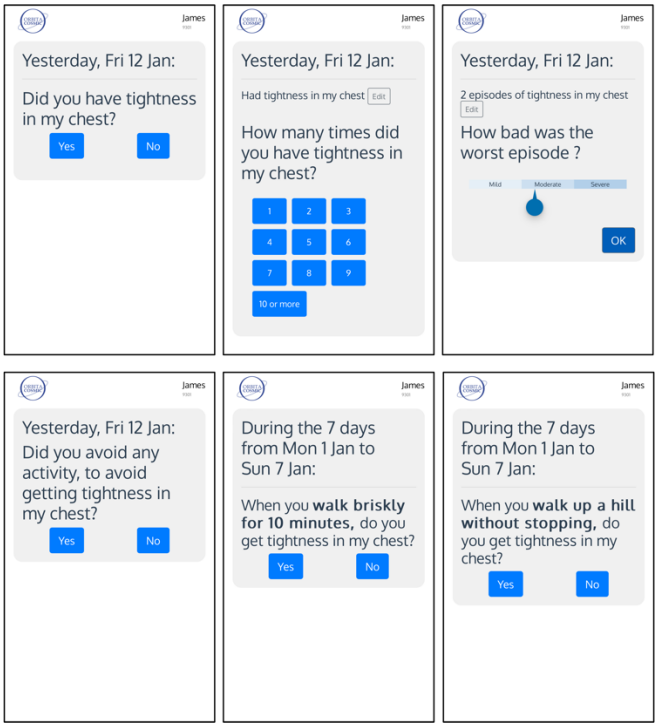
155	1	14	No	No	No
156	2	14	No	No	No
157	3	14	No	No	No
158	4	14	No	No	No
159	5	14	No	No	No
160	6	14	No	No	No
161	7	14	No	No	No
162	8	14	No	No	No
163	9	14	No	No	No
164	10 or more	14	No	No	No
165	0	15	No	No	No
166	1	15	No	No	No
167	2	15	No	No	No
168	3	15	No	No	No
169	4	15	No	No	No
170	5	15	No	No	No
171	6	15	No	No	No
172	7	15	No	No	No
173	8	15	No	No	No
174	9	15	No	No	No
175	10 or more	15	No	No	No
176	0	16	No	No	No
177	1	16	No	No	No
178	2	16	No	No	No
179	3	16	No	No	No

180	4	16	No	No	No
181	5	16	No	No	No
182	6	16	No	No	No
183	7	16	No	No	No
184	8	16	No	No	No
185	9	16	No	No	No
186	10 or more	16	No	No	No
187	0	17	No	No	No
188	1	17	No	No	No
189	2	17	No	No	No
190	3	17	No	No	No
191	4	17	No	No	No
192	5	17	No	No	No
193	6	17	No	No	No
194	7	17	No	No	No
195	8	17	No	No	No
196	9	17	No	No	No
197	10 or more	17	No	No	No
198	0	18	No	No	No
199	1	18	No	No	No
200	2	18	No	No	No
201	3	18	No	No	No
202	4	18	No	No	No
203	5	18	No	No	No
204	6	18	No	No	No

205	7	18	No	No	No
206	8	18	No	No	No
207	9	18	No	No	No
208	10 or more	18	No	No	No
209	0	19	No	No	No
210	1	19	No	No	No
211	2	19	No	No	No
212	3	19	No	No	No
213	4	19	No	No	No
214	5	19	No	No	No
215	6	19	No	No	No
216	7	19	No	No	No
217	8	19	No	No	No
218	9	19	No	No	No
219	10 or more	19	No	No	No
220	0	20	No	No	No
221	1	20	No	No	No
222	2	20	No	No	No
223	3	20	No	No	No
224	4	20	No	No	No
225	5	20	No	No	No
226	6	20	No	No	No
227	7	20	No	No	No
228	8	20	No	No	No
229	9	20	No	No	No

230	10 or more	20	No	No	No
231	NA	NA	Yes	No	No
232	NA	NA	No	Yes	No
233	NA	NA	No	No	Yes

Supplementary figure S1: screenshots of the ORBITA-COSMIC smartphone symptom application



Medications management standard operating procedure

On enrolment, all participants were started on dual antiplatelet therapy (aspirin 75mg once daily and clopidogrel 75mg once daily), a proton-pump inhibitor for gastric protection and atorvastatin (target dose ≥40mg daily). No protocolised changes were made to antianginal medication once enrolled in the trial. If the antianginal medication was altered by the treating physician, this was reported to the study team and documented. If medication changes were made, they were adjusted to match the enrolment medications at all follow-up assessments, including CMR, where possible.

Supplementary Table S4: Units of antianginal medication for use in the angina ordinal outcome scale

Medication	Total daily dose in mg
Bisoprolol	5
Atenolol	25
Propranolol	60

Nebivolol	2.5
Metoprolol	100
Carvedilol	25
Amlodipine	2.5
Nifedipine	20
Diltiazem	120
Lercanidipine	5
Felodipine	5
Isosorbide mononitrate MR	30
Isosorbide mononitrate SR	25
Isosorbide dinitrate	30
Nicorandil	20
Ranolazine	750
Ivabradine	5

Coronary sinus reducer implantation protocol

All patients had 9Fr venous access in the right internal jugular vein, right atrial pressure measurement, peripheral intravenous heparin administration (5000 units) and coronary sinus venogram acquisition using a diagnostic catheter in the distal coronary sinus (Multipurpose or Amplatzer) in the LAO 30° position. Patients were then sedated to a deep level of conscious sedation and were randomised.

If randomised to the CSR arm *(Neovasc Reducer, Shockwave Medical)*, a 180cm 0.035 guidewire was advanced through the diagnostic catheter to the distal coronary sinus. The diagnostic catheter was inserted into the Neovasc Reducer 9Fr guide catheter *(Cordis)*, utilising a “mother and child” technique. The multipurpose catheter

and guide catheter were advanced together to the coronary sinus. The multipurpose catheter was exchanged for the Neovasc Reducer CSR catheter with the device positioned in the desired implantation position in the coronary sinus. The guide catheter was withdrawn to the proximal marker on the CSR delivery catheter. The CSR was deployed to 4 to 6atm, aiming for 10% oversizing, confirmed with an IV contrast injection. The guidewire was temporarily withdrawn at this point and the CSR catheter connected to the pressure transducer to measure the CS wedge pressure.

The CSR balloon was then serially deflated at least five times to ensure adequate purging of contrast. The guide was then readvanced into the neck of the CSR and the balloon was withdrawn into the guide catheter. The guide catheter was withdrawn and the final venogram was acquired using a multipurpose catheter. A final non-contrast image was acquired demonstrating the CSR in situ.

Protamine (50mg) was administered to patients in both groups, and venous access removed with manual haemostasis.

Mechanisms of blinding and blinding index

The management of blinding is described in detail in Table 3.

Supplementary table S5: DITTO blinding framework

Domain	Placebo optimisation strategy in ORBITA-COSMIC Trial
Sensory manipulation	Patients received incremental doses of intravenous opiate and benzodiazepine to achieve a deep level of conscious sedation such that the patient was unresponsive to verbal or tactile stimulus, with maintained airway, ventilation, and cardiovascular function. Physiological support with oxygenation and intravenous fluids was administered as necessary. The additional steps for sensory manipulation are detailed below.
Visual masking	The positioning of the patient and the sterile drape, with the drape between the patient and the operator screen, meant that the operator screen was not visible to them.
Verbal cues	Patients were not able to hear any verbal cues due to sedation and auditory isolation. The handover of treatment allocation from the

	research team to the operator was communicated away from the patient to prevent inadvertent leakage of information.
Auditory cues	Auditory isolation and sedation minimised any possible auditory difference between CSR and placebo procedures.
Physical cues	Before the procedure began, patients were counselled that they may experience some discomfort during the procedure. Sheath implantation and coronary sinus venography took place prior tom randomisation.
Visual cues	Although patients were sedated, the positioning of the sterile drape in from of their face meant that the operator screen was also not visible to the patient.
Auditory masking	Over-the-ear headphones with music continuously playing throughout the invasive procedure to provided auditory isolation to all patients. These were worn prior to sedation and randomisation to prevent the patient hearing any communication between the clinical team.
Olfactory cues	There were no olfactory differences between the treatment groups.
Use of devices to optimise blinding	In both the CSR and placebo groups, the catheterisation laboratory table and equipment table were set up for CSR implantation. All patients underwent internal jugular access with a 9Fr sheath and had coronary sinus venography undertaken prior to randomisation.
Mimicked Timings	The randomisation procedure comprised sterile draping, local anaesthetic, ultrasound guided right internal jugular access with a 9Fr venous sheath, right atrial pressure measurement with a diagnostic catheter, coronary sinus venography prior to establishing a deep level of conscious sedation. Once randomised, a coronary sinus reducer implantation from this point would take approximately 15 minutes, which is mimicked by the 15 minutes of maintained sedation without intervention in the placebo group. The benzodiazepines used for sedation had a secondary effect of amnesia regarding the length of procedure.
Restricting interaction between blinded and unblinded personnel	The blinded ward staff managed all patients as if they had undergone CSR for post procedural monitoring and care. The catheter laboratory staff involved in the procedure were not permitted any contact or communication with the patient after handover.
Omission of intervention details in trial paperwork	The online case reporting form (Redcap) had a dedicated page for treatment allocation. This was only place where randomisation allocation was documented. The unblinded fellow entered the treatment allocation to a pre-allocated page of the online case reporting form to which none of the other members of the research team had access. All the communication with the patient after discharge and during follow up was conducted by a blinded fellow. At the 6-month point the blinded fellow contacted the unblinded fellow to confirm that all the assessments had been performed, only at that time was the treatment allocation communication. Following this, the patient, the research team, and the clinical team became unblinded and no further research data collection was undertaken.
Intervention not specified in patient notes	A standardised protocol was used for the management of all documentation in the catheter laboratory in all centres. During the procedure, the nurses documented that the patient had participated in the ORBITA-COSMIC trial. They did not document treatment allocation or any details of the procedure in the medical notes. After the procedure, the handover between the catheter laboratory staff and ward nursing staff was carefully managed to include only location of access sites and medication given (which was identical for the two randomised arms, as all patients required heparin for physiological assessment and all patients received sedation). The

	handover did not indicate the treatment allocation and therefore did not indicate whether a CSR was implanted. Additionally, during the handover process patients continued to have auditory isolation with music via headphones. The unblinded fellow prepared a standardised discharge letter at the end of the procedure which informed the reader that a blinded procedure had taken place, that this procedure was a coronary sinus venogram +/- CSR implantation and that all medications should remain unchanged, including continuation of dual antiplatelet therapy, until trial follow-up was complete. The letter stated that they should receive standard post CSR care, which is the same as post PCI care, until full details of the procedure were provided after unblinding at 6 months. This standardised letter was approved by the local ethics committee and was given to all patients and their general practitioners on discharge.
Patient billing delayed or withheld	Not applicable in National Health Service (NHS) of United Kingdom
Unblinded operator delivering component of intervention	The unblinded operator who performed the procedure was not permitted to attend to the patient after completion of the interventional procedure. This meant that the unblinded operator was not able to review or have any communication with the patient in recovery. Furthermore, the unblinded operator was not permitted to have any contact with the patient during the 6-month blinded follow-up period, until the patient had completed the trial and been unblinded to treatment allocation.

Blinding index assessment

The blinding index assessment protocol checked for accidental disclosure or leakage of treatment allocation information to patients or staff. At the point of discharge on the day of their randomisation procedure, patients and staff were asked to guess the treatment allocation using all information available to them with the options 1) CSR 2) Placebo 3) Don't know. They were then asked to give a score for the certainty of their answer using 1-5 scale. For completeness this blinding assessment was also reassessed at the conclusion of follow-up assessments, prior to unblinding. However, because at this point the patient can incorporate their own symptom response into their answer, questioning at this timepoint is not a true assessment of blinding but can also incorporate "wishful thinking" and pre-conceived ideas about treatment response.

Additional statistical methods

Priors for the Bayesian analyses

The priors were previously specified in the Statistical Analysis Plan: • For the intercepts the priors are induced by a Dirichlet distribution on the cell probabilities when all covariates are set to their means. This enforces 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 is normal with mean zero and standard deviation chosen so to that the prior probability that the OR < 0.25 equals the prior probability OR > 4 with both equalling 0.05. Thus, the analysis is skeptical about the treatment effect being large in either direction. Besides being more convincing to a skeptic (should there be evidence for benefit), the skeptical prior "pulls back" the OR more at early data looks to help avoid making a mistake in stopping a treatment arm early. For covariates a virtually flat prior will be used, i.e., a distribution with mean 0 and standard deviation of 100 on a normalised covariate scale.

Supplementary table S6: secondary CMR outcomes

Imaging Secondary Outcomes	
CMR	MPR in ischaemic segments, non-ischaemic segments, and global MPR
	Rest MBF in ischaemic segments, non-ischaemic segments, and global rest MBF
	Stress MBF in ischaemic segments with inferior and inferoseptal segments excluded
	MPR in ischaemic segments with inferior and inferoseptal segments excluded
	Rest MBF in ischaemic segments with inferior and inferoseptal segments excluded
	Endocardial:epicardial ratio of stress MBF
	Endocardial:epicardial ratio of MPR
	Endocardial:epicardial ratio of rest MBF
	Myocardial strain
	Myocardial scar burden

Supplementary table S7: secondary symptom outcomes

Symptom Secondary Outcomes	
Physician Assessed	CCS
Patient Reported	Angina symptom score
	SAQ angina frequency
	SAQ angina physical limitation
	SAQ quality of life
	SAQ treatment satisfaction
	SAQ angina stability
	EQ-5D-5L descriptive system
	EQ-5D-5L visual analogue scale
	Angina related quality of life rated by the MacNew questionnaire
Other	Treadmill exercise time

Supplementary results

Supplementary table S8: blood results

	CSR (N=25) [1]	Placebo (N=26) [1]	Overall (n=51) [1]
Haemoglobin (g/L)	136.0 (123.0 to 142.0)	126.5 (122.0 to 144.8)	129.0 (122.5 to 144.0)
HbA1c (mmol/mol)	50.0 (41.0 to 54.0)	52.0 (41.25 to 60.50)	51.0 (41.0 to 56.5)
Creatinine (μmol/L)	75.0 (66.0 to 99.0)	86.5 (75.0 to 101.8)	82.0 (67.0 to 101.0)
Triglycerides (mmol/L)	1.16 (0.99 to 1.78)	1.52 (1.17 to 2.08)	1.41 (1.03 to 2.03)
Total cholesterol (mmol/L)	3.40 (2.90 to 4.10)	3.17 (2.80 to 3.78)	3.30 (2.80 to 3.84)
HDL cholesterol (mmol/L)	1.06 (0.92 to 1.19)	1.13 (0.91 to 1.21)	1.08 (0.91 to 1.20)
LDL cholesterol (mmol/L)	1.67 (1.19 to 2.22)	1.27 (1.00 to 1.94)	1.47 (1.01 to 2.05)
[1] Median (IQR)			

Supplementary table S9: volumetric CMR data

	CSR, N = 25[1]	**Placebo**, N = 26[1]	**Overall**, N = 51[1]
Left ventricle			
LV end diastolic volume (ml)	151.0 (121.0 to 167.0)	157.0 (126.5 to 173.8)	152.0 (122.0 to 167.5)
LV end diastolic volume index (ml/m^2)	75.0 (66.0 to 85.0)	77.0 (67.0 to 82.0)	77.0 (66.0 to 84.0)
LV end systolic volume (ml)	53.0 (47.0 to 78.0)	58.50 (42.5 to 65.8)	57.0 (43 to 73)
LV end systolic volume index (ml/m^2)	28.0 (21.0 to 38.0)	28.5 (25.0 to 31.8)	28.0 (21.5 to 36.0)
LV mass (g)	120.0 (104.0 to 134.0)	120.0 (104.0 to 139.3)	120.0 (103.5 to 137.5)

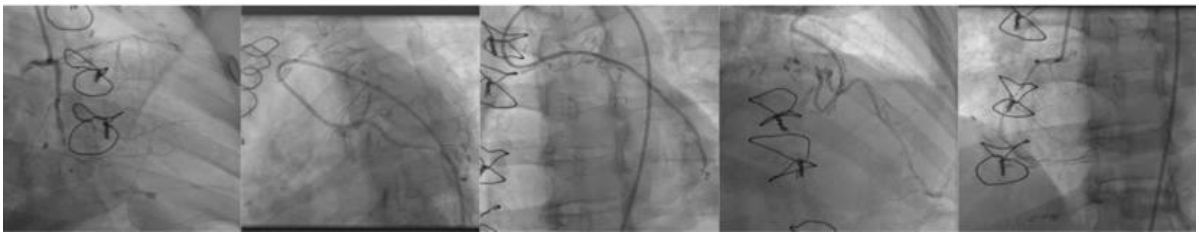
LV mass index (g/m^2)	64.0 (57.0 to 66.0)	60.5 (55.0 to 69.0)	64.0 (55.0 to 67.0)
LV stroke volume (ml)	84.0 (73.0 to 104.0)	94.5 (71.0 to 105.8)	92.0 (73.0 to 104.5)
LV stroke volume index (ml/m^2)	45.0 (40.0 to 51.0)	45.5 (38.0 to 51.8)	45.0 (39.5 to 51.5)
LV ejection fraction (%)	61.0 (55.0 to 69.0)	63.0 (58.3 to 66.8)	62.0 (57.0 to 67.0)
Right ventricle			
RV end diastolic volume (ml)	142.5 (121.0 to 161.0)	142.0 (129.0 to 174.0)	142. (121.0 to 164.0)
RV end diastolic volume index (ml/m^2)	74.5 (65.5 to 83.0)	75.0 (61.0 to 85.0)	75.0 (64.0 to 84.0)
RV end systolic volume (ml)	57.5 (50.3 to 69.5)	60.0 (50.0 to 67.0)	58.0 (50.0 to 67.0)
RV end systolic volume index (ml/m^2)	30.0 (25.8 to 35.0)	29.0 (25.0 to 34.0)	30.0 (25.0 to 34.0)

[1] Median (IQR)

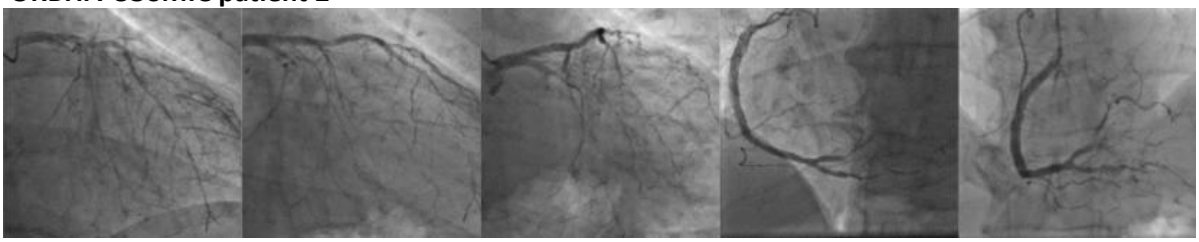
Coronary angiography

Supplementary figure S2- coronary angiograms of all patients randomised in ORBITA-COSMIC

