EuroIntervention
2023;19:e216-e223 published online ahead of print January 2024
published online e-edition February 2024
DOI: 10.4244/EIJ-D-23-00567

A double-blind, randomised, placebo-controlled trial of the coronary sinus Reducer in refractory angina: design and rationale of the ORBITA-COSMIC trial

Michael J. Foley[1,2], MBBS, BSc; Christopher A. Rajkumar[1,2], MBBS, BSc; Fiyyaz Ahmed-Jushuf[1], MBBS, BSc; Florentina Simader[1], MD; Rachel H. Pathimagaraj[1,2], MBChB, BSc; Sukhjinder Nijjer[1,2], MBBS, PhD; Sayan Sen[1,2], MBBS, PhD; Ricardo Petraco[1,2], MBBS, PhD; Gerald Clesham[3], MA, PhD, FRCP; Thomas Johnson[4], MBBS, MD, FRCP; Frank E. Harrell Jr[5], PhD; Peter Kellman[6], PhD; Darrel Francis[1,2], MA, MBBChir, MD; Matthew Shun-Shin[1,2], MA, BMBCh, PhD; James Howard[1,2], MA, MBBChir, PhD; Graham D. Cole[1,2], MA, MBBChir, PhD; Rasha Al-Lamee[1,2]*, MA, MBBS, PhD

**Corresponding author: National Heart and Lung Institute, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0HS, United Kingdom. E-mail: r.al-lamee13@imperial.ac.uk*

The authors' affiliations can be found at the end of this article.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00567

ABSTRACT

The coronary sinus Reducer (CSR) is an hourglass-shaped device which creates an artificial stenosis in the coronary sinus. Whilst placebo-controlled data show an improvement in angina, these results are unreplicated and are the subject of further confirmatory research. The mechanism of action of this unintuitive therapy is unknown. The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia, and Microvascular Resistance (ORBITA-COSMIC) trial is a randomised, placebo-controlled, double-blind trial investigating the efficacy of the CSR. Patients with (i) established epicardial coronary artery disease, (ii) angina on maximally tolerated antianginal medication, (iii) evidence of myocardial ischaemia and (iv) no further options for percutaneous coronary intervention or coronary artery bypass grafting will be enrolled. Upon enrolment, angina and quality-of-life questionnaires, treadmill exercise testing and quantitative stress perfusion cardiac magnetic resonance (CMR) imaging will be performed. Participants will record their symptoms daily on a smartphone application throughout the trial. After a 2-week symptom assessment phase, participants will be randomised in the cardiac catheterisation laboratory to CSR or a placebo procedure. After 6 months of blinded follow-up, all prerandomisation tests will be repeated. A prespecified subgroup will undergo invasive coronary physiology assessment at prerandomisation and follow-up. The primary outcome is stress myocardial blood flow on CMR. Secondary outcomes include angina frequency, quality of life and treadmill exercise time. (ClinicalTrials.gov: NCT04892537)

KEYWORDS: clinical trials, innovation, other technique, stable angina

SUBMITTED ON 14/07/2023 - REVISION RECEIVED ON 12/10/2023 - ACCEPTED ON 12/11/2023

The coronary sinus Reducer (CSR; Shockwave Medical [previously Neovasc]) is an hourglass-shaped, stainless-steel mesh, currently used in patients with angina, which is refractory to antianginal medication and conventional antianginal procedures including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). It is the only currently utilised intervention for stable angina which is thought to improve myocardial ischaemia by acting on the cardiac venous circulation and has placebo-controlled evidence of angina relief[1,2].

The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) study reported a placebo-controlled reduction in physician-assessed Canadian Cardiovascular Society (CCS) angina class[1]. However, the mechanism of action of this device is unintuitive and remains unknown. All previous antianginal therapies are considered to work by improving myocardial ischaemia. Many mechanistic theories have been offered for the CSR[3,4]. However, these have principally been derived from animal models of myocardial infarction.

In humans, the effect of the CSR on myocardial ischaemia has been investigated in a single-arm unblinded registry. While global myocardial perfusion did not change, segments that were determined to be ischaemic at baseline appeared to improve[5]. The impact that randomisation, a control group, placebo subtraction, blinded reporting, and quantification of myocardial blood flow (MBF) might have had on this result is unknown.

The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (ORBITA-COSMIC) trial will investigate the placebo-controlled efficacy of the CSR on quantified myocardial perfusion and stable angina.

Impact on daily practice

ORBITA-COSMIC will provide placebo-controlled data on the efficacy of the CSR on myocardial perfusion and angina. The results will inform our daily practice in patients with angina, epicardial CAD, no further options for revascularisation and maximum antianginal medication. Knowledge of the mechanism of action of the device and its antianginal efficacy will determine if, and when, this device should be offered.