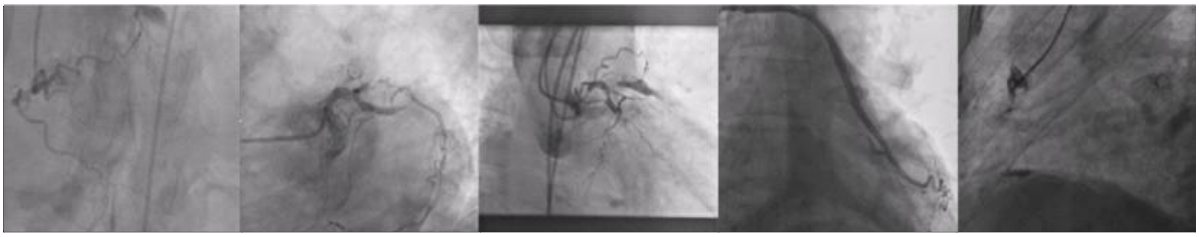
ORBITA-COSMIC patient 1



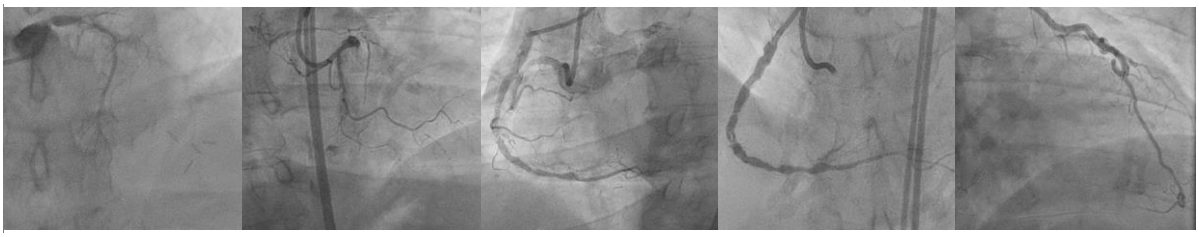
ORBITA-COSMIC patient 2



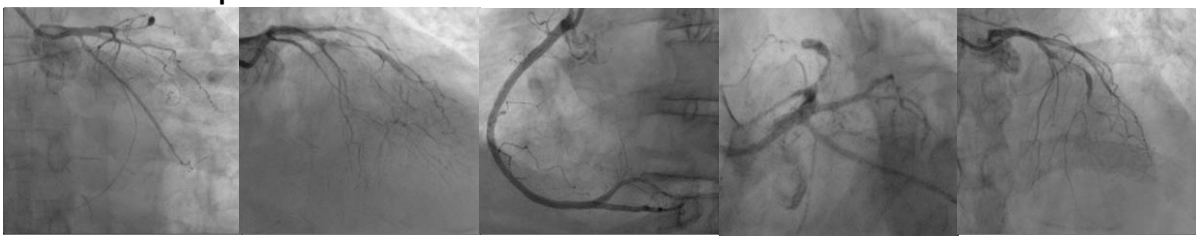
ORBITA-COSMIC patient 3



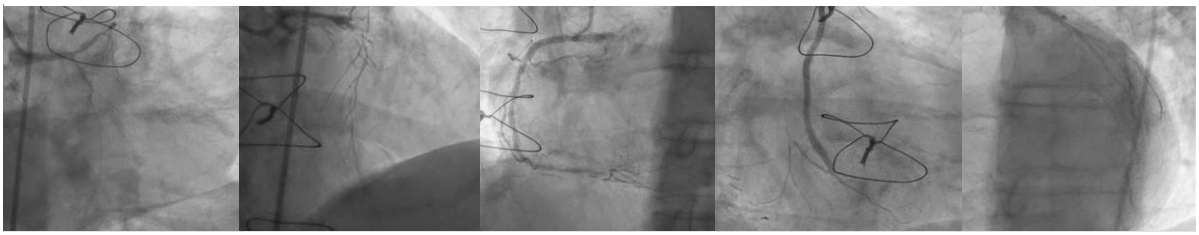
ORBITA-COSMIC patient 4



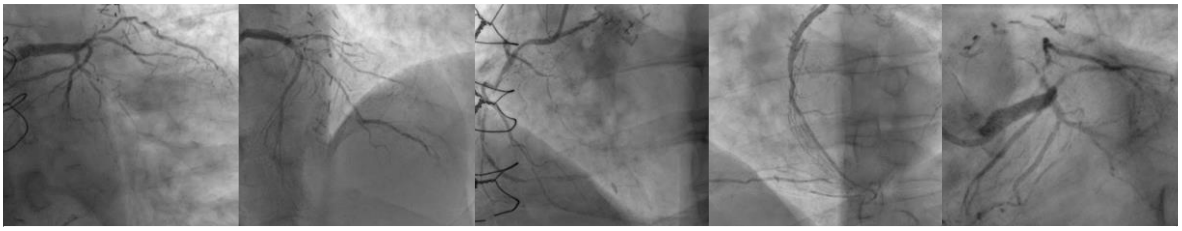
ORBITA-COSMIC patient 5



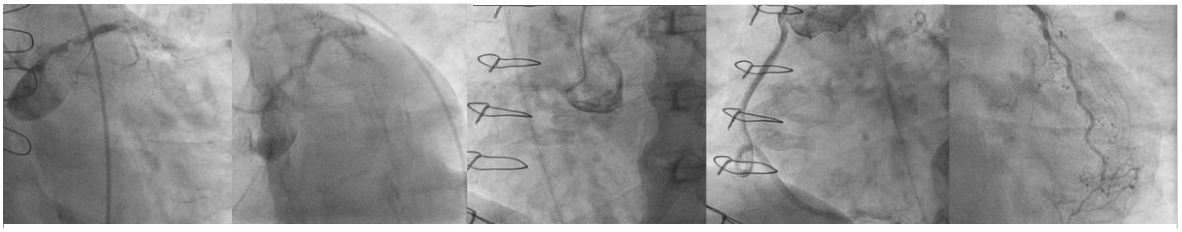
ORBITA-COSMIC patient 6



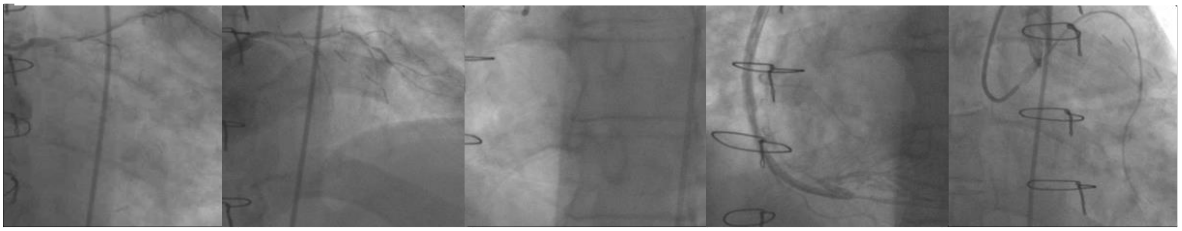
ORBITA-COSMIC patient 7



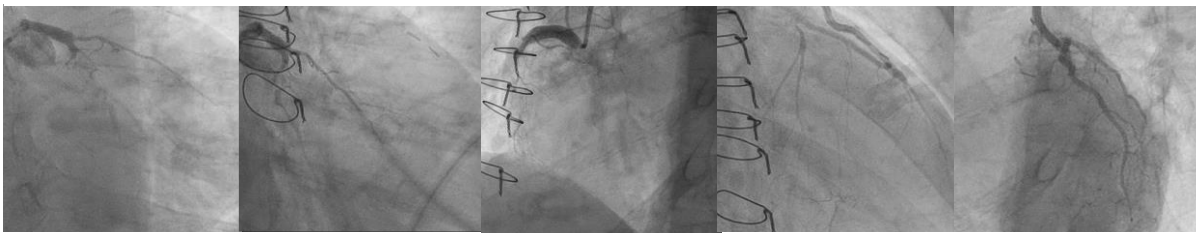
ORBITA-COSMIC patient 8



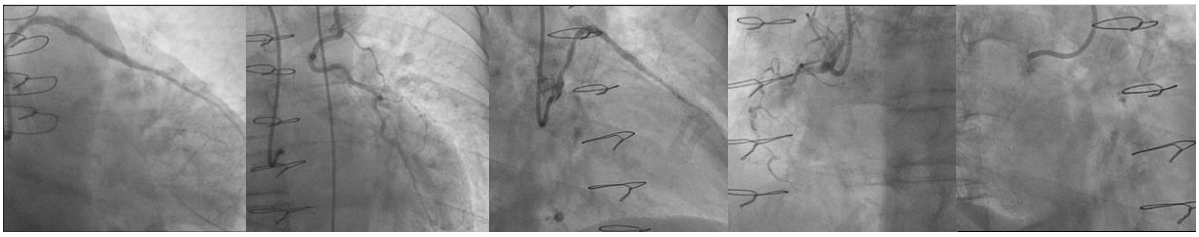
ORBITA-COSMIC patient 9



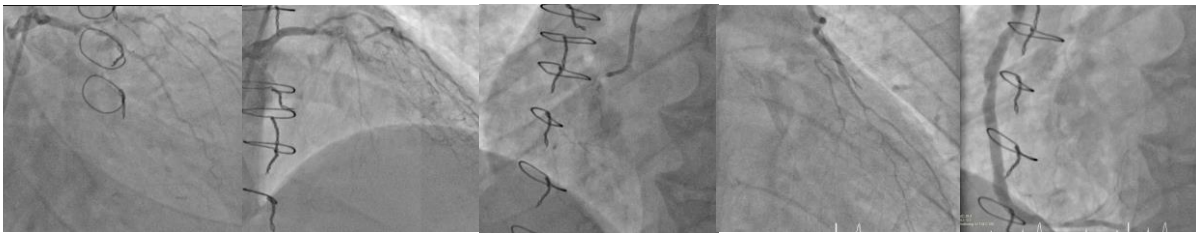
ORBITA-COSMIC patient 10



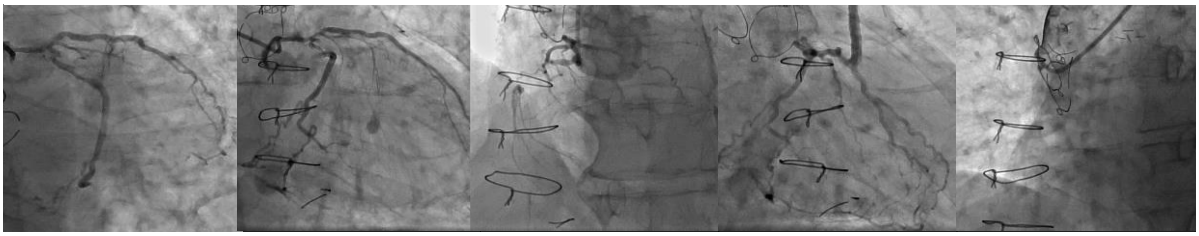
ORBITA-COSMIC patient 11



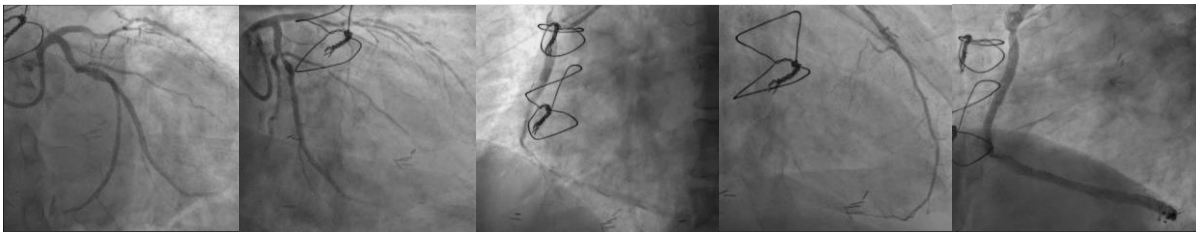
ORBITA-COSMIC patient 12



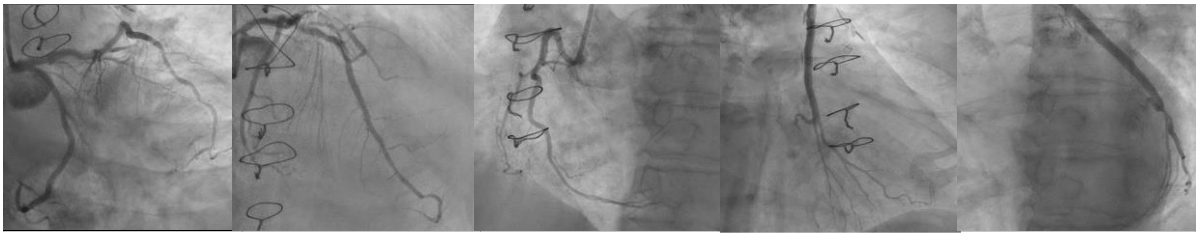
ORBITA-COSMIC patient 13



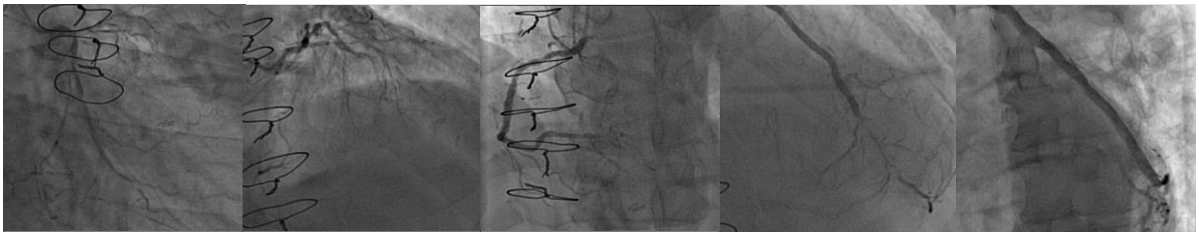
ORBITA-COSMIC patient 14



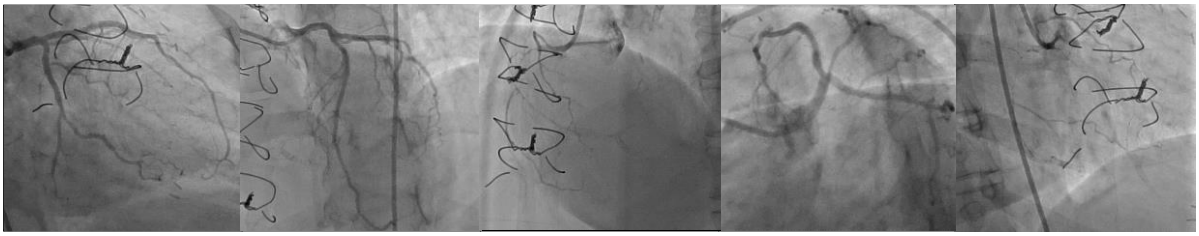
ORBITA-COSMIC patient 15



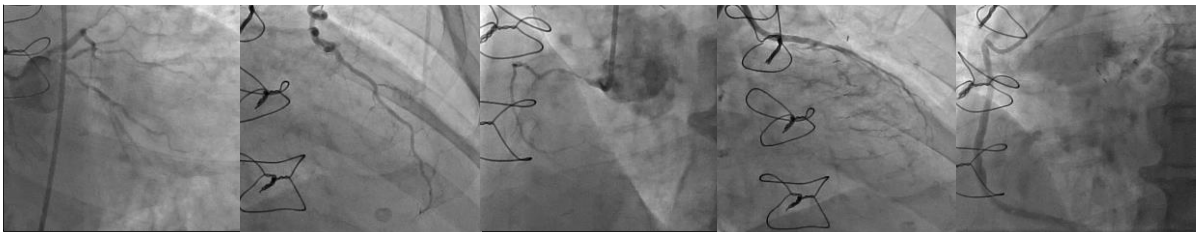
ORBITA-COSMIC patient 16



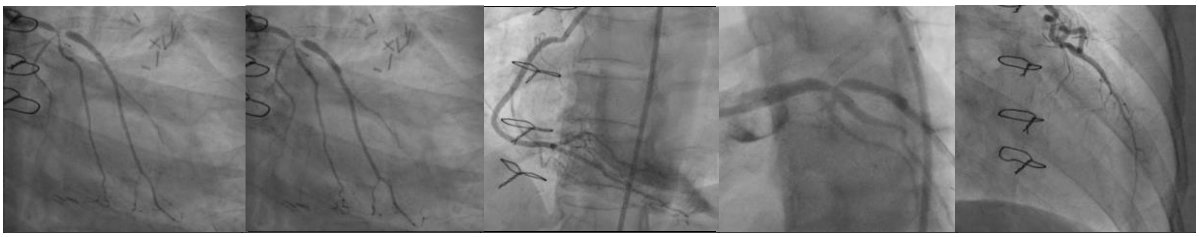
ORBITA-COSMIC patient 17



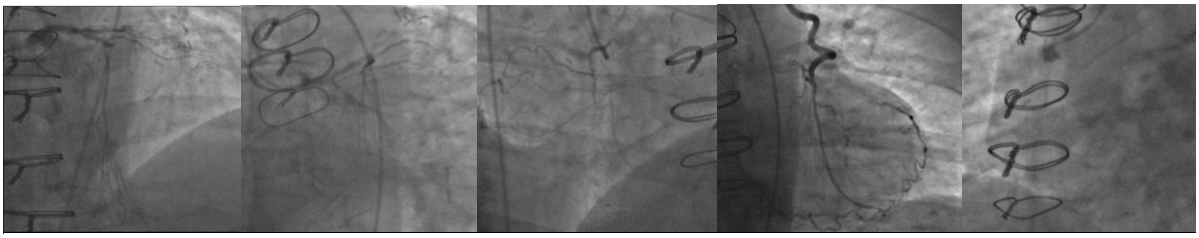
ORBITA-COSMIC patient 18



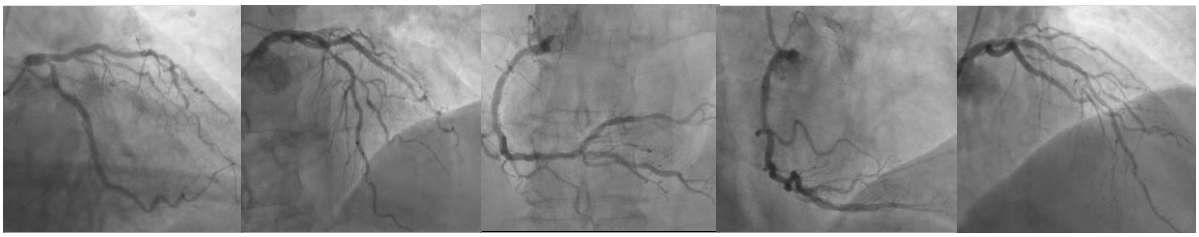
ORBITA-COSMIC patient 19



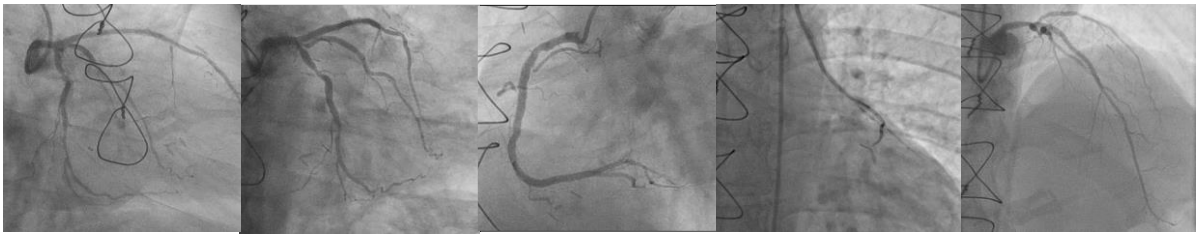
ORBITA-COSMIC patient 20



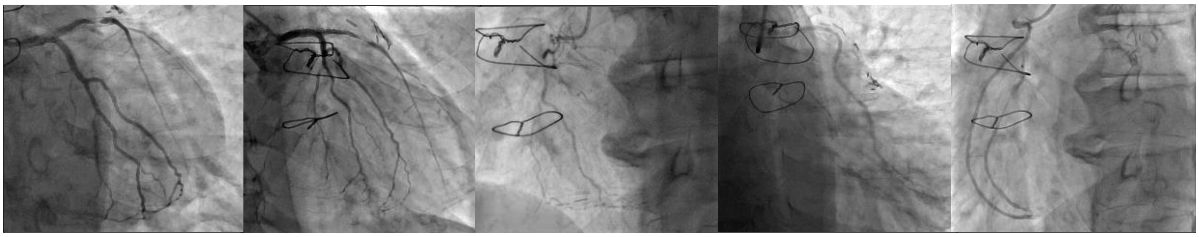
ORBITA-COSMIC patient 21



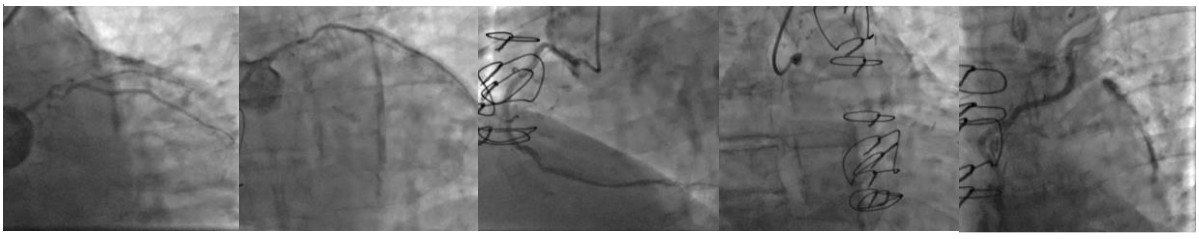
ORBITA-COSMIC patient 22



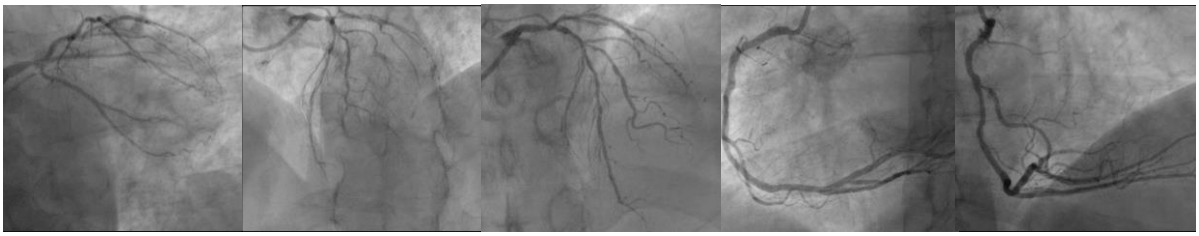
ORBITA-COSMIC patient 23



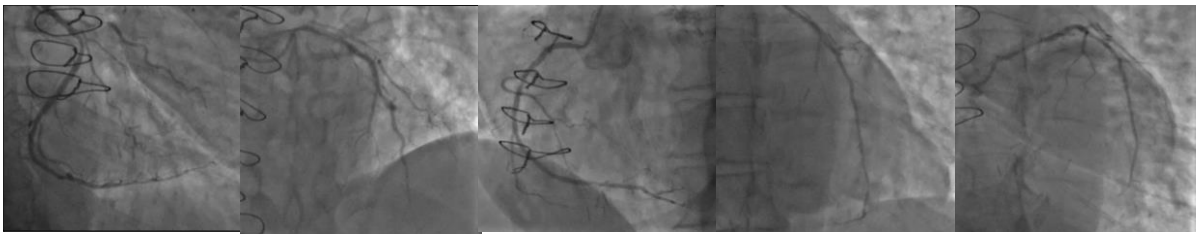
ORBITA-COSMIC patient 24



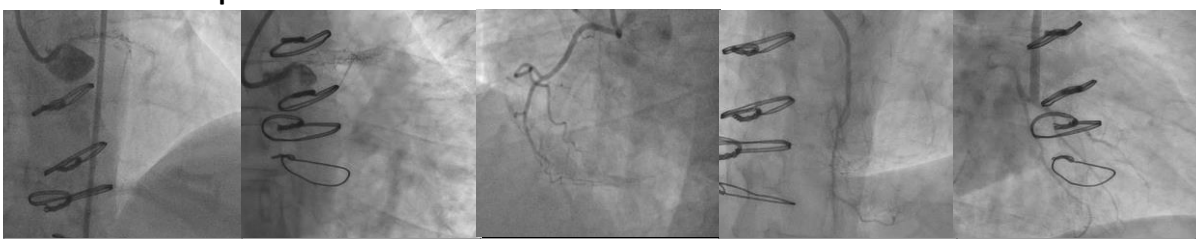
ORBITA-COSMIC patient 25



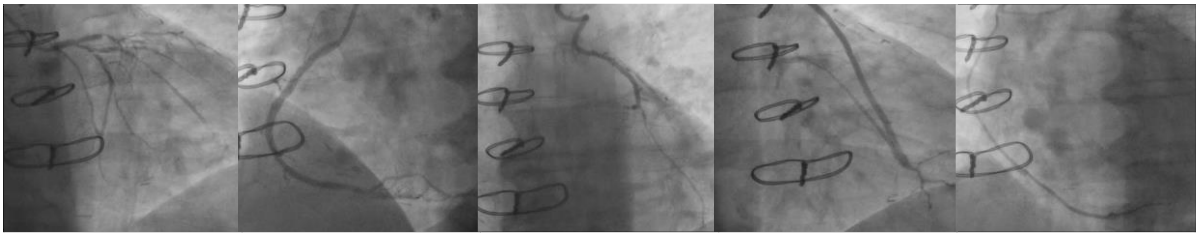
ORBITA-COSMIC patient 26



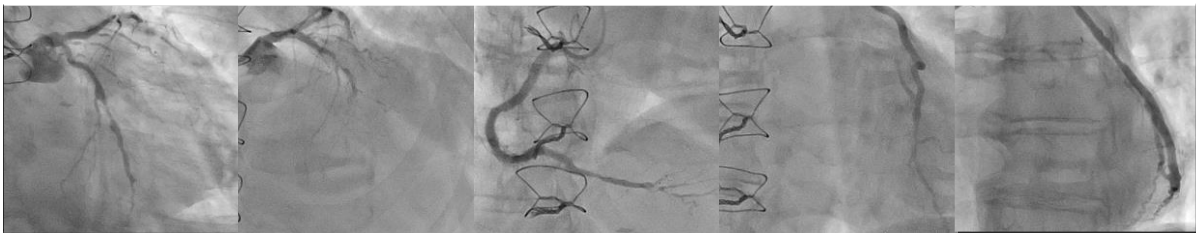
ORBITA-COSMIC patient 27



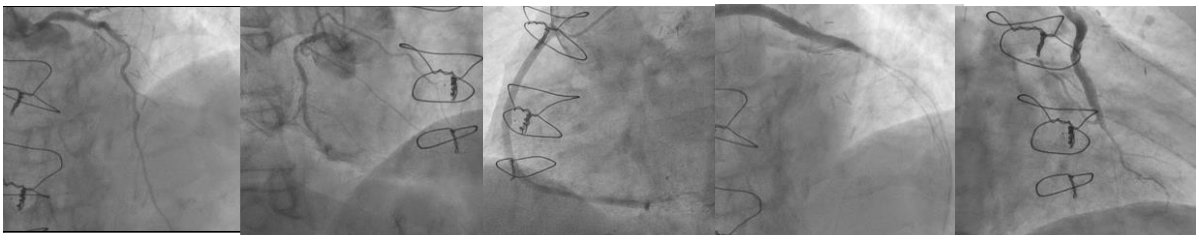
ORBITA-COSMIC patient 28



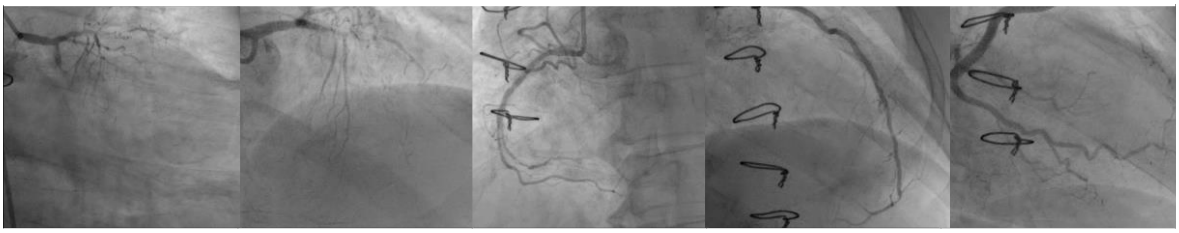
ORBITA-COSMIC patient 29



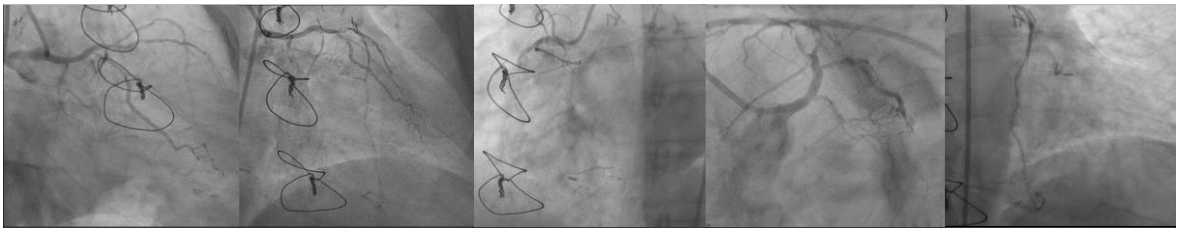
ORBITA-COSMIC patient 30



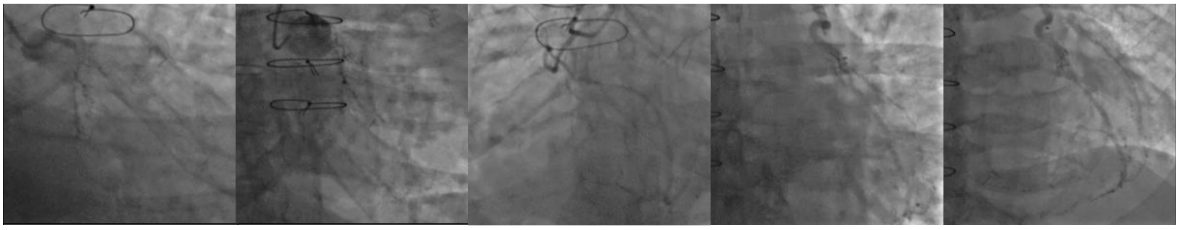
ORBITA-COSMIC patient 31



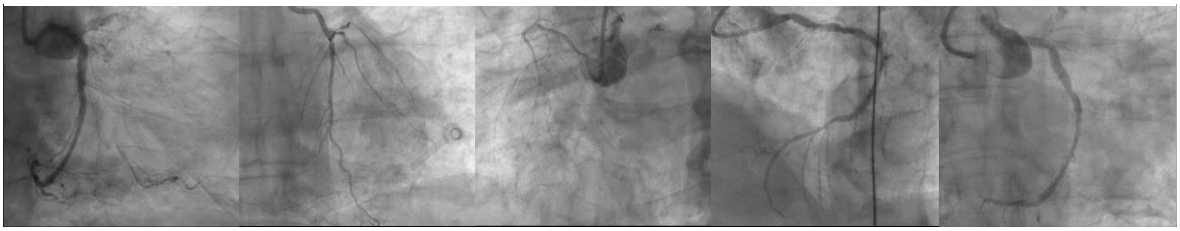
ORBITA-COSMIC patient 32



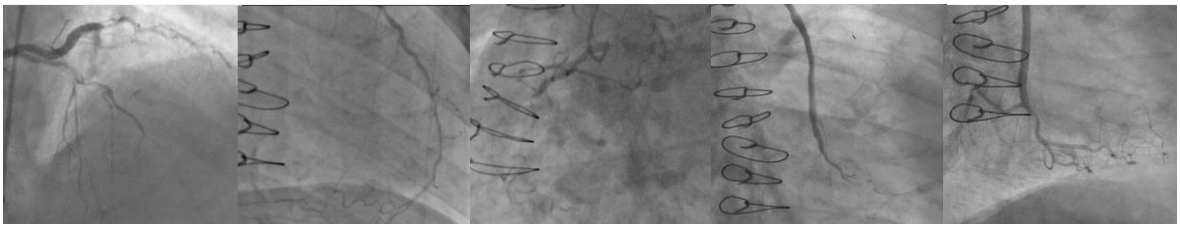
ORBITA-COSMIC patient 33



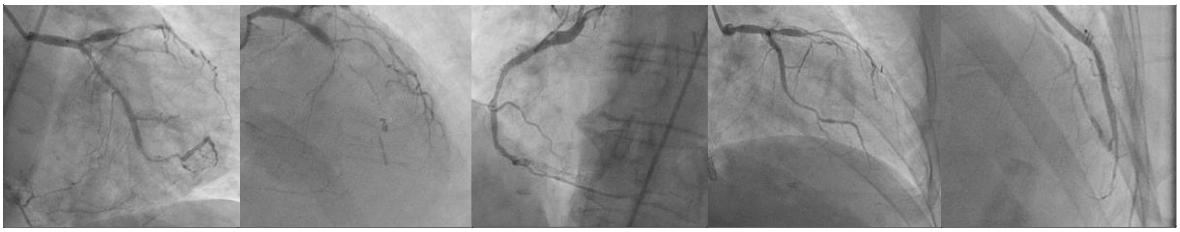
ORBITA-COSMIC patient 34



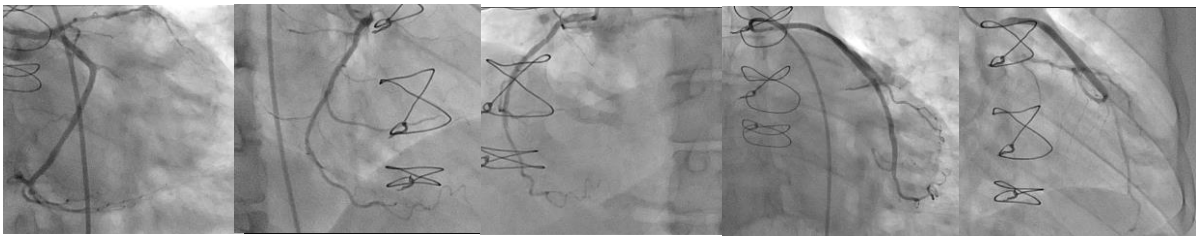
ORBITA-COSMIC patient 35



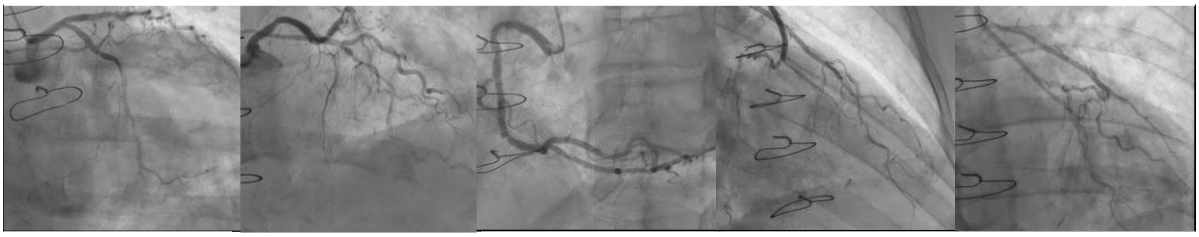
ORBITA-COSMIC patient 36



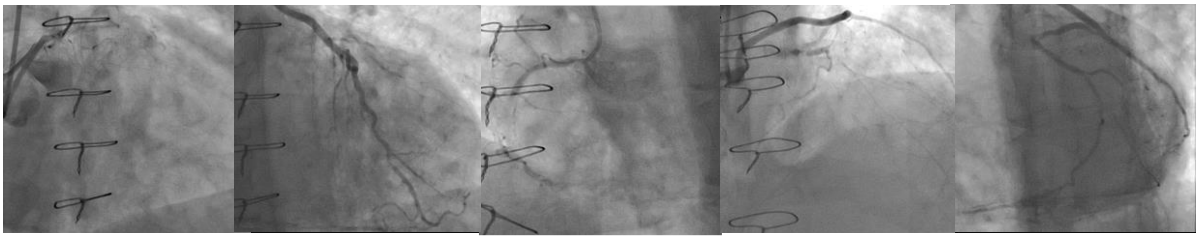
ORBITA-COSMIC patient 37



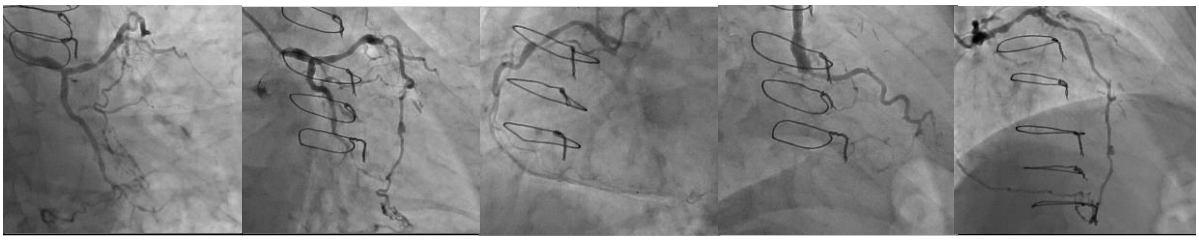
ORBITA-COSMIC patient 38



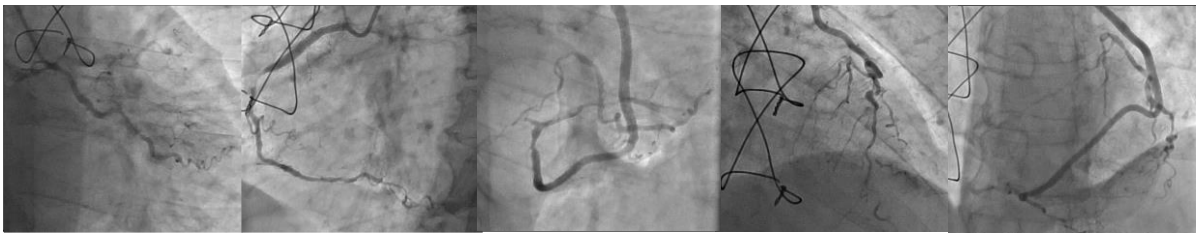
ORBITA-COSMIC patient 39



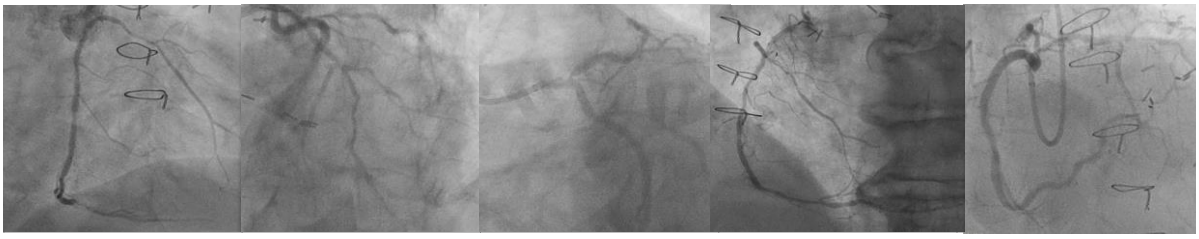
ORBITA-COSMIC patient 40



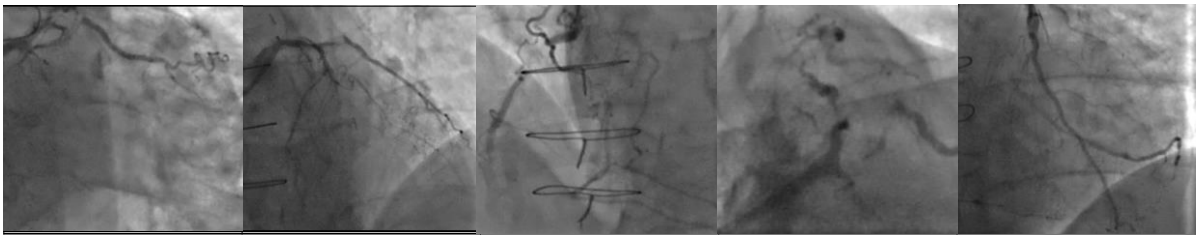
ORBITA-COSMIC patient 41



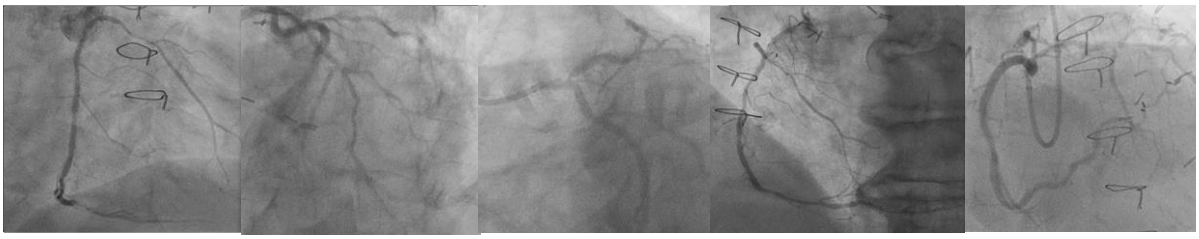
ORBITA-COSMIC patient 42



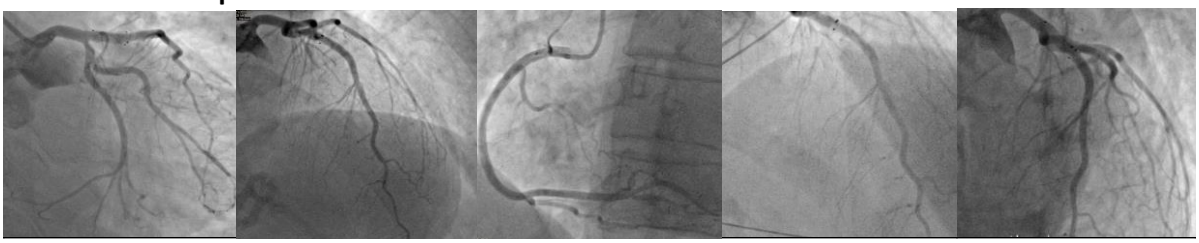
ORBITA-COSMIC patient 43



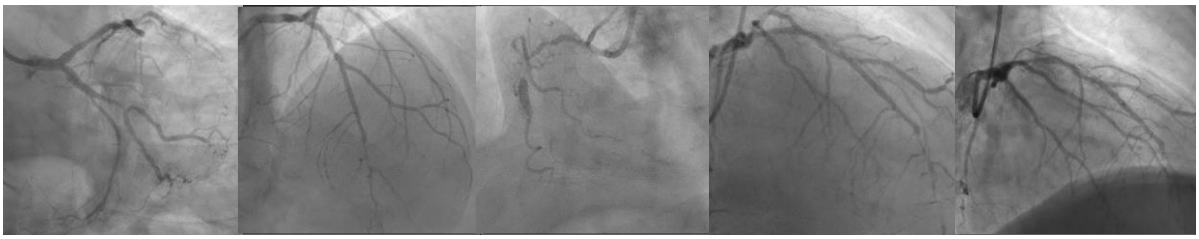
ORBITA-COSMIC patient 44



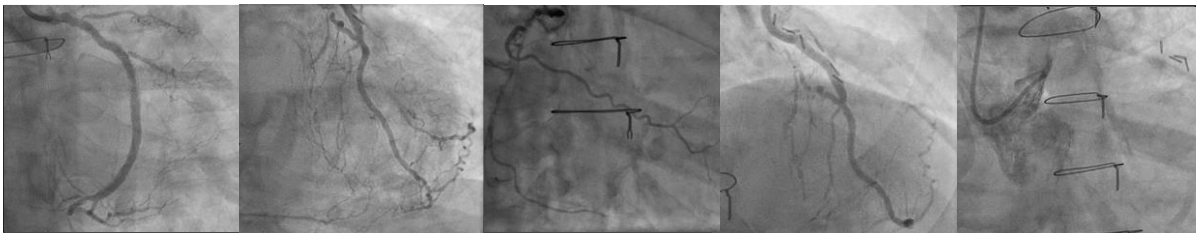
ORBITA-COSMIC patient 45



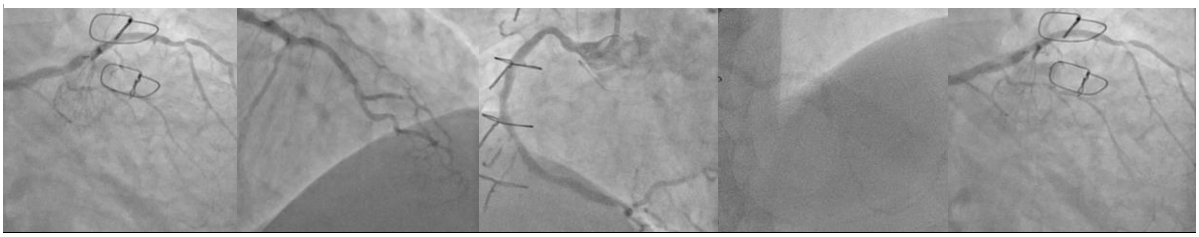
ORBITA-COSMIC patient 46



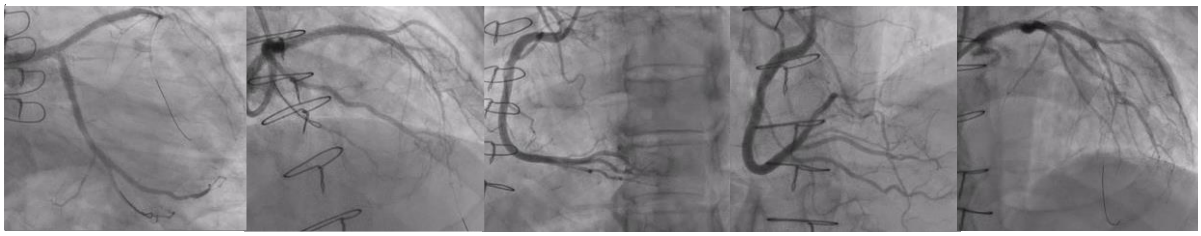
ORBITA-COSMIC patient 47



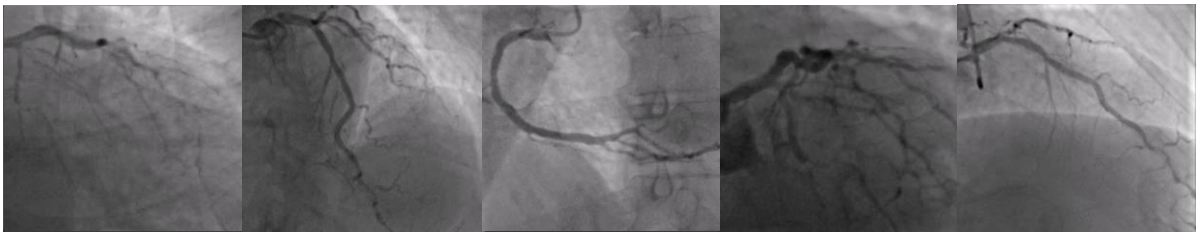
ORBITA-COSMIC patient 48



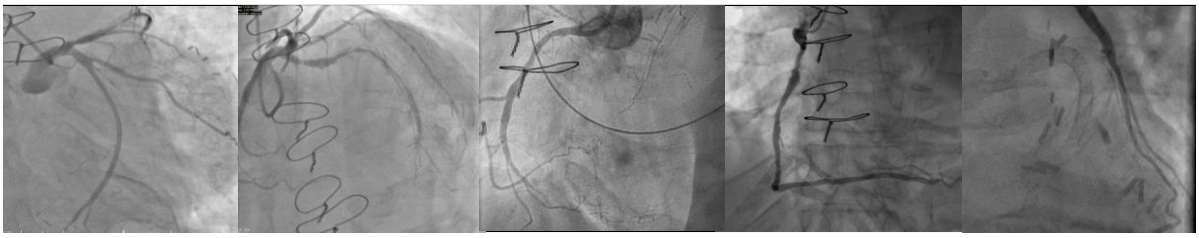
ORBITA-COSMIC patient 49



ORBITA-COSMIC patient 50



ORBITA-COSMIC patient 51



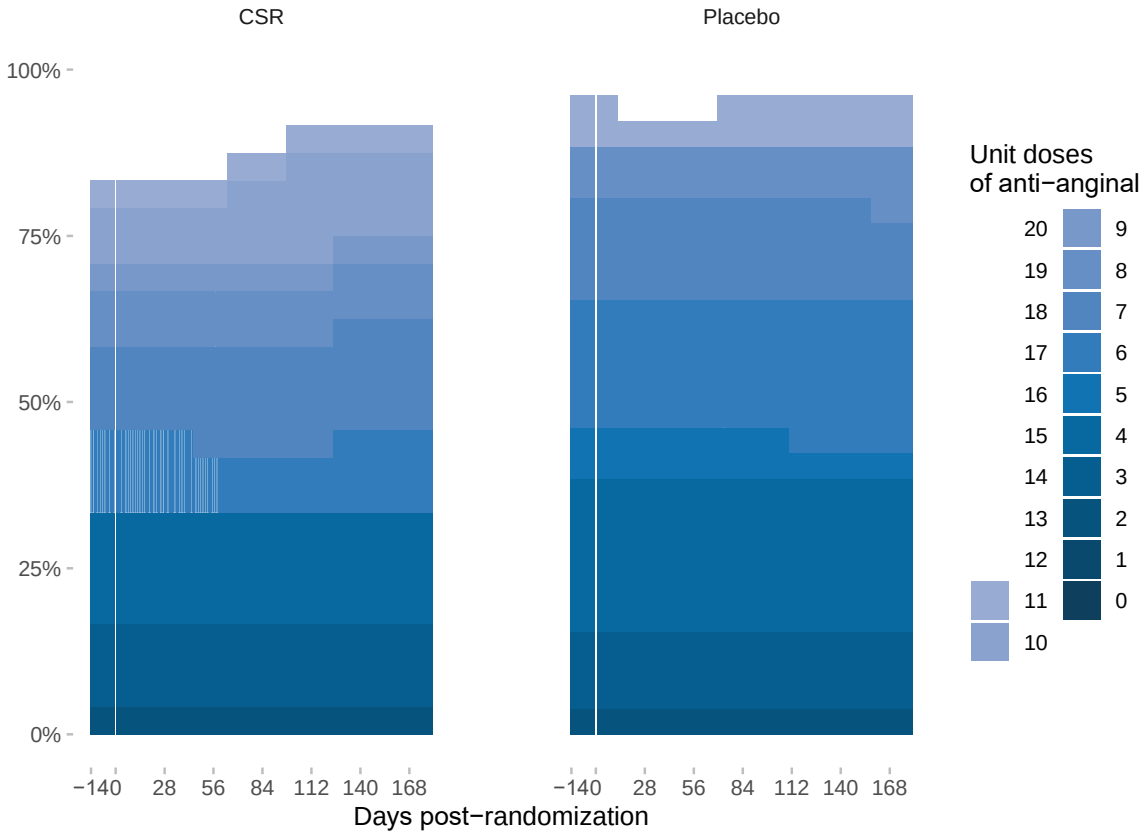
Antianginal prescribing

Within the 6 month follow up in ORBITA-COSMIC, only 8 antinaginal medication changes were made, 4 in each arm. These are detailed below.

Supplementary table 10: antianginal medication changes

ORBITA-COSMIC ID	Treatment	Day	Antianginal unit change
10023-COSMIC	Placebo	13	3
10022-COSMIC	CSR	45	1
50001-COSMIC	CSR	64	-2
10023-COSMIC	Placebo	70	-3
60001-COSMIC	CSR	98	-2
10034-COSMIC	CSR	125	-4
20002-COSMIC	Placebo	111	1
10016-COSMIC	Placebo	158	1

Supplementary figure S3: antianginal prescribing



Antianginal units are defined above in Supplementary table S4.

Serious adverse events

Supplementary table S11: serious adverse events

Patient	Arm	Event	Details
20001	CSR	Retinal Detachment	Spontaneous retinal detachment requiring urgent surgery. Recovered well. Some right eye visual loss. No change to DAPT. Adjudicated to be serious adverse event unrelated to the study protocol.
30001	CSR	CSR embolisation	CSR dislodged from delivery balloon during

			deployment. Device embolised to lungs and managed conservatively. Patient remained blinded and well throughout study. Analysis according to intention to treat.
10004	CSR	CSR embolisation	CSR embolisation on withdrawal of the balloon. Unsuccessful attempt to retrieve with snare via femoral access. Device embolised to lungs. Managed conservatively. Patient remained well. Unblinded and withdrawn from the trial because the patient had not been consented for second access point.
10005	CSR	Failure to deploy CSR	Patient randomised to CSR. Due to significant tortuosity of the coronary sinus with a steep angulation from the right atrium and an ostial valve, CSR could not be deployed despite multiple delivery catheters and operators. Blinding was maintained until final follow up.

Primary outcomes

Primary symptom outcome: daily angina episodes

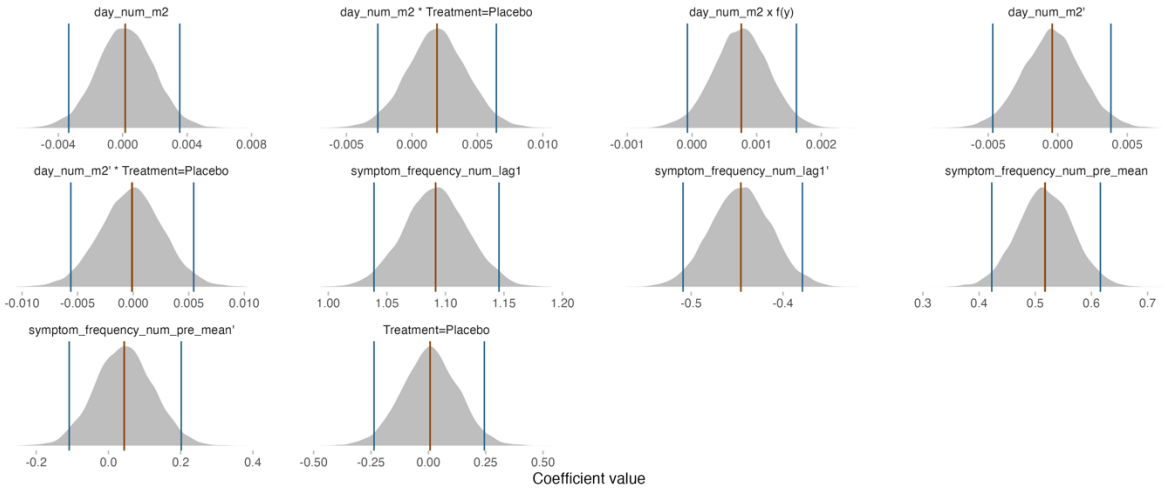
Supplementary table S12: daily transition odds ratio for daily angina episodes

Post-randomisation day	Odds ratio for benefit of CSR over placebo	Pr(Benefit>1
2	1.009 (95% CrI 0.795 - 1.284)	0.531
3	1.011 (95% CrI 0.798 - 1.279)	0.538
4	1.013 (95% CrI 0.803 - 1.277)	0.544
5	1.015 (95% CrI 0.808 - 1.274)	0.551
6	1.016 (95% CrI 0.812 - 1.271)	0.559
7	1.018 (95% CrI 0.811 - 1.260)	0.566
14	1.032 (95% CrI 0.848 - 1.248)	0.625
21	1.045 (95% CrI 0.884 - 1.239)	0.694
28	1.059 (95% CrI 0.915 - 1.230)	0.775
35	1.073 (95% CrI 0.942 - 1.226)	0.853
42	1.087 (95% CrI 0.961 - 1.224)	0.914
49	1.101 (95% CrI 0.981 - 1.239)	0.948
56	1.116 (95% CrI 0.992 - 1.256)	0.965
63	1.130 (95% CrI 1.003 - 1.282)	0.975
70	1.145 (95% CrI 1.003 - 1.298)	0.981
77	1.160 (95% CrI 1.016 - 1.331)	0.985
84	1.175 (95% CrI 1.023 - 1.350)	0.989
91	1.190 (95% CrI 1.033 - 1.365)	0.993
98	1.205 (95% CrI 1.052 - 1.382)	0.996
105	1.221 (95% CrI 1.072 - 1.397)	0.999
112	1.237 (95% CrI 1.087 - 1.400)	1.000
119	1.252 (95% CrI 1.107 - 1.407)	1.000
126	1.268 (95% CrI 1.128 - 1.425)	1.000
133	1.284 (95% CrI 1.145 - 1.451)	1.000
140	1.301 (95% CrI 1.147 - 1.475)	1.000
147	1.317 (95% CrI 1.146 - 1.517)	1.000
154	1.334 (95% CrI 1.140 - 1.570)	1.000
161	1.351 (95% CrI 1.129 - 1.627)	0.999
168	1.368 (95% CrI 1.109 - 1.682)	0.998
175	1.386 (95% CrI 1.091 - 1.746)	0.997
182	1.403 (95% CrI 1.079 - 1.827)	0.994

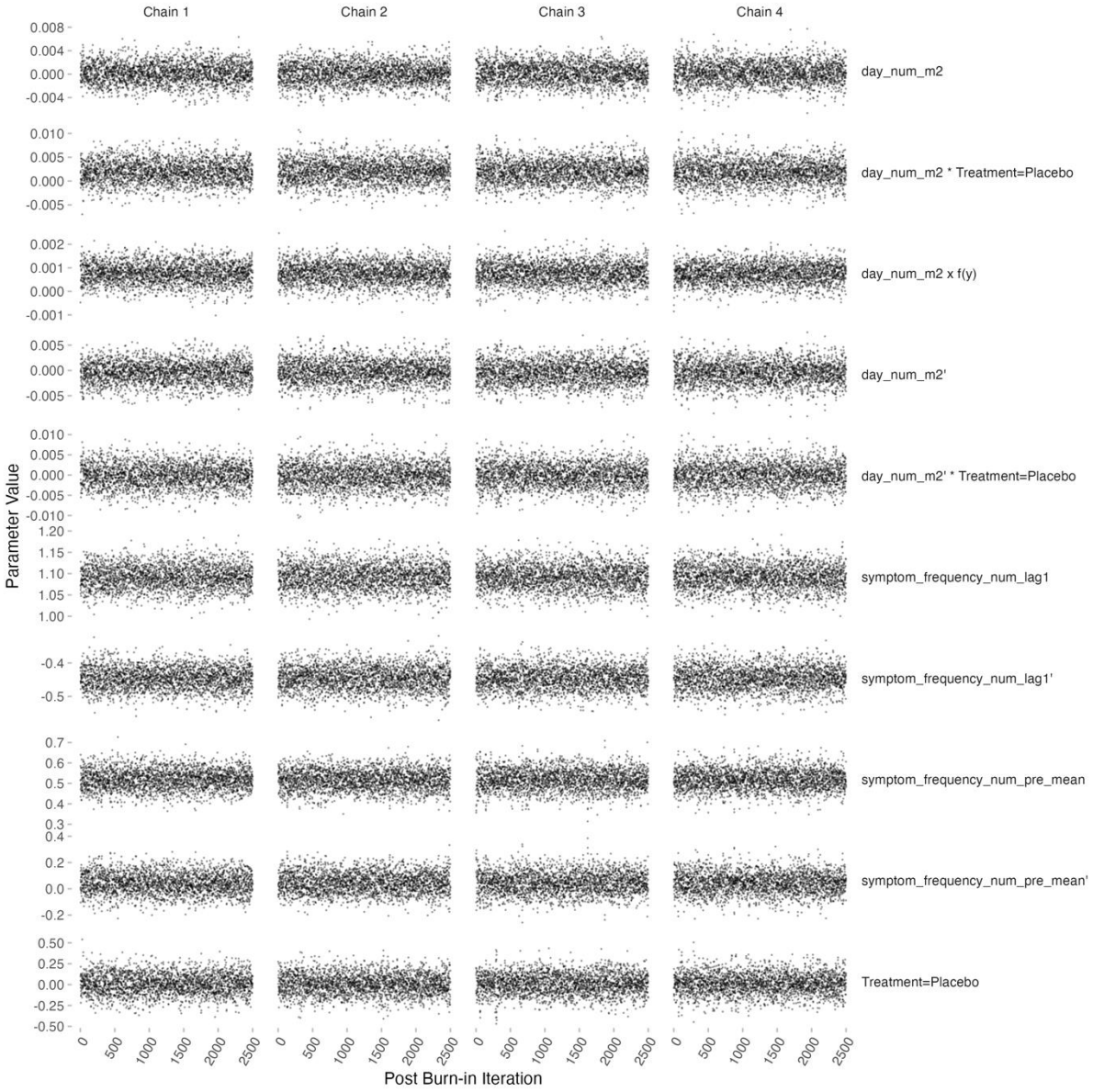
Regression model and coefficients for daily angina episodes

```
Bayesian Constrained Partial Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.215 for Intercepts

blrm(formula = symptom_frequency_num ~ rcs(symptom_frequency_num_lag1,
    c(1, 3, 5)) + rcs(day_num_m2, 3) * Treatment + rcs(symptom_frequency_num_pre_mean,
    3), ppo = ~day_num_m2, cppo = function(y) y, keepsep = "^Treatment=CSR$",
    data = main_analysis_d, priorsdppo = c(rep(100, 4), sap_treatment_sd_prior,
        rep(100, 5)), iter = 5000, chains = 4, refresh = 100,
    progress = "./output/symptom_freq_res3.txt", loo = FALSE,
    ppairs = NULL, method = "sampling", file = "./output/symptom_freq_res3.blrm.rds")


Frequencies of Responses

   0    1    2    3    4    5    6    7    8    9   10
4066 1362 1305  763  397  211   86   86  120   46  276

                 Mixed Calibration/                Discrimination                 Rank Discrim.
               Discrimination Indexes                      Indexes                       Indexes
  Obs 8718     B   0.15 [0.149, 0.15]    g  2.735 [2.666, 2.803]    C   0.844 [0.843, 0.844]
Draws10000                               gp  0.36 [0.354, 0.365]    Dxy 0.687 [0.686, 0.688]
  Chains 4                               EV 0.405 [0.393, 0.417]
Time183.3s                               v  7.214 [6.832, 7.576]
  p      9                               vp 0.101 [0.098, 0.104]

                                  Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
symptom_frequency_num_lag1         1.0917    1.0916     0.0272  1.0390  1.1458 1.0000     1.01
symptom_frequency_num_lag1'       -0.4458   -0.4459     0.0329 -0.5088 -0.3788 0.0000     1.02
day_num_m2                         0.0002    0.0002     0.0018 -0.0034  0.0035 0.5358     0.97
day_num_m2'                       -0.0004   -0.0004     0.0021 -0.0047  0.0038 0.4245     1.00
Treatment=Placebo                  0.0075    0.0079     0.1226 -0.2367  0.2440 0.5270     1.00
symptom_frequency_num_pre_mean     0.5177    0.5171     0.0492  0.4226  0.6159 1.0000     1.01
symptom_frequency_num_pre_mean'    0.0439    0.0434     0.0797 -0.1087  0.2016 0.7055     1.02
day_num_m2 * Treatment=Placebo     0.0019    0.0019     0.0023 -0.0026  0.0064 0.8012     1.02
day_num_m2' * Treatment=Placebo   -0.0001   -0.0001     0.0028 -0.0056  0.0054 0.4846     1.01
day_num_m2 x f(y)                  0.0008    0.0008     0.0004 -0.0001  0.0016 0.9616     0.97
```