Methods

STUDY DESIGN

ORBITA-COSMIC is a randomised, placebo-controlled trial of the CSR investigating the efficacy of the CSR on myocardial perfusion and angina. It is registered on ClinicalTrials.gov (NCT04892537) and approved by the London Research Ethics Committee (reference 21/LO/0203). The study design is shown in **Figure 1**. A list of the ORBITA-COSMIC investigators is included in **Supplementary Appendix 1**.

ELIGIBILITY CRITERIA

ORBITA-COSMIC will randomise participants who have the following:

1. Angina on maximally tolerated antianginal medication,
2. Epicardial coronary artery disease (CAD),
3. Evidence of ischaemia on cardiac magnetic resonance (CMR) imaging,
4. No further options for CABG or PCI.

Angina is diagnosed by the referring clinician. Medical therapy is considered maximal when the patient is established on ≥3 antianginal medications at target doses or has documented intolerance to additional antianginals. Epicardial disease is defined as visual angiographic stenosis ≥50% in at least one major epicardial coronary artery or previous CABG or PCI. Documented ischaemia on stress perfusion CMR is required for enrolment. The absence of further options for CABG or PCI is determined by the clinical site's Heart Team, prior to referral. These teams consist of invasive cardiologists, general cardiologists, imaging cardiologists and cardiac surgeons.

Confirmation of eligibility will be performed by the ORBITA-COSMIC multidisciplinary team (COSMIC-MDT). This team is comprised of interventional cardiologists from the trial sites, with extensive experience in managing complex CAD, including chronic total occlusions and post-CABG CAD. To progress to enrolment, the COSMIC-MDT must reach a consensus that there are no reasonable PCI or additional antianginal medication options.

The inclusion and exclusion criteria are listed in **Table 1**.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome is the between-group difference in myocardial blood flow (MBF) on adenosine stress CMR at 6-month follow-up in the segments designated to be ischaemic at baseline. This imaging outcome will be analysed using Bayesian methodology, in which stress MBF at 6 months is

Abbreviations

CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CFR	coronary flow reserve
CMR	cardiac magnetic resonance
COSIRA	Coronary Sinus Reducer for Treatment of Refractory Angina
COSMIC-MDT	ORBITA-COSMIC multidisciplinary team
CSR	coronary sinus Reducer
EQ-5D-5L	EuroQol questionnaire
IMR	index of microcirculatory resistance
MBF	myocardial blood flow
MPR	myocardial perfusion reserve
MRR	microvascular resistance reserve
OR	odds ratio
ORBITA-COSMIC	Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia, and Microvascular Resistance
PCI	percutaneous coronary intervention
SAQ	Seattle Angina Questionnaire

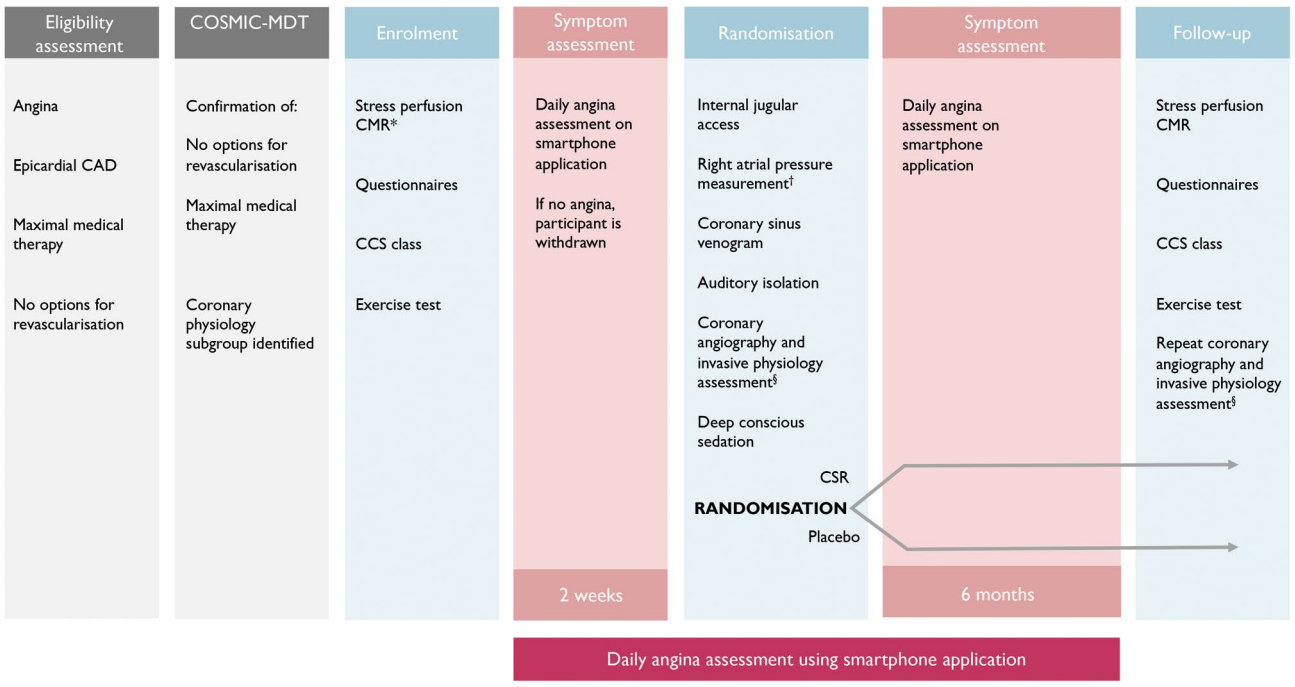


Figure 1. *ORBITA-COSMIC study design. Questionnaires and CCS class assessment additionally administered immediately prior to randomisation. *If there is no ischaemia outside of the inferior wall on this scan, the participant is removed from the study at this stage and does not proceed to randomisation. †Participants with a right atrial pressure ≥15 mmHg will not proceed to randomisation and will be removed from the study. §For those patients identified as eligible during the COSMIC-MDT assessment. CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; CMR: cardiac magnetic resonance; COSMIC-MDT: ORBITA-COSMIC multidisciplinary team; CSR: coronary sinus Reducer*

conditioned on the enrolment value and treatment arm. The MBF at rest and stress will be quantified using validated perfusion mapping with automated analysis using the Gadgetron (open source framework)[6-11]. Enrolment and follow-up CMR will have matched adenosine dose and duration and will be performed by a blinded research team. An example quantitative CMR is shown in **Figure 2**. A single-arm study has suggested an improvement in the endocardial-epicardial perfusion gradient with the CSR[12]. This will be investigated as a secondary imaging outcome. The primary symptom outcome is the daily angina episodes component of the angina symptom score[13]. Outcomes are listed in **Table 2**.