Supplementary figure S4: coefficient density plots: daily angina episodes



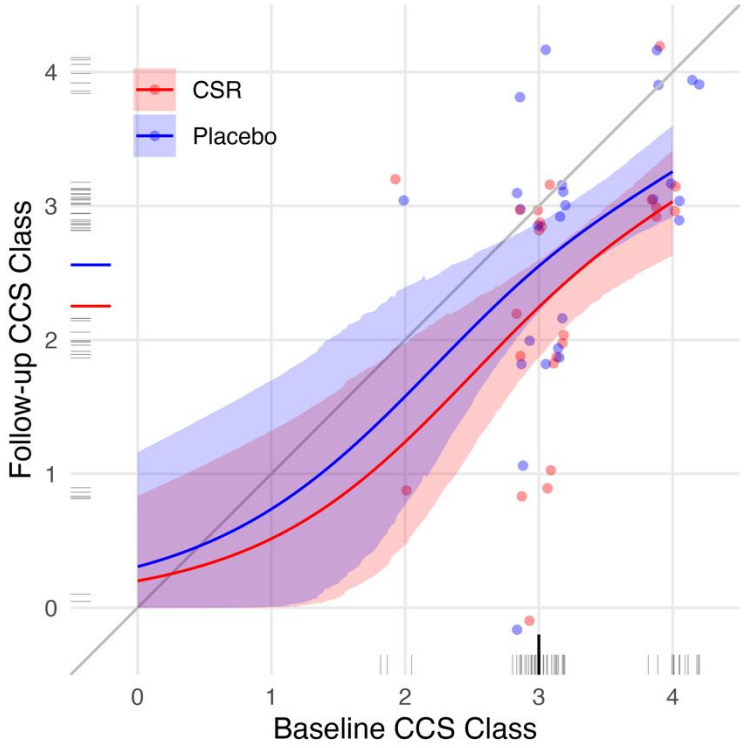
Supplementary figure S5: chain plot of MCMC draws for daily angina episodes



Secondary symptom outcomes

Secondary outcome: Canadian Cardiovascular Society (CCS) class

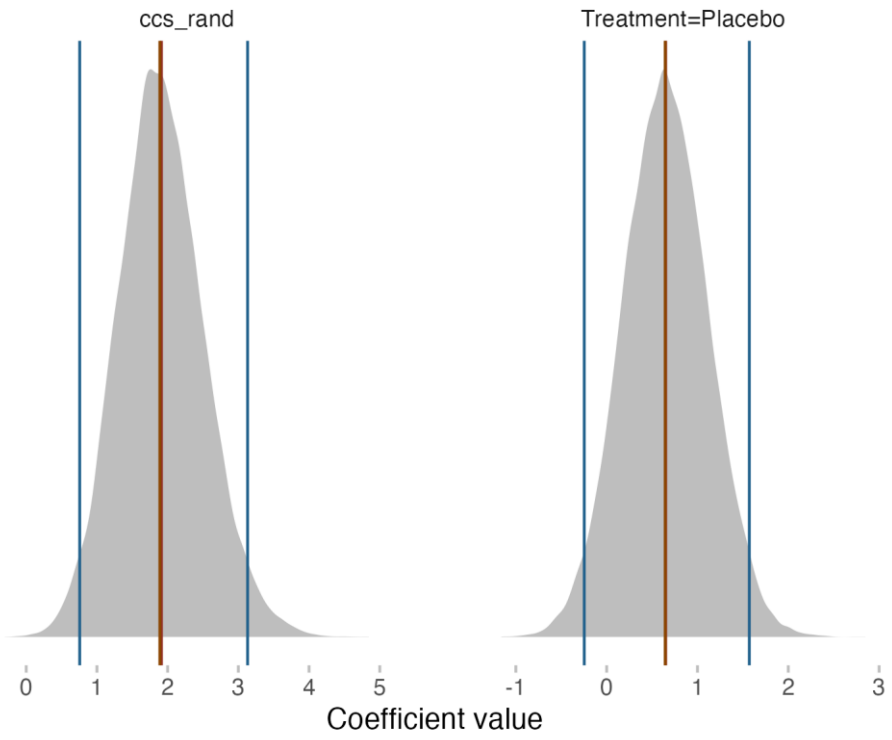
Supplementary figure S6: result: CCS class



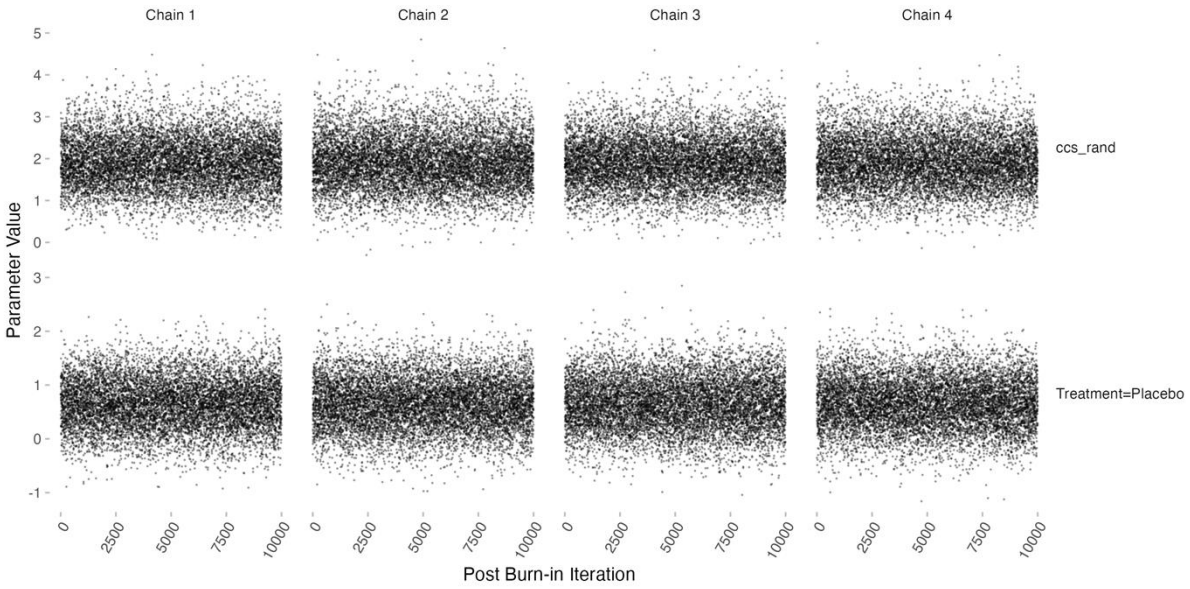
Regression model and coefficients for CCS class

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.392 for Intercepts

blrm(formula = ccs_fu ~ ccs_rand + Treatment, data = ccs_res1_d,
    pcontrast = con, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "res1.txt"), loo = FALSE,
    ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

 0  1  2  3  4
 2  5 12 24  7

                Mixed Calibration/            Discrimination              Rank Discrim.
              Discrimination Indexes                  Indexes                    Indexes
   Obs  50    B 0.205 [0.196, 0.222]    g  1.229 [0.621, 1.816]    C   0.797 [0.683, 0.809]
Draws40000                             gp  0.221 [0.138, 0.29]     Dxy 0.594 [0.365, 0.617]
   Chains4                             EV 0.188 [0.068, 0.291]
  Time2.6s                             v  1.436 [0.326, 2.932]
   p     2                             vp  0.044 [0.016, 0.07]

                  Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
y>=1              -2.7779   -2.7609     1.9274  -6.6222  0.9584 0.0723     0.96
y>=2              -4.3537   -4.3015     1.8657  -8.0617 -0.7591 0.0068     0.92
y>=3              -5.8851   -5.8287     1.9064  -9.6094 -2.1500 0.0004     0.92
y>=4              -8.8163   -8.7342     2.1886 -13.0867 -4.5279 0.0000     0.88
ccs_rand           1.9134    1.8926     0.5970   0.7534  3.0874 0.9998     1.10
Treatment=Placebo  0.6481    0.6514     0.4559  -0.2705  1.5214 0.9236     1.00

Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S7: coefficient density plots: CCS class

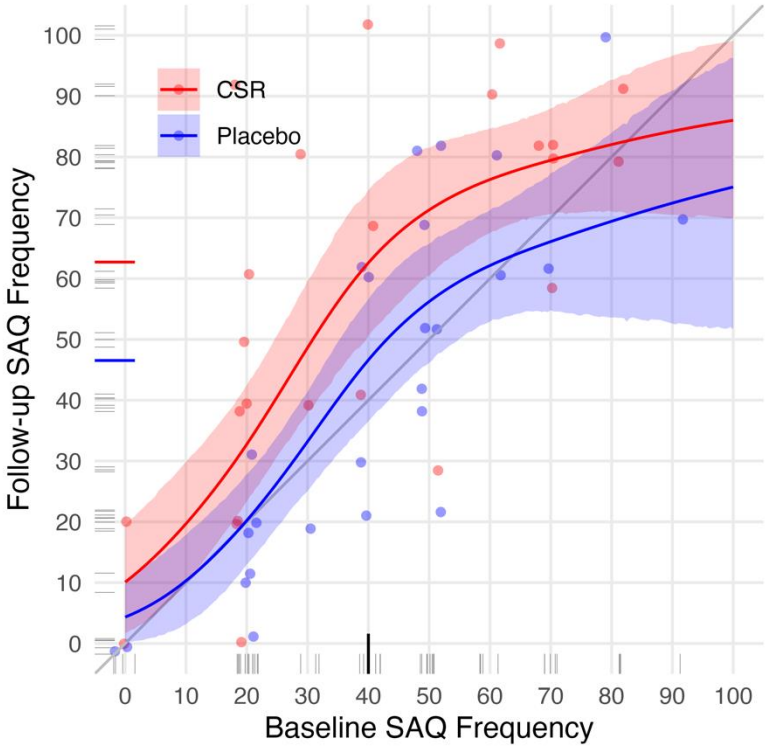


Supplementary figure S8: chain plot of MCMC draws for CCS class



Secondary outcome: SAQ angina frequency

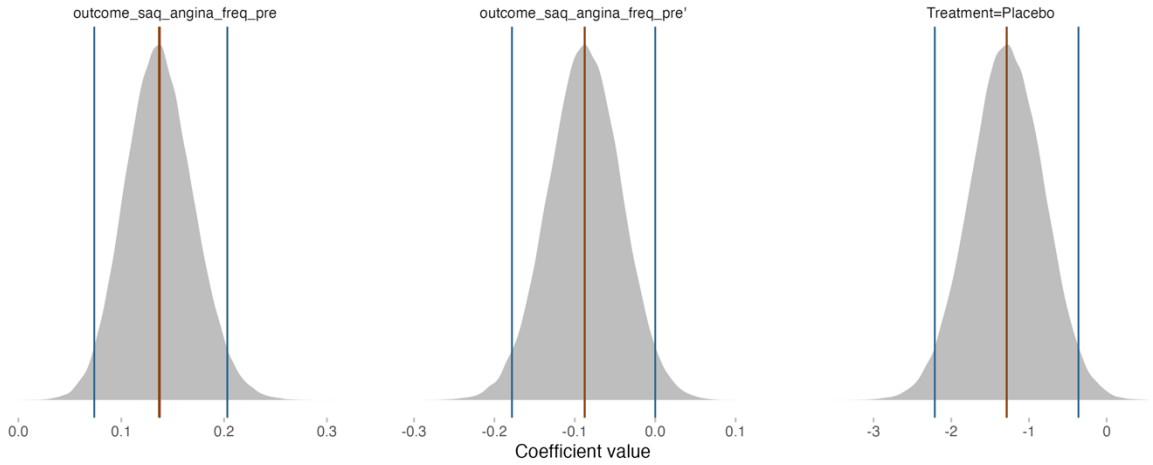
Supplementary figure S9: result: SAQ angina frequency



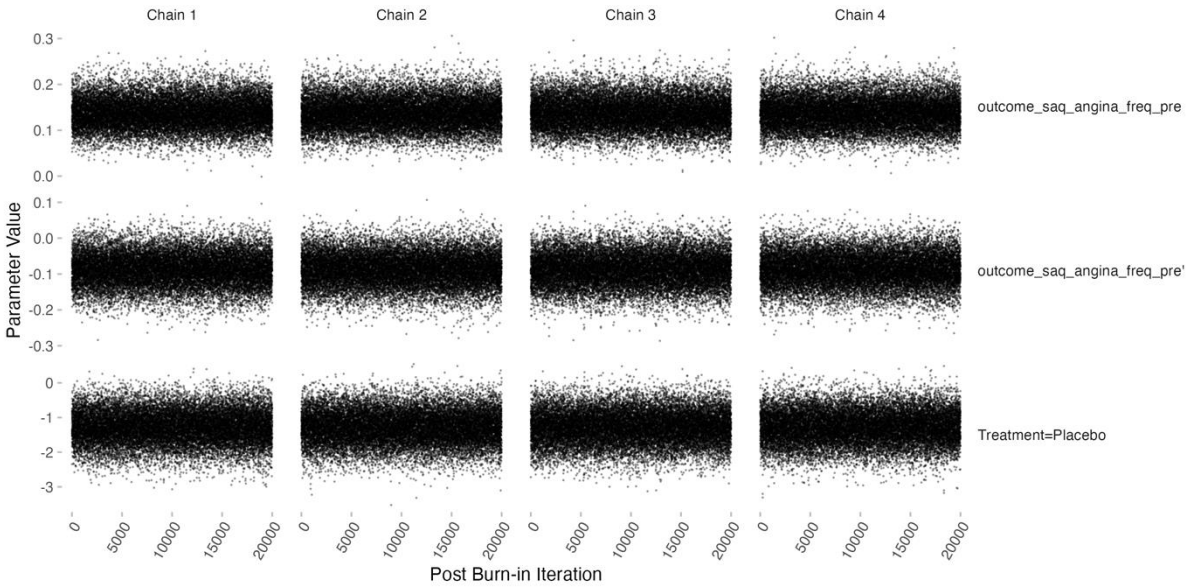
Regression model and coefficients for SAQ angina frequency

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.215 for Intercepts

blrm(formula = outcome_saq_angina_freq_post ~ rcs(outcome_saq_angina_freq_pre,
    3) + Treatment, data = saq_freq_res1_d, pcontrast = con,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, method = "sampling",
    file = file.path(output_dir, "res1.blrm.rds"))


Frequencies of Responses

  0  10  20  30  40  50  60  70  80  90 100
  5   2   8   3   6   3   6   3   8   3   3

                Mixed Calibration/              Discrimination              Rank Discrim.
              Discrimination Indexes                    Indexes                    Indexes
   Obs  50    B  0.151 [0.14, 0.165]    g  2.449 [1.788, 3.303]    C   0.83 [0.813, 0.839]
Draws40000                             gp 0.372 [0.314, 0.423]    Dxy 0.66 [0.626, 0.679]
   Chains4                             EV  0.43 [0.286, 0.551]
  Time3.1s                             v   4.89 [2.212, 8.052]
   p     3                             vp  0.107 [0.073, 0.14]

                           Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
outcome_saq_angina_freq_pre   0.1378    0.1367     0.0332  0.0726  0.2027 1.0000     1.09
outcome_saq_angina_freq_pre' -0.0882   -0.0874     0.0453 -0.1765  0.0014 0.0248     0.98
Treatment=Placebo            -1.2884   -1.2839     0.4783 -2.2322 -0.3579 0.0034     0.97


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S10: coefficient density plots: SAQ angina frequency

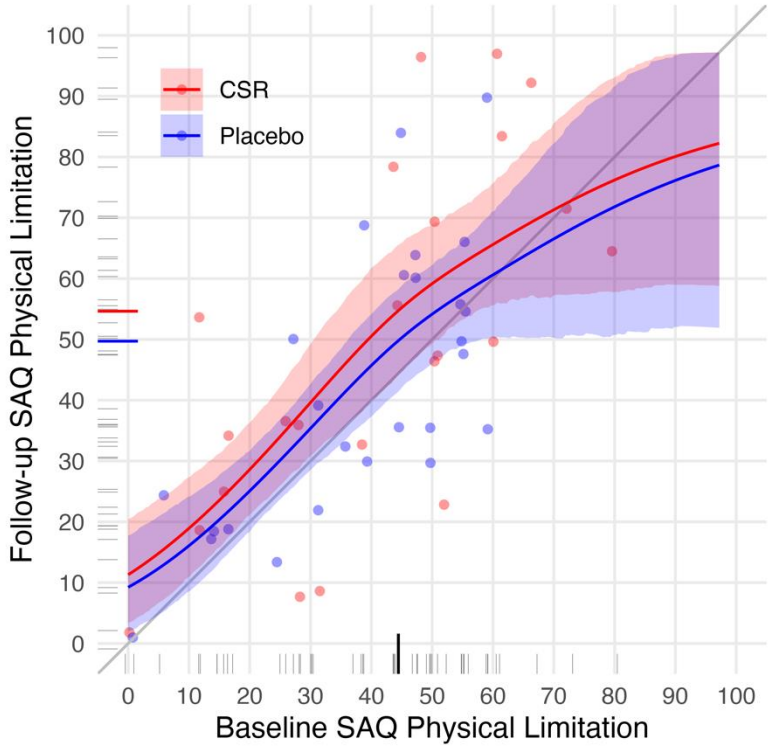


Supplementary figure S11: chain plot of MCMC draws for SAQ angina frequency



Secondary outcome: SAQ physical limitation

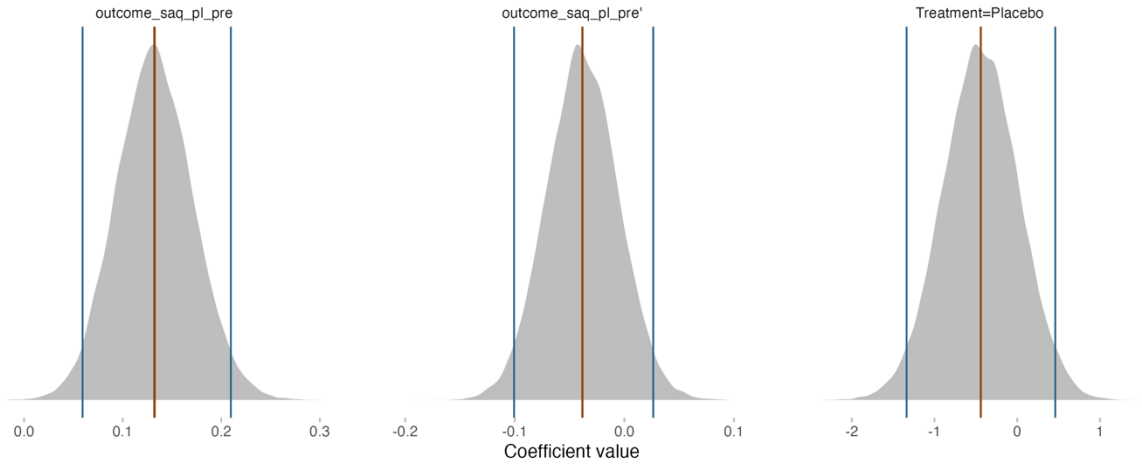
Supplementary figure S12: result: SAQ physical limitation



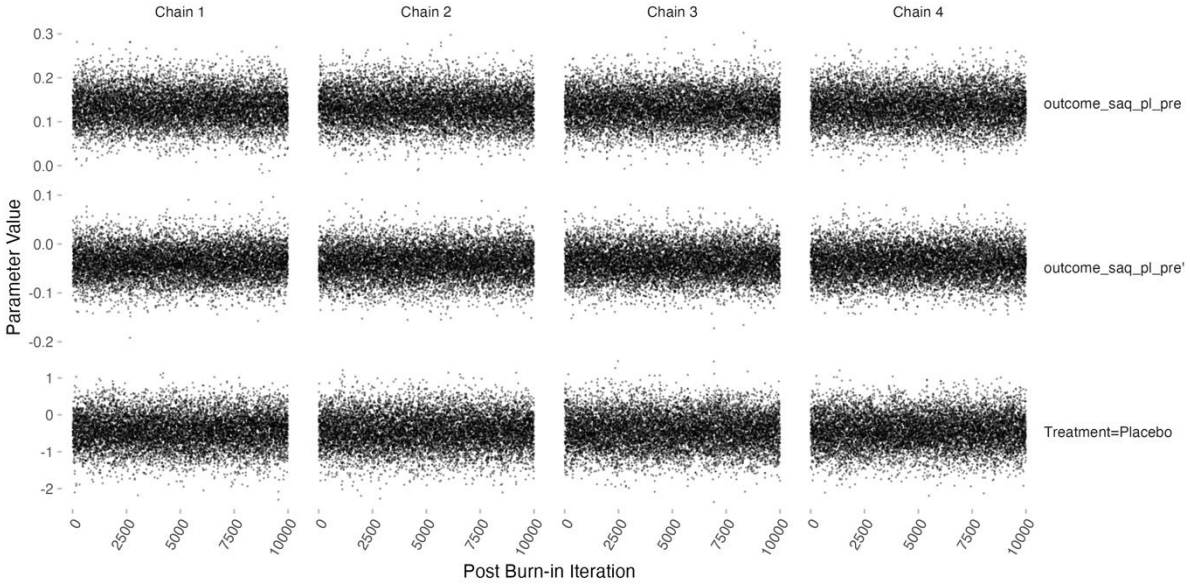
Regression model and coefficients for SAQ physical limitation

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.088 for Intercepts

blrm(formula = outcome_saq_pl_post ~ rcs(outcome_saq_pl_pre,
    3) + Treatment, data = saq_pl_res1_d, pcontrast = con, iter = 20000,
    chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, method = "sampling",
    file = file.path(output_dir, "res1.blrm.rds"))


Frequencies of Responses

               0 2.77777777777778 8.33333333333333 13.8888888888889 16.6666666666667 19.4444444444444 19.4444444444444 22.2222222222222
               1                1                2                1                1                2                1                1
22.2222222222222               25 30.5555555555556 33.3333333333333 36.1111111111111 36.1111111111111 38.8888888888889 47.2222222222222
               1                2                2                3                4                1                1                3
              50 52.7777777777778 55.5555555555556 55.5555555555556 61.1111111111111 63.8888888888889 66.6666666666667 69.4444444444444
               3                1                1                2                2                2                1                2
72.2222222222222 77.7777777777778 83.3333333333333 88.8888888888889 91.6666666666667 97.2222222222222
               1                1                2                1                1                2

                  Mixed Calibration/              Discrimination              Rank Discrim.
                Discrimination Indexes                    Indexes                   Indexes
   Obs  49    B  0.153 [0.14, 0.173]    g  2.144 [1.395, 2.791]    C   0.757 [0.737, 0.768]
Draws40000                              gp  0.343 [0.28, 0.397]    Dxy 0.514 [0.476, 0.539]
   Chains4                              EV 0.374 [0.257, 0.506]
  Time4.8s                              v  3.897 [1.576, 6.219]
   p     3                              vp  0.093 [0.059, 0.12]

                   Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
outcome_saq_pl_pre    0.1323    0.1315     0.0391  0.0544 0.2074 0.9999     1.07
outcome_saq_pl_pre' -0.0378   -0.0379     0.0330 -0.1019 0.0272 0.1251     1.01
Treatment=Placebo   -0.4400   -0.4397     0.4547 -1.3251 0.4440 0.1672     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S13: coefficient density plots: SAQ physical limitation

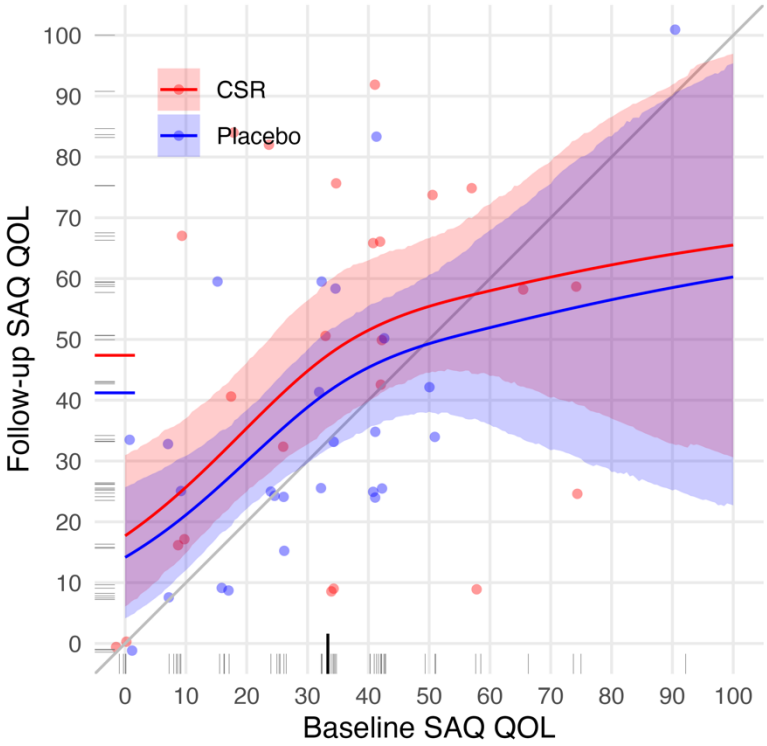


Supplementary Figure S14: Chain plot of MCMC draws for SAQ physical limitation



Secondary outcome: SAQ quality of life

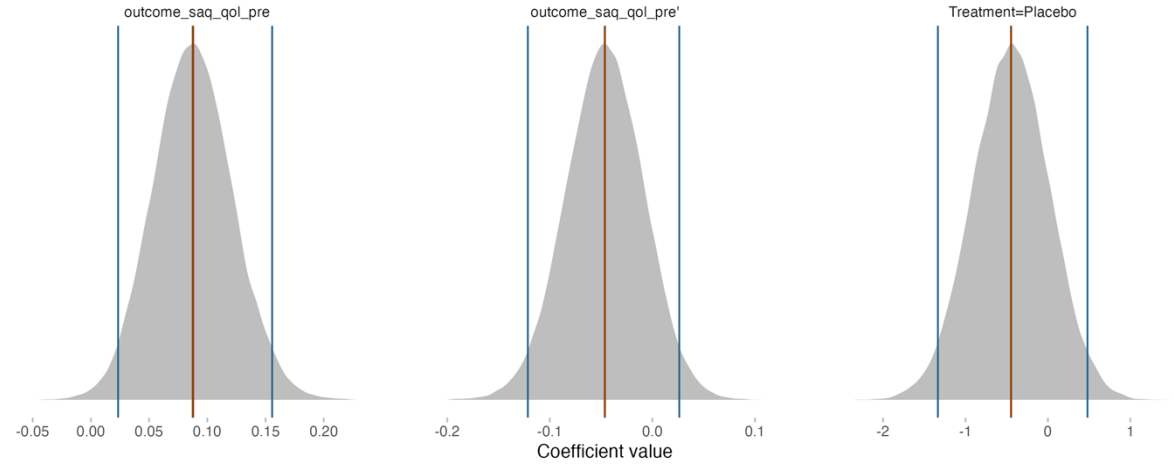
Supplementary figure S15: result: SAQ quality of life



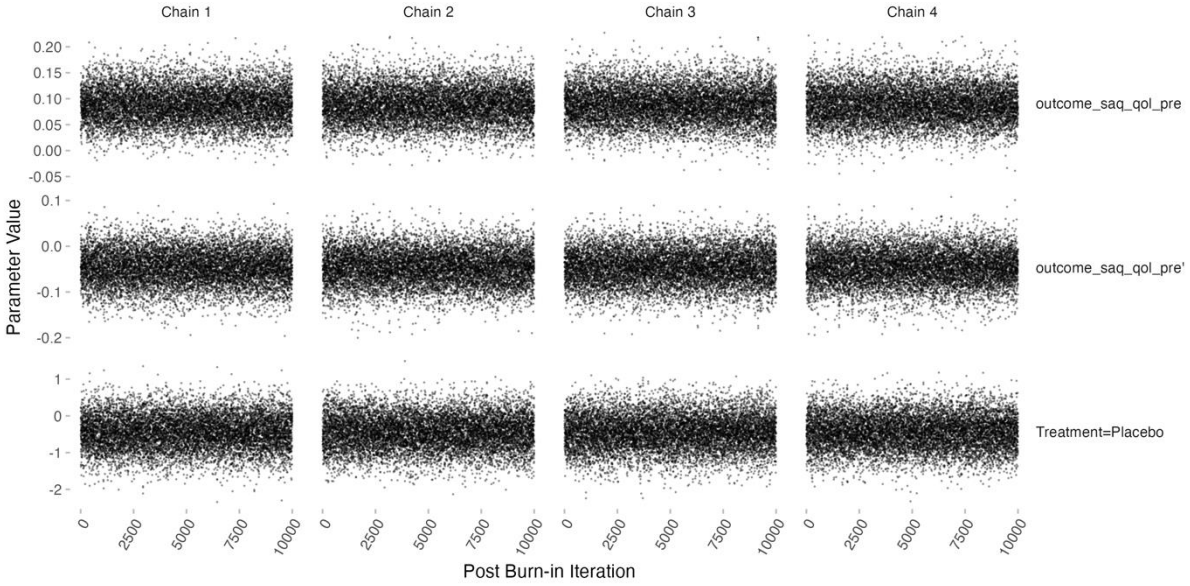
Regression model and coefficients for SAQ quality of life

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.187 for Intercepts

blrm(formula = outcome_saq_qol_post ~ rcs(outcome_saq_qol_pre,
    3) + Treatment, data = saq_qol_res1_d, pcontrast = con, iter = 20000,
    chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, method = "sampling",
    file = file.path(output_dir, "res1.blrm.rds"))


Frequencies of Responses

               0 8.33333333333333 16.6666666666667              25 33.3333333333333 41.6666666666667              50 58.3333333333333
               3                  6                 3               9                  6                 4               3                 5
66.6666666666667              75 83.3333333333333 91.6666666666667             100
               3                  3                 3               1                  1


                    Mixed Calibration/           Discrimination              Rank Discrim.
                  Discrimination Indexes                 Indexes                   Indexes
   Obs  50    B 0.222 [0.209, 0.239]    g  1.323 [0.63, 1.908]    C   0.684 [0.643, 0.709]
Draws40000                              gp 0.26 [0.162, 0.348]    Dxy 0.368 [0.287, 0.417]
   Chains4                              EV 0.23 [0.082, 0.373]
  Time4.5s                              v    1.5 [0.32, 2.819]
   p     3                              vp 0.056 [0.019, 0.09]

                    Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
outcome_saq_qol_pre   0.0879    0.0875     0.0340  0.0191 0.1527 0.9964     1.03
outcome_saq_qol_pre' -0.0466   -0.0463     0.0380 -0.1185 0.0301 0.1106     0.98
Treatment=Placebo    -0.4489   -0.4501     0.4649 -1.3562 0.4675 0.1671     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S16: coefficient density plots: SAQ quality of life

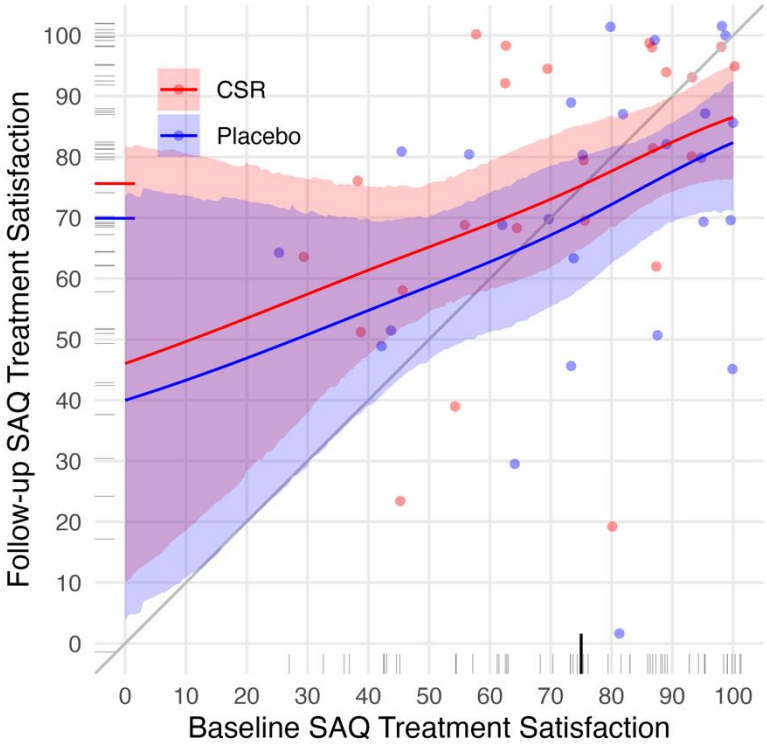


Supplementary figure S17: chain plot of MCMC draws for SAQ quality of life



Secondary outcome: SAQ treatment satisfaction

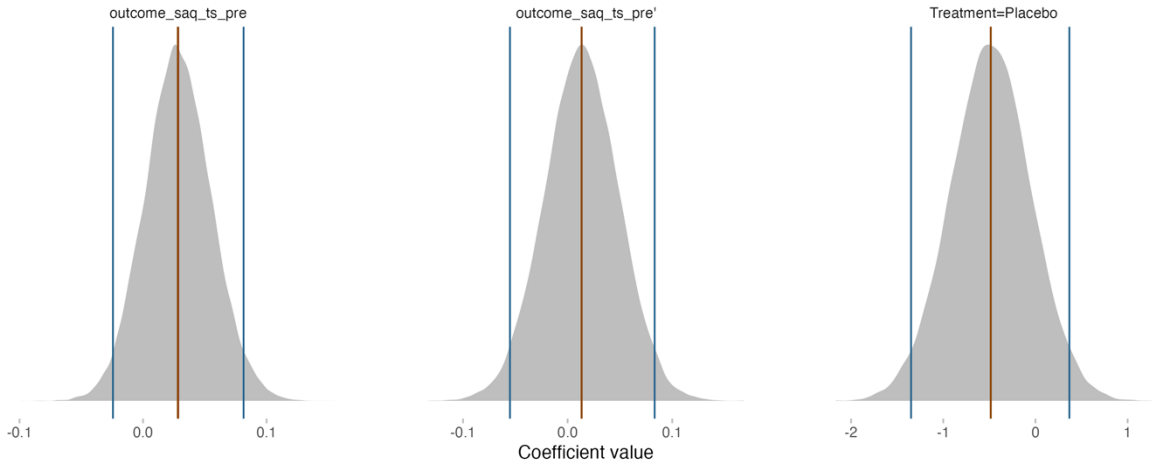
Supplementary figure S18: result: SAQ treatment satisfaction



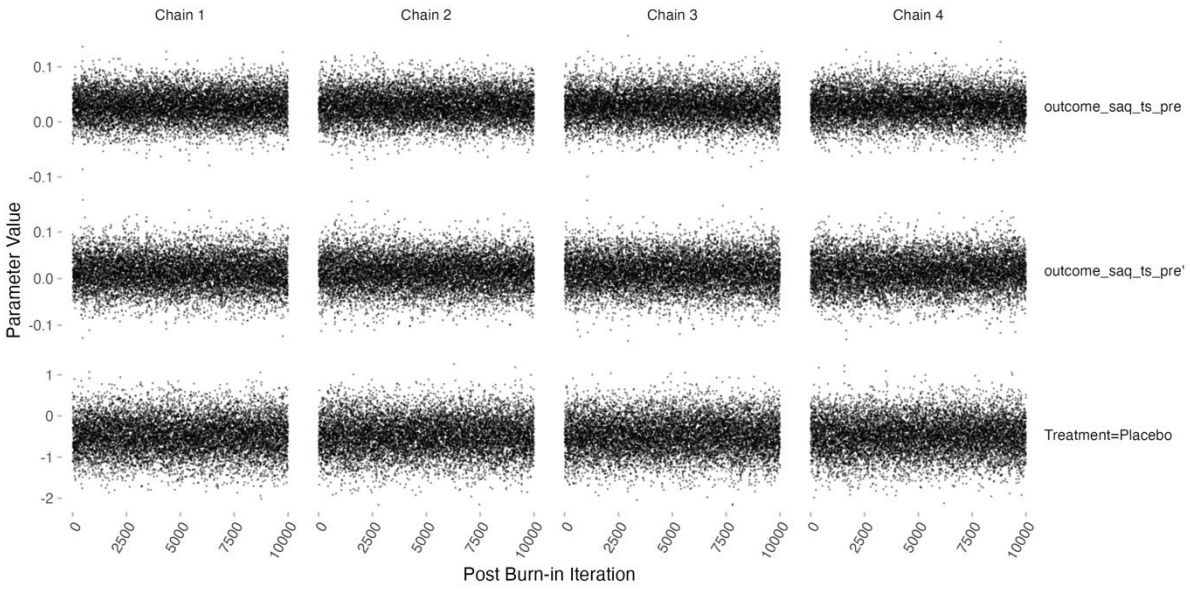
Regression model and coefficients for SAQ treatment satisfaction

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.165 for Intercepts

blrm(formula = outcome_saq_ts_post ~ rcs(outcome_saq_ts_pre,
    3) + Treatment, data = saq_ts_res1_d, pcontrast = con, iter = 20000,
    chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, method = "sampling",
    file = file.path(output_dir, "res1.blrm.rds"))


Frequencies of Responses

    0 18.75    25 31.25  37.5 43.75    50 56.25  62.5 68.75    75 81.25  87.5 93.75   100
    1     1     1     1     1     2     4     1     4     7     1     8     4     5     9

                 Mixed Calibration/              Discrimination                Rank Discrim.
               Discrimination Indexes                    Indexes                    Indexes
   Obs  50    B 0.214 [0.198, 0.237]    g  0.983 [0.472, 1.524]    C   0.657 [0.609, 0.682]
Draws40000                             gp 0.212 [0.111, 0.299]    Dxy 0.314 [0.218, 0.365]
   Chains4                             EV 0.148 [0.034, 0.277]
  Time3.8s                             v  0.818 [0.086, 1.648]
   p     3                             vp 0.037 [0.009, 0.069]

                    Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
outcome_saq_ts_pre    0.0285    0.0283     0.0270 -0.0253 0.0806 0.8558     1.04
outcome_saq_ts_pre'   0.0132    0.0132     0.0355 -0.0566 0.0833 0.6444     0.99
Treatment=Placebo    -0.4834   -0.4800     0.4384 -1.3339 0.3833 0.1338     0.99

Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
.
```

Supplementary figure S19: coefficient density plots: SAQ treatment satisfaction

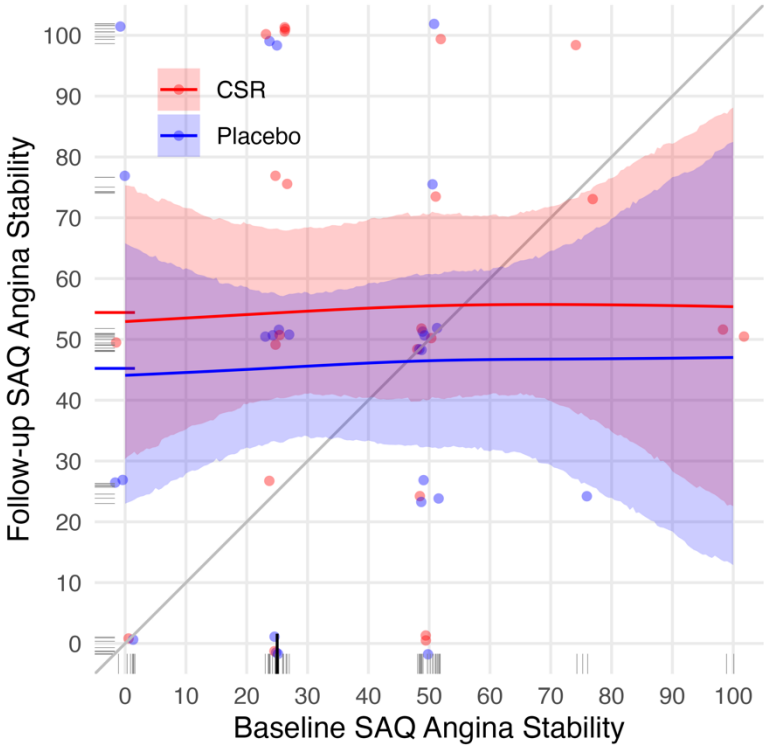


Supplementary figure S20: chain plot of MCMC draws for SAQ treatment satisfaction



Secondary outcome: SAQ angina stability

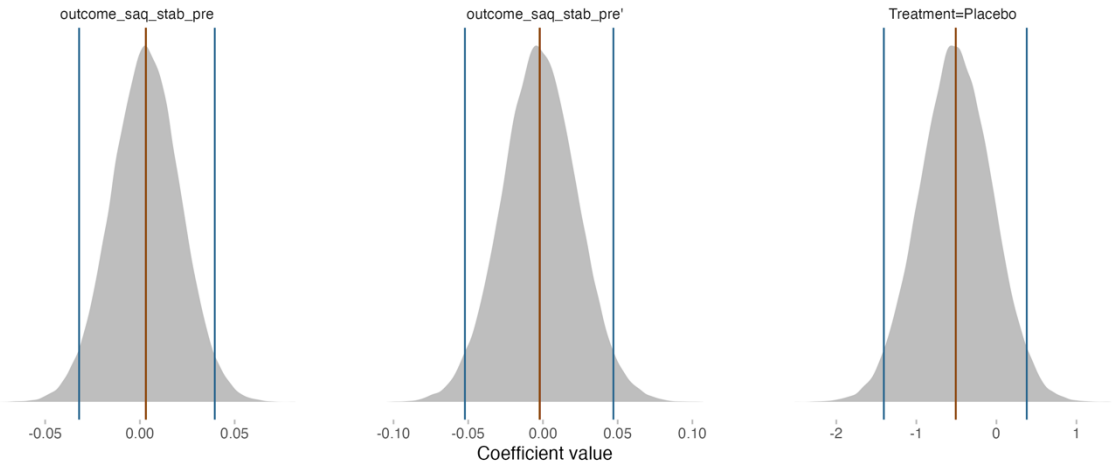
Supplementary figure S21: result: SAQ angina stability



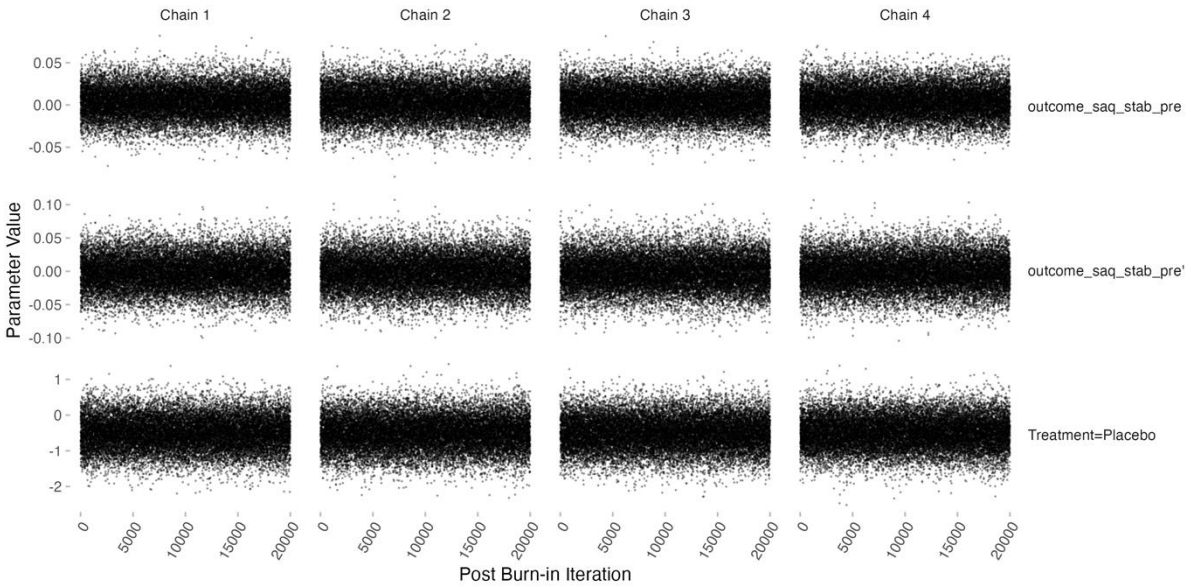
Regression model and coefficients for SAQ angina stability

```
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) + Treatment, data = saq_stab_res1_d, pcontrast = con,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, method = "sampling",
    file = file.path(output_dir, "res1.blrm.rds"))


Frequencies of Responses

  0  25  50  75 100
  9   8  17   6  10

                Mixed Calibration/              Discrimination                Rank Discrim.
              Discrimination Indexes                    Indexes                      Indexes
   Obs  50    B 0.229 [0.216, 0.247]    g   0.49 [0.102, 0.897]    C    0.543 [0.447, 0.594]
Draws40000                             gp 0.102 [0.019, 0.182]    Dxy 0.086 [-0.105, 0.188]
   Chains4                             EV 0.046 [0.002, 0.118]
  Time2.5s                             v  0.248 [0.007, 0.636]
   p     3                             vp      0.01 [0, 0.027]

                     Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
y>=25                 1.7708    1.7595     0.7090  0.3803 3.1418 0.9952     1.04
y>=50                 0.8636    0.8565     0.6812 -0.4518 2.2056 0.8998     1.03
y>=75                -0.6195   -0.6177     0.6711 -1.9387 0.6807 0.1791     1.01
y>=100               -1.3023   -1.2957     0.6879 -2.6709 0.0324 0.0286     0.98
outcome_saq_stab_pre  0.0032    0.0032     0.0181 -0.0319 0.0389 0.5707     0.98
outcome_saq_stab_pre' -0.0022   -0.0024     0.0250 -0.0517 0.0472 0.4615     1.01
Treatment=Placebo     -0.5090   -0.5064     0.4586 -1.3888 0.3899 0.1347     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S22: coefficient density plots: SAQ angina stability



Supplementary figure S23: chain plot of MCMC draws for SAQ angina stability

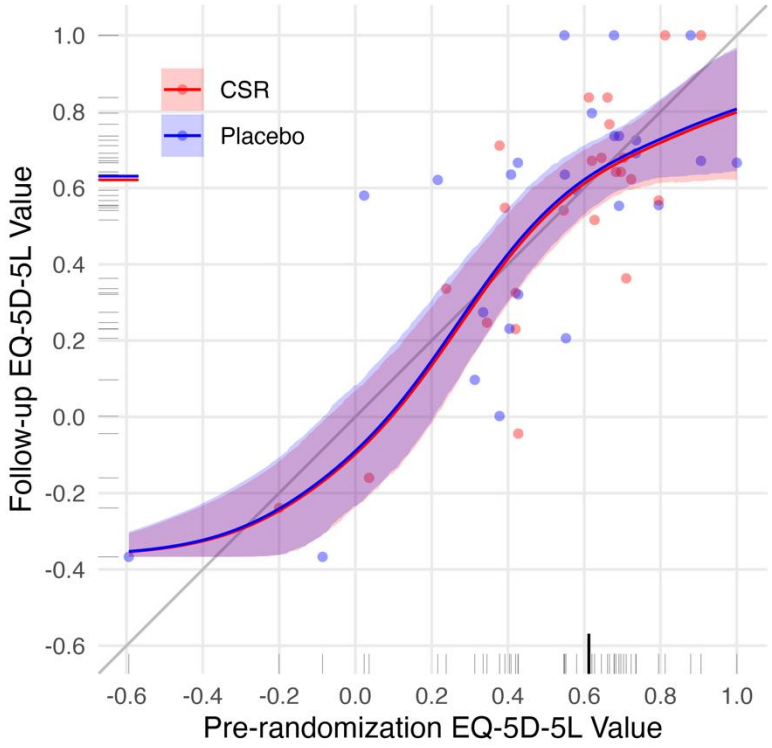


Secondary outcome: SAQ angina freedom

Very few patients in either group became free from angina (2/24 (8.3%) in the CSR group and 0/26 (0%) in the placebo group), with no evidence of difference between the groups (1·6%, 95% CrI -7·2% to 11·2%, Pr(Benefit)=0%). As this is only based on data from 3 patients, the prior appropriately pulls the effect estimate back towards zero and the small amount of data is reflected in the wide credible interval.

Secondary outcome: EQ-5D-5L index value

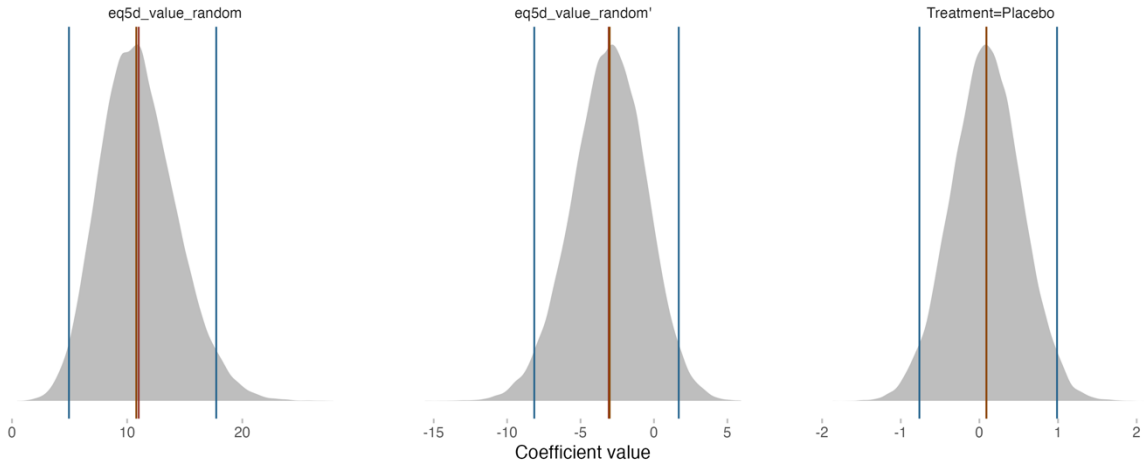
Supplementary figure S24: result: EQ-5D-5L index value



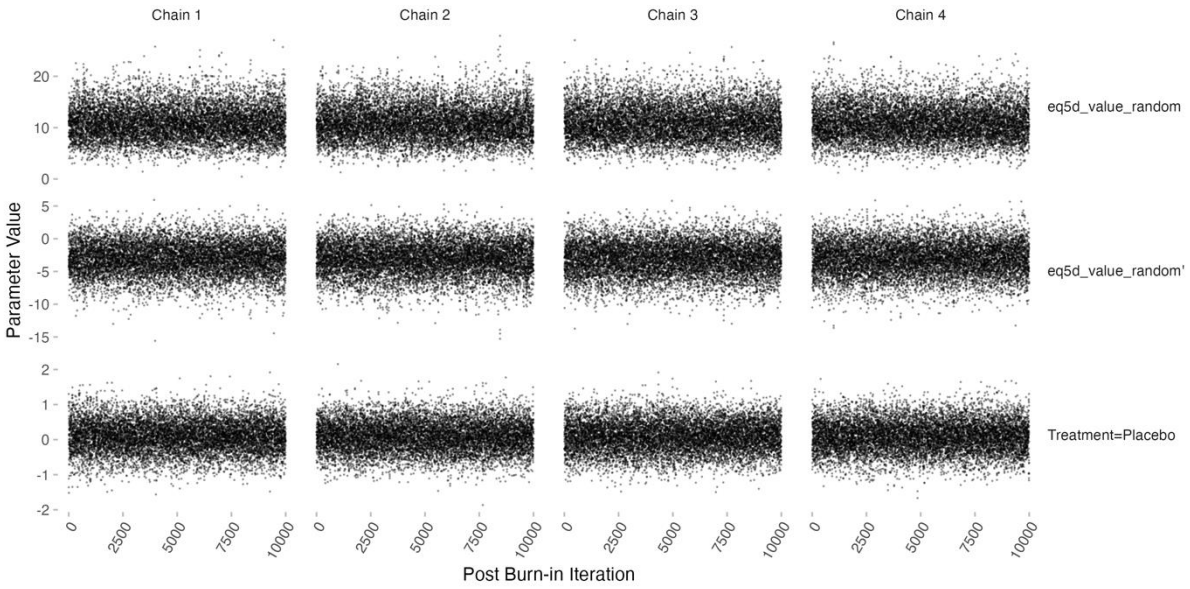
Regression model and coefficients for EQ-5D-5L index value

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.071 for Intercepts

blrm(formula = eq5d_value_fu ~ rcs(eq5d_value_random, 3) + Treatment,
    data = eq5d_res1_d, pcontrast = con, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

-0.367 -0.239  -0.16 -0.044  0.002  0.097  0.206   0.23  0.231  0.247  0.274  0.321  0.325  0.336  0.363  0.516  0.541  0.548  0.553  0.555  0.567
     2      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1      1
  0.58  0.594  0.621  0.623  0.635  0.642  0.666  0.671  0.679  0.691  0.711  0.725  0.736  0.767  0.796  0.837      1
     1      1      1      1      2      2      2      2      2      1      1      1      2      1      1      2      5

                 Mixed Calibration/              Discrimination              Rank Discrim.
               Discrimination Indexes                    Indexes                   Indexes
   Obs  50    B 0.019 [0.013, 0.025]    g    2.542 [1.539, 3.44]    C    0.73 [0.715, 0.744]
Draws40000                             gp   0.071 [0.029, 0.12]    Dxy 0.461 [0.429, 0.487]
   Chains4                             EV  0.654 [0.362, 0.872]
  Time7.2s                             v  7.553 [1.476, 13.515]
   p     3                             vp  0.024 [0.007, 0.043]

                   Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
eq5d_value_random  10.9628   10.7281     3.3057  4.8701 17.6525 1.0000     1.22
eq5d_value_random' -3.0740   -3.0020     2.5269 -8.1010  1.8012 0.1086     0.93
Treatment=Placebo   0.0896    0.0885     0.4475 -0.7677  0.9745 0.5796     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S25: coefficient density plots: EQ-5D-5L index value

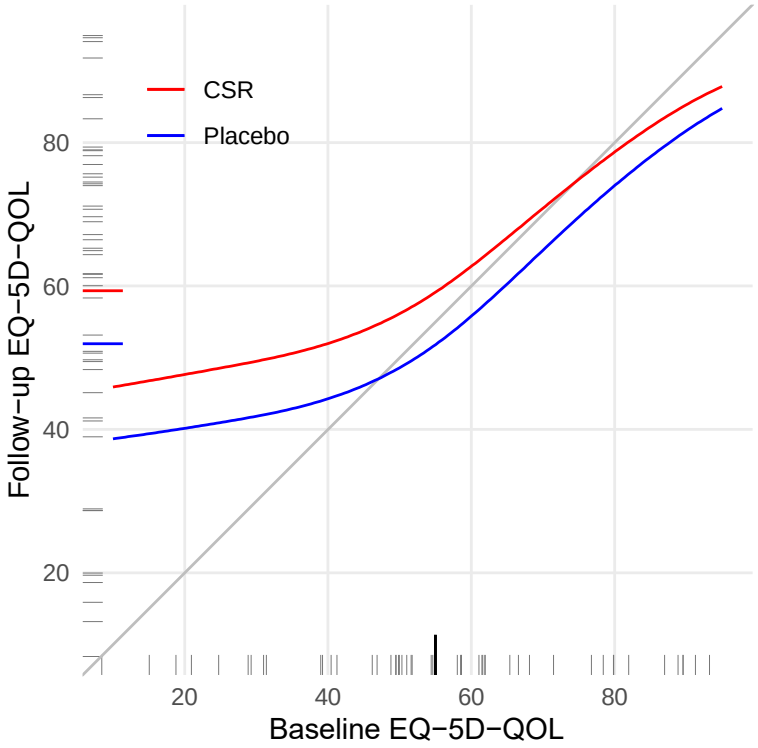


Supplementary figure S26: chain plot of MCMC draws for EQ-5D-5L index value



Secondary outcome: EQ-5D-5L visual analogue scale

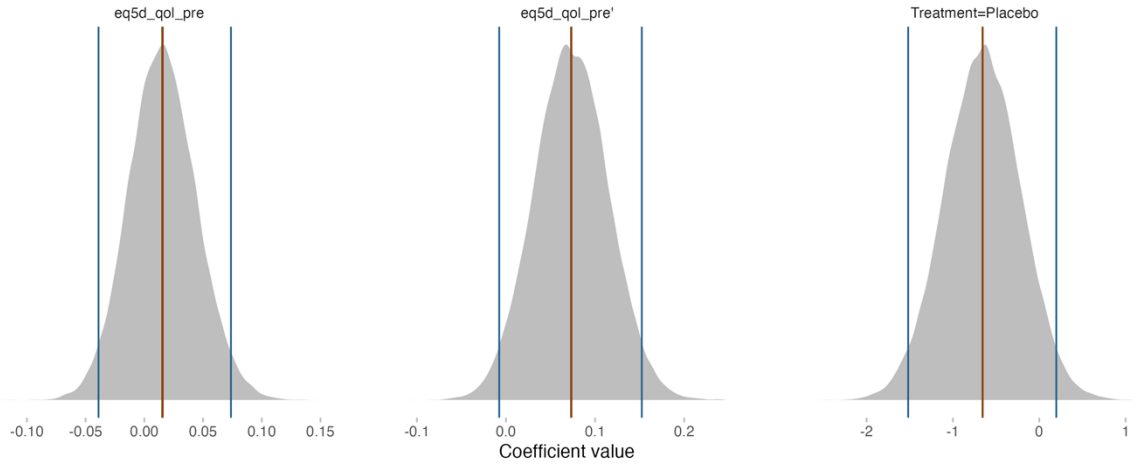
Supplementary figure S27: result: EQ-5D-5L visual analogue scale



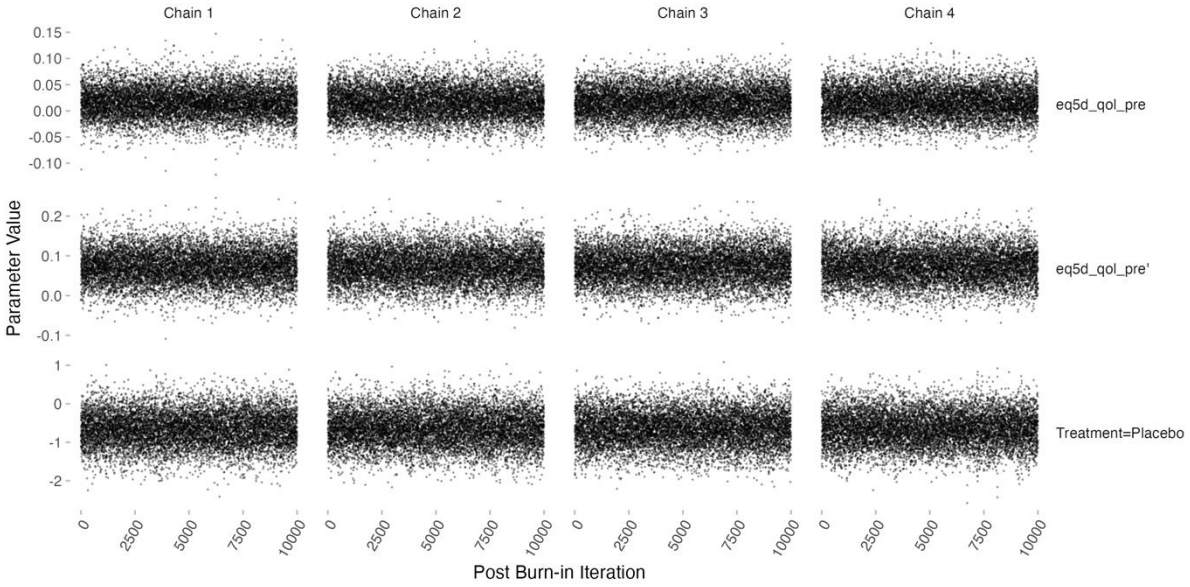
Regression model and coefficients for EQ-5D-5L visual analogue scale

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.148 for Intercepts

blrm(formula = eq5d_qol_post ~ rcs(eq5d_qol_pre, 3) + Treatment,
    data = eq5d_qol_res1_d, pcontrast = con, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

10 15 20 30 40 45 50 55 60 65 67 70 75 80 85 90 95
 1  2  3  3  3  1  5  1  5  3  2  4  6  4  3  1  3

                Mixed Calibration/              Discrimination              Rank Discrim.
              Discrimination Indexes                   Indexes                    Indexes
   Obs  50    B 0.213 [0.203, 0.229]    g  1.633 [0.946, 2.343]    C   0.724 [0.692, 0.742]
Draws40000                             gp 0.286 [0.203, 0.364]    Dxy 0.448 [0.384, 0.484]
   Chains4                             EV 0.266 [0.129, 0.403]
  Time4.5s                             v  2.381 [0.549, 4.467]
   p     3                             vp 0.066 [0.031, 0.099]

                  Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
eq5d_qol_pre       0.0153    0.0149     0.0287 -0.0409 0.0724 0.7027     1.04
eq5d_qol_pre'      0.0740    0.0739     0.0414 -0.0080 0.1539 0.9638     1.02
Treatment=Placebo -0.6576   -0.6568     0.4419 -1.5337 0.2095 0.0667     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S28: coefficient density plots: EQ-5D-5L visual analogue scale



Supplementary figure S29: chain plot of MCMC draws for EQ-5D-5L visual analogue scale



Supplementary Table 13: EQ-5D-5L Domains

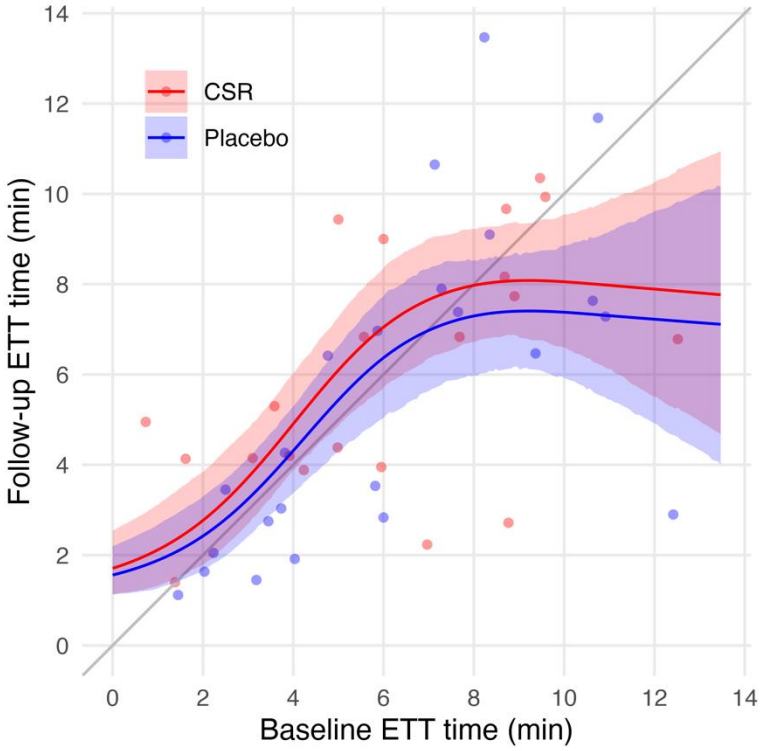
Dimension	CSR		Placebo	
	Enrolment	Follow-up	Enrolment	Follow-up
Mobility				
No problems	4/24 (16.7%)	5/24 (20.8%)	5/26 (19.2%)	8/26 (30.8%)
Slight problems	7/24 (29.2%)	5/24 (20.8%)	6/26 (23.1%)	1/26 (3.9%)
Moderate problems	7/24 (29.2%)	9/24 (37.5%)	10/26 (38.5%)	11/26 (42.3%)
Severe problems	5/24 (20.8%)	4/24 (16.7%)	4/26 (15.4%)	5/26 (19.2%)
Unable to walk about	1/24 (4.2%)	1/24 (4.2%)	1/26 (3.9%)	1/26 (3.9%)
Self-care				
No problems	17/24 (70.8%)	15/24 (62.5%)	14/26 (53.8%)	15/26 (57.7%)
Slight problems	5/24 (20.8%)	4/24 (16.7%)	7/26 (26.9%)	3/26 (11.5%)
Moderate problems	0/24 (0.0%)	3/24 (12.5%)	2/26 (7.7%)	6/26 (23.1%)
Severe problems	2/24 (8.3%)	1/24 (4.2%)	1/26 (3.9%)	0/26 (0.0%)
Unable to wash/dress	0/24 (0.0%)	1/24 (4.2%)	2/26 (7.7%)	2/26 (7.7%)
Usual activities				
No problems	1/24 (4.2%)	8/24 (33.3%)	4/26 (15.4%)	7/26 (26.9%)
Slight problems	10/24 (41.7%)	8/24 (33.3%)	9/26 (34.6%)	7/26 (26.9%)
Moderate problems	11/24 (45.8%)	4/24 (16.7%)	6/26 (23.1%)	6/26 (23.1%)
Severe problems	2/24 (8.3%)	2/24 (8.3%)	5/26 (19.2%)	4/26 (15.4%)
Unable to do usual activities	0/24 (0.0%)	2/24 (8.3%)	2/26 (7.7%)	2/26 (7.7%)
Pain/discomfort				
No pain/discomfort	3/24 (12.5%)	3/24 (12.5%)	3/26 (11.5%)	3/26 (11.5%)
Slight pain/discomfort	6/24 (25.0%)	6/24 (25.0%)	7/26 (26.9%)	6/26 (23.1%)
Moderate pain/discomfort	9/24 (37.5%)	9/24 (37.5%)	8/26 (30.8%)	9/26 (34.6%)
Severe pain/discomfort	5/24 (20.8%)	4/24 (16.7%)	6/26 (23.1%)	6/26 (23.1%)
Extreme pain/discomfort	1/24 (4.2%)	2/24 (8.3%)	2/26 (7.7%)	2/26 (7.7%)
Anxiety/depression				
Not anxious/depressed	8/24 (33.3%)	8/24 (33.3%)	9/26 (34.6%)	8/26 (30.8%)

Slightly anxious/depressed	2/24 (8.3%)	9/24 (37.5%)	7/26 (26.9%)	9/26 (34.6%)
Moderately anxious/depressed	11/24 (45.8%)	3/24 (12.5%)	8/26 (30.8%)	6/26 (23.1%)
Severely anxious/depressed	2/24 (8.3%)	2/24 (8.3%)	1/26 (3.9%)	1/26 (3.9%)
Extremely anxious/depressed	1/24 (4.2%)	2/24 (8.3%)	1/26 (3.9%)	2/26 (7.7%)

Supplementary table: EQ-5D-5L domains
CSR = coronary sinus reducer

Secondary outcome: treadmill exercise time

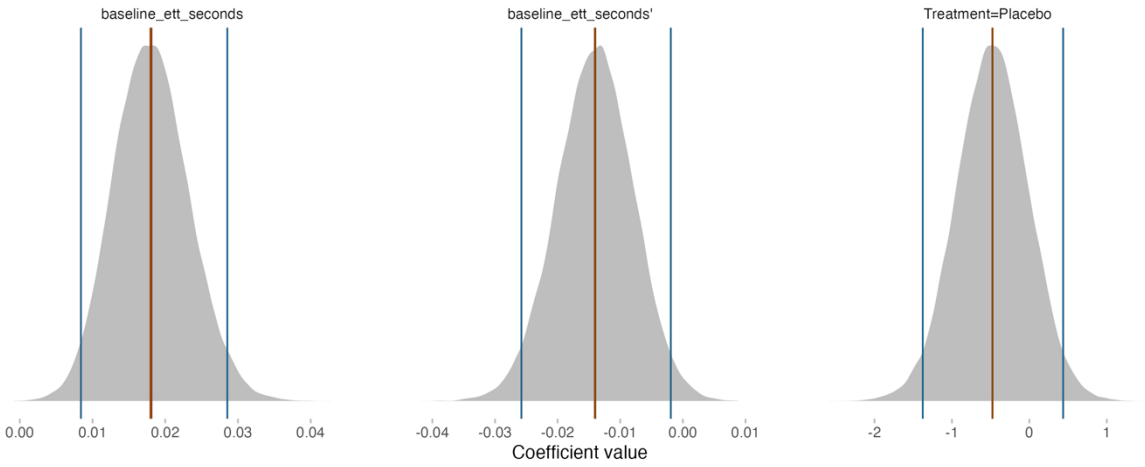
Supplementary figure S30: result: treadmill exercise time



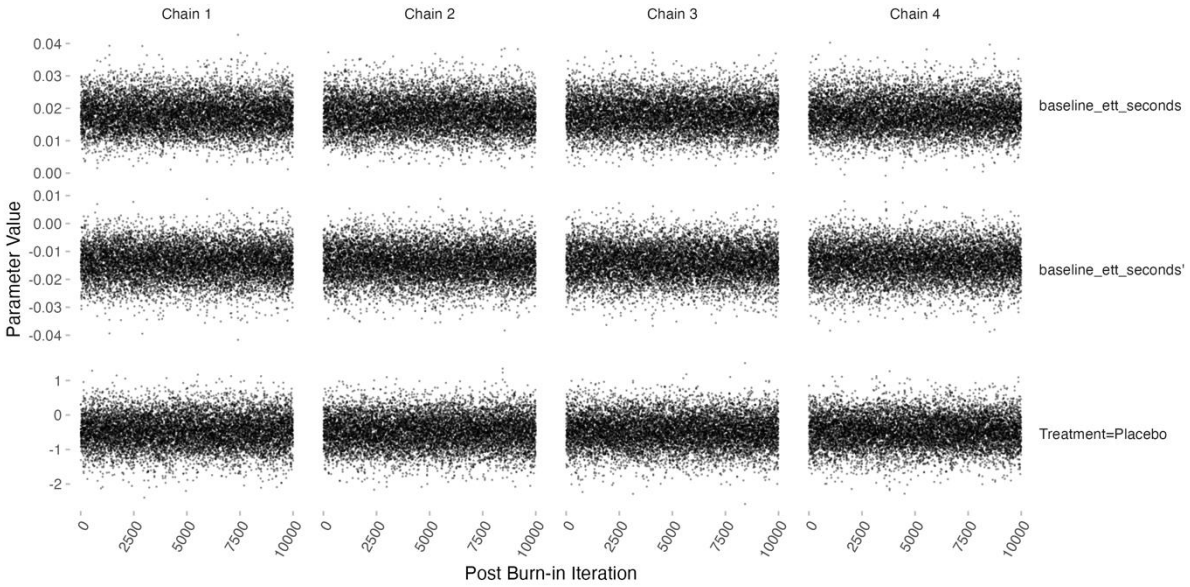
Regression model and coefficients for treadmill exercise time

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.063 for Intercepts

blrm(formula = fu_ett_seconds ~ rcs(baseline_ett_seconds, 3) +
    Treatment, data = ett_res1_d, pcontrast = con, backend = "cmdstan",
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

 67  84  87  98 115 123 134 163 165 170 174 182 207 212 233 237 248 249 252 256 263 297 318 385 388 407 410 418 437 443 458 464 474 490 540 546 566
  1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   2   1   1   1   1   1   1   1   1   1   1
580 596 621 639 701 808
  1   1   1   1   1   1

                Mixed Calibration/              Discrimination             Rank Discrim.
              Discrimination Indexes                    Indexes                   Indexes
   Obs  44    B  0.02 [0.013, 0.027]    g  1.993 [1.269, 2.847]    C    0.73 [0.71, 0.75]
Draws40000                              gp     0.041 [0, 0.113]    Dxy 0.46 [0.42, 0.501]
   Chains4                              EV 0.109 [0.001, 0.311]
  Time7.4s                              v   3.38 [1.184, 6.279]
   p     3                              vp      0.005 [0, 0.02]

                     Mode Beta Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
baseline_ett_seconds   0.0177    0.0181    0.0180     0.0051  0.0084  0.0284 0.9999     1.07
baseline_ett_seconds' -0.0138   -0.0141   -0.0140     0.0061 -0.0261 -0.0022 0.0093     0.98
Treatment=Placebo     -0.4697   -0.4763   -0.4766     0.4614 -1.3826  0.4372 0.1480     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S31: coefficient density plots: treadmill exercise time

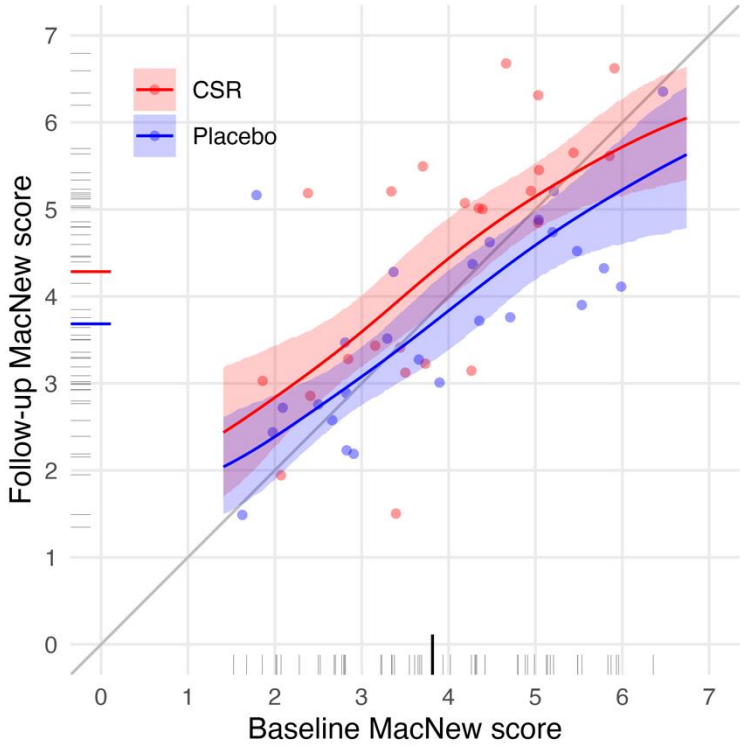


Supplementary figure S32: chain plot of MCMC draws for treadmill exercise time



Secondary outcome: MacNew heart disease health-related quality of life

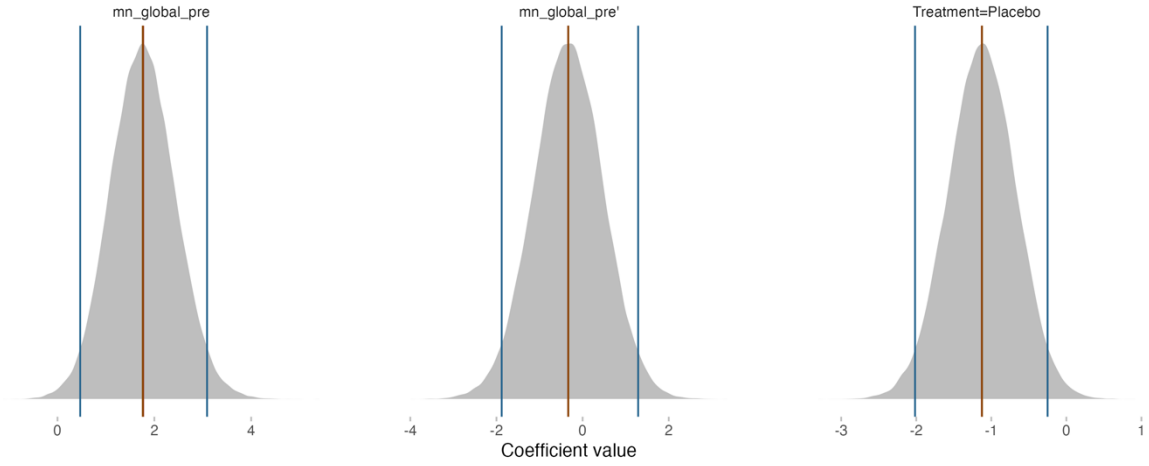
Supplementary figure S33: result: MacNew heart disease health-related quality of life



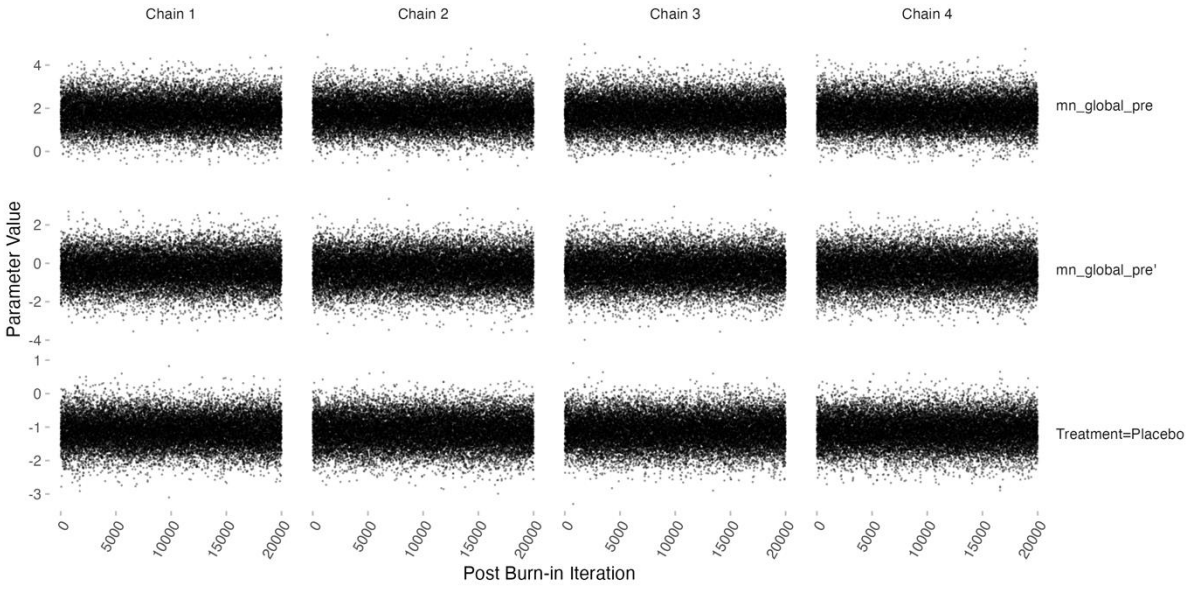
Regression model and coefficients for MacNew heart disease health-related quality of life

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.063 for Intercepts

blrm(formula = mn_global_post ~ rcs(mn_global_pre, 3) + Treatment,
    data = mn_res1_d, pcontrast = con, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

1.40740740740741 1.44444444444444                2 2.14814814814815 2.18518518518519 2.37037037037037 2.62962962962963  2.7037037037037
               1                1                1                1                1                1                1               1
2.85185185185185 2.88888888888889 2.92592592592593 2.96296296296296 3.07407407407407 3.25925925925926  3.2962962962963 3.37037037037037
               1                1                1                1                3                1                2               1
3.40740740740741 3.48148148148148 3.55555555555556 3.74074074074074 3.81481481481481 3.85185185185185 4.18518518518519  4.2962962962963
               1                1                1                1                1                1                1               1
4.40740740740741 4.44444444444444 4.55555555555556  4.7037037037037 4.77777777777778 4.88888888888889 5.03703703703704 5.07407407407407
               1                1                1                2                1                1                2               1
5.14814814814815 5.18518518518519 5.22222222222222 5.40740740740741 5.44444444444444 5.55555555555556 5.62962962962963  6.2962962962963
               2                1                2                1                1                1                1               1
6.37037037037037 6.55555555555556 6.74074074074074
               1                1                1

                  Mixed Calibration/              Discrimination              Rank Discrim.
                Discrimination Indexes                    Indexes                   Indexes
   Obs  50    B   0.016 [0.01, 0.02]    g  2.465 [1.495, 3.174]    C    0.778 [0.76, 0.789]
Draws40000                             gp     0.038 [0, 0.104]    Dxy 0.556 [0.521, 0.581]
   Chains4                             EV     0.101 [0, 0.286]
  Time7.1s                             v   4.729 [1.693, 7.59]
   p     3                             vp     0.004 [0, 0.017]

                  Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
mn_global_pre      1.7655    1.7560     0.6681  0.4648  3.0776 0.9968     1.05
mn_global_pre'    -0.3272   -0.3184     0.8029 -1.8904  1.2680 0.3415     0.98
Treatment=Placebo -1.1295   -1.1301     0.4529 -2.0275 -0.2572 0.0056     0.98


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S34: coefficient density plots: MacNew heart disease health-related quality of life



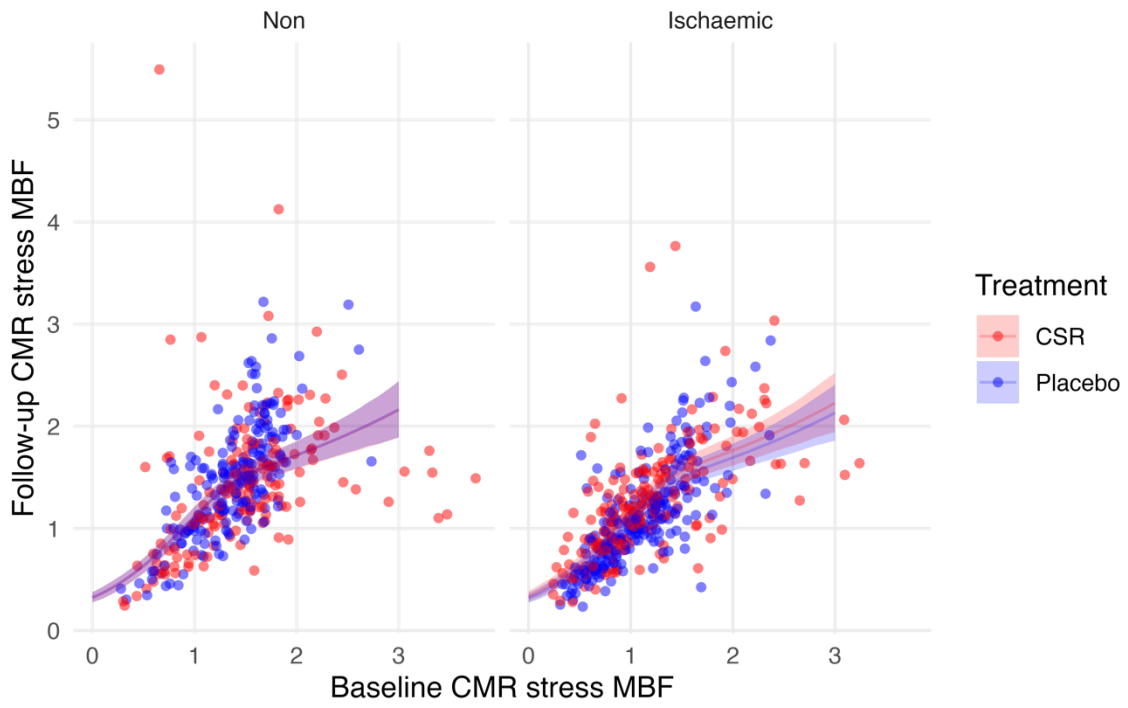
Supplementary figure S35: chain plot of MCMC draws for MacNew heart disease health-related quality of life



Secondary imaging outcomes

Secondary outcome: stress myocardial blood flow in segments ischaemic (primary outcome) and non-ischaemic at enrolment