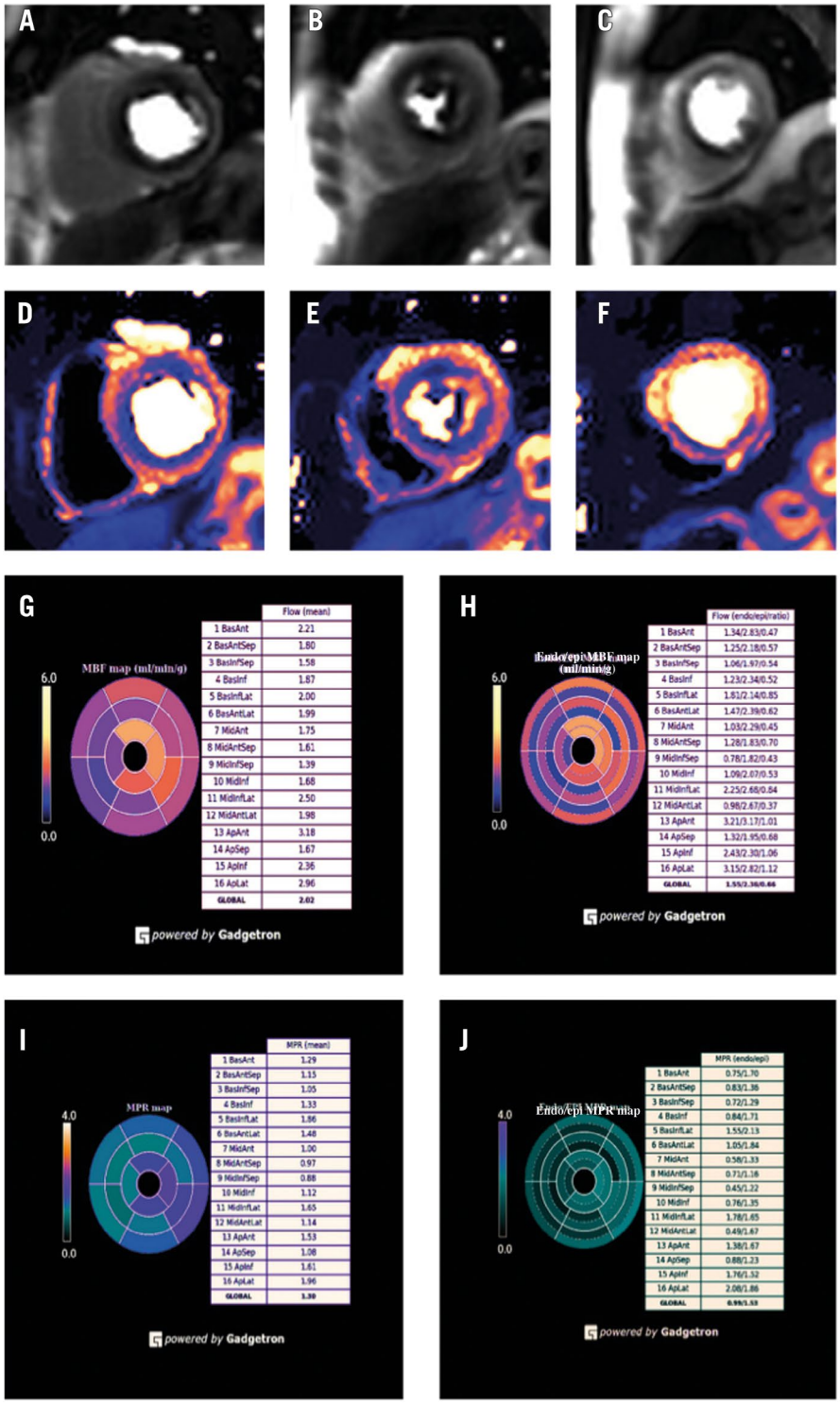
ENROLMENT

At enrolment, eligibility will be rechecked, and written consent will be obtained. Symptoms will be assessed by Canadian Cardiovascular Society (CCS) class and symptom questionnaires including the Seattle Angina Questionnaire (SAQ), Rose Angina Questionnaire, EuroQol (EQ-5D-5L) and the MacNew Heart Disease Health-Related Quality of Life Questionnaire. The participants will be taught to use the ORBITA-COSMIC smartphone application for documentation of daily angina symptoms **(Supplementary Appendix 2, Supplementary Table 1, Supplementary Table 2)**[13,14]. Participants will undergo treadmill exercise testing, utilising

Table 1. ORBITA-COSMIC inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Established epicardial CAD • Angina on maximally tolerated antianginal 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 (LVEF <25%) • Indication for CRT • Right atrial pressure ≥15 mmHg • Life expectancy <1 year • Severe renal impairment (eGFR <15 ml/min) • Contraindication to CMR • Contraindication to adenosine • Ischaemia isolated to inferior wall • Ongoing participation in a separate interventional study

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CMR: cardiac magnetic resonance; CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention



	Flow (mean)
1 BasAnt	2.21
2 BasAntSep	1.80
3 BasInfSep	1.58
4 BasInf	1.87
5 BasInfLat	2.00
6 BasAntLat	1.99
7 MidAnt	1.75
8 MidAntSep	1.61
9 MidInfSep	1.39
10 MidInf	1.68
11 MidInfLat	2.50
12 MidAntLat	1.98
13 ApAnt	3.18
14 ApSep	1.67
15 ApInf	2.36
16 ApLat	2.96
GLOBAL	2.02

	Flow (endo/epi/ratio)
1 BasAnt	1.34/2.83/0.47
2 BasAntSep	1.25/2.18/0.57
3 BasInfSep	1.06/1.97/0.54
4 BasInf	1.23/2.34/0.52
5 BasInfLat	1.81/2.14/0.85
6 BasAntLat	1.47/2.39/0.62
7 MidAnt	1.03/2.29/0.45
8 MidAntSep	1.28/1.83/0.70
9 MidInfSep	0.78/1.82/0.43
10 MidInf	1.09/2.67/0.53
11 MidInfLat	2.25/2.68/0.84
12 MidAntLat	0.98/2.67/0.37
13 ApAnt	3.21/3.17/1.01
14 ApSep	1.32/1.95/0.68
15 ApInf	2.43/2.30/1.06
16 ApLat	3.15/2.82/1.12
GLOBAL	1.55/2.36/0.66

	MPR (mean)
1 BasAnt	1.29
2 BasAntSep	1.15
3 BasInfSep	1.05
4 BasInf	1.33
5 BasInfLat	1.86
6 BasAntLat	1.48
7 MidAnt	1.00
8 MidAntSep	0.97
9 MidInfSep	0.88
10 MidInf	1.12
11 MidInfLat	1.65
12 MidAntLat	1.14
13 ApAnt	1.53
14 ApSep	1.08
15 ApInf	1.61
16 ApLat	1.96
GLOBAL	1.30

	MPR (endo/epi)
1 BasAnt	0.75/1.70
2 BasAntSep	0.83/1.36
3 BasInfSep	0.72/1.29
4 BasInf	0.84/1.71
5 BasInfLat	1.55/2.13
6 BasAntLat	1.05/1.84
7 MidAnt	0.58/1.33
8 MidAntSep	0.71/1.16
9 MidInfSep	0.45/1.22
10 MidInf	0.76/1.35
11 MidInfLat	1.78/1.65
12 MidAntLat	0.49/1.67
13 ApAnt	1.38/1.67
14 ApSep	0.88/1.23
15 ApInf	1.76/1.32
16 ApLat	2.08/1.86
GLOBAL	0.99/1.53

Figure 2. *Quantitative perfusion mapping in a patient with refractory angina. A-C) Shows first-pass perfusion images during maximal hyperaemia induced by adenosine stress in the basal, mid-, and apical short-axis slices. There are subendocardial perfusion defects in the LAD and RCA territories. D-F) Shows perfusion maps of myocardial blood flow on a pixel-by-pixel basis in the same basal, mid-, and apical short-axis slices. G) Shows myocardial blood flow on stress by segment, and for the epicardial (epi) and endocardial (endo) component of each segment (H), provided inline during the scan in an automated bias-resistant manner using the Gadgetron framework. Myocardial perfusion reserve by segment (I) and for epicardial and endocardial components of each segment (J) are also automated and are provided after the rest perfusion images. In this case, the bull's-eye plots demonstrate reduced myocardial blood flow on stress and reduced MPR in segments in the anterior, anteroseptal, inferoseptal and inferior walls. LAD: left anterior descending artery; MPR: myocardial perfusion reserve; RCA: right coronary artery*

Table 2. ORBITA-COSMIC trial outcomes.