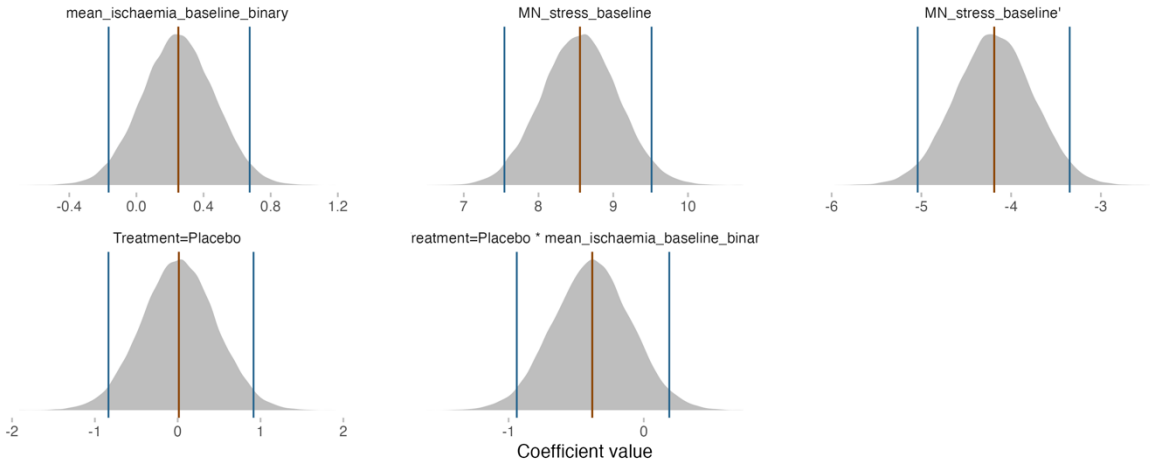
Supplementary figure S36: result: stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



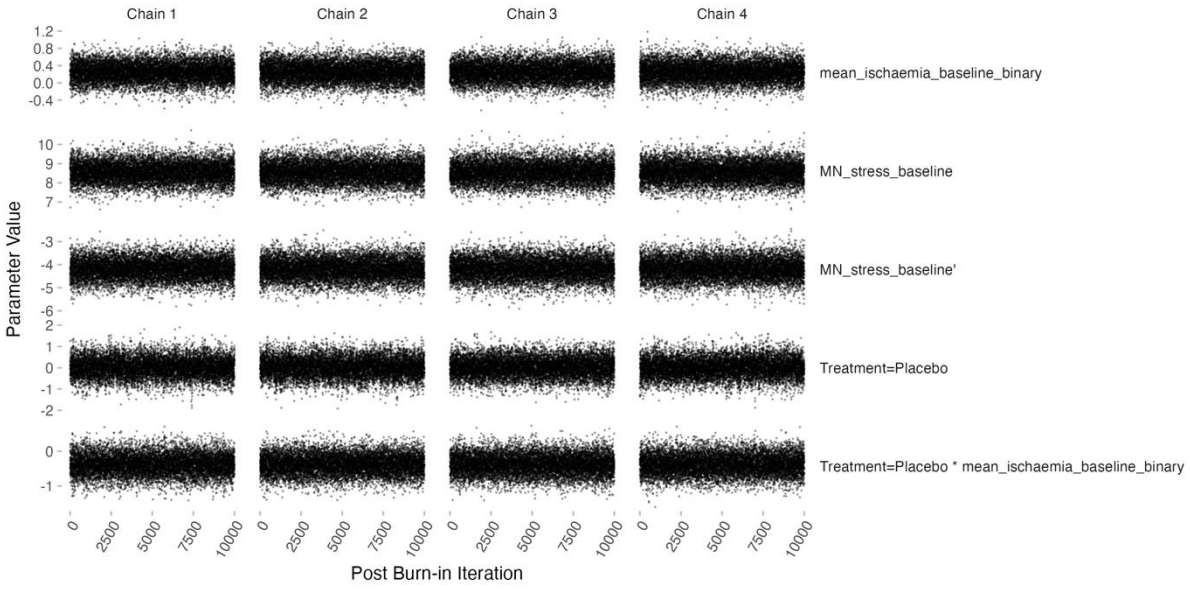
Regression model and coefficients for stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = MN_stress_followup ~ rcs(MN_stress_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))


                                    Mixed Calibration/              Discrimination              Rank Discrim.
                                  Discrimination Indexes                    Indexes                    Indexes
Obs                          768  B 0.001 [0.001, 0.001]   g    2.88 [2.57, 3.148]   C   0.77 [0.763, 0.774]
Draws                      40000                          gp     0.001 [0, 0.003]   Dxy 0.54 [0.526, 0.547]
Chains                         4                          EV     0.008 [0, 0.026]
Time                       619.6s                         v  6.706 [5.432, 8.047]
p                              5                          vp             0 [0, 0]
Cluster on                orbita_id
Clusters                      48
sigma gamma 1.6528 [1.3044, 2.0515]

                                                    Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
MN_stress_baseline                                   8.5547    8.5547     0.5051  7.5439  9.5125 1.0000     1.02
MN_stress_baseline'                                 -4.1882   -4.1879     0.4336 -5.0412 -3.3475 0.0000     0.99
Treatment=Placebo                                    0.0134    0.0142     0.4482 -0.8360  0.9155 0.5133     1.00
mean_ischaemia_baseline_binary                       0.2504    0.2496     0.2151 -0.1654  0.6750 0.8779     1.00
Treatment=Placebo * mean_ischaemia_baseline_binary -0.3813   -0.3806     0.2884 -0.9393  0.1886 0.0925     1.01


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
.
```

Supplementary figure S37: coefficient density plots: stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



Supplementary Figure S38: Chain plot of MCMC draws for stress myocardial blood flow in segments non-ischaemic at enrolment

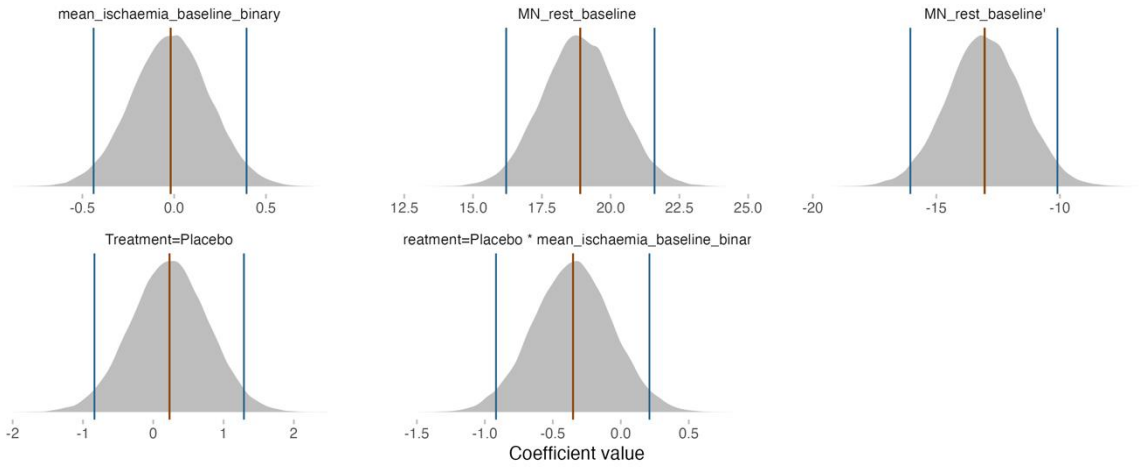


Secondary outcome: rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

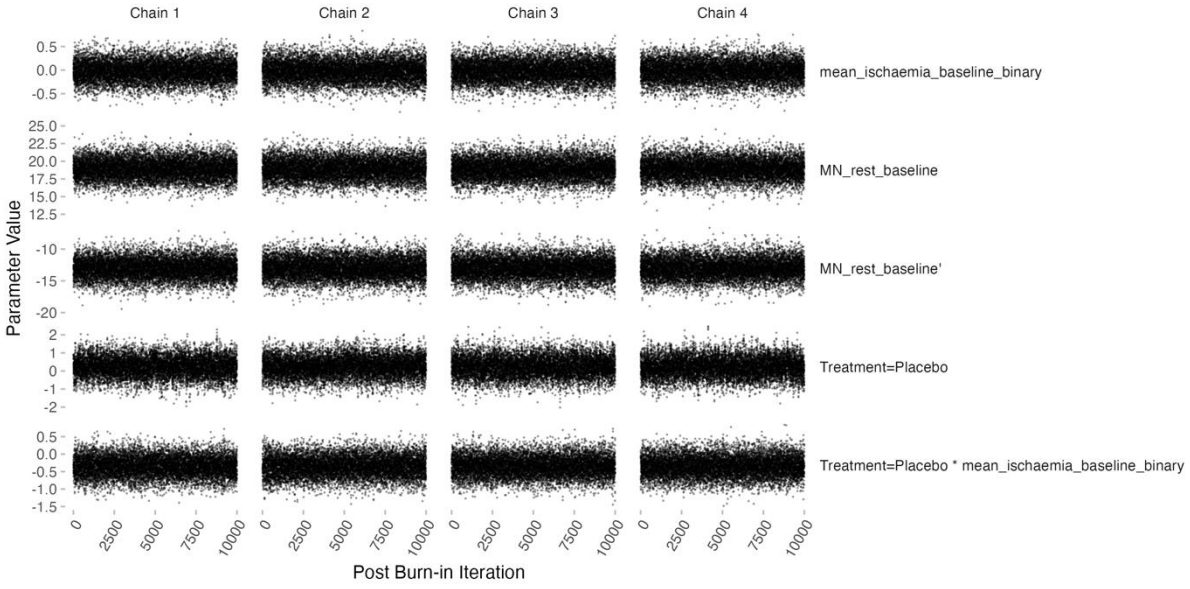
Regression model and coefficients for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

```
Frequencies of Missing Values Due to Each Variable
              MN_rest_followup                MN_rest_baseline                      Treatment mean_ischaemia_baseline_binary
                             0                              32                                0                                     0
            cluster(orbita_id)
                             0

Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = MN_rest_followup ~ rcs(MN_rest_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))

                                      Mixed Calibration/             Discrimination             Rank Discrim.
                                    Discrimination Indexes                   Indexes                   Indexes
Obs                           768   B 0.002 [0.001, 0.003]   g  2.571 [2.284, 2.929]   C   0.73 [0.722, 0.734]
Draws                       40000                            gp     0.003 [0, 0.006]   Dxy 0.46 [0.443, 0.468]
Chains                          4                            EV 0.498 [0.076, 0.787]
Time                        693.9s                            v  5.498 [4.242, 6.999]
p                                5                            vp     0.001 [0, 0.002]
Cluster on                orbita_id
Clusters                        48
sigma gamma 2.3348 [1.8645, 2.8705]

                                                  Mean Beta Median Beta S.E.   Lower    Upper    Pr(Beta>0) Symmetry
MN_rest_baseline                                   18.8995   18.8906    1.3783  16.2034  21.5949 1.0000     1.02
MN_rest_baseline'                                 -13.0410  -13.0525    1.5272 -16.0523 -10.1010 0.0000     1.00
Treatment=Placebo                                   0.2309    0.2324    0.5450  -0.8367   1.2897 0.6642     0.98
mean_ischaemia_baseline_binary                     -0.0193   -0.0185    0.2121  -0.4386   0.3942 0.4668     0.99
Treatment=Placebo * mean_ischaemia_baseline_binary -0.3517   -0.3506    0.2875  -0.9178   0.2105 0.1114     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S39: coefficient density plots: for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



Supplementary figure S40: chain plot of MCMC draws for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



Secondary outcome: myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

Regression model and coefficients for myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = MN_mpr_followup ~ rcs(MN_mpr_baseline, 3) + Treatment *
    mean_ischaemia_baseline_binary + cluster(orbita_id), data = main_analysis_d,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "res1.txt"), loo = FALSE,
    ppairs = NULL, file = file.path(output_dir, "res1.blrm.rds"))
```

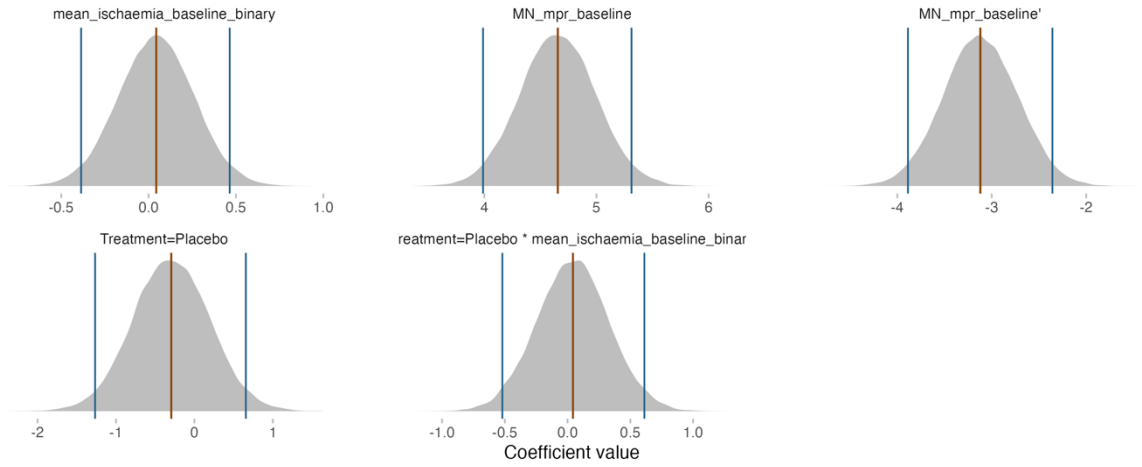
		Mixed Calibration/ Discrimination Indexes		Discrimination Indexes		Rank Discrim. Indexes
Obs	766	B 0.001 [0.001, 0.001]	g	2.204 [1.93, 2.468]	C	0.742 [0.735, 0.746]
Draws	40000		gp	0 [0, 0.002]	Dxy	0.484 [0.469, 0.492]
Chains	4		EV	0.004 [0, 0.013]		
Time	895.2s		v	3.876 [2.951, 4.798]		
p	5		vp	0 [0, 0]		
Cluster on	orbita_id					
Clusters	48					

sigma gamma 1.929 [1.5289, 2.3953]

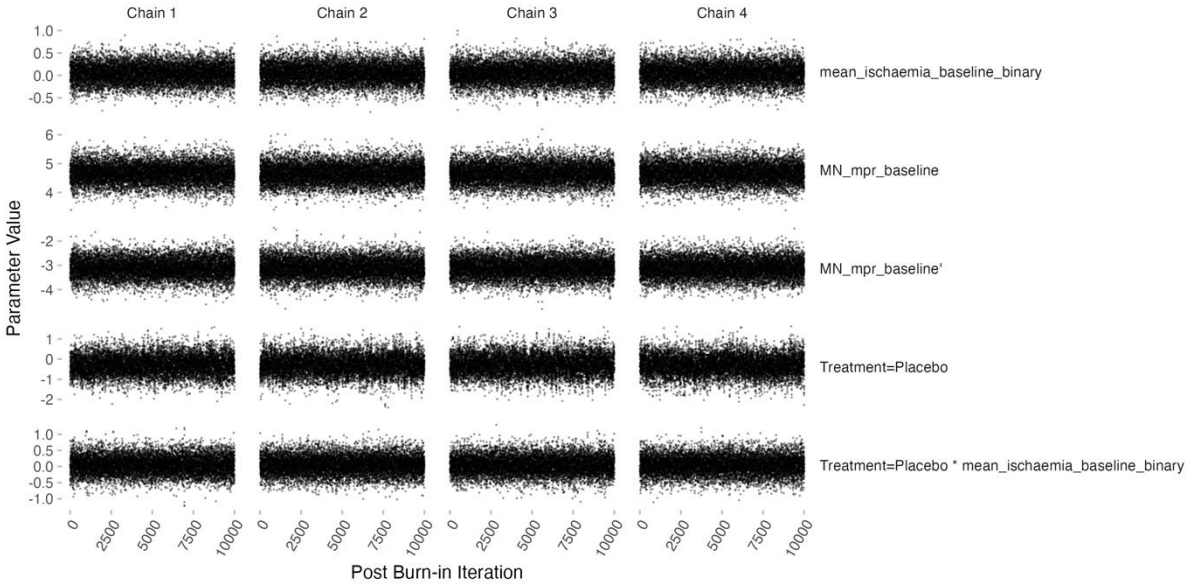
	Mean Beta	Median Beta	S.E.	Lower	Upper	Pr(Beta>0)	Symmetry
MN_mpr_baseline	4.6560	4.6541	0.3374	3.9889	5.3121	1.0000	1.02
MN_mpr_baseline'	−3.1191	−3.1221	0.3927	−3.8869	−2.3576	0.0000	1.00
Treatment=Placebo	−0.2941	−0.2964	0.4896	−1.2667	0.6558	0.2731	1.01
mean_ischaemia_baseline_binary	0.0436	0.0438	0.2154	−0.3862	0.4643	0.5820	1.00
Treatment=Placebo * mean_ischaemia_baseline_binary	0.0427	0.0434	0.2881	−0.5197	0.6116	0.5596	1.02

```
Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S41: coefficient density plots: for myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment



Supplementary figure S42: chain plot of MCMC draws for myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

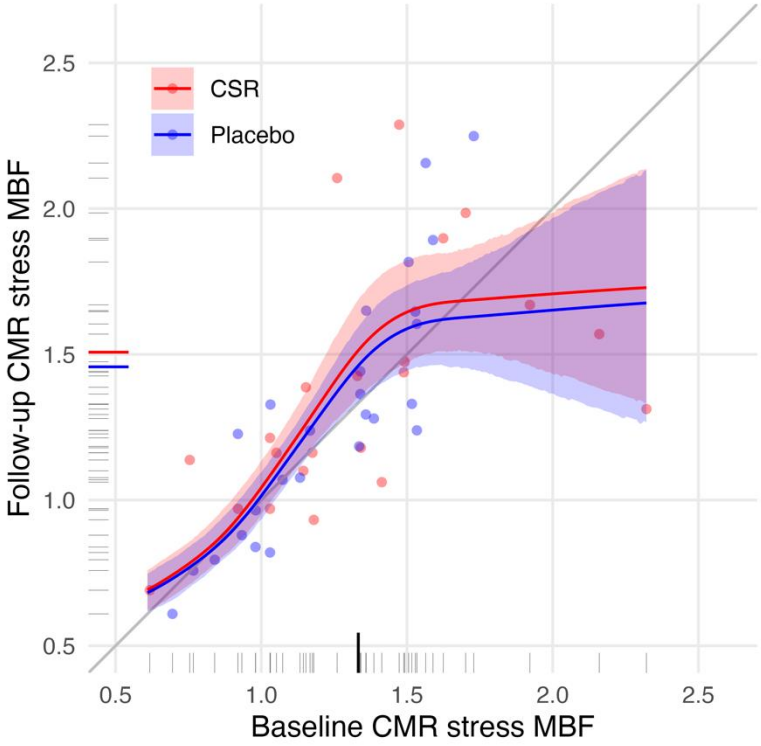


Secondary outcome: global stress MBF

Supplementary table 14 global myocardial perfusion

	Difference at follow up for CSR vs placebo	Probability of benefit with CSR vs placebo
Global myocardial perfusion		
Stress MBF (ml/min/g)	0.05 (95% CrI -0.11 to 0.21)	73.9%
Rest MBF (ml/min/g)	-0.01 (95% CrI -0.06 to 0.05)	39.6%
MPR	0.01 (95% CrI -0.21 to 0.23)	53.1%
Endo:epi ratio		
Stress MBF (ml/min/g)	0.03 (95% CrI -0.01 to 0.07)	95.2%
Rest MBF (ml/min/g)	0.02 (95% CrI -0.02 to 0.05)	85.8%
MPR	0.02 (95% CrI -0.03 to 0.08)	80.3%

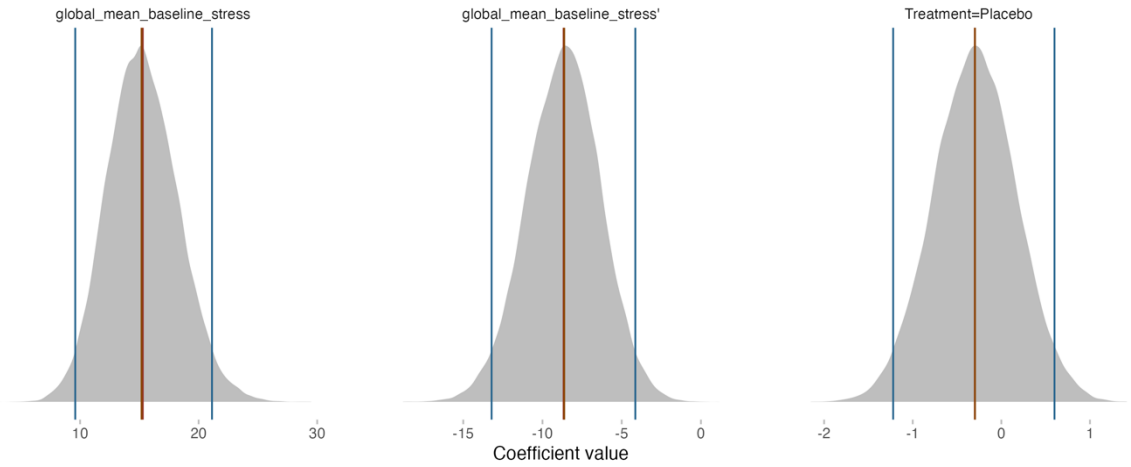
Supplementary figure S43: result: global stress myocardial blood flow



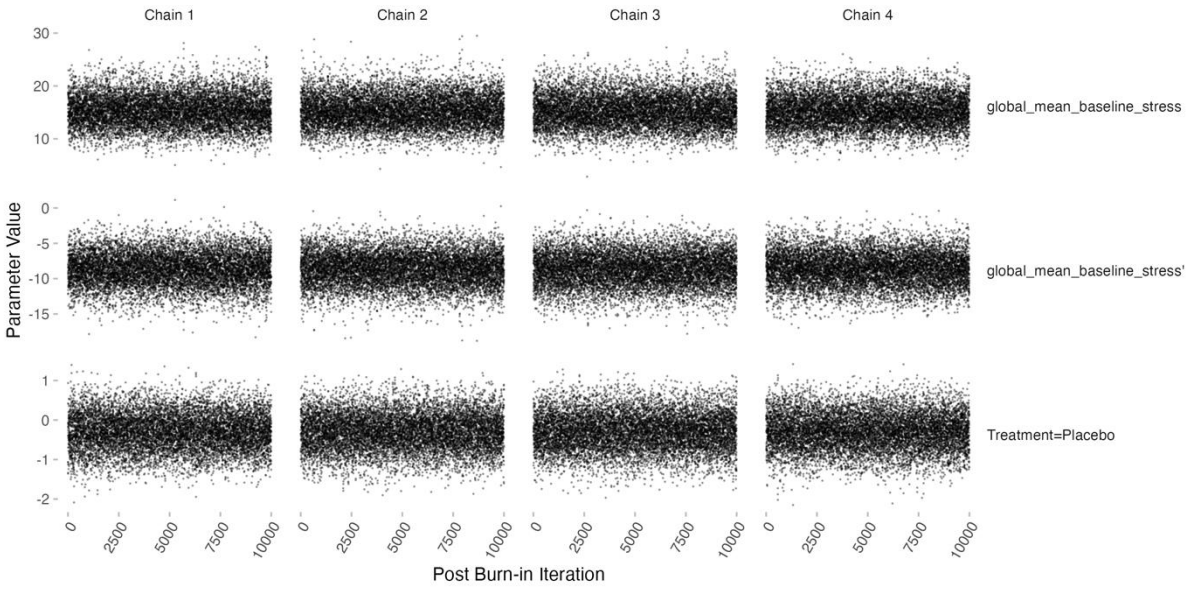
Regression model and coefficients for global stress myocardial blood flow

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.058 for Intercepts

blrm(formula = global_mean_followup_stress ~ rcs(global_mean_baseline_stress,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

0.609402 0.690665 0.758063 0.795188     0.82 0.838834  0.87951 0.932023 0.964817     0.97   1.0614  1.06946  1.07683  1.10018  1.13758  1.16193
       1        1        1        1        1        1        1        1        1        2        1        1        1        1        1        1
 1.16254  1.17944  1.18421  1.21331  1.22693  1.23827  1.23919  1.27978  1.29355  1.31235  1.32777  1.33001   1.3637  1.38696   1.4259  1.43832
       1        1        1        1        1        1        1        1        1        1        1        1        1        1        1        1
 1.44179  1.47445  1.56955   1.6041   1.6466     1.65  1.66979  1.81673  1.89215  1.89819  1.98519  2.10488  2.15637  2.24888  2.28807
       1        1        1        1        1        1        1        1        1        1        1        1        1        1        1

                Mixed Calibration/              Discrimination               Rank Discrim.
              Discrimination Indexes                    Indexes                    Indexes
   Obs  48    B 0.018 [0.013, 0.022]    g  3.105 [2.092, 4.137]    C    0.802 [0.782, 0.82]
Draws40000                             gp     0.034 [0, 0.089]    Dxy 0.605 [0.564, 0.641]
   Chains4                             EV 0.233 [0.002, 0.512]
  Time7.7s                             v      8.51 [3.194, 14]
   p     3                             vp     0.006 [0, 0.022]

                           Mode Beta Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
global_mean_baseline_stress  15.1962   15.2903   15.1828     2.9741   9.5925 21.1264 1.0000     1.10
global_mean_baseline_stress' -8.7140   -8.6685   -8.6276     2.3121 -13.2126 -4.1411 0.0001     0.96
Treatment=Placebo            -0.3116   -0.2996   -0.2976     0.4643  -1.2208  0.5997 0.2609     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S44: coefficient density plots: global stress myocardial blood flow



Supplementary figure S45: chain plot of MCMC draws for global stress myocardial blood flow

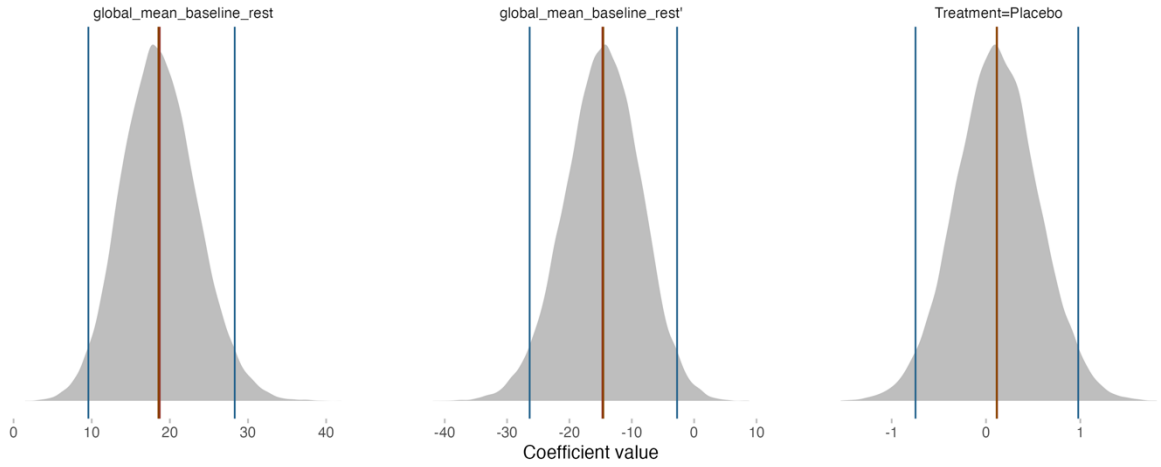


Secondary outcome: global rest MBF

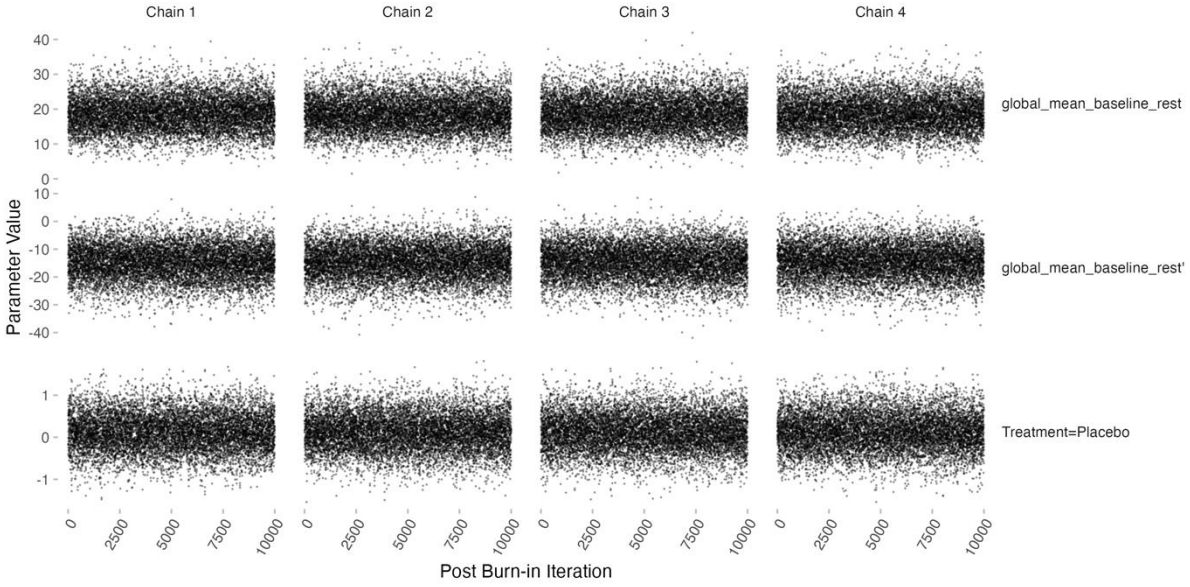
Regression model and coefficients for global rest myocardial blood flow

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.057 for Intercepts

blrm(formula = global_mean_followup_rest ~ rcs(global_mean_baseline_rest,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

0.406706 0.465457 0.465587 0.517919 0.518816 0.557544 0.561765 0.569772 0.589199     0.59 0.592532 0.608798 0.614614     0.62 0.643368  0.64838
       1        1        1        1        1        1        1        1        1        1        1        1        1        1        1        1
0.664789 0.674282 0.674377 0.712052 0.719645 0.722503 0.737668 0.739414 0.741094 0.741647 0.752501     0.76 0.761548 0.780425 0.785085 0.796888
       1        1        1        1        1        1        1        1        1        1        1        1        1        1        1        1
0.800939     0.83 0.833172 0.833446 0.836749 0.850767 0.865056 0.874999 0.897628  0.92255 0.927028 0.949687 0.963557     1.09  1.10956  1.30834
       1        1        1        1        1        1        1        1        1        1        1        1        1        1        1        1

                Mixed Calibration/              Discrimination               Rank Discrim.
              Discrimination Indexes                    Indexes                    Indexes
   Obs  48    B 0.024 [0.019, 0.036]    g  2.015 [1.272, 2.664]    C    0.747 [0.73, 0.756]
Draws40000                             gp     0.037 [0, 0.091]    Dxy 0.495 [0.461, 0.512]
   Chains4                             EV 0.206 [0.001, 0.472]
  Time7.3s                             v  3.437 [1.289, 5.838]
   p     3                             vp     0.006 [0, 0.023]

                          Mode Beta Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
global_mean_baseline_rest   17.9920   18.7006   18.5336    4.7915   9.5746 28.2992 1.0000     1.09
global_mean_baseline_rest' -14.0344  -14.7055  -14.5651    6.0355 -26.3819 -2.7391 0.0057     0.94
Treatment=Placebo            0.1083    0.1165    0.1131    0.4379  -0.7476  0.9777 0.6044     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),     | contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S46: coefficient density plots: global rest myocardial blood flow



Supplementary figure S47: chain plot of MCMC draws for global rest myocardial blood flow

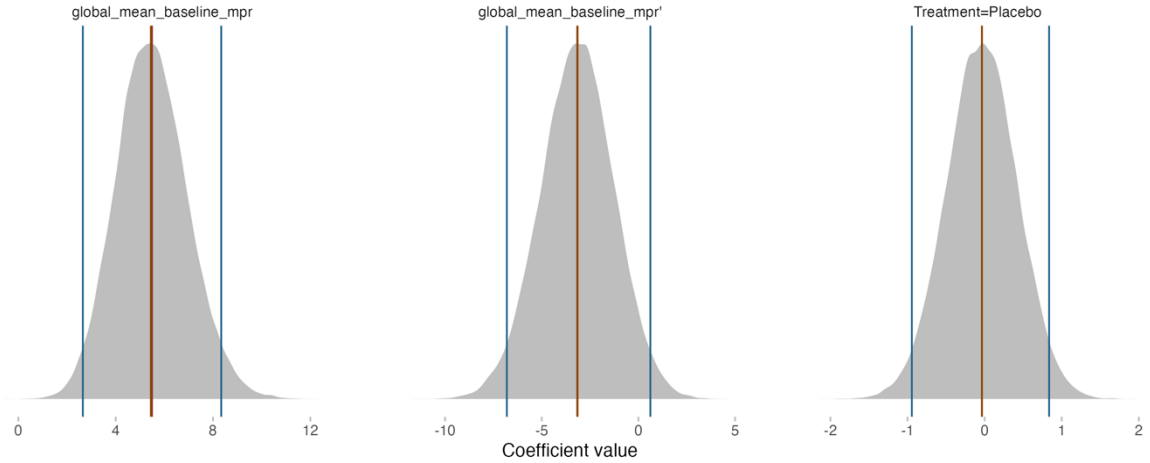


Secondary outcome: global MPR

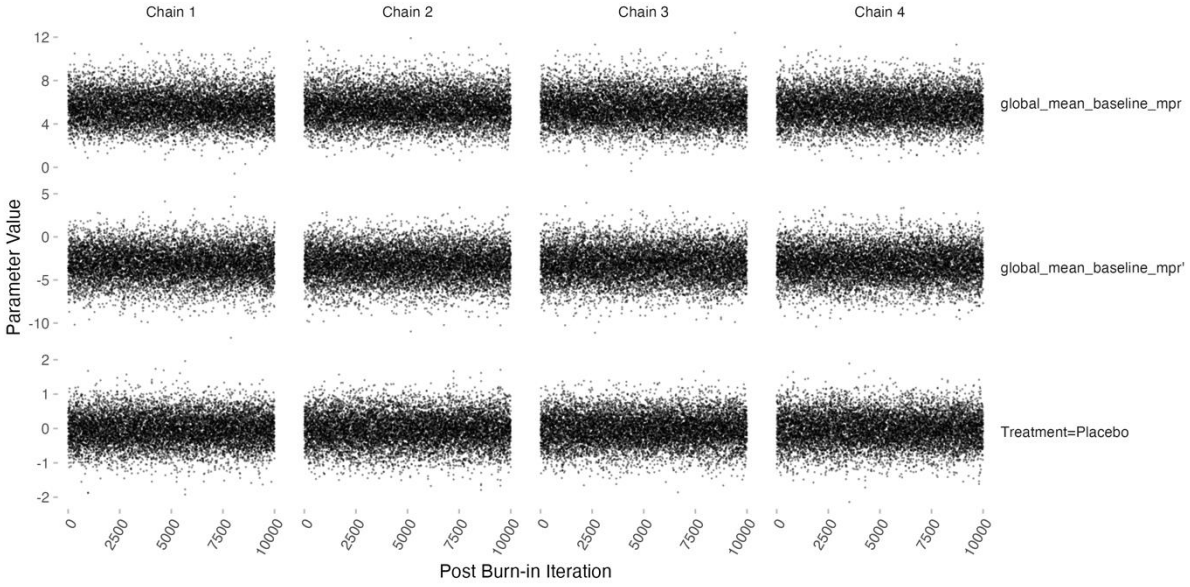
Regression model and coefficients for global myocardial perfusion reserve

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.057 for Intercepts

blrm(formula = global_mean_followup_mpr ~ rcs(global_mean_baseline_mpr,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

0.903651814934376 0.909552628484629  0.98140018764077  1.11755713465835  1.12027360094767  1.16582248819352  1.16867469879518  1.27631578947368
                1                 1                 1                 1                 1                 1                 1                 1
  1.3000929143919   1.30792849899955   1.3312330383026   1.37785275247291   1.38983050847458   1.4392390656333   1.51376146788991   1.52273416165746
                1                 1                 1                 1                 1                 1                 1                 1
 1.59784952412106  1.59792145125989  1.60331816668516  1.62719881084318  1.63891918932251  1.69469431701042  1.71141132923334  1.74883440084382
                1                 1                 1                 1                 1                 1                 1                 1
 1.77621387919243  1.80489830085126  1.8196095995444  1.85026001144452  1.86285040331922  1.86785515664586  1.95519121920995  1.99556856357163
                1                 1                 1                 1                 1                 1                 1                 1
 2.03981236244265   2.1226944580438  2.15981771737292   2.1628888136809  2.22093682292339  2.31449815766829  2.31987096774194  2.40229805665599
                1                 1                 1                 1                 1                 1                 1                 1
  2.4142559278991  2.49562380392923  2.49763136014712  2.69709453182561  2.92758875967797  3.22997849056481   3.3828477908028  3.65337050774349
                1                 1                 1                 1                 1                 1                 1                 1

                 Mixed Calibration/              Discrimination              Rank Discrim.
               Discrimination Indexes                    Indexes                   Indexes
   Obs  48    B  0.025 [0.02, 0.041]    g  2.297 [1.527, 3.235]    C   0.759 [0.746, 0.768]
Draws40000                             gp     0.032 [0, 0.091]    Dxy 0.519 [0.491, 0.535]
   Chains4                             EV     0.144 [0, 0.409]
  Time7.3s                             v  4.473 [1.758, 8.133]
   p     3                             vp     0.004 [0, 0.02]

                        Mode Beta Mean Beta Median Beta S.E.   Lower   Upper  Pr(Beta>0) Symmetry
global_mean_baseline_mpr    5.3026    5.4919     5.4449     1.4553  2.6499 8.3370 1.0000     1.10
global_mean_baseline_mpr'  -3.1181   -3.1630    -3.1463     1.8887 -6.8045 0.6181 0.0453     0.98
Treatment=Placebo          -0.0366   -0.0364    -0.0352     0.4564 -0.9442 0.8363 0.4686     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S48: coefficient density plots: global myocardial perfusion reserve



Supplementary figure S49: chain plot of MCMC draws for global myocardial perfusion reserve

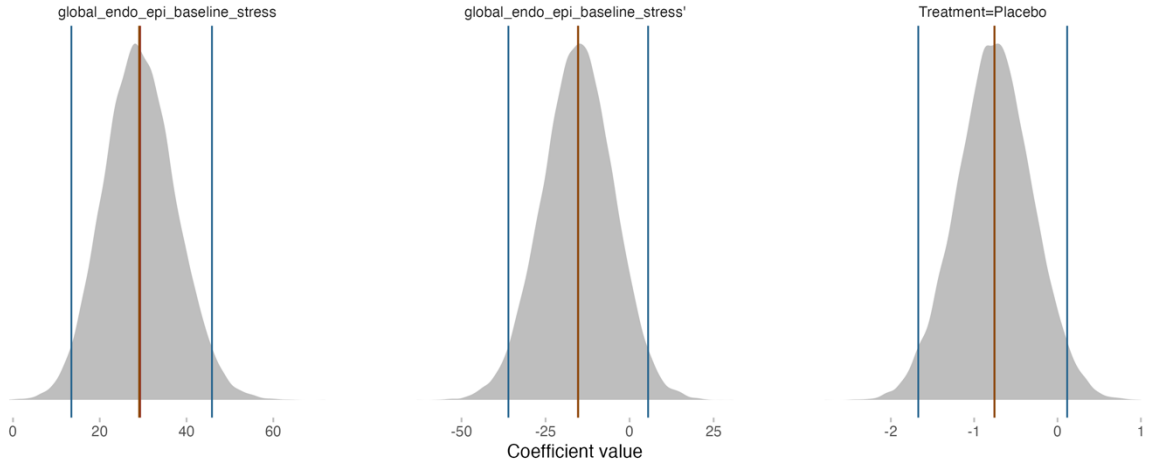


Secondary outcome: global endo:epi stress MBF

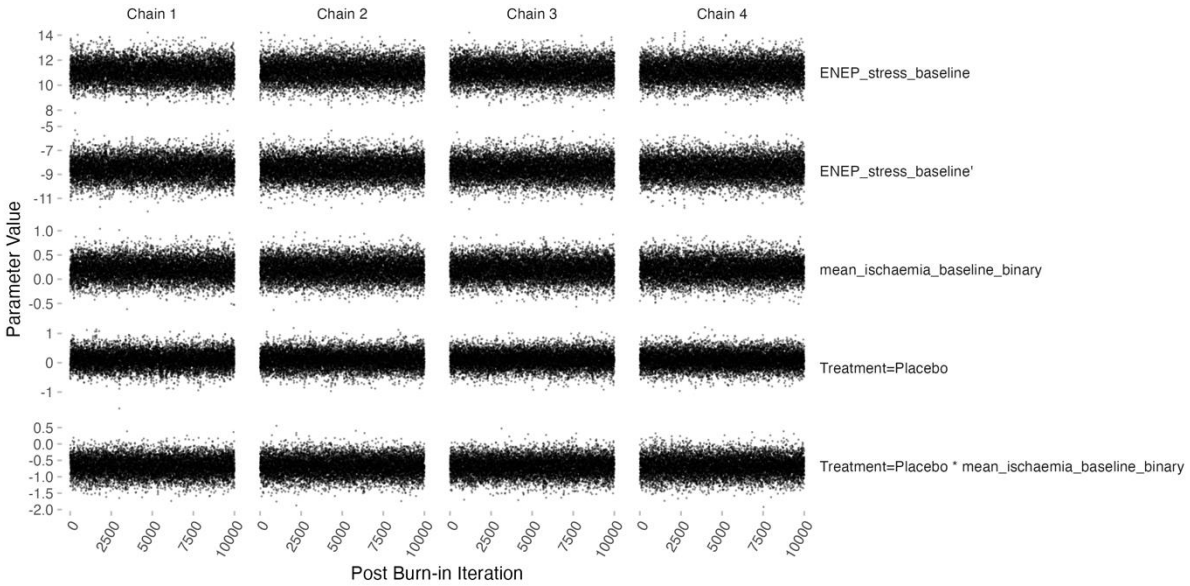
Regression model and coefficients for global endo:epi stress myocardial blood flow

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.057 for Intercepts

blrm(formula = global_endo_epi_followup_stress ~ rcs(global_endo_epi_baseline_stress,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

0.652748636841937 0.656396121357841 0.663132058211523 0.671369020645931 0.671735497968183 0.677444441966111 0.688782359258422 0.703039245904505
                1                 1                 1                 1                 1                 1                 1                 1
0.711711711711712 0.712891498313077  0.73769746588694 0.738594140254599 0.742225435868027 0.743119266055046 0.757087388579744 0.758022963354593
                1                 1                 1                 1                 1                 1                 1                 1
0.762615533964742 0.772481737370181 0.774354028607986 0.775291478790755 0.783641421076723 0.788946610752957 0.800803837861763 0.803184597931085
                1                 1                 1                 1                 1                 1                 1                 1
0.808988764044944 0.815903610803597 0.818955654427223  0.82005890462464  0.82918932943822 0.831346589877787 0.847218718262208 0.850628473185821
                1                 1                 1                 1                 1                 1                 1                 1
0.851244861963771 0.854818943787528 0.855771034663293 0.860803840091704  0.87006176298822 0.877060974482859 0.895953757225434 0.898679258136485
                1                 1                 1                 1                 1                 1                 1                 1
0.901281260055175 0.912228774128161   0.9144306222446 0.992102029194017  1.03145209450941  1.08361212823687  1.19382994579254  1.38145123073063
                1                 1                 1                 1                 1                 1                 1                 1


                   Mixed Calibration/              Discrimination              Rank Discrim.
                 Discrimination Indexes                    Indexes                   Indexes
   Obs  48    B 0.017 [0.013, 0.021]    g  2.423 [1.546, 3.289]    C   0.771 [0.756, 0.78]
Draws40000                              gp     0.039 [0, 0.103]    Dxy 0.541 [0.512, 0.56]
   Chains4                              EV     0.105 [0, 0.305]
  Time7.6s                              v  4.819 [1.817, 8.385]
   p     3                              vp     0.004 [0, 0.018]

                               Mode Beta Mean Beta Median Beta S.E.    Lower    Upper   Pr(Beta>0) Symmetry
global_endo_epi_baseline_stress   28.9763   29.3070   29.0774     8.3060  13.4560 45.8596 0.9999     1.07
global_endo_epi_baseline_stress' -15.6803  -15.3578  -15.2873    10.6276 -36.0523  5.5083 0.0727     0.98
Treatment=Placebo                 -0.7396   -0.7574   -0.7556     0.4534  -1.6706  0.1159 0.0482     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S50: coefficient density plots: for global endo:epi stress myocardial blood flow



Supplementary figure S51: chain plot of MCMC draws for global endo:epi stress myocardial blood flow

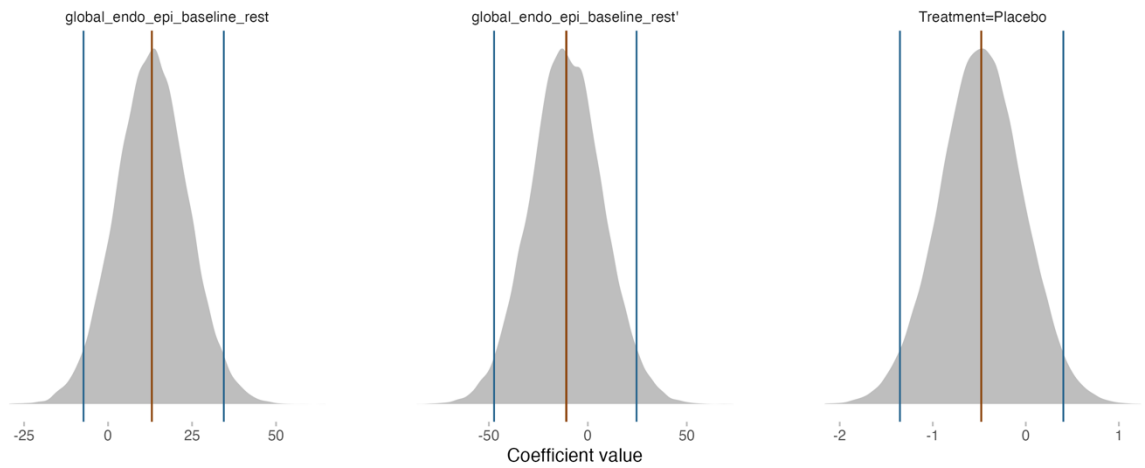


Secondary outcome: global endo:epi rest MBF

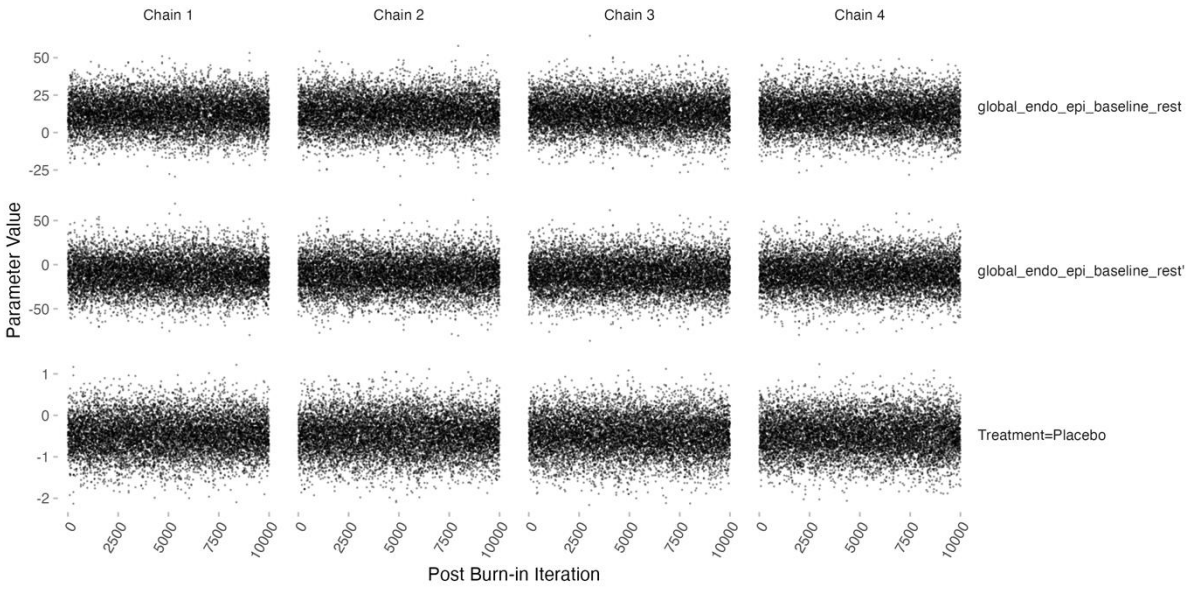
Regression model and coefficients for global endo:epi rest myocardial blood flow

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.057 for Intercepts

blrm(formula = global_endo_epi_followup_rest ~ rcs(global_endo_epi_baseline_rest,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

0.858719031307257 0.892955666858299 0.950647696289765 0.960314082924776 0.961038961038961 0.961610444664923 0.974607143306481 0.980289850632528
                1                 1                 1                 1                 1                 1                 1                 1
0.984811779983445 0.986197940261544 0.987951807228916 0.988889597460479 0.992610937436564 0.993898632997968 0.998598875492348  1.00181135266484
                1                 1                 1                 1                 1                 1                 1                 1
 1.00441948430295  1.01323074971228  1.02070178998879  1.02313024205815  1.02720230761149  1.03250568047704  1.03541743738822  1.03738317757009
                1                 1                 1                 1                 1                 1                 1                 1
 1.03877627796051  1.04046170674138  1.04177294323581  1.04232739236558   1.0448515466368  1.05185951871816  1.05567919455485  1.05673958027517
                1                 1                 1                 1                 1                 1                 1                 1
 1.06190286981376  1.06644425050541   1.0672845872426  1.06788948024869  1.06896551724138  1.08333333333333  1.10217317195525  1.11684192869953
                1                 1                 1                 1                 1                 1                 1                 1
 1.13544663665556  1.14548174977705  1.14869886827261   1.1519283681112   1.1558574031199  1.16306717190948  1.19110299309158  1.28884469166095
                1                 1                 1                 1                 1                 1                 1                 1

                   Mixed Calibration/              Discrimination              Rank Discrim.
                 Discrimination Indexes                    Indexes                   Indexes
   Obs  48    B  0.02 [0.016, 0.022]    g  0.783 [0.281, 1.336]    C    0.583 [0.526, 0.62]
Draws40000                              gp      0.016 [0, 0.05]    Dxy 0.166 [0.051, 0.239]
   Chains4                              EV     0.014 [0, 0.058]
  Time9.2s                              v  0.559 [0.045, 1.348]
   p     3                              vp     0.001 [0, 0.003]

                              Mode Beta Mean Beta Median Beta S.E.    Lower    Upper   Pr(Beta>0) Symmetry
global_endo_epi_baseline_rest   12.7945   13.0449   13.0447    10.6358  -7.3082 34.4466 0.8902     1.01
global_endo_epi_baseline_rest' -11.1245  -10.7887  -10.9407    18.3380 -47.3634 24.6157 0.2748     1.02
Treatment=Placebo               -0.4684   -0.4793   -0.4786     0.4468  -1.3528  0.4035 0.1418     0.98


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S52: coefficient density plots: for global endo:epi rest myocardial blood flow



Supplementary figure S53: chain plot of MCMC draws for global endo:epi rest myocardial blood flow

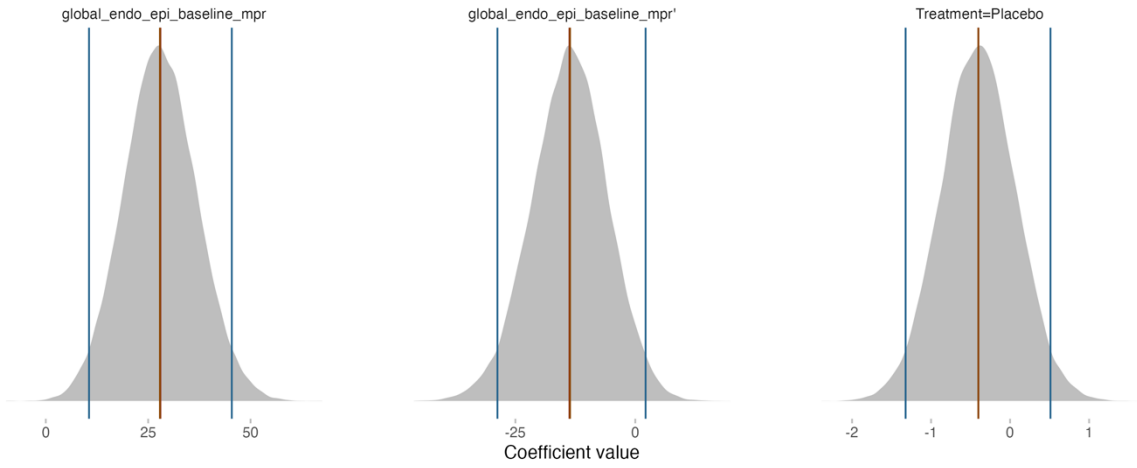


Secondary outcome: global endo:epi MPR

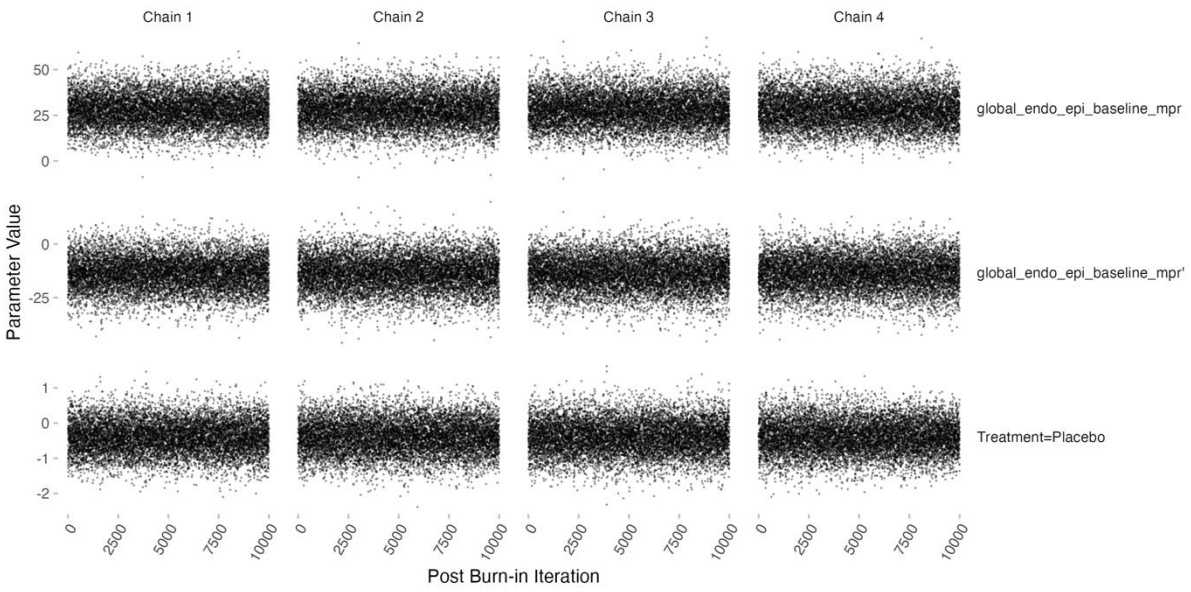
Regression model and coefficients for global endo:epi myocardial perfusion reserve

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.057 for Intercepts

blrm(formula = global_endo_epi_followup_mpr ~ rcs(global_endo_epi_baseline_mpr,
    3) + Treatment, data = main_analysis_d, pcontrast = pcon,
    iter = 20000, chains = 4, refresh = 100, progress = file.path(output_dir,
        "mri_res1.txt"), loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "mri_res1.blrm.rds"))


Frequencies of Responses

 0.59140570515241  0.59851373260571 0.636274416871609 0.642549673977085  0.65500068307406 0.660811914090848 0.661323792808019 0.661883999340767
                1                 1                 1                 1                 1                 1                 1                 1
0.675859162761879 0.690472531432682 0.720391122830147 0.721668373362298 0.722735546388176 0.725125626696553  0.73209302915073 0.739791705360183
                1                 1                 1                 1                 1                 1                 1                 1
0.740115326854658 0.740883434684277  0.74262595873839 0.746058265465105 0.749700456615998 0.754121549744195 0.754760258077602 0.756795940558173
                1                 1                 1                 1                 1                 1                 1                 1
0.773202676044957 0.773245722787007 0.773408644871122 0.788284868950991 0.793825942271029 0.809594745676485 0.813579208472791 0.817731081637843
                1                 1                 1                 1                 1                 1                 1                 1
0.820546302341673 0.825070475914481 0.825540864545912 0.835421945763077 0.836226607236863 0.863667135343436  0.86800235452291 0.872791133358569
                1                 1                 1                 1                 1                 1                 1                 1
0.891605718049255 0.899940186387053 0.943338727116873 0.968124100629515 0.977050698573579 0.999487303410276  1.14595983082881  1.29436070495472
                1                 1                 1                 1                 1                 1                 1                 1

               Mixed Calibration/              Discrimination              Rank Discrim.
             Discrimination Indexes                    Indexes                   Indexes
   Obs  48    B 0.017 [0.013, 0.021]    g  1.518 [0.874, 2.227]    C   0.683 [0.656, 0.699]
Draws40000                             gp     0.031 [0, 0.083]    Dxy 0.365 [0.312, 0.399]
   Chains4                             EV     0.079 [0, 0.253]
  Time6.8s                             v    2.024 [0.4, 3.711]
   p     3                             vp     0.003 [0, 0.012]

                            Mode Beta Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
global_endo_epi_baseline_mpr   26.8583   27.9877   27.8678    8.8778  10.5572 45.4153 0.9996     1.04
global_endo_epi_baseline_mpr' -12.9383  -13.7259  -13.6074    7.8630 -28.7489  2.1526 0.0389     0.95
Treatment=Placebo              -0.3894   -0.4021   -0.4022    0.4703  -1.3224  0.5109 0.1966     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S54: coefficient density plots: for global endo:epi myocardial perfusion reserve



Supplementary figure S55: chain plot of MCMC draws for global endo:epi myocardial perfusion reserve

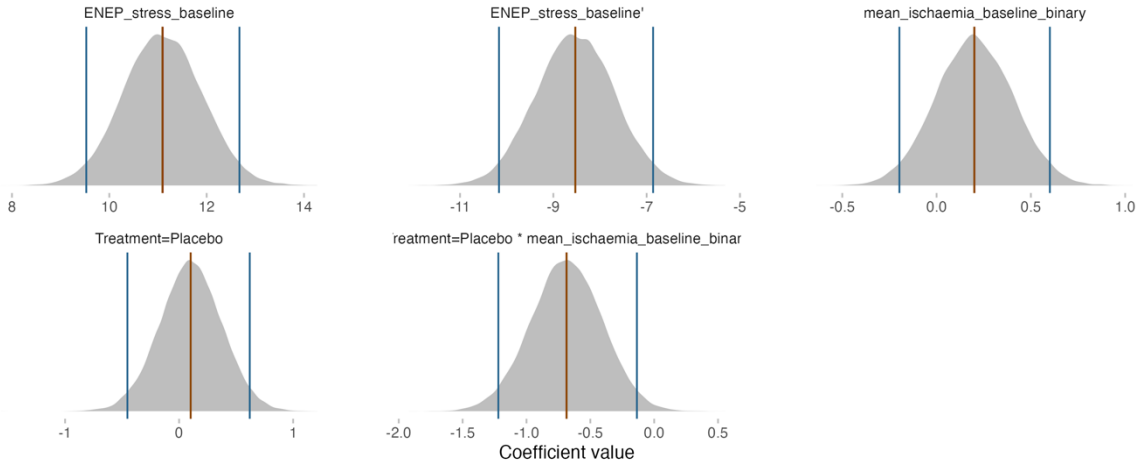


Secondary outcome: endo:epi stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

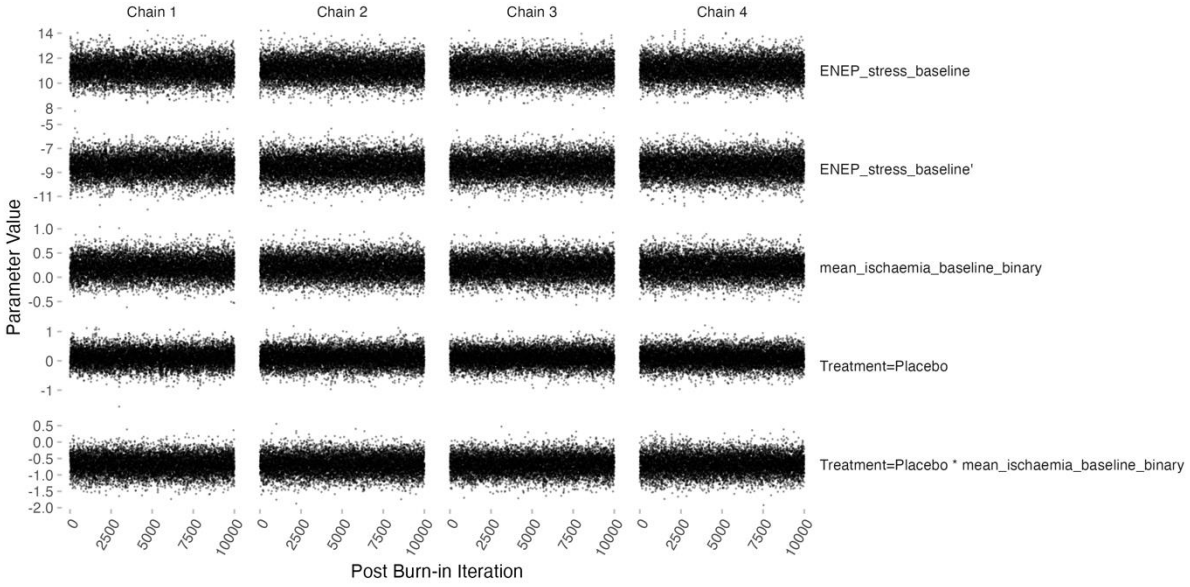
Regression model and coefficients for: endo:epi stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = ENEP_stress_followup ~ rcs(ENEP_stress_baseline,
    3) + Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))

                                      Mixed Calibration/             Discrimination              Rank Discrim.
                                    Discrimination Indexes                   Indexes                   Indexes
Obs                           768   B 0.001 [0.001, 0.001]   g  1.747 [1.542, 1.936]   C    0.728 [0.724, 0.73]
Draws                       40000                            gp     0.002 [0, 0.006]   Dxy 0.455 [0.447, 0.461]
Chains                          4                            EV     0.011 [0, 0.036]
Time                        812.7s                           v  2.471 [1.897, 2.999]
p                                5                           vp             0 [0, 0]
Cluster on                orbita_id
Clusters                        48
sigma gamma 0.7066 [0.4986, 0.9337]

                                                    Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
ENEP_stress_baseline                                 11.0979   11.0908     0.8058   9.5267 12.6738 1.0000     1.00
ENEP_stress_baseline'                                -8.5287   -8.5302     0.8452 -10.1646 -6.8620 0.0000     1.01
Treatment=Placebo                                     0.1011    0.1010     0.2724  -0.4536  0.6195 0.6487     0.99
mean_ischaemia_baseline_binary                        0.2009    0.1997     0.2039  -0.1972  0.6007 0.8378     1.01
Treatment=Placebo * mean_ischaemia_baseline_binary -0.6869   -0.6858     0.2775  -1.2202 -0.1352 0.0062     0.98


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S56: coefficient density plots: endo:epi stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



Supplementary figure S57: chain plot of MCMC draws for endo:epi stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

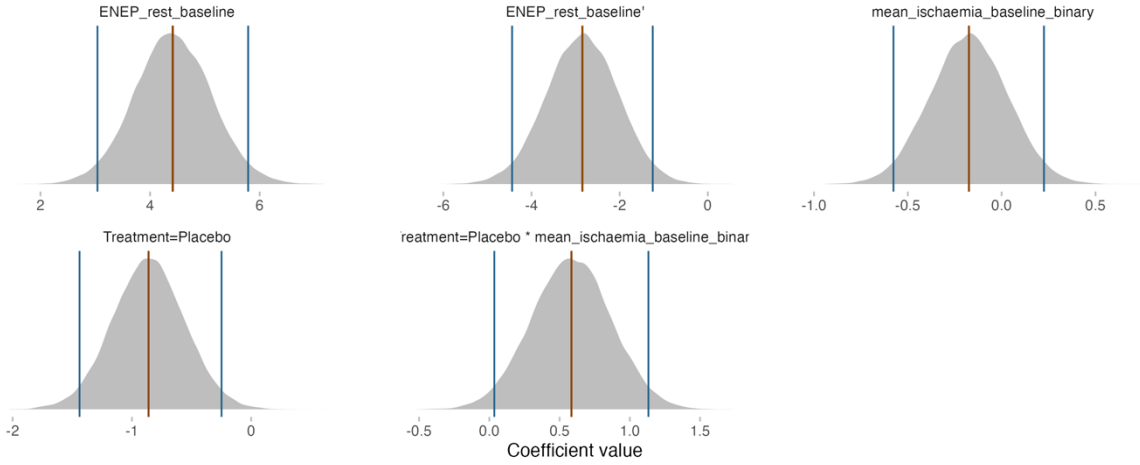


Secondary outcome: endo:epi rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

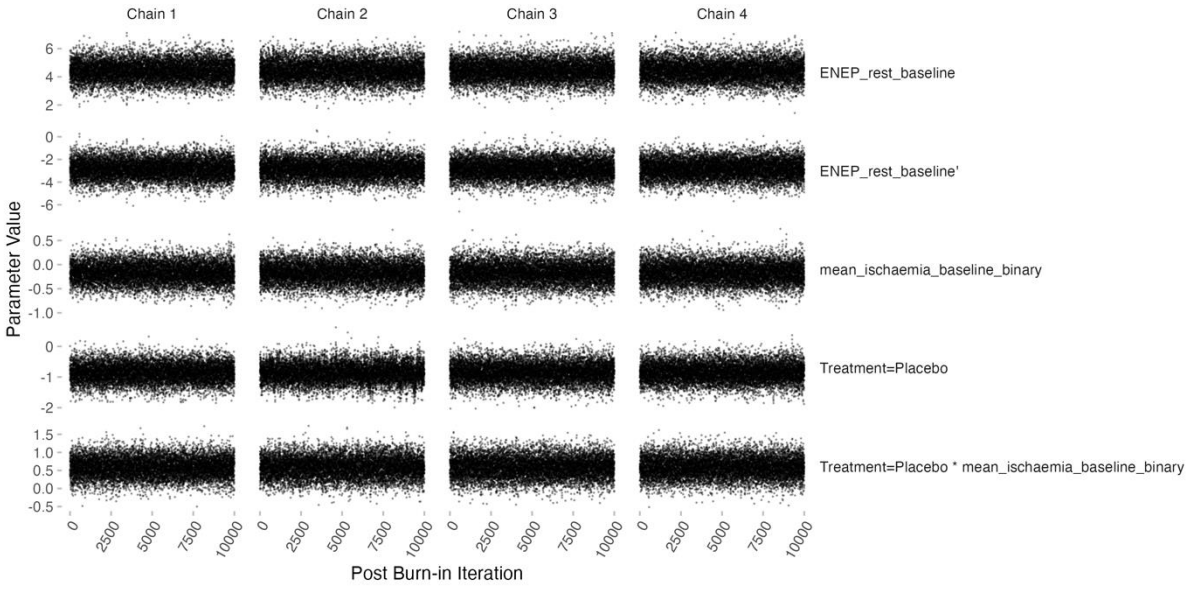
Regression model and coefficients for endo:epi rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = ENEP_rest_followup ~ rcs(ENEP_rest_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))

                                     Mixed Calibration/              Discrimination              Rank Discrim.
                                   Discrimination Indexes                    Indexes                    Indexes
Obs                            765   B 0.233 [0.229, 0.238]    g  0.666 [0.488, 0.875]    C   0.598 [0.587, 0.606]
Draws                        40000                             gp  0.15 [0.107, 0.187]    Dxy 0.195 [0.173, 0.212]
Chains                           4                             EV 0.075 [0.039, 0.109]
Time                         569s                              v    0.4 [0.217, 0.631]
p                                5                             vp  0.019 [0.01, 0.027]
Cluster on                orbita_id
Clusters                        48
sigma gamma 0.8787 [0.6507, 1.1269]

                                                 Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
ENEP_rest_baseline                                4.4164    4.4103     0.6984  3.0399  5.7900 1.0000     1.01
ENEP_rest_baseline'                              -2.8481   -2.8429     0.8133 -4.4399 -1.2500 0.0003     0.98
Treatment=Placebo                                -0.8607   -0.8601     0.3032 -1.4388 -0.2485 0.0026     1.00
mean_ischaemia_baseline_binary                   -0.1748   -0.1742     0.2057 -0.5766  0.2254 0.1980     1.00
Treatment=Placebo * mean_ischaemia_baseline_binary  0.5839    0.5849     0.2811  0.0355  1.1321 0.9813     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)

1
```

Supplementary figure S58: coefficient density plots: endo:epi rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment



Supplementary figure S59: chain plot of MCMC draws for endo:epi rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment

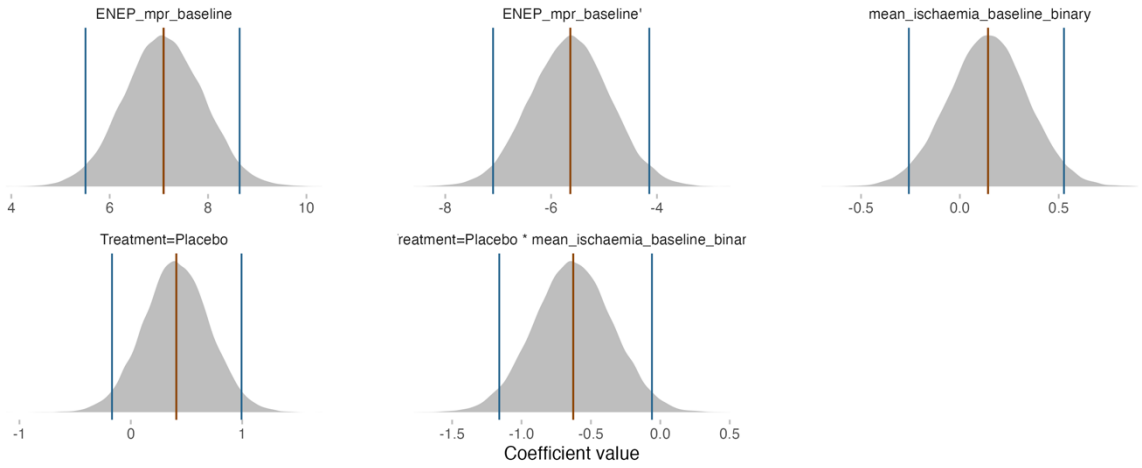


Secondary outcome: endo:epi myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

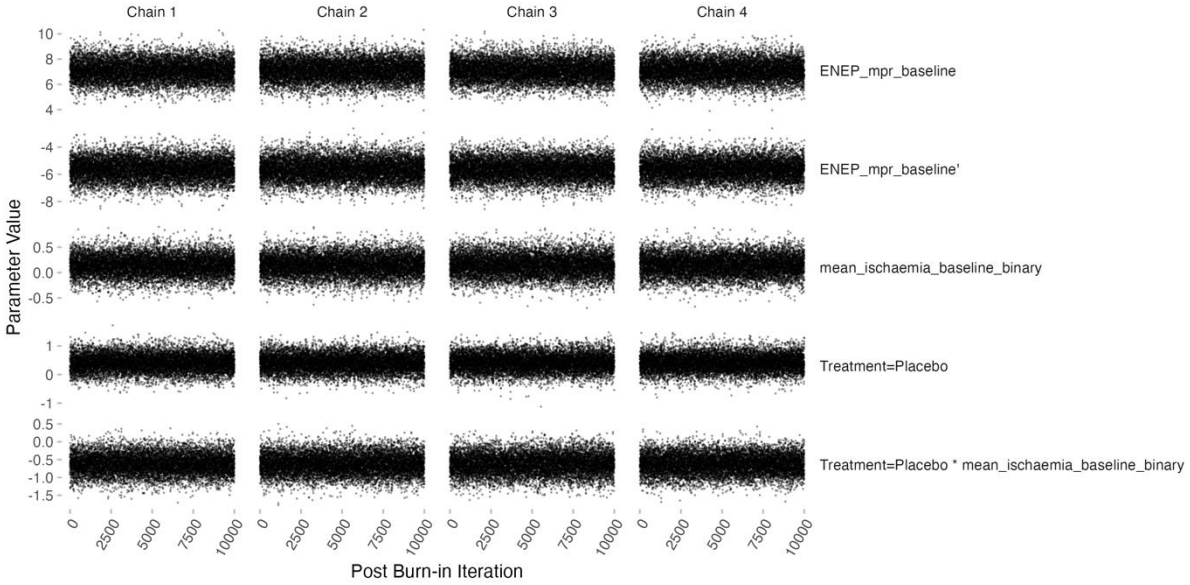
Regression model and coefficients for endo:epi myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.004 for Intercepts

blrm(formula = ENEP_mpr_followup ~ rcs(ENEP_mpr_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "res1.txt"),
    loo = FALSE, ppairs = NULL, file = file.path(output_dir,
        "res1.blrm.rds"))

                                    Mixed Calibration/              Discrimination              Rank Discrim.
                                  Discrimination Indexes                    Indexes                    Indexes
Obs                          765    B 0.217 [0.215, 0.222]    g      1 [0.831, 1.173]    C   0.657 [0.649, 0.662]
Draws                      40000                              gp 0.213 [0.185, 0.244]    Dxy 0.314 [0.299, 0.323]
Chains                         4                              EV 0.143 [0.108, 0.183]
Time                       485.5s                             v   0.85 [0.599, 1.176]
p                              5                              vp 0.036 [0.027, 0.045]
Cluster on              orbita_id
Clusters                      48
sigma gamma 0.8182 [0.6, 1.0665]

                                                  Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
ENEP_mpr_baseline                                  7.0990    7.0930     0.8032  5.5087  8.6414 1.0000     1.00
ENEP_mpr_baseline'                                -5.6382   -5.6357     0.7521 -7.0966 -4.1447 0.0000     1.01
Treatment=Placebo                                  0.4091    0.4078     0.2963 -0.1690  0.9940 0.9166     1.00
mean_ischaemia_baseline_binary                     0.1423    0.1429     0.2005 -0.2581  0.5267 0.7638     0.99
Treatment=Placebo * mean_ischaemia_baseline_binary -0.6268   -0.6279     0.2802 -1.1602 -0.0604 0.0124     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S60: coefficient density plots: endo:epi myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment



Supplementary figure S61: chain plot of MCMC draws for endo:epi myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment

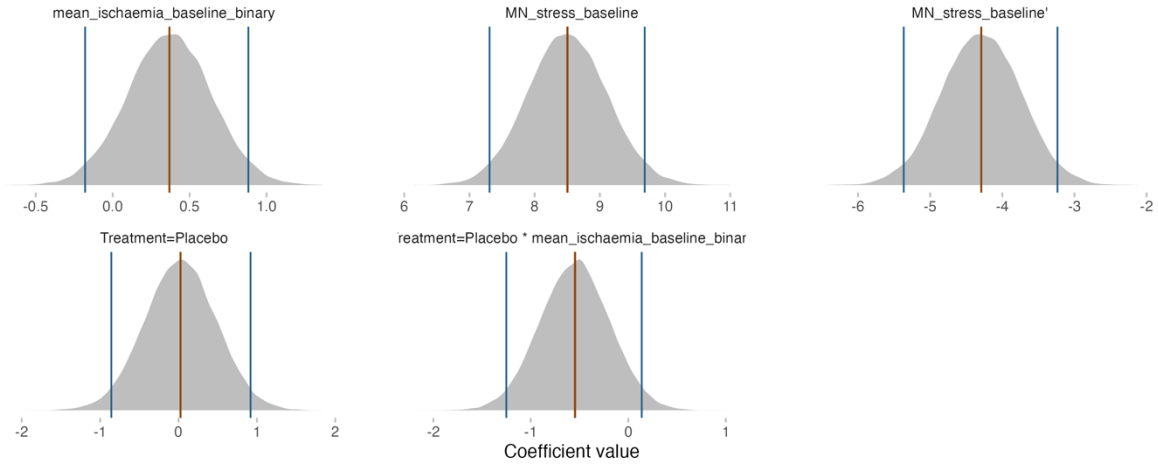


Secondary outcome: stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

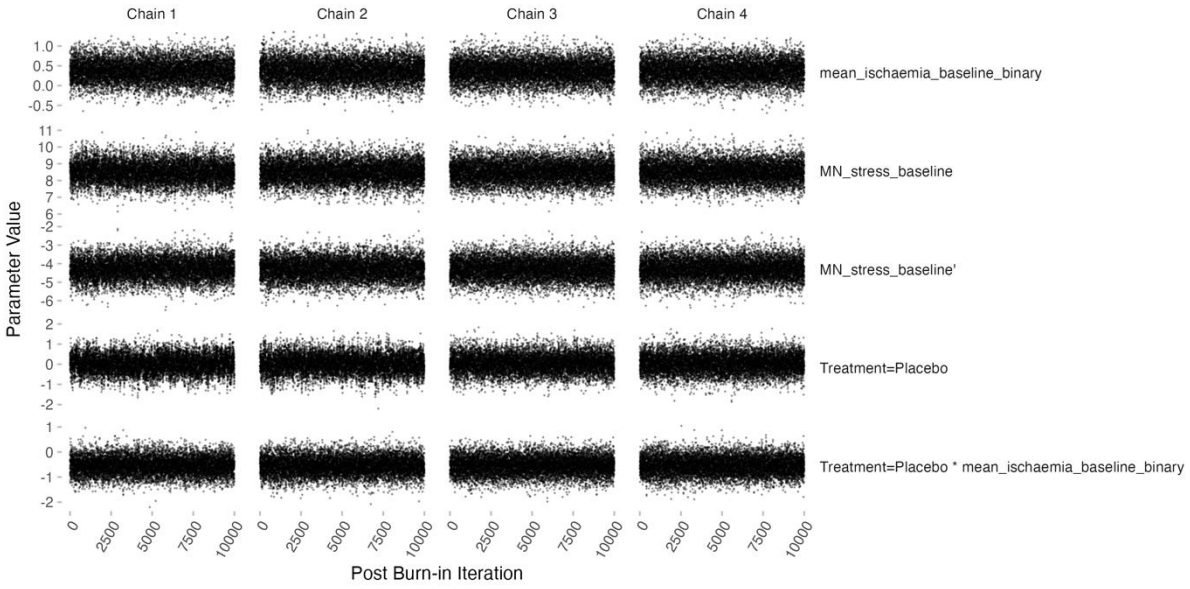
Regression model and coefficients for stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.006 for Intercepts

blrm(formula = MN_stress_followup ~ rcs(MN_stress_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "mri_res1.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "mri_res1.blrm.rds"))

                                      Mixed Calibration/             Discrimination              Rank Discrim.
                                    Discrimination Indexes                   Indexes                   Indexes
Obs                           528   B 0.002 [0.002, 0.002]   g  2.919 [2.564, 3.211]   C   0.767 [0.761, 0.77]
Draws                       40000                            gp     0.001 [0, 0.004]   Dxy 0.534 [0.523, 0.54]
Chains                          4                            EV     0.011 [0, 0.037]
Time                        274.4s                            v     6.852 [5.2, 8.22]
p                               5                            vp             0 [0, 0]
Cluster on                orbita_id
Clusters                       48
sigma gamma 1.681 [1.3028, 2.1204]

                                                  Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
MN_stress_baseline                                 8.5052    8.5001     0.6072  7.3078  9.6878 1.0000     1.02
MN_stress_baseline'                               -4.2920   -4.2912     0.5432 -5.3671 -3.2358 0.0000     0.99
Treatment=Placebo                                  0.0254    0.0266     0.4557 -0.8569  0.9187 0.5240     0.99
mean_ischaemia_baseline_binary                     0.3685    0.3691     0.2701 -0.1793  0.8818 0.9132     1.00
Treatment=Placebo * mean_ischaemia_baseline_binary -0.5480   -0.5447     0.3560 -1.2515  0.1379 0.0619     1.00


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd =
0.842807127883599)
```

Supplementary figure S62: coefficient density plots: for stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded



Supplementary figure S63: chain plot of MCMC draws for stress myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