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 (PressureWire X; Abbott) and an intracoronary saline infusion catheter (RayFlow; Hexacath)
	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)

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

the Modified Bruce Protocol **(Supplementary Appendix 3)**. The management of medications is described in **Supplementary Appendix 4**.

STRESS CMR CONFIRMATION OF ISCHAEMIA

At enrolment, all participants will undergo a quantitative perfusion CMR[7] **(Supplementary Appendix 5)**. For inclusion, ischaemia is defined as present or absent by the reporting clinical cardiologist. No minimum ischaemia threshold or a relationship between anatomical stenosis and myocardial ischaemia is required. This is to ensure that patients with a broad range of ischaemia are randomised. Patients with ischaemia involving the inferior wall will be included if they have additional ischaemia in other territories.

Scans will be assessed by a core imaging laboratory of 3 CMR experts. They will double report every CMR, blinded to all clinical data, the randomisation arm, and time point. They will determine the location of ischaemia and scar, by segment, for use in the assessment of the primary outcome.

SYMPTOM EVALUATION

Once enrolled, participants will enter the 2-week prerandomisation symptom assessment phase. If asymptomatic, they will be withdrawn. Angina will be assessed daily throughout the trial using the symptom smartphone application **(Supplementary Appendix 3)**. Participants will have additional symptom and quality-of-life assessment performed at enrolment, prerandomisation, and follow-up.

CORONARY PHYSIOLOGY SUBGROUP

A subgroup of participants will be eligible for invasive physiological assessment if they have a patent native coronary artery which can be safely investigated. Eligibility will be determined by the COSMIC-MDT.

This subgroup will undergo invasive assessment at prerandomisation and follow-up. The aim is to measure macro- and microvascular coronary function using multiple modalities. Measurements will be preferentially performed in the left main coronary artery and the ostial right coronary artery, where coronary anatomy permits. This will be performed before sedation and randomisation and will include absolute coronary flow and resistance using continuous thermodilution with the RayFlow catheter (Hexacath) and PressureWire X guidewire (Abbott), coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) using bolus thermodilution with the PressureWire X and CFR using Doppler velocity with the ComboWire (Philips). The full protocol is described in **Supplementary Appendix 6**.

RANDOMISATION PROCEDURE AND BLINDING

Randomisation procedures will occur in 6 high-volume PCI centres in the United Kingdom with a proctor in attendance. Procedures will be performed with standard electrocardiogram and haemodynamic monitoring. A 9 Fr sheath will be implanted into the right internal jugular vein with ultrasound guidance under local anaesthetic. Right atrial pressure will be measured in end-expiration. Participants with a mean right atrial pressure ≥15 mmHg will be withdrawn.

Coronary sinus access will be obtained with a diagnostic catheter, and a coronary sinus venogram will be acquired in

the left anterior oblique position to confirm coronary sinus size and anatomy are suitable for implantation.

Auditory isolation will be obtained using over-the-ear headphones playing music. A bolus of 5,000 units of intravenous heparin will be administered. Incremental doses of intravenous benzodiazepines and opiates will be administered to establish a deep level of conscious sedation. Carbon dioxide capnography will be utilised according to local practice. Ventilatory and circulatory status will be monitored throughout the procedure. Once adequately sedated, participants will be randomised 1:1 to CSR or placebo using a dedicated computer randomisation software (Randi; open source software).

In the CSR group, device implantation will be conducted according to standard clinical protocol **(Supplementary Appendix 7)**. During CSR balloon inflation, coronary sinus wedge pressure will be measured where possible. In the placebo group, sedation will be maintained for 15 minutes without further intervention. At the end of the procedure, protamine will be administered, and the venous sheath will be removed under sedation.

A standardised handover to the blinded recovery team will be performed. Participants, caregivers and all staff outside the catheter laboratory, including ward and research staff involved in follow-up assessment and data analysis, will be blinded to treatment allocation. Following ward recovery with routine haemodynamic monitoring, all participants will be discharged with dual antiplatelet therapy for 6 months and standardised discharge documentation. An assessment of the blinding of participants and clinical staff will be made at the time of discharge **(Supplementary Appendix 8)**.

BLINDED FOLLOW-UP EVALUATION

Participants will continue daily completion of the smartphone symptom application and will have access to the blinded research team at any time. Symptom questionnaires, CCS class assessment, treadmill exercise testing and CMR will be repeated at 6 months by a blinded research team.

BLINDING INDEX

Fidelity of the blinding of the patient, clinical and research teams will be assessed and reported prior to discharge after the randomisation procedure and at 6-month follow-up **(Supplementary Appendix 8)**. The blinding index will be assessed using previously reported methodology[15].

UNBLINDING AND TRIAL END

After the completion of follow-up and blinding assessment, participants will be unblinded and return to routine care. The placebo group will be offered the opportunity to undergo CSR implantation as part of clinical care. Any actions after unblinding will not contribute to outcome data. To date, 51 patients in ORBITA-COSMIC have been randomised, and 40 have completed follow-up.

DATA MONITORING

ORBITA-COSMIC will be overseen by a trial steering committee with an independent chair. All safety events and participant crossovers will be reported to an independent data safety and monitoring board. Data management is detailed in **Supplementary Appendix 9**.

STATISTICAL ANALYSIS

The sample size was calculated to detect a change in the between-group difference in myocardial perfusion reserve (MPR) 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, 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[5] and (2) a reproducibility standard deviation of MPR of 18%[9].

Conservatively estimating the change in ischaemic segments to be 10% with an 18% reproducibility standard deviation, to have a 90% power with a 5% alpha level will require 38 participants. We estimate a crossover and dropout rate of 10% and, therefore, plan to randomise 50 participants.

Categorical variables will be summarised as proportions; continuous variables will be summarised as quartiles. All data will be analysed according to the intention-to-treat principle.

The mechanism of action of the CSR is unknown. The analytical approach is designed to take into consideration previously published concepts: perfusion may improve only in segments which are ischaemic[5], normally perfused segments may have reduced perfusion at follow-up[3], transmurally infarcted segments will not have reliable perfusion quantification, and ischaemic thresholds in quantified perfusion are arbitrary.

To enable an analysis that can draw multiple simultaneously valid conclusions, 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), clustered by participant. An indicator variable, based on whether the segment was classified as ischaemic at enrolment, will also be included as an interaction with the treatment arm.

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

PRIMARY OUTCOME

The primary efficacy analysis will be derived from the model and the effect of the treatment arm within the ischaemic segments. Particular probabilities of OR intervals will be computed, along with 2-sided 0.95 Bayesian credible intervals.

SECONDARY OUTCOMES ESTIMATED FROM THE PRIMARY MODEL

The outcomes of the effect in the designated "non-ischaemic" segments and the effect on global myocardial perfusion will be computed from the same model and presented.

A detailed discussion of the analysis plan for secondary outcomes, including the primary symptom outcome, is included in the statistical analysis plan.

Discussion

The coronary sinus Reducer is recommended in patients with angina, epicardial CAD, no further revascularisation options and optimal antianginal medication[16]. While the device is hypothesised to redistribute myocardial perfusion to improve ischaemic segments, the mechanism of action of this device

is poorly understood and unintuitive, with only single-arm data in humans[5,12]. This may explain why, despite placebo-controlled evidence of angina improvement[1] and guideline recommendations[16], the CSR is not widely used in current clinical practice.

ORBITA-COSMIC is the first placebo-controlled trial to investigate the hypothesised improvement in myocardial perfusion. It incorporates key factors in the design to ensure that assessments are reliable, with the potential to inform clinical practice. Firstly, randomisation will avoid misattribution of regression to the mean to a treatment effect. Secondly, inclusion of a placebo control group will allow quantification of the true physical component of treatment by accounting for the contribution of placebo to the overall effect. Whilst blinding in trials of interventional procedures is complex and challenging, requiring a systemic and reproducible approach, it is certainly possible and important[17]. It is essential for symptomatic endpoints, where the differences between unblinded and blinded effect sizes are substantial[18-24]. And finally, robust blinding methodology, including auditory isolation, deep levels of conscious sedation, standardised management of blinded clinical and research teams and reporting of blinding fidelity, will ensure that any potential impact of unblinding will be minimised and measured.

To optimise the power of the trial to detect a between-group difference, multiple methodological steps have been incorporated. CMR quantitative perfusion mapping will improve the ability to detect regional changes in myocardial blood flow. Daily collection of patient-reported angina data will increase the ability of the trial to detect change. This contrasts with conventional angina assessment, which is restricted to specific time points with the possibility of recall and reporting biases. Bayesian statistical methodology will be used so that direct inferential statements can be made.

Limitations

The study is only recruiting from centres in the United Kingdom, which may impact the generalisability of the data. Although, these centres serve diverse populations, all efforts will be made to ensure the participants represent the local population. While the study is adequately powered for the primary outcome, the size of this effect will determine our ability to detect changes in the secondary outcomes. Only a proportion of patients will be anatomically suitable to undergo coronary physiology assessment, given the advanced nature of their coronary artery disease.