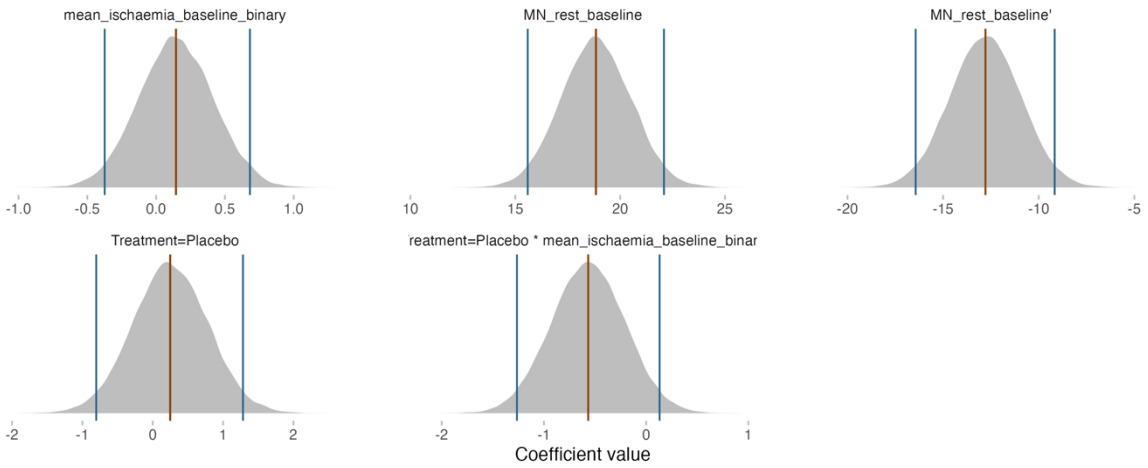


Secondary outcome: rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

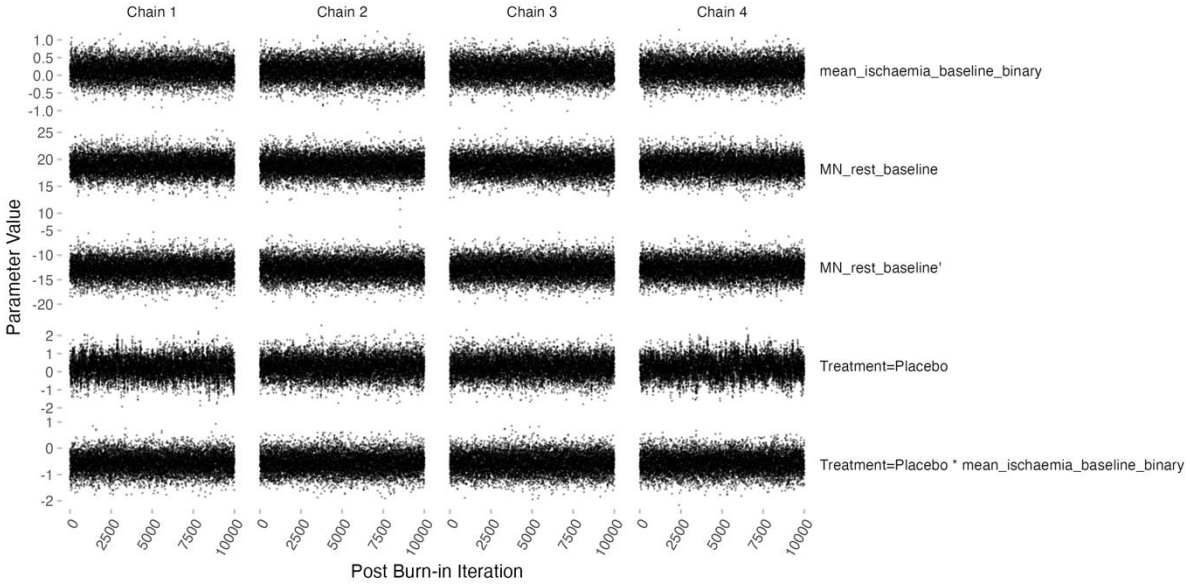
Regression model and coefficients for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.006 for Intercepts

blrm(formula = MN_rest_followup ~ rcs(MN_rest_baseline, 3) +
    Treatment * mean_ischaemia_baseline_binary + cluster(orbita_id),
    data = main_analysis_d, pcontrast = pcon, iter = 20000, chains = 4,
    refresh = 100, progress = file.path(output_dir, "mri_res1.txt"),
    loo = FALSE, ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "mri_res1.blrm.rds"))

                                      Mixed Calibration/              Discrimination              Rank Discrim.
                                    Discrimination Indexes                    Indexes                    Indexes
Obs                           528   B 0.004 [0.002, 0.005]   g  2.507 [2.133, 2.867]   C   0.728 [0.72, 0.732]
Draws                       40000                            gp     0.005 [0, 0.009]   Dxy 0.456 [0.44, 0.463]
Chains                          4                            EV 0.561 [0.061, 0.847]
Time                        370.5s                           v  5.339 [3.676, 6.689]
p                                5                           vp     0.002 [0, 0.004]
Cluster on                orbita_id
Clusters                        48
sigma gamma 2.2108 [1.7508, 2.7439]

                                                  Mean Beta Median Beta S.E.   Lower    Upper   Pr(Beta>0) Symmetry
MN_rest_baseline                                   18.8529   18.8418    1.6649  15.5947 22.0893 1.0000     1.01
MN_rest_baseline'                                 -12.7862  -12.7842    1.8550 -16.4360 -9.1671 0.0000     1.00
Treatment=Placebo                                   0.2499    0.2456    0.5327  -0.8035  1.2826 0.6815     0.99
mean_ischaemia_baseline_binary                      0.1450    0.1436    0.2700  -0.3740  0.6818 0.7048     1.01
Treatment=Placebo * mean_ischaemia_baseline_binary -0.5675   -0.5671    0.3588  -1.2642  0.1316 0.0558     1.00

Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S64: coefficient density plots: for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded



Supplementary figure S65: chain plot of MCMC draws for rest myocardial blood flow in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

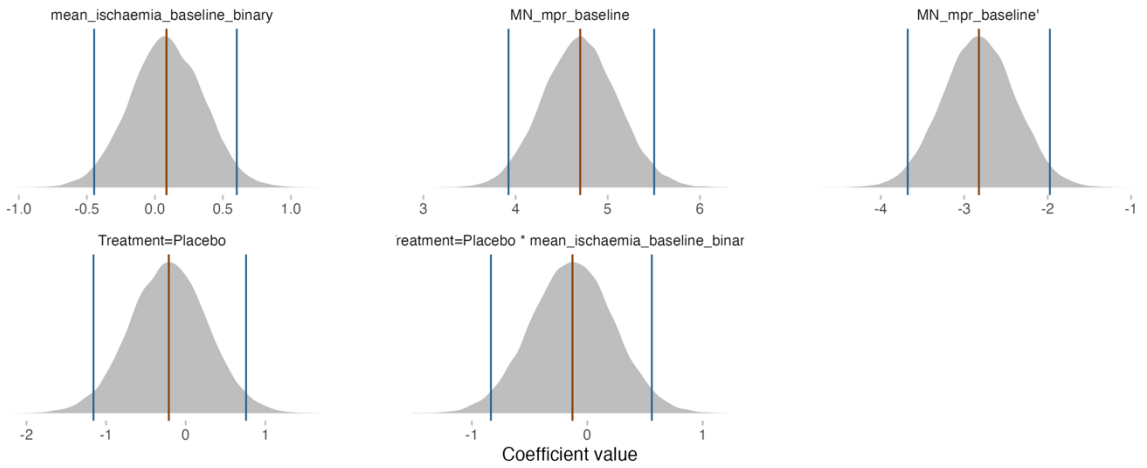


Secondary outcome: myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

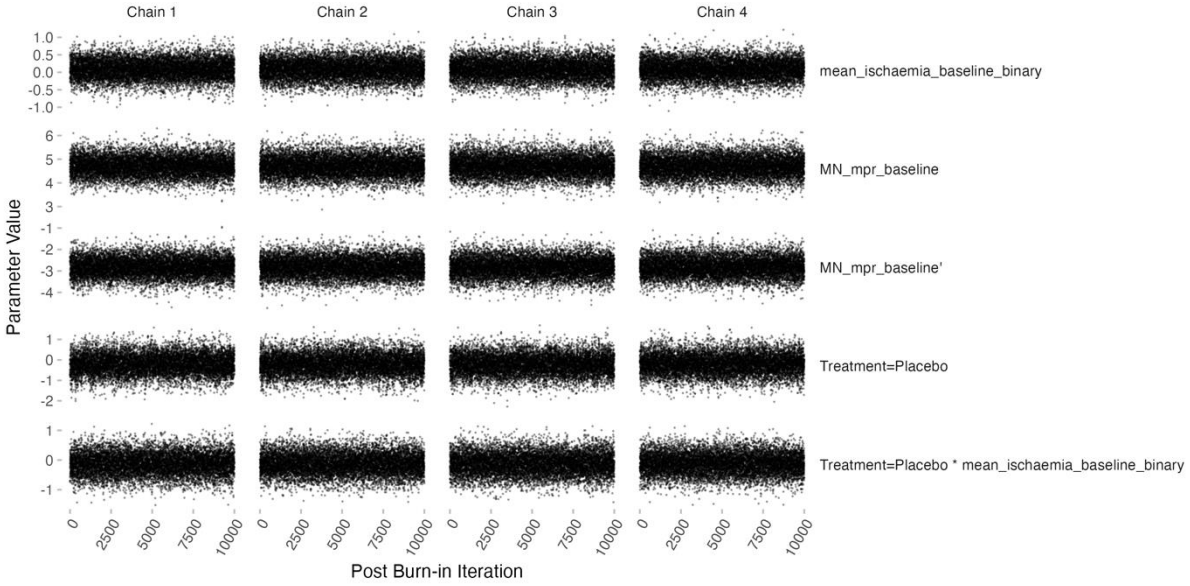
Regression model and coefficients myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.005 for Intercepts

blrm(formula = MN_mpr_followup ~ rcs(MN_mpr_baseline, 3) + Treatment *
    mean_ischaemia_baseline_binary + cluster(orbita_id), data = main_analysis_d,
    pcontrast = pcon, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "mri_res1.txt"), loo = FALSE,
    ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "mri_res1.blrm.rds"))

                                    Mixed Calibration/              Discrimination              Rank Discrim.
                                  Discrimination Indexes                    Indexes                    Indexes
Obs                          526  B 0.002 [0.002, 0.002]   g   2.28 [1.976, 2.575]   C   0.739 [0.732, 0.742]
Draws                      40000                            gp     0.001 [0, 0.002]   Dxy 0.477 [0.464, 0.484]
Chains                         4                            EV     0.005 [0, 0.017]
Time                       490.4s                           v  4.183 [3.107, 5.292]
p                               5                           vp             0 [0, 0]
Cluster on                orbita_id
Clusters                       48
sigma gamma 1.8422 [1.4381, 2.3012]

                                                    Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
MN_mpr_baseline                                      4.7021    4.6999     0.4053  3.9230  5.5037 1.0000     1.03
MN_mpr_baseline'                                    -2.8229   -2.8232     0.4374 -3.6765 -1.9733 0.0000     1.00
Treatment=Placebo                                   -0.2130   -0.2121     0.4856 -1.1583  0.7585 0.3305     0.99
mean_ischaemia_baseline_binary                       0.0861    0.0848     0.2692 -0.4464  0.6022 0.6250     0.99
Treatment=Placebo * mean_ischaemia_baseline_binary -0.1291   -0.1278     0.3557 -0.8347  0.5583 0.3594     1.00

Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599)
```

Supplementary figure S66: coefficient density plots: for myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded



Supplementary figure S67: chain plot of MCMC draws myocardial perfusion reserve in segments ischaemic and non-ischaemic at enrolment, inferior and inferoseptal segments excluded



Secondary outcome: myocardial strain

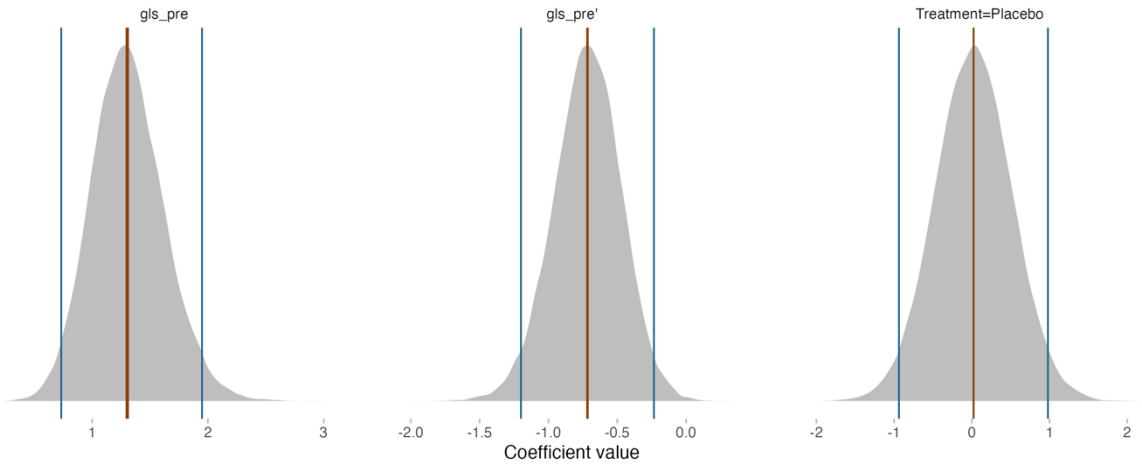
Supplementary table 15: myocardial strain

Secondary imaging outcomes – myocardial strain – global longitudinal strain %			
	CSR	Placebo	Pr(Benefit)
n	21	21	
Baseline median	15·9		
Follow-up	16·3 (15·3 to 17·3)	16·3 (15·5 to 17·1)	
Increment	0·4 (-0·6 to 1·4)	0·4 (-0·4 to 1·2)	
Benefit of CSR over placebo	-0·0 (-1·1 to 1·0)		48·2%

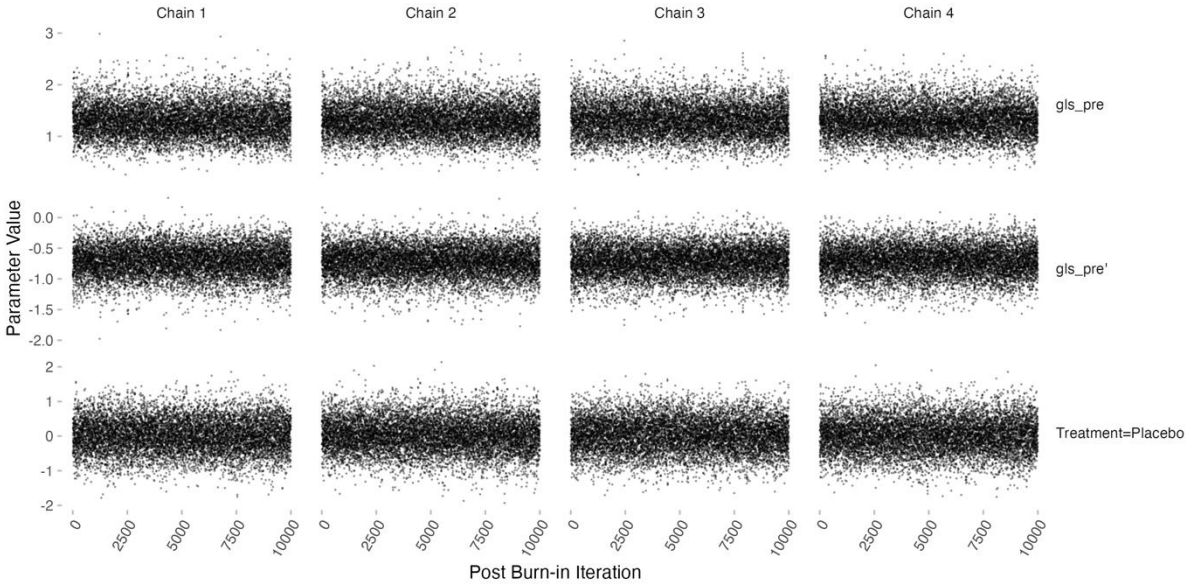
Regression model and coefficients myocardial strain

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.073 for Intercepts

blrm(formula = gls_post ~ rcs(gls_pre, 3) + Treatment, data = gls_res1_d,
    pcontrast = con, iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "res1.txt"), loo = FALSE,
    ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "res1.blrm.rds"))


Frequencies of Responses

10.9 11.3 11.5 11.9 12.2 12.4 12.6 13.5 13.7 13.8 14.1 14.3 14.5 14.7 14.8 15.5 15.7 15.8 15.9   16 16.2 16.3 16.5 16.6 16.9   17 17.1 17.5   18 18.1
   1    1    1    1    1    1    2    1    1    1    1    1    1    1    2    1    1    2    3    1    1    1    1    1    1    1    1    1    1
18.2 18.3 18.4 19.1 19.5 20.4 22.8
   1    1    1    1    1    1    1

                Mixed Calibration/              Discrimination              Rank Discrim.
              Discrimination Indexes                    Indexes                   Indexes
   Obs  42    B 0.018 [0.014, 0.024]    g   2.363 [1.603, 3.416]    C   0.758 [0.736, 0.769]
Draws40000                             gp      0.044 [0, 0.107]    Dxy 0.516 [0.472, 0.538]
   Chains4                             EV  0.223 [0.001, 0.511]
  Time5.3s                             v  5.944 [1.989, 11.288]
   p     3                             vp      0.008 [0, 0.028]

                 Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
gls_pre           1.3107    1.2964     0.3114  0.7115  1.9277 1.0000     1.13
gls_pre'         -0.7202   -0.7129     0.2452 -1.2141 -0.2545 0.0009     0.93
Treatment=Placebo  0.0182    0.0205     0.4879 -0.9372  0.9706 0.5166     0.99


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S68: coefficient density plots: for myocardial strain



Supplementary figure S69: chain plot of MCMC draws myocardial strain



Secondary outcome: myocardial scar

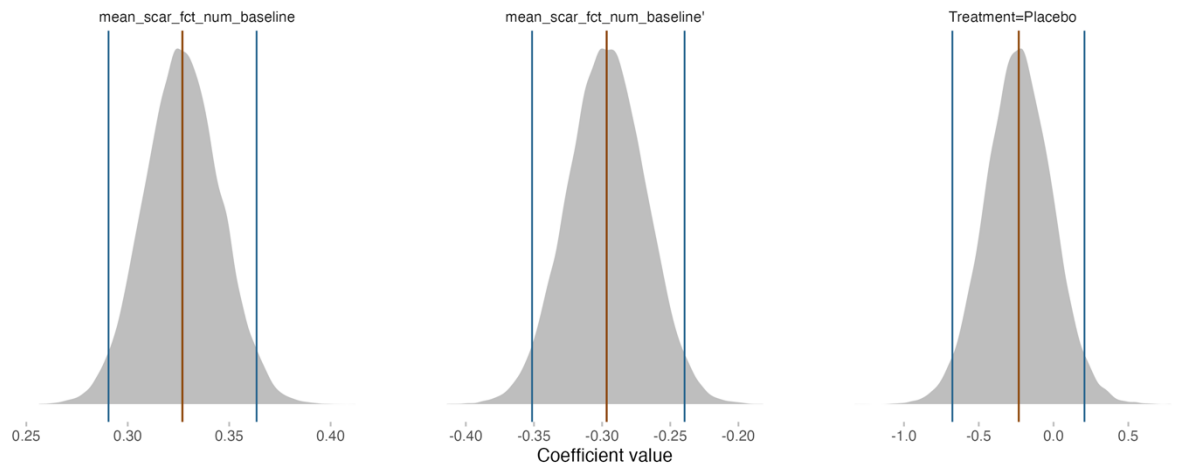
Supplementary table 16: myocardial scar

Secondary imaging outcomes – myocardial scar			
	CSR	Placebo	Pr(Benefit)
Segments (n)	408	442	
Mean % scar	8·1		
Follow-up	7·4 (6·1 to 8·8)	6·5 (5·4 to 7·7)	
Increment	-0·7 (-2·0 to -0·7)	-1·6 (-2·8 to -0·4)	
Benefit of CSR over placebo	0·9 (-0·8 to 2·5)		14·9%

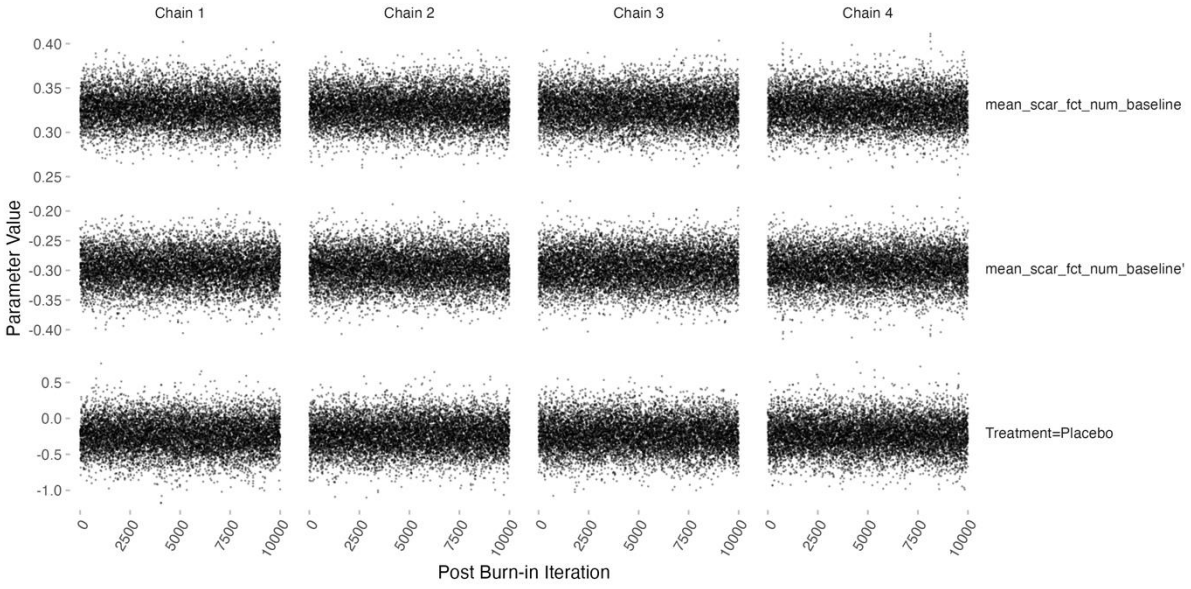
Regression model and coefficients myocardial scar

```
Bayesian Proportional Odds Ordinal Logistic Model

Dirichlet Priors With Concentration Parameter 0.025 for Intercepts

blrm(formula = mean_scar_fct_num_followup ~ rcs(mean_scar_fct_num_baseline,
    3) + Treatment + cluster(orbita_id), data = mri_res1_d, pcontrast = con,
    backend = "cmdstan", iter = 20000, chains = 4, refresh = 100,
    progress = file.path(output_dir, "mri_res1.txt"), loo = FALSE,
    ppairs = NULL, method = "sampling", file = file.path(output_dir,
        "mri_res1.blrm.rds"))

                                      Mixed Calibration/             Discrimination              Rank Discrim.
                                    Discrimination Indexes                   Indexes                    Indexes
Obs                           850    B  0.118 [0.116, 0.12]    g  2.715 [2.476, 3.003]    C   0.889 [0.883, 0.89]
Draws                       40000                              gp 0.348 [0.329, 0.364]    Dxy 0.777 [0.767, 0.78]
Chains                          4                              EV 0.475 [0.423, 0.531]
Time                        106.7s                             v  7.708 [6.216, 9.092]
p                               3                              vp 0.117 [0.104, 0.128]
Cluster on                orbita_id
Clusters                       50
sigma gamma 0.592 [0.3613, 0.849]

                          Mean Beta Median Beta S.E.   Lower   Upper   Pr(Beta>0) Symmetry
mean_scar_fct_num_baseline   0.3270    0.3269     0.0186  0.2905  0.3635 1.0000     1.01
mean_scar_fct_num_baseline' -0.2967   -0.2966     0.0286 -0.3514 -0.2395 0.0000     1.00
Treatment=Placebo           -0.2322   -0.2326     0.2241 -0.6764  0.2068 0.1474     1.01