Conclusions

The CSR is the only interventional procedure for angina relief with a site of action in the cardiac venous circulation. The placebo-controlled mechanism of action and efficacy of the CSR is uncertain. ORBITA-COSMIC will assess the impact of the CSR compared to a placebo procedure on myocardial perfusion and angina in a double-blind, randomised controlled trial.

Authors' affiliations

1. National Heart and Lung Institute, Imperial College London, London, United Kingdom; 2. Imperial College Healthcare NHS Trust, London, United Kingdom; 3. Essex Cardiothoracic Centre, Basildon, United Kingdom; 4. Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom; 5. Vanderbilt University School of Medicine, Nashville, TN, USA; 6. National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Acknowledgements

We thank Raquel Trujllio, Craig Robertson and Katherine March for their dedication and support.

Funding

The trial is sponsored by Imperial College London and funded by the Medical Research Council (MR/V001620/1). Michael Foley, Christopher Rajkumar and Fiyyaz Ahmed-Jushuf are funded by the Medical Research Council (MR/V001620/1, MR/S021108/1 and MR/W000520/1). James Howard, Rasha Al-Lamee and Darrel Francis are funded by the British Heart Foundation (FS/ICRF/22/26039, FS/ICRF/22/26051 and RG/RG/F/22/110059). The CSR devices used in the trial are funded by a grant from the Imperial Healthcare Charity (Nissen Fund). Graham D. Cole is supported by the National Institute of Health Research (NIHR) Imperial Biomedical Research Centre (BRC).

Conflict of interest statement

M.J. Foley has received speaker honoraria from Menarini and Philips/Volcano. C.A. Rajkumar has received speaker honoraria from Menarini and Philips/Volcano. F. Simader has received financial support from Servier. S. Nijjer has received speaker honoraria from Philips/Volcano, Pfizer, Bayer, AstraZeneca, Ingelheim, and Amarin. R. Petraco has received speaker and consultant fees from Philips and Abbott. J. Howard reports shares in Mycardium AI. G.D. Cole reports shares in Mycardium AI. R. Al-Lamee reports advisory board positions for Janssen Pharmaceuticals, Abbott, and Philips; and speaker honoraria for Abbott, Philips, Medtronic, Servier, Omniprex, and Menarini. The other authors have no conflicts of interest to declare.

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Supplementary data

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00567

Supplementary data

Supplementary Appendix 1. ORBITA-COSMIC investigators.

Dr Rasha Al-Lamee, Prof Darrel Francis, Dr Ghadha Mikhail, Dr Graham Cole, Dr James Howard, Dr Matthew Shun-Shin, Dr Jamil Mayet, Dr Sukhjinder Nijjer, Dr Ricardo Petraco, Dr Sayan Sen, Dr Gerald Clesham, Dr Tom Johnson, Dr Ranil De Silva, Dr Jonathan Hill, Dr John Davies, Dr Thomas Keeble, Dr Tushar Kotecha, Dr Peter O'Kane, Dr Helen Routledge, Dr James Spratt, Dr Claudia Cosgrove.

Supplementary Appendix 2. ORBITA-COSMIC smartphone application development, design and ordinal outcomes scale.

The ORBITA-COSMIC smartphone application is similar in concept and design to the ORBITA-2 application. In consultation with patients with lived experience of severe, refractory angina, two key changes have been made. The first is 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 is 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 will be 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 will additionally select 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 will be encouraged to undertake these activities at least once a week.

Throughout the trial, from enrolment to trial exit, participants will be 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 will also be asked if they experienced angina with the two pre-specified angina triggering activities.

The angina frequency reported on the smartphone application will be 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 Appendix 3. Exercise test.

The test will be 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 will be assessed by two blinded assessors who are unaware of the timing of the test (pre-randomisation or follow-up) or the randomisation arm (CSR or placebo).

Supplementary Appendix 4. Medications management.

On enrolment, all participants will be 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 will be made to antianginal medication once enrolled in the trial. If the antianginal medication is changed by the treating physician during the course of the trial, this will be reported to the study team and documented. If medication changes are made, they will be adjusted to match the enrolment medications at all follow-up assessments, including CMR, where possible.

Supplementary Appendix 5. CMR protocol.

Patients will undergo 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. For stress, adenosine will be 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 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 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. The same CMR protocol will be used at pre-randomisation and follow-up. Patients will abstain 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 will be 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 has shown no artefact and we do not expect this to cause problems with image interpretation or unblinding. This is the first study of its kind utilising quantitative CMR perfusion mapping and CSR. Problematic device-related artefact will be documented and reported.

Supplementary Appendix 6. Coronary physiology protocol.