Contrasts Given Priors

[1] list(c1 = list(Treatment = "CSR"), c2 = list(Treatment = "Placebo"),      contrast = expression(c1 - c2), sd = 0.842807127883599, mu = 0)
```

Supplementary figure S70: coefficient density plots: for myocardial scar



Supplementary figure S71: chain plot of MCMC draws myocardial scar



Blinding index at follow-up

At this time-point patients had experience of any change in symptoms, which could therefore have influenced their guess. The blinding index for patients in the CSR arm was 0.29 (95% CI -0.00 to 0.59) and in the placebo arm was 0.31 (95% CI 0.01 to 0.60).

The medical team completed their blinding questionnaire immediately before speaking to the patient at the follow-up visit. The blinding index for staff in the CSR arm was 0.12 (95% CI -0.01 to 0.26) and in the placebo arm was 0.12 (95% CI -0.05 to 0.28).

The fidelity of blinding was also assessed at the point of CMR reporting. Reporters were instructed to report if they could detect a CSR on any of the available sequences. In only 2 instances across the 606 scan reports did a reporter feel able to give an answer. In one instance they were correct and in the other they were incorrect.

REFERENCES

1Kellman P, Hansen MS, Nielles-Vallespin S, *et al.* Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. *J Cardiovasc Magn Reson* 2017; **19**: 43.

2Ganesananthan S, Rajkumar CA, Foley M, Francis D, Al-Lamee R. Remote digital smart device follow-up in prospective clinical trials: early insights from ORBITA-2, ORBITA-COSMIC, and ORBITA-STAR. *European Heart Journal Supplements* 2022; **24**: H32–42.

Study protocol

Imperial College London

ORBITA-COSMIC

ORBITA-COSMIC – Coronary sinus reducer Objective impact on Symptoms, MRI Ischaemia and microvascular Resistance

Study Management Group

Principal Investigator: Dr Rasha Al-Lamee

Co-investigators:
Professor Darrel Francis
Dr Matthew Shun-Shin (statistician)
Dr Frank Harrell (statistician)
Dr Graham Cole
Dr James Howard
Dr Michael Foley
Dr John Davies
Dr Peter O'Kane
Dr Jonathan Hill
Dr James Spratt
Dr Claudia Cosgrove
Dr Tushar Kotecha

MAIN SPONSOR: Imperial College London
FUNDERS: Medical Research Council, The Nissen Fund
STUDY COORDINATION CENTRE: The National Heart and Lung Institute, B Block, Hammersmith Hospital, Du Cane Road, W12 0HS
IRAS Project ID: **288725**
REC reference: **21/LO/0203**

Protocol authorised by:

Imperial College London

Name & Role	Date	Signature
Dr Rasha Al-Lamee Principal Investigator	06/01/2021	

Clinical Queries

Clinical queries should be directed to Dr Michael Foley who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

This protocol describes the ORBITA-COSMIC study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Principal Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research It will be conducted in compliance with the protocol, Data Protection Act 2018 and General Data Protection Regulations (Europe) and other regulatory requirements as appropriate.

Keywords

Imperial College London

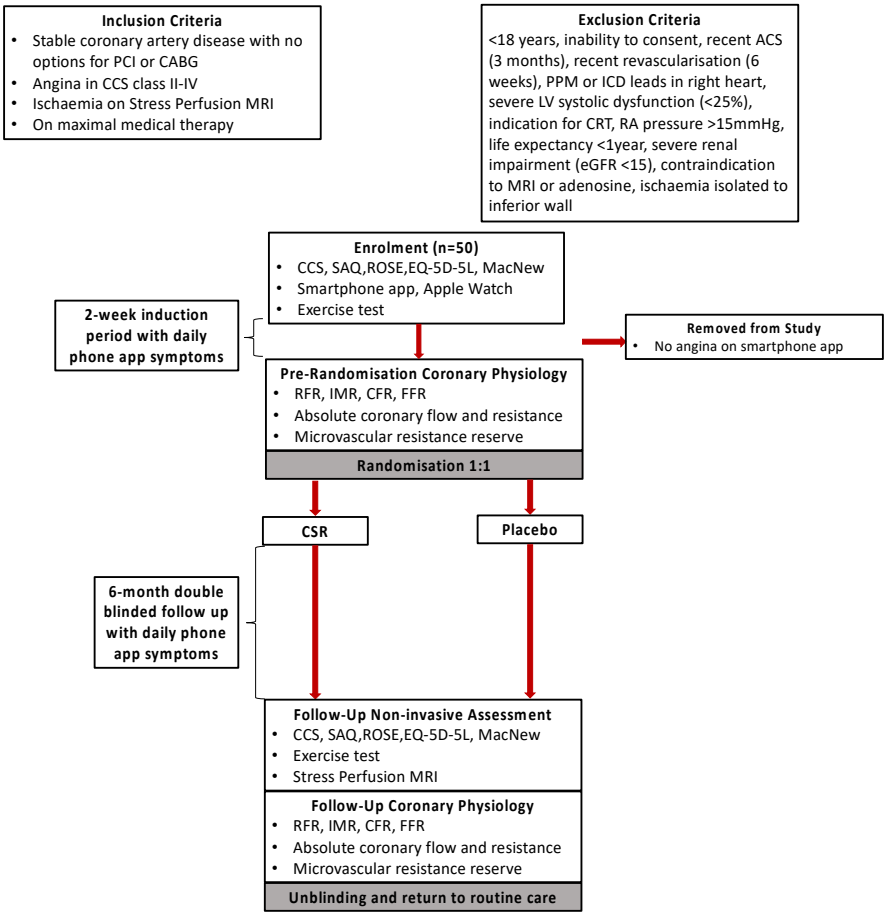
Coronary Sinus Reducer, Refractory Angina, Myocardial Ischaemia, Microvascular Resistance

Study Summary

TITLE	ORBITA-COSMIC: Coronary sinus reducer Objective impact on Symptoms, MRI Ischaemia and microvascular Resistance
DESIGN	Double blinded, randomised, placebo-controlled trial
AIMS	To investigate the mechanism of action of the coronary sinus reducer and its placebo-controlled impact on myocardial ischaemia, coronary flow, microvascular resistance and symptoms
OUTCOME MEASURES	Primary outcome: Change in myocardial blood flow on MRI between the groups
POPULATION	Patients with refractory angina
ELIGIBILITY	Refractory angina, stable coronary artery disease with no further options for revascularisation
DURATION	6 months

Reference Diagram

Imperial College London



Imperial College London

Table of Contents

Imperial College London

1. INTRODUCTION

1.1 Background

Approximately 10% of patients referred for coronary angiography have angina which is refractory to all conventional therapies (refractory angina). (1) This group of patients has a high symptom burden, significant healthcare use and poor quality of life. The coronary sinus reducer (CSR) is a novel device which has been developed for the treatment of refractory angina.

The CSR is a wire mesh device, mounted upon a single sized delivery balloon and is delivered into the coronary sinus using an over-the-wire technique under fluoroscopy. Following implantation, inflammation surrounding the struts causes the spaces to close off, leaving the 3mm lumen as the only route of drainage through the coronary sinus. In an animal model, coronary sinus ligation increased blood flow to ischaemic areas of myocardium and increased sub-endocardial: sub-epicardial perfusion gradient. (2) This is the hypothesised mechanism for angina relief in humans, though this has never been demonstrated. Its use is supported by the placebo-controlled double-blinded randomised Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) trial which showed improvement in angina symptoms with the device.(3) It is now recommended in the European Society of Cardiology guidelines for the treatment of refractory angina however, the mechanism of action of the device is unknown.(4)

1.2 Study Rationale

This study is designed to investigate the mechanism of action of the CSR and to identify which patients receive the most benefit. It will utilise quantitative MRI perfusion, coronary pressure wire assessments, symptom assessments and exercise time in a randomised, double-blinded, placebo-controlled study. This will fill a vital knowledge gap, advancing our understanding of the CSR and will support physicians and patients managing refractory angina to access appropriate therapy.

2. STUDY OBJECTIVES

Primary Objective

- To discover the mechanism of action of the CSR in patients with refractory angina.

Secondary Objective

- To discover which patients are most likely to benefit from the coronary sinus reducer.
- Investigate the double-blinded, placebo-controlled impact of the CSR on myocardial perfusion on stress perfusion cardiac MRI scans in patients with refractory angina.
- Investigate the double-blinded, placebo-controlled impact of the CSR on coronary pressure wire assessed index of microcirculatory resistance.

- Investigate the double-blinded, placebo-controlled impact of the CSR on exercise time, physician-assessed and patient-reported angina symptoms.

Other Objectives

- This study will be the setting for a Medical Research Council funded Clinical Research Training Fellowship for Dr Michael Foley. It will form the basis of his doctoral degree.

3. STUDY DESIGN

Type of Study: A randomised, double-blinded, placebo-controlled trial, in 50 participants with refractory angina

Recruitment methods: Participants will be recruited from a number of sources including

- Joint Cardiology Cardiothoracic Meeting
- Cardiac catheterisation laboratory
- Cardiology outpatient clinics

If participants have angina which is refractory to medical therapy, they will be referred to the research fellow. The research fellow will provide each participant with a patient information sheet and will discuss the trial in detail, explaining the protocol, the risks and the benefits. The potential participant will then have at least 24 hours to consider participation before a follow up consultation with the research fellow. If the potential participant is interested in participating, a trial consent form will be completed at this stage.

Study Design

Patients will be assessed at 3 time points: enrolment, pre-randomisation coronary physiology assessment and follow up. Enrolment assessment will consist of symptom questionnaires, establishing a smartphone application (app) for daily angina symptom scoring, and reviewing the stress perfusion cardiac MRI (CMR) (needed on clinical grounds for enrolment to the study). There will be a 2-week period prior to randomisation during which participants input their angina symptoms into the smartphone app. They will also undergo a treadmill exercise test.

On the day of randomisation participants will have a coronary angiogram and invasive measures of coronary flow (Coronary flow reserve, Absolute Flow, fractional flow reserve, FFR) will be taken as well as a measure of microvascular resistance (IMR). These will be acquired using coronary pressure wires (Pressure Wire X, Abbott, Combowire, Phillips) and the Rayflow Catheter.

Participants will be randomly allocated 1:1 to CSR implantation or placebo with blinding maintained for participants with over the ear headphones for auditory isolation and a deep level of conscious sedation. Over the next 6 months, participants will complete their smartphone app. After 6 months, participants will return for repeat questionnaires, exercise treadmill tests, cardiac catheter lab assessment and CMR.

Study Outcomes – Table 1

Study Primary Outcome	
CMR	MBF on CMR*
Imaging Secondary Outcomes	
CMR	MPR in ischaemic segments, non-ischaemic segments, and global MPR
	Rest MBF in ischaemic segments, non-ischaemic segments, and global rest MBF Stress MBF in ischaemic segments with inferior and inferoseptal segments excluded
	MPR in ischaemic segments with inferior and inferoseptal segments excluded
	Rest MBF in ischaemic segments with inferior and inferoseptal segments excluded
	Endocardial:epicardial ratio of stress MBF
	Endocardial:epicardial ratio of MPR
	Endocardial:epicardial ratio of rest MBF
	Myocardial strain
	Myocardial scar burden
Symptom Primary Outcome	
Patient Reported	Episodes of angina component of angina symptom score
Symptom Secondary Outcomes	
Physician Assessed	CCS
Patient Reported	Angina symptom score
	SAQ angina frequency
	SAQ angina physical limitation
	SAQ quality of life
	SAQ treatment satisfaction
	SAQ angina stability
	EQ-5D-5L descriptive system
	EQ-5D-5L visual analogue scale
	Angina related quality of life rated by the MacNew questionnaire

Other	Treadmill exercise time
Invasive Physiology Substudy Outcomes	
Invasive Physiology	Absolute Flow assessed by a pressure and temperature sensor wire (*PressureWireX, Abbott, USA)* and an intracoronary saline infusion catheter *(RayFlow™, Hexacath, France)*
	Absolute Resistance assessed by a pressure and temperature sensor wire and an intracoronary saline infusion catheter
	MRR assessed by a pressure and temperature sensor wire and an intracoronary saline infusion catheter
	CFR assessed by a pressure and temperature sensor wire
	IMR assessed by a pressure and temperature sensor wire
	CFR assessed by a pressure and doppler sensor wire (*Combowire, Philips, USA)*

*Table 1. MBF = myocardial blood flow, CMR = cardiac magnetic resonance, MPR = myocardial perfusion reserve, CCS = Canadian Cardiovascular Society Class, SAQ = Seattle Angina Questionnaire, EQ-5D-5L = EuroQol Questionnaire, MRR = microvascular resistance reserve CFR = coronary flow reserve, IMR = index of microcirculatory resistance. *MBF is measured during adenosine stress and will be calculated in segments which were designated ischaemic on the baseline CMR.*

Duration of Study

The study will last from January 2021 to January 2024 (36 months)

Number of Participants

This study will enrol 50 participants

4. PARTICIPANT RECRUITMENT

4.1 Pre-recruitment evaluations

In order to be eligible for the CSR in clinical guidelines, patients must have evidence of ischaemia on a non-invasive test. In clinical practice, this test is a stress perfusion CMR.

Imperial College London

4.2 Inclusion Criteria

These are clinical criteria for CSR eligibility. We are investigating the patient group for whom the CSR is intended and in routine clinical practice.

Inclusion Criteria:

- Stable coronary artery disease (CAD) not eligible for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)
- Evidence of ischaemia on stress perfusion CMR
- Angina – Canadian Cardiovascular Society Class II-VI on maximal medical therapy

4.3 Exclusion Criteria

Exclusion Criteria:

- Age<18 years
- Pregnancy
- Inability to consent
- Recent acute coronary syndrome (3 months)
- Recent revascularisation (6 weeks)
- Permanent pacemaker or defibrillator leads in the right heart
- Severe left ventricular impairment (<25%)
- Indication for cardiac resynchronisation therapy (CRT)
- Right atrial pressure ≥15mmHg
- Life expectancy <1 year
- Severe renal impairment (eGFR<15)
- Contraindication to CMR
- Contraindication to adenosine
- Ischaemia isolated to inferior wall
- Ongoing participation in a separate interventional study

Patients who have had recent acute coronary syndrome (ACS) and recent PCI will be excluded because CSR is not clinically indicated and has not been studied in these patients. Patients with a left ventricular ejection fraction<25% have not previously been investigated with the CSR. This group are also likely to have a large burden of myocardial scar and their CMR will be difficult to interpret. Patients with an indication for CRT will be excluded because the coronary sinus is needed for CRT pacing. CMR ischaemia is the primary outcome of the study therefore patients who cannot tolerate CMR will be excluded. The protocol involves adenosine stress during CMR therefore patients with a contraindication to adenosine will be excluded. CMR will have the coronary sinus and inferior wall blanked by an unblinded researcher. Therefore, patients with isolated inferior wall ischaemia on CMR will be excluded.

Imperial College London

4.4 Withdrawal Criteria

A participant will be able to withdraw from the study at any time. This will be discussed and documented during the consent process. Pseudonymised data which has already been collected will continue to be used in the study if they consent.

Participants will be withdrawn from the study if they have no angina on the symptom smartphone app during the 2-week induction period.

5. ADVERSE EVENTS

5.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 Reporting Procedures

All AEs will be reported. Any questions concerning adverse event reporting will be directed to the Principal Investigator in the first instance. All adverse events will be reviewed by an independent trial Data Safety and Monitoring Board.

5.2.1 Non serious AEs

All such events, whether expected or not, will be recorded.

5.2.2 Serious AEs

A Serious Adverse Event (SAE) form will be completed and emailed to the Principal Investigator within 24 hours. However, relapse and death due to non-cardiac pre-existing conditions and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London Central Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- ‘related’, ie resulted from the administration of any of the research procedures; and
- ‘unexpected’, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Incidental findings which are discovered in the this study will be reported the patient and their general practitioner.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)

Please send SAE forms to: Dr Rasha Al-Lamee, r.allamee13@imperial.ac.uk
Tel: 0207 594 5735 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW UP

Participants with stable CAD with no further options for revascularisation, angina on maximal medical therapy (CCS-class II-IV) and evidence of ischaemia on a non-invasive imaging will be approached for enrolment. Patients who are potential candidates for the CSR on clinical grounds will be referred for a stress perfusion CMR. Patients will undergo CMR at 1.5T (Aera, Siemens Healthineers, Erlangen, Germany) using a standard clinical protocol including cine imaging, stress and rest perfusion and late gadolinium enhancement. For stress, adenosine will be infused at 140mcg/kg/min for 4 minutes (increased to 175mcg/kg/min and then 210mcg/kg/min for a further 2 minutes if the heart rate increases by <10% or there are no symptoms). At the end of the infusion a gadolinium-based contrast agent (Gadovist, Bayer, Leverkusen, Germany) will be injected peripherally at 4.5mls/s at a dose of 0.05mmol/kg and 70 images will be acquired for three short-axis left ventricular slices. Rest perfusion images will be acquired at least 5 minutes after the end of adenosine infusion.

Images will be analysed in clinically available software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada) which has functionality to analyse endocardial and epicardial perfusion distinctly. Myocardial perfusion reserve, and the gradient of sub-endocardial to sub-epicardial perfusion will be calculated. Patients who do not have any evidence of perfusion abnormality on stress perfusion CMR, or who do not have appropriate coronary sinus anatomy for CSR implantation, are not eligible for the CSR and will not be approached for enrolment into the study.

6.1 Enrolment Assessment

At enrolment, participants will undertake the following questionnaires: Seattle Angina Questionnaire (SAQ), Rose chest pain questionnaire, MacNew Heart Disease Health-related Quality of Life Questionnaire, Quality of Life Questionnaire (European EQ-5D-5L) and CCS angina class. The clinical interview with the patient will be a voluntary, semi-structured video interview conducted under GDPR-compliant standardised conditions, for which the patient will be consented. Before the recording starts, patients will be reminded not to reveal any personal information during the recording. Language interpretation will be provided as required. Participants will begin by providing a descriptive narrative of symptoms, in their own words. They will then be asked to answer a set of structured questions. The video recordings will be stored on a secure NHS computer for 10 years, as with other study data. This is to facilitate future analyses of the patient descriptions of angina and analysis of non-verbal communication. This recording will be transcribed by a member of the research team and stored on a secure computer (transcripts will not include any personal identifiers such as name or address).

Patients will be established on a smartphone symptom app (participants without a smartphone will be provided with one for the duration of the study) and will begin daily scoring of angina on this, using a visual analogue scale. Participants without any angina during the 2-week induction period will exit the study and return to routine clinical practice.

They will then undergo a treadmill exercise test. This will be undertaken according to standard clinical protocols with ECG and non-invasive blood pressure monitoring, with medical supervision. The smoothed modified Bruce Protocol will be used. The test will be terminated when the participant can no longer keep up with the treadmill or significant ST segment depression develops. All participants will be started on dual antiplatelet therapy in anticipation of CSR implantation.

6.2 Invasive Coronary Physiology Assessment

All participants will be screened for suitability for coronary physiology assessment. The following criteria will be used for to screen for participants for whom the invasive physiology assessment is not suitable:

- Previous coronary artery bypass grafting with patent grafts.
- Only open vessel is right coronary artery.
- Significant tortuosity in target coronary artery which would preclude pressure wire and Rayflow catheter passage.

- Significant stenosis or calcification in target coronary artery which would preclude pressure wire and Rayflow catheter passage.

Participants who are not suitable for the coronary physiology assessment will proceed directly to randomisation after their enrolment assessment.

Suitable participants will attend the cardiac catheterisation laboratory and will complete a consent form for coronary angiography, pressure wire assessment +/- CSR implantation. Risk of complications will be quoted as 1%. Auditory isolation will be maintained throughout the procedure using over the ear headphones.

Venous access will be obtained via the right internal jugular vein under ultrasound guidance with a 6Fr venous sheath implanted under local anaesthetic. The right atrial pressure will be measured using a multipurpose catheter. Participants with right atrial pressure >15mmHg are not eligible for the CSR; they will be removed from the study at this stage and will return to routine clinical practice.

Arterial access will be gained under local anaesthetic, preferentially via the right or left radial artery. Standard doses of 2.5mg of verapamil and 3000 units of heparin will be administered into the arterial sheath and a guide catheter will be used to intubate the left main coronary ostium. Diagnostic coronary angiography of the left coronary system will be performed.

Additional heparin will be given to a total dose of 100 units/Kg. A Combowire *(Phillips Volcano)* will be placed in the distal epicardial coronary artery, depending on the coronary anatomy of the participant. This will measure coronary flow at rest. An infusion of adenosine will then be administered (140mcg/kg/min) and coronary flow at maximal hyperaemia will be measured, allowing calculation of coronary flow reserve (CFR).

Pressure Wire^{TM} X *(Abbott)* will be placed in the distal epicardial coronary artery, depending on the coronary anatomy of the participant. Bolus injections of room temperature saline will be administered through the guide catheter to calculate coronary transit times at rest. Maximal hyperaemia will be induced with adenosine as above and the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) will be calculated after repeat saline boluses.

A RayFlow^{TM} catheter *(Hexacath)* will be passed over the wire to a position at least 40-60mm from the sensor on the Pressure Wire X^{TM}. An infusion of room temperature saline at 10ml/min will be started through the RayFlow^{TM} catheter until a steady state temperature is achieved. The flow will then be increased in the RayFlow^{TM} catheter to 20ml/min. Once steady state temperature and pressure reading is achieved (approximately 30 seconds), the Pressure Wire X will be pulled back so that the pressure and temperature sensor is at the tip of the RayFlow^{TM} catheter. The Pressure Wire X^{TM} and Rayflow^{TM} catheter positions will be stored as fluoroscopic images.

The following measurements will be calculated by the Coroventis software system:

- Absolute Blood Flow (Q)
  - Q (ml/min) = Infusion rate (ml/min) x $\frac{\text{Infusion temperature (°C)}}{\text{Steady State Mixed Temperature (°C)}}$

- Resistance
  - Q (ml/min) / Pd (distal coronary pressure) (mmHg)
- FFR
  - Pd / Pa (aortic pressure) (at maximal hyperaemia)

- Microvascular Resistance Reserve
  - Resistance (low flow)/Resistance (high flow)

6.3 Sedation, Randomisation and Blinding

After completion of the coronary physiology assessment, participants will be sedated using incremental doses of intravenous benzodiazepines and intravenous opiates to a deep level of conscious sedation such that they are unresponsive to verbal or tactile stimulus but that airway, ventilation and cardiovascular function are maintained. Auditory isolation will be maintained from the start of the coronary physiology assessment, with over the ear headphones playing music. Participants will then be randomised 1:1 to CSR or placebo procedure using an online randomisation tool (https://icch.med.ic.ac.uk/randi/index). Once randomised the treatment allocation must be adhered to. Any deviation from the treatment allocation will be considered a protocol violation.

Participants randomised to placebo will be kept in the coronary catheterisation laboratory for 15 minutes before returning to the ward. The venous sheath will be removed in the cardiac catheterisation laboratory.

The post randomisation documentation in ORBITA-COSMIC will be managed according to a standardised protocol. During the procedure, nursing staff will document that the patient is an ORBITA-COSMIC participant and will not document the treatment allocation or any details of the CSR implantation post procedure. Handover to the recovery staff will be carefully managed, to ensure that only access sites and medications administered will be documented. All participants will be managed in recovery as if they have had a coronary sinus reducer implant. No staff from the cardiac catheterisation laboratory will have any interaction with the participant after handover.

A standardised discharge letter will be given to all patients and their GPs which will inform the reader that a blinded procedure had taken place, that this procedure was a coronary angiogram and pressure wire assessment +/- CSR implantation, that all medications should remain unchanged, including continuation of dual antiplatelet therapy, until trial follow-up is complete. The letter will state that they should receive usual post-CSR care until full details of the procedure are provided after unblinding at 6 months.

An unblinded fellow will enter the treatment allocation into a pre-allocated page of the online case reporting form to which none of the other members of the research team will have access. The blinded team will perform all the communication with the patient after discharge and will perform all the follow-up tests (stress perfusion CMR, exercise test, questionnaires). At 6 months, the blinded team will contact the unblinded fellow to confirm that all the assessments had been performed, and only at that time will the unblinded fellow

communicate the treatment allocation. From that time, the patient, the research team, and the clinical team will become unblinded.

Our protocol will assess for accidental disclosure of information to staff and to patients, which could influence blinding. The ward clinical staff will be asked to guess the treatment allocation at the time of discharge from the blinded procedure. The blinded research staff will be asked to guess the treatment allocation from all information available to them at the follow-up visit prior to speaking to the patient. Patient blinding will be assessed at the time of discharge from the randomised blinded procedure. For completeness the same question will also be asked when they attend for follow-up, but at that time they will have the benefit of knowing the symptomatic responses and therefore this will no longer strictly be a valid measure of blinding. Patients and staff will be asked to guess one of the following: (1) CSR, (2) Placebo, (3) Don't know. Patients and medical staff will be asked to state the certainty of their answers grade 1-5 with 5 being most sure.

6.4 Coronary Sinus Reducer Implantation

The CSR will be implanted according to established clinical protocols. The 6Fr venous sheath will be exchanged for a 9Fr CSR delivery sheath. In the 30-degree left anterior oblique C-arm position, a multipurpose catheter will be guided fluoroscopically to the coronary sinus ostium. A coronary sinus venogram will be taken to identify anatomy, implantation site and side branches. A guidewire is advanced deep into the coronary sinus and the multipurpose catheter is removed. The 9Fr CSR guiding catheter is advanced into the CS and the guide catheter is withdrawn slightly, revealing the CSR which is guided to the correct position (2-4cm from the coronary sinus ostium, avoiding side branches. The CSR balloon is inflated to 4-6 atm, aiming for a 10-20% oversize of the CSR. At this stage, a coronary sinus wedge pressure will be taken. The balloon is deflated and carefully withdrawn to avoid displacement of the CSR. A final venogram is taken to confirm correct positioning and exclude complications and the catheter is removed. The venous sheath will be removed in the cardiac catheterisation laboratory.

6.5 Follow Up Assessment

Participants will be followed up for 6 months from randomisation, with all communication to a blinded research fellow. They will input their angina symptoms every day into a smartphone app. They will be given the telephone number of a dedicated trial telephone held by the blinded research fellow for any questions and queries. At the end of the follow up period, participants will attend for follow up assessments. They will repeat their exercise tests, angina questionnaires and stress perfusion CMR.

In the follow-up CMR, the image acquisition and the image interpretation will be undertaken by two separate researchers. The unblinded researcher will acquire the stress perfusion CMR images according to the same protocol outlined above. The second, blinded researcher, will control the adenosine infusion and will judge the timing of adequate myocardial stress. The unblinded researcher will blank the coronary sinus and in the inferior wall in all images. They will also blank the coronary sinus and inferior wall from the baseline

CMR images. The stress perfusion CMR images will be interpreted under conditions blinded to treatment arm and scan order.

Participants who underwent the baseline coronary physiology protocol will undergo repeat assessment with a coronary angiogram and pressure wire assessment. The Combowire, Pressure Wire X™ and Rayflow™ catheter will be placed in the same positions as the baseline assessment, using the stored fluoroscopic images as a guide. Invasive physiology measurements will be repeated.

6.6 Unblinding and Study End

At their last visit, patients will be unblinded and will return to routine care. In total a patient will be enrolled in the study for 182 days. If patients have no ongoing indication for dual antiplatelet therapy, they will return to a single antiplatelet agent. The end of study is defined as the last study visit.

7. STATISTICS AND DATA ANALYSIS

7.1 Sample Size Calculation

The sample size is calculated in order to meet the requirements of the primary outcome: The difference in change of myocardial perfusion in myocardial segments ischaemic on baseline stress CMR, between baseline and follow up, between the control and treatment groups.

We aim to detect a 10% difference in the ischaemic myocardial segments. The only study of perfusion on CMR with the CSR has shown a variable effect, with an 8% difference from baseline to follow up in the global MPR and a 35% difference in ischaemic segments. (5) Recent data show that the reproducibility standard deviation of MPR is 18% (6)

Conservatively estimating the change in ischaemic segments to be 10%, with a 18% reproducibility standard deviation, to have a 90% power with a 5% alpha level we require 38 participants. Accounting for 10% participant dropout, we therefore plan to enrol 50.

7.2 Data Analysis

Data analysis will be undertaken using R. Normally distributed data will be summarised as mean and standard deviation. Non-normally distributed data will be summarised as median and interquartile range. Results will be analysed according to the intention to treat principle. The data will be analysed using the methodology outlined in the ORBITA-COSMIC statistical analysis plan.

Data will be stored for a minimum of 10 years after completion of the study, including the follow up period.

Imperial College London

8. REGULATORY ISSUES

8.1 Ethics approval

The Study Coordination Centre has obtained approval from the London Riverside Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and at least 48 hours allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. Participants will not receive payment for entering the study but reasonable travel expenses related to additional research visits will be reimbursed. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8.4 Indemnity

Imperial College London holds negligent harm insurance policies which apply to this study.

Imperial College London

8.5 Sponsor

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

The Medical Research Council are the funder of this study as a Clinical Research Training Fellowship for Dr Michael Foley (MR/V001620/1). Financial support for the CSR devices has been provided by a grant from the Nissen Foundation at Imperial. Researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

8.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. PUBLICATION POLICY

The data from this study will be submitted for presentation in International Scientific Fora and publication in peer reviewed journals. All patient information will be anonymised. Participants will be informed of the study results in a leaflet which will thank them for their contribution.

10. REFERENCES

1. Mannheimer C. The problem of chronic refractory angina. Report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002 Mar 1;23(5):355–70.

2. Konigstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. Eur Heart J. 2018 Mar 14;39(11):925–33.

3. Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, et al. Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina. N Engl J Med. 2015 Feb 5;372(6):519–27.

4. Knuuti J. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Russ J Cardiol. 2020 Mar 11;25(2):119–80.

5. Giannini F, Palmisano A, Baldetti L, Benedetti G, Ponticelli F, Rancoita PMV, et al. Patterns of Regional Myocardial Perfusion Following Coronary Sinus Reducer

Implantation: Insights by Stress Cardiac Magnetic Resonance. Circ Cardiovasc Imaging [Internet]. 2019 Sep [cited 2020 Nov 13];12(9). Available from: https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.119.009148

6. Brown LAE, Onciul SC, Broadbent DA, Johnson K, Fent GJ, Foley JRJ, et al. Fully automated, inline quantification of myocardial blood flow with cardiovascular magnetic resonance: repeatability of measurements in healthy subjects. J Cardiovasc Magn Reson. 2018 Dec;20(1):48.

Statistical analysis plan

ORBITA-COSMIC Statistical Plan

V1.0 November 2022

Sponsor

Imperial College London

Statistical Working Group

Frank Harrell – Senior Statistician

Matthew Shun-Shin –Clinical Senior Lecturer

Rasha Al-Lamee – Reader in Cardiology

Overview

ORBITA-COSMIC is a double-blind, randomised, placebo-controlled trial of the coronary sinus reducer (CSR) in refractory angina. It follows from the COSIRA trial which demonstrated placebo-controlled benefit of the CSR in this population. The CSR is an hourglass shaped, stainless steel, wire mesh device which is implanted in the coronary sinus percutaneously in the cardiac catheterisation laboratory. There has never been a study which has demonstrated how the CSR causes a benefit in patients with angina, it is unknown if the CSR has any effect on ischaemia (the physiological substrate for angina) and the placebo-controlled symptom data are unreplicated.

ORBITA-COSMIC will enrol patients with angina, ischaemia and no options for revascularisation with PCI or CABG (as determined by a dedicated multi-disciplinary team). All participants will undergo a stress perfusion cardiac MRI (CMR) utilising quantitative perfusion mapping (Kellman Sequence). This has the advantage of automatically quantifying myocardial blood flow at rest and at stress in each segment of the left ventricular myocardium (16 segment model). Participants without any inducible ischaemia on this test will be withdrawn from the study at this stage. Participants will also complete symptom questionnaires, a treadmill exercise test and will be established on a smartphone symptom app to document their symptoms on a daily basis.

Participants will then attend for a research cardiac catheter lab procedure. They will have a 9Fr venous sheath implanted with ultrasound guidance under local anaesthetic. Selected patients will additionally have a coronary angiogram and physiology study as part of a coronary physiology subgroup. After measurement of right atrial pressure, coronary sinus pressure and acquisition of a coronary sinus venogram, participants will be randomised 1:1 to CSR or placebo. Blinding will be maintained utilising an invasive blinding protocol which includes auditory isolation and a deep level of conscious sedation for all patients. The

success of blinding will be assessed at hospital discharge with calculation of a blinding index.

Participants will enter a 6-month period of double-blind follow-up, during which the smartphone symptom app is completed daily. They will attend for a follow-up visit in which they have a quantitative stress perfusion CMR scan, questionnaires and treadmill exercise test. Participants who had an invasive coronary physiology study at baseline will have this repeated at follow-up. After completion of all follow-up assessments, the blinding index will be repeated before planned unblinding of the participant and return to routine care.

Study Objectives

Hypotheses

We hypothesise that the CSR improves ischaemia in patients with refractory angina. We further hypothesise that the CSR improves angina in these patients.

Primary Objective

The primary objective is to determine if the CSR improves ischaemia compared with placebo, as assessed by quantitative stress perfusion CMR.

Secondary Objective

The secondary objective is to determine if the CSR improves angina symptoms, assessed by a smartphone app, symptom questionnaires, blinded physician assessment of angina and treadmill exercise time.

Exploratory Objectives

The exploratory objectives include investigating if the CSR causes a reduction in coronary flow or resistance, assessed in a pressure wire assessment in a coronary physiology subgroup. We also aim to investigate if the quantity or location of ischaemia on baseline stress MRI can predict the benefit of CSR on angina symptoms.

Study Design

Description of Study Design

Participants will be enrolled and undergo a quantitative stress perfusion CMR scan along with a treadmill exercise test and symptom questionnaires. They will complete a 2-week pre-randomisation symptom assessment phase, completing a smartphone symptom application, documenting their angina frequency and severity on a daily basis. After 2 weeks they will attend for a randomisation procedure in which participants are sedated, have auditory isolation established and are randomised 1:1 to CSR implantation or placebo. CSR arm participants have a CSR implanted according to standard clinical protocols, placebo arm patients are kept sedated for 15 minutes without further intervention. Participants will enter 6 months of double blind follow up, completing their angina diary on a daily basis and undertaking repeat blinded CCS class assessment and symptom questionnaires at 12 weeks. At 6 months, participants will have a repeat CMR, treadmill test and symptom questionnaires.

Mechanistic Outcomes

Primary Mechanistic Outcome (Primary Study Outcome)

The primary study and primary mechanistic outcome is quantified myocardial perfusion, assessed using Kellman Sequence CMR (Stress Myocardial Blood Flow (MBF)), in the cardiac segments deemed at enrolment to be ischaemic (excluding transmurally infarcted segments).

Secondary Mechanistic CMR Outcomes

Secondary CMR Endpoints from the primary model:

- Stress MBF in the non-ischaemic segments.
- Global stress MBF

Other Mechanistic Outcomes:

- MPR in ischaemic segments, non-ischaemic segments, and global MPR
- Rest MBF in ischaemic segments, non-ischaemic segments, and global rest MBF
- Stress MBF in ischaemic segments with inferior and inferoseptal segments excluded
- MPR in ischaemic segments with inferior and inferoseptal segments excluded
- Rest MBF in ischaemic segments with inferior and inferoseptal segments excluded
- Endocardial:epicardial ratio of stress MBF
- Endocardial:epicardial ratio of MPR
- Endocardial:epicardial ratio of rest MBF
- Myocardial strain
- Myocardial scar burden

Secondary Mechanistic Invasive Physiology Outcomes

A proportion of patients deemed eligible by the COSMIC-MDT will undergo a paired invasive coronary physiology assessment prior to randomisation and at 6-month follow-up. These changes may underpin changes in myocardial perfusion detectable on CMR. We will assess multiple measures of coronary flow and resistance using multiple modalities.

- Absolute Flow assessed by a pressure and temperature sensor wire (*Pressure Wire X, Abbott, USA)* and an intracoronary saline infusion catheter *(RayFlow™, Hexacath, France)*
- Absolute Resistance assessed by a pressure and temperature sensor wire and an intracoronary saline infusion catheter
- Microvascular Resistance Reserve (MRR) assessed by a pressure and temperature sensor wire (PressureWireX) and an intracoronary saline infusion catheter *(RayFlow™)*
- Coronary Flow Reserve (CFR) assessed by a pressure and temperature sensor wire (*PressureWireX)*
- Index of Microcirculatory Resistance (IMR) assessed by a pressure and temperature sensor wire (*PressureWireX)*
- CFR assessed by a pressure and doppler sensor wire (*Combowire, Philips, USA)*

Symptom Endpoints

Primary Symptom Outcome

In ORBITA-COSMIC patients report their symptoms on a daily basis via a mobile phone application, and we are notified of all antianginal medication changes, such as up-titration or down-titration, such that for every day in the trial we known which and what does of antianginals participants are taking. In addition, we also monitor events including unblinding due to intolerable angina, acute coronary syndromes and death. We have previously developed the [illegible] which combines these into an ordinal scale multiplexing the number of episodes of angina, the number of antianginal medications and these over-riding clinical events. This score allows us to track on a daily basis the angina state of a patient.

In ORBITA-COSMIC, patients are already on maximal antianginal therapy, and overriding events are expected to be low. Therefore, if there is any efficacy in patient symptoms, we expect it to be driven by changes in the number of episodes of angina each day. For this reason, and to aid interpretation, our primary ***symptom*** outcome will be the angina episodes component of the ORBITA Score, followed by the overall ORBITA Score.

Secondary Symptom Outcomes

Secondary symptom outcomes will also include the treadmill exercise time, physician assessed Canadian Cardiovascular Society (CCS) angina class, Seattle angina questionnaire (SAQ), Euro-Qol (EQ-5D-5L) and MacNew quality of life questionnaires.

Summary of Outcomes

Study Primary, Mechanistic Primary Outcome	
	The quantified myocardial blood flow at stress in segments ischaemic at baseline
Mechanistic Secondary Outcomes	
CMR	
	MPR in ischaemic segments, non-ischaemic segments, and global MPR
	Rest MBF in ischaemic segments, non-ischaemic segments, and global rest MBF
	Stress MBF in ischaemic segments with inferior and inferoseptal segments excluded
	MPR in ischaemic segments with inferior and inferoseptal segments excluded
	Rest MBF in ischaemic segments with inferior and inferoseptal segments excluded
	Endocardial:epicardial ratio of stress MBF
	Endocardial:epicardial ratio of MPR
	Endocardial:epicardial ratio of rest MBF
	Myocardial strain
	Myocardial scar burden
Invasive Physiology	
	Absolute Flow assessed by a pressure and temperature sensor wire (Pressure Wire X, Abbott, USA) and an intracoronary saline infusion catheter (RayFlowTM, Hexacath, France)
	Absolute Resistance assessed by a pressure and temperature sensor wire and an intracoronary saline infusion catheter

	Microvascular Resistance Reserve (MRR) assessed by a pressure and temperature sensor wire (PressureWireX) and an intracoronary saline infusion catheter (RayFlowTM)
	Coronary Flow Reserve (CFR) assessed by a pressure and temperature sensor wire (PressureWireX)
	Index of Microcirculatory Resistance (IMR) assessed by a pressure and temperature sensor wire (PressureWireX)
	CFR assessed by a pressure and doppler sensor wire (Combowire, Philips, USA)
Symptom, Primary Outcome	
	Episodes of angina component of ORBITA Score
Symptom, Secondary Outcomes	
	ORBITA Score
Physician Assessed	CCS
	Treadmill Exercise Time
Patient Reported	SAQ Angina Frequency
	SAQ Angina Physical Limitation
	SAQ Quality of Life
	SAQ Treatment Satisfaction
	SAQ Angina Stability
	EQ-5D-5L Descriptive System
	EQ-5D-5L Visual Analogue Scale
	MacNew

Study Visits

- Enrolment
- Randomisation
- Follow-Up

Participant Completion

The participant will have completed the study after the follow-up visit, when all follow-up assessments have taken place and the participant has been unblinded and returned to routine care.

Participant Stopping Rules and Withdrawal Criteria

A participant may withdrawn from the trial for the following reasons:

- The participant withdraws consent for future study activities
- The participant is lost to follow up and attempts to contact them are unsuccessful
- The participant dies

Study Stopping Rules

The Data Safety and Monitoring Board (DSMB) has the authority to terminate the study early if they have safety concerns.

Selection of Participants and Clinical Sites

Rationale for Study Population

ORBITA-COSMIC will randomise patients with refractory angina, meaning they have angina with no good options for further treatment with CABG, PCI or medical therapy. This is the patient group who were investigated in the COSIRA trial, in whom we have placebo-controlled efficacy data. ORBITA-COSMIC aims to discover the impact of the CSR on ischaemia in this patient group, in a randomised, placebo-controlled setting. Participants must have evidence of ischaemia, which can be thought of as the pathophysiological substrate for angina symptoms, and ischaemia change is the primary endpoint.

Participants with ischaemia isolated to the inferior wall will be excluded. This is because the inferior wall has venous drainage through the middle cardiac vein, which joins the coronary sinus proximal to the CSR implantation site. As such, the physiological effects seen with the CSR are not thought to occur in the inferior wall. Pacemaker or ICD leads may lead to artefact which could interfere with perfusion imaging so patients with these devices are excluded. Participants who have a CRT indication are excluded, as the CSR makes CRT

implantation more challenging. Very severe LV and renal impairment are excluded, as are clinical factors which preclude perfusion imaging, which forms the primary endpoint.

Inclusion Criteria

1. Angina on maximally tolerated antianginal medication

2. Epicardial CAD

3. Evidence of ischaemia on cardiac magnetic resonance (CMR) imaging

4. No further options for CABG or PCI

Exclusion Criteria

• Contraindication to CMR

• Contraindication to adenosine

• Ischaemia isolated to inferior wall

• Ongoing participation in a separate interventional study

Selection of Clinical Sites

Sites must be tertiary cardiothoracic centres, managing a large volume of patients with complex coronary artery disease. They must have an existing CSR program or the facility to establish one for the purposes of the trial. Currently 6 sites are included.

Data Handling

Sources of Data used in Analyses

The data used in the analysis will come from Redcap (an online case report form) and the ORBITA-COSMIC smartphone application.

Access to Source Data

Source data are considered to be the original documentation where subject information and assessments are recorded. All source data will be made available to the Data Monitor.

Methods for Handling Missing Data

For the primary endpoint, participants who do not complete the enrolment MRI will not progress to randomisation. Participants who do not complete their follow up MRI will not form part of the primary endpoint analysis.

The daily number of episodes of angina is obtained by an application. The application is designed in such a way, with alerts and notifications from the study team, that means missing data is greatly minimised. If a patient is unblinded due to intolerable angina, development of an acute coronary syndrome or death, the symptom data up until the overriding clinical endpoint and the clinical endpoint are used. For visualisation, the last value carried forward will be used for the remaining study, but, for statistical analysis only days with data will be included in the analysis.

The specified date of final follow-up is 6 months following randomisation, however this is allowed in the protocol to vary by up to a month due to logistical factors (i.e. difficulty in obtaining slots for CMR, patient travel, covid restrictions). Again, for visualisation of the daily ORBITA Score and its components, the last value carried forwards will be used, and in patients whose follow up is after 6 months it will be curtailed, however, for statistical analysis only dates with valid data will be used, and symptom data after 6 months will not be used.

For analysis of other outcomes such as CMR, other symptoms and coronary physiology, is based on the data obtained at follow-up, adjusted for that at baseline. If either value is absent, the patient will be excluded from analysis, no imputation will be performed.

Analysis Plan

Measures to Minimise Bias

Randomisation

Participants will be allocated to CSR or placebo in a 1:1 ratio with randomly varying block sizes using a central, secure, online, computer-generated random number system (Randi) immediately prior to delivery of the intervention (or placebo).

Blinding

Blinding will be maintained for the participant using an invasive blinding protocol. Auditory isolation with noise cancelling headphones will be established near the start of the case, immediately following the insertion of a 9Fr right internal jugular venous sheath under ultrasound guidance. All participants will then have right atrial pressure and coronary sinus pressure measured, followed by acquisition of a coronary sinus venogram. Eligible participants will then undergo the coronary physiology protocol. Participants will then be administered incremental doses of benzodiazepines and opioids to a deep level of conscious sedation, to the extent that they are unresponsive to verbal or tactile stimulus but airway, breathing and circulatory status are maintained.

All assessments in the follow up period will be undertaken by the blinded team.

Procedure for unblinding

Participants will be unblinded on completion of all follow up assessments.

Analysis Populations

The intention to treat principle will include all randomised participants regardless of the treatment they received. Participants who are randomised to CSR but a CSR is not implanted due the technical difficulty of the procedure will be kept blinded and analysed according to the intention to treat principle. Participants who have CSR embolisation and device snaring, cardiac tamponade or another complication which necessitates unblinding, will not contribute MRI or symptom data as this data will be unblinded. There are no circumstances in which a participant randomised to placebo would receive a CSR.

Missing data

The primary analysis will include all randomised participants who undertook a stress perfusion CMR at enrolment and follow up. Phone application data forming secondary symptom endpoints is expected to be complete as participants receive text reminders if they miss more than 3 days. Significant missing data is not anticipated.

MRI Endpoints

Primary MRI end-point and associated primary and secondary outcomes

The mechanism of action of the CSR is unknown. The analytical approach is designed to take into consideration the following concepts that have been discussed in the literature:

1. Only the ischaemic segments may have an increase in blood flow with CSR treatment.
2. The increase in blood flow may come at the expense of a reduction elsewhere (redistribution).
3. As a consequence of (1) and (2) global blood flow may or may not be changed.
4. Perfusion values are available in segments that have a full-thickness infarct but are unlikely to be comparable to segments without infarct.
5. Specific cut-off values to designate a segment as ischemic are arbitrary and often rely on a complex relationship with the surrounding segments. Consequently, expert review will be required of the MRI scans at baseline to designate segments as ischaemic (and to identify full-thickness infarct).

To enable an analysis that can draw multiple simultaneously valid conclusions for these questions a Bayesian modelling approach will be taken.

The data from every segment will be used in a model that conditions the stress MBF at follow-up on the stress MBF at enrolment and the treatment arm (CSR or placebo), and clustered by patient. An indicator variable based on if the segment was designated to be ischaemic at enrolment (based on the consensus of blinded experts) will also be included as an interaction with the treatment arm.

The ordinal model will be constructed to include:

1. The follow-up stress MBF for each individual segment (excluding transmurally infarcted segments) as the dependent variable.
2. The baseline stress MBF for each individual segment (excluding infarcted segments) as an independent variable.
3. The treatment arm.
4. An indicator variable for if each segment has been designated as ischaemic at baseline by the consensus of experts, blinded to the follow-up scan. This will be allowed to interact with the treatment arm.

From this model the posterior density function for the treatment effect (log OR) will be provided, along with the cumulative posterior distribution.

Primary Endpoint

The primary efficacy analysis will be derived from the model and the effect of treatment arm within the ischaemic segments. Particular probabilities of OR intervals will be computed, along with two-sided 0.95 Bayesian credible intervals.

Secondary Endpoints estimated from the primary model

The end-points of the effect in the designated “non-ischaemic” segments will be computed from the same model and presented. The effect on global perfusion will be computed from a similar model conditioned on the global perfusion value and the treatment arm.

The additional MRI endpoints will be analysed with a similar approach to the primary end-point.

The CMR derived global longitudinal strain will be analysed using a Bayesian model with the follow-up GLS conditioned on the enrolment GLS and the treatment arm.

Additional analyses of the MRI end-points

It has been suggested in the literature that there may be a differential effect of the coronary sinus reducer on the endo- and epicardial sub-segments. To test this each of the individual segments will be split into two 2 sub-segments - an endo- and epicardial sub-segment. An indicator variable for the endo- and epicardial classification and this is included as an additional interaction term in the model.

We will also test if there is an additional interaction between stress MBF at baseline and treatment arm beyond the expert designated ischaemia, i.e. is the information provided by stress MBF as baseline greater than that provided by the consensus of experts.

Symptom endpoints

Primary symptom endpoint: Episodes of angina component of angina symptom score

The number of daily anginal episodes are recorded on a daily basis throughout the trial using a mobile phone application by the participant for the 14 days before randomisation until unblinding (26 weeks, 6 months) after.

This data is combined with the number of units of antianginals and if the patient was (1) intolerable angina requiring unblinding, (2) an acute coronary syndrome, or (3) death to form a daily ordinal score - the Angina Symptom Score.

The primary symptom end-point (and Angina Symptom Score) will be analysed using a longitudinal, first-order Markov ordinal model within a Bayesian framework. This approach enables the utilisation of the >100 daily symptoms assessments from each patient, their medication changes, and other clinical events.

This Markov model accounts for the within-patient correlation in serial measurements.

The model will include as the dependent variable the “episodes of angina component” (post-randomisation). Independent variable will include a summary of the pre-randomisation “episodes of angina component and treatment arm, and will take into account the clustering of scores within patients. In addition a time *x* treatment interaction will be included.

The per-patient serial data will be handled in the following manner. A first-order Markov model will be used, so that the proportional odds model is for transitions in outcome states over consecutive days. Probabilities of an outcome level y or worse on a given day, given the outcome status on the previous day, are conditionally independent. The Markov model is similar to an AR(1) autocorrelation model but models the dependence within patient on the raw outcome scale. This allows intra-patient correlation to be arbitrarily large or small, and allows for correlations of outcomes within patient to be higher when measurements are closer together in time.

Letting Y(t) denote the outcome level on day t and expit denote the inverse logit transform, the Markov proportional odds model is stated as

$$P(Y(t) \geq y|X, Y(t-1)) = \text{expit}(\alpha_y + X + f(Y(t-1), t))$$

where is X a vector of covariates including treatment and f is a flexible function of the prior day's outcome Y(t-1) and days since randomisation including possible interactions. Time will be modelled as a restricted cubic spline or a quadratic polynomial. This is a non-homogeneous Markov model since transition probabilities are allowed to change with time.

The model to be used is a constrained partial proportional odds model, where the one non-proportional odds part of the model is related to follow-up time.

In the Bayesian proportional odds model, prior distributions will be specified as follows:

- For the intercepts the priors are induced by a Dirichlet distribution on the cell probabilities when all covariates are set to their means. This enforces 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 is normal with mean zero and standard deviation chosen so to that the prior probability that the OR < 0.25 equals the prior probability OR > 4 with both equalling 0.05. Thus the analysis is skeptical about the treatment effect being large in either direction. Besides being more convincing to a skeptic (should there be evidence for benefit), the skeptical prior "pulls back" the OR more at early data looks to help avoid making a mistake in stopping a treatment arm early.
- For covariates a virtually flat prior will be used, I.e., a distribution with mean 0 and standard deviation of 100 on a normalised covariate scale.

Primary outcome: Odds ratio of improvement in episodes of angina component of the angina symptom score with the CSR as compared to placebo.

Secondary outcomes: Efficacy estimands derived from the same model can include mean number of days with a score of 0, mean number of days with a [illegible] estimands is the transition odds ratio treatment effect.

Sensitivity analyses will be performed and reported for a range of possible prior distributions, especially using a flat prior for the treatment effect.

The R rmsb package written by Dr Harrell (see http://hbiostat.org/R/rmsb), and the rstan package will be used to do model fitting and posterior sampling for the Bayesian analysis, and 4000 posterior samples at a minimum will be used in calculations.

Other Secondary Symptom Endpoints

For the following end-points an ordinal Bayesinal model will be constructed with the follow-up value conditioned on the enrolment value and treatment arm.

- Physician assessed angina class (CCS)
- Angina symptom score
- SAQ physical limitation
- SAQ angina stability
- SAQ treatment satisfaction scale
- SAQ quality of life
- Angina related quality of life assessed by the MacNew Questionnaire
- Quality of life assessed by the EQ-5D-5L Questionnaire
- Treadmill exercise time

Interim Analyses

The interim analysis will concern serious adverse events, not efficacy data. All adverse events will be reported to an independent Data Safety Monitoring Board who have the authority to terminate the trial if they have participant safety concerns. Reports to the DSMB will occur every 6 months or every 5 adverse events, or every 1 serious adverse event, whichever comes first.

Sample Size Considerations

The sample size was calculated to detect a change in the primary outcome: the between-group difference in stress MBF on CMR, at follow-up. For simplification, a frequentist approach was used for sample size calculation, as an approximation of the performance of the Bayesian model. The calculation was informed by: (1) the only study of perfusion change with the CSR, which was unblinded and single arm, and reported a variable effect, with an 8% difference from baseline to follow up in the global perfusion and a 35% difference in ischaemic segments and (2) a reproducibility standard deviation of stress MBF of 17%.

Conservatively estimating the change in ischaemic segments to be 17% (half the published unblinded effect size) with a 17% reproducibility standard deviation, to have a 90% power with a 5% alpha level, will require 44 participants. We estimate a crossover and dropout rate of 10% and therefore plan to randomise 50 participants.

Tables

Table 1. Ordinal Clinical Outcome Scale for Angina

Grade	Number of angina episodes in a day	Units of anti-anginal medication	Unblinding due to intolerable angina	Acute coronary syndrome	Death
0	0	0	No	No	No
1	1	0	No	No	No
2	2	0	No	No	No
3	3	0	No	No	No
4	4	0	No	No	No
5	5	0	No	No	No
6	6	0	No	No	No
7	7	0	No	No	No
8	8	0	No	No	No
9	9	0	No	No	No
10	10 or more	0	No	No	No
11	0	1	No	No	No
12	1	1	No	No	No
13	2	1	No	No	No
14	3	1	No	No	No
15	4	1	No	No	No
16	5	1	No	No	No
17	6	1	No	No	No
18	7	1	No	No	No
19	8	1	No	No	No
20	9	1	No	No	No
21	10 or more	1	No	No	No
22	0	2	No	No	No
23	1	2	No	No	No
24	2	2	No	No	No
25	3	2	No	No	No
26	4	2	No	No	No
27	5	2	No	No	No
28	6	2	No	No	No

29	7	2	No	No	No
30	8	2	No	No	No
31	9	2	No	No	No
32	10 or more	2	No	No	No
33	0	3	No	No	No
34	1	3	No	No	No
35	2	3	No	No	No
36	3	3	No	No	No
37	4	3	No	No	No
38	5	3	No	No	No
39	6	3	No	No	No
40	7	3	No	No	No
41	8	3	No	No	No
42	9	3	No	No	No
43	10 or more	3	No	No	No
44	0	4	No	No	No
45	1	4	No	No	No
46	2	4	No	No	No
47	3	4	No	No	No
48	4	4	No	No	No
49	5	4	No	No	No
50	6	4	No	No	No
51	7	4	No	No	No
52	8	4	No	No	No
53	9	4	No	No	No
54	10 or more	4	No	No	No
55	0	5	No	No	No
56	1	5	No	No	No
57	2	5	No	No	No
58	3	5	No	No	No
59	4	5	No	No	No
60	5	5	No	No	No
61	6	5	No	No	No
62	7	5	No	No	No
63	8	5	No	No	No

64	9	5	No	No	No
65	10 or more	5	No	No	No
66	0	6	No	No	No
67	1	6	No	No	No
68	2	6	No	No	No
69	3	6	No	No	No
70	4	6	No	No	No
71	5	6	No	No	No
72	6	6	No	No	No
73	7	6	No	No	No
74	8	6	No	No	No
75	9	6	No	No	No
76	10 or more	6	No	No	No
77	0	7	No	No	No
78	1	7	No	No	No
79	2	7	No	No	No
80	3	7	No	No	No
81	4	7	No	No	No
82	5	7	No	No	No
83	6	7	No	No	No
84	7	7	No	No	No
85	8	7	No	No	No
86	9	7	No	No	No
87	10 or more	7	No	No	No
88	0	8	No	No	No
89	1	8	No	No	No
90	2	8	No	No	No
91	3	8	No	No	No
92	4	8	No	No	No
93	5	8	No	No	No
94	6	8	No	No	No
95	7	8	No	No	No
96	8	8	No	No	No
97	9	8	No	No	No
98	10 or more	8	No	No	No

99	0	9	No	No	No
100	1	9	No	No	No
101	2	9	No	No	No
102	3	9	No	No	No
103	4	9	No	No	No
104	5	9	No	No	No
105	6	9	No	No	No
106	7	9	No	No	No
107	8	9	No	No	No
108	9	9	No	No	No
109	10 or more	9	No	No	No
110	0	10	No	No	No
111	1	10	No	No	No
112	2	10	No	No	No
113	3	10	No	No	No
114	4	10	No	No	No
115	5	10	No	No	No
116	6	10	No	No	No
117	7	10	No	No	No
118	8	10	No	No	No
119	9	10	No	No	No
120	10 or more	10	No	No	No
121	0	11	No	No	No
122	1	11	No	No	No
123	2	11	No	No	No
124	3	11	No	No	No
125	4	11	No	No	No
126	5	11	No	No	No
127	6	11	No	No	No
128	7	11	No	No	No
129	8	11	No	No	No
130	9	11	No	No	No
131	10 or more	11	No	No	No
132	0	12	No	No	No
133	1	12	No	No	No

134	2	12	No	No	No
135	3	12	No	No	No
136	4	12	No	No	No
137	5	12	No	No	No
138	6	12	No	No	No
139	7	12	No	No	No
140	8	12	No	No	No
141	9	12	No	No	No
142	10 or more	12	No	No	No
143	0	13	No	No	No
144	1	13	No	No	No
145	2	13	No	No	No
146	3	13	No	No	No
147	4	13	No	No	No
148	5	13	No	No	No
149	6	13	No	No	No
150	7	13	No	No	No
151	8	13	No	No	No
152	9	13	No	No	No
153	10 or more	13	No	No	No
154	0	14	No	No	No
155	1	14	No	No	No
156	2	14	No	No	No
157	3	14	No	No	No
158	4	14	No	No	No
159	5	14	No	No	No
160	6	14	No	No	No
161	7	14	No	No	No
162	8	14	No	No	No
163	9	14	No	No	No
164	10 or more	14	No	No	No
165	0	15	No	No	No
166	1	15	No	No	No
167	2	15	No	No	No
168	3	15	No	No	No

169	4	15	No	No	No
170	5	15	No	No	No
171	6	15	No	No	No
172	7	15	No	No	No
173	8	15	No	No	No
174	9	15	No	No	No
175	10 or more	15	No	No	No
176	0	16	No	No	No
177	1	16	No	No	No
178	2	16	No	No	No
179	3	16	No	No	No
180	4	16	No	No	No
181	5	16	No	No	No
182	6	16	No	No	No
183	7	16	No	No	No
184	8	16	No	No	No
185	9	16	No	No	No
186	10 or more	16	No	No	No
187	0	17	No	No	No
188	1	17	No	No	No
189	2	17	No	No	No
190	3	17	No	No	No
191	4	17	No	No	No
192	5	17	No	No	No
193	6	17	No	No	No
194	7	17	No	No	No
195	8	17	No	No	No
196	9	17	No	No	No
197	10 or more	17	No	No	No
198	0	18	No	No	No
199	1	18	No	No	No
200	2	18	No	No	No
201	3	18	No	No	No
202	4	18	No	No	No
203	5	18	No	No	No

204	6	18	No	No	No
205	7	18	No	No	No
206	8	18	No	No	No
207	9	18	No	No	No
208	10 or more	18	No	No	No
209	0	19	No	No	No
210	1	19	No	No	No
211	2	19	No	No	No
212	3	19	No	No	No
213	4	19	No	No	No
214	5	19	No	No	No
215	6	19	No	No	No
216	7	19	No	No	No
217	8	19	No	No	No
218	9	19	No	No	No
219	10 or more	19	No	No	No
220	0	20	No	No	No
221	1	20	No	No	No
222	2	20	No	No	No
223	3	20	No	No	No
224	4	20	No	No	No
225	5	20	No	No	No
226	6	20	No	No	No
227	7	20	No	No	No
228	8	20	No	No	No
229	9	20	No	No	No
230	10 or more	20	No	No	No
231	NA	NA	Yes	No	No
232	NA	NA	No	Yes	No
233	NA	NA	No	No	Yes

Table 2. Total daily dose of antianginal medication considered to be one unit

Medication	Total daily dose in mg
Bisoprolol	5
Atenolol	25
Amlodipine	2.5
Nifedipine	20
Isosorbide mononitrate MR	30
Isosorbide mononitrate SR	25
Diltiazem	120
Nicorandil	20
Ranolazine	750
Ivabradine	5