Participants will be excluded from the coronary physiology subgroup study if the following criteria are met:

- Previous coronary artery bypass grafting with patent grafts to the target vessel
- Only open vessel is right coronary artery
- Significant tortuosity, stenosis or calcification in target coronary artery which would preclude physiology assessment

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 coronary artery of interest, as determined by the COSMIC-MDT. Diagnostic coronary angiography will be performed.

Additional heparin will be given to a total dose of 100 units/Kg and 300mcg of intracoronary nitrates will be administered. A Combowire *(Philips, USA)* will be placed in the epicardial coronary artery. This will measure coronary flow velocity at rest. An infusion of adenosine will then be administered (140mcg/kg/min) and coronary flow velocity at maximal stable hyperaemia will be measured, allowing calculation of coronary flow reserve (CFR).

PressureWire™X *(Abbott, USA)* will be placed in the same epicardial coronary artery. 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 repeated saline boluses. The adenosine will then be stopped.

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

For the purposes of calculations, measurements taken 10ml/min infusion rate will be resting (i.e. Q_{rest}, Pa_{rest}, Pd_{rest}) and measurements taken at 20ml/min infusion rate will be maximal or hyperaemic (i.e Q_{max}, $Pd_{hyperaemia}$).

The following measurements will be calculated by the Coroventis software system *(Coroflow, Uppsala, Sweeden)*:

Absolute Blood Flow (Q)

$$Q = 1.08 \frac{T_i}{T} Qi$$

Q_{rest} will be calculated at 10ml/min infusion rate and Q_{max} will be calculated at 20ml/min infusion rate.

Resistance (R)

$$R = \frac{Pd}{Q}$$

R_{rest} will be calculated at 10ml/min infusion rate and $R_{hyperaemia}$ will be calculated at 20ml/min infusion rate.

Fractional Flow Reserve (FFR)

$$FFR = \frac{Pd_{hyperaemia}}{Pa_{hyperaemia}}$$

Microvascular Resistance Reserve (MRR)

$$MRR = \left(\frac{Q_{max}}{Q_{rest}}\right).\left(\frac{Pa_{rest}}{Pd_{hyperaemia}}\right)$$

Supplementary Appendix 7. CSR implantation.

At the point of randomisation, all patients will have had 9Fr venous access into the right internal jugular vein, right atrial pressure measurement, peripheral intravenous heparin administration and coronary sinus venogram acquisition using a diagnostic catheter in the distal coronary sinus (Multipurpose or Amplatzer) in the LAO 30° position.

Upon randomisation to the CSR arm, a 180cm 0.035 guidewire will be advanced through the diagnostic catheter to the distal coronary sinus. The diagnostic catheter will be inserted into

the Neovasc Reducer 9Fr guide catheter *(Cordis)*, to utilise a "mother and child" technique. The multipurpose catheter and guide catheter will be advanced together to the coronary sinus. The multipurpose catheter will be exchanged for the Neovasc Reducer CSR catheter with the device positioned in the desired implantation position in the coronary sinus. The guide catheter will be withdrawn to the proximal marker on the CSR delivery catheter. The CSR will be deployed to 4 to 6atm, aiming for 10% oversizing, confirmed with an IV contrast injection. The guidewire will be temporarily withdrawn at this point and the CSR catheter connected to the pressure transducer to measure the CS wedge pressure.

The CSR balloon will then be deflated at least five times to ensure adequate purging of contrast. The guide will be readvanced into the neck of the CSR and the balloon will be withdrawn into the guide catheter. The guide catheter will be withdrawn and the final venogram will be acquired using a multipurpose catheter. A final non-contrast image will be acquired demonstrating the CSR in situ. Protamine will be administered, and venous access removed with satisfactory haemostasis.

Supplementary Appendix 8. Blinding index assessment.

The efficacy of blinding will be assessed at two timepoints: prior to discharge on the day of the randomisation procedure for both clinical staff and the research participant, and again at 6-month follow-up. Blinding assessment will involve asking the staff member and participant to guess the randomisation allocation (CSR or placebo) with the options: 1) CSR, 2) Placebo, and 3) Don't Know. They will additionally be asked to give an indication of the certainty of their answer on a scale 1-5 with 5 being the most certain. Blinding index will be reassessed prior to planned unblinding at the end of 6 months of follow-up (however this guess may be influenced by symptomatic response or "wishful thinking" in the follow-up period, therefore this is not strictly a true assessment of blinding at this timepoint).

Supplementary Appendix 9. Data management.

All data will be entered on to an electronic clinical record form (RedCap). Smartphone data will be stored on a central server. Data will be stored for a minimum of 10 years from the completion of the study.

Supplementary Table 1. Ordinal clinical outcomes scale for angina.

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 Table 2. Standardised units of antianginal medication
On enrolment to the trial, participants will be maintained on their existing antianginal medication. During follow-up, any changes to the medication will be reported to the research team. The medications below are defined as one unit of antianginal medication for the ordinal outcome scale. Where patients are on alternative antianginal medication, the research team will adjudicate the unit equivalence at enrolment.

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