Coronary sinus reducer for the treatment of refractory angina (ORBITA-COSMIC): a randomised, placebo-controlled trial

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Summary

Background The coronary sinus reducer (CSR) is proposed to reduce angina in patients with stable coronary artery disease by improving myocardial perfusion. We aimed to measure its efficacy, compared with placebo, on myocardial ischaemia reduction and symptom improvement.

Methods ORBITA-COSMIC was a double-blind, randomised, placebo-controlled trial conducted at six UK hospitals. Patients aged 18 years or older with angina, stable coronary artery disease, ischaemia, and no further options for treatment were eligible. All patients completed a quantitative adenosine-stress perfusion cardiac magnetic resonance scan, symptom and quality-of-life questionnaires, and a treadmill exercise test before entering a 2-week symptom assessment phase, in which patients reported their angina symptoms using a smartphone application (ORBITA-app). Patients were randomly assigned (1:1) to receive either CSR or placebo. Both participants and investigators were masked to study assignment. After the CSR implantation or placebo procedure, patients entered a 6-month blinded follow-up phase in which they reported their daily symptoms in the ORBITA-app. At 6 months, all assessments were repeated. The primary outcome was myocardial blood flow in segments designated ischaemic at enrolment during the adenosine-stress perfusion cardiac magnetic resonance scan. The primary symptom outcome was the number of daily angina episodes. Analysis was done by intention-to-treat and followed Bayesian methodology. The study is registered with ClinicalTrials.gov, NCT04892537, and completed.

Findings Between May 26, 2021, and June 28, 2023, 61 patients were enrolled, of whom 51 (44 [86%] male; seven [14%] female) were randomly assigned to either the CSR group (n=25) or the placebo group (n=26). Of these, 50 patients were included in the intention-to-treat analysis (24 in the CSR group and 26 in the placebo group). 454 (57%) of 800 imaged cardiac segments were ischaemic at enrolment, with a median stress myocardial blood flow of 1·08 mL/min per g (IQR 0·77–1·41). Myocardial blood flow in ischaemic segments did not improve with CSR compared with placebo (difference 0·06 mL/min per g [95% CrI –0·09 to 0·20]; Pr(Benefit)=78·8%). The number of daily angina episodes was reduced with CSR compared with placebo (OR 1·40 [95% CrI 1·08 to 1·83]; Pr(Benefit)=99·4%). There were two CSR embolisation events in the CSR group, and no acute coronary syndrome events or deaths in either group.

Interpretation ORBITA-COSMIC found no evidence that the CSR improved transmural myocardial perfusion, but the CSR did improve angina compared with placebo. These findings provide evidence for the use of CSR as a further antianginal option for patients with stable coronary artery disease.

Funding Medical Research Council, Imperial College Healthcare Charity, National Institute for Health and Care Research Imperial Biomedical Research Centre, St Mary's Coronary Flow Trust, British Heart Foundation.

Lancet 2024; 403: 1543–53

Published Online April 8, 2024 https://doi.org/10.1016/S0140-6736(24)00256-3

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Introduction

The coronary sinus reducer (CSR) is an hourglass-shaped stainless-steel mesh that is percutaneously implanted in the coronary sinus to reduce angina.[1] It is the only antianginal therapy that acts on the cardiac venous circulation, and it is hypothesised to work by redistributing myocardial perfusion from more perfused to less perfused areas. This theory is based on a study in dogs with myocardial infarction treated with coronary sinus occlusion and on single-arm studies of CSR in humans.[2,3] However, no randomised trials to date have verified this proposed mechanism of action.

CSR is currently used for patients with angina and no further options for antianginal medication, percutaneous coronary intervention, or coronary artery bypass grafting. This practice is based on evidence of efficacy in this group

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Research in context

Evidence before this study

The coronary sinus reducer (CSR) device is believed to reduce angina by diverting blood flow from more perfused to less perfused areas of the myocardium. We did a literature search on PubMed, on Oct 20, 2019 (before the start of this trial), using the search terms "coronary sinus reducer" and "randomised controlled trial". This search confirmed that only one randomised trial of the coronary sinus reducer—the COSIRA trial—has been reported so far. This trial showed no improvement in patient-reported angina, but a distinct improvement in physician-assessed angina status. An additional search on the same date, using the terms "coronary sinus narrowing", "coronary sinus reducer", and "mechanism", showed that the effect of coronary sinus narrowing has been investigated in dogs and pigs, and that the mechanism of action of the CSR has only been investigated in observational single-arm registries. The mechanism of action of the CSR remains unclear. The literature search was updated annually.

Added value of this study

ORBITA-COSMIC is a double-blind, placebo-controlled trial of CSR in patients with angina, stable coronary artery disease, ischaemia, and no further antianginal medication or revascularisation options available. To our knowledge, it is the only trial of the CSR to mandate procedural auditory isolation, a deep level of conscious sedation during the randomisation procedure, and reporting of blinding fidelity for patients and research staff. It is also the only trial of the CSR to quantify perfusion in all myocardial segments at enrolment and follow-up by means of a bias-resistant cardiac magnetic resonance sequence, and to collect patient-reported angina episodes every day for the duration of the trial. We did not find strong evidence of an increase in perfusion of ischaemic areas. However, we found clear evidence of reduction in patient-reported angina episodes. This reduction developed gradually over a period of weeks and was sustained at 6 months.

Implications of all the available evidence

Physicians should favour placebo-controlled data when making symptom-focused treatment recommendations to patients. Although the mechanism of action of the CSR remains uncertain, ORBITA-COSMIC produced placebo-controlled data showing an improvement in patient-reported angina in a population with stable coronary artery disease, ischaemia, and no further options for antianginal therapy. The results of this trial provide evidence supporting the use of CSR as an additional treatment option for patients with stable coronary artery disease.

from one randomised controlled trial and from single-arm observational data.[4,5] In the randomised COSIRA trial,[4] patients were given the option of receiving either headphones or sedation, and the efficacy of blinding was not reported. No improvement in angina frequency was reported by patients, although there was a clear improvement in physician-evaluated angina severity.[4]

The CSR currently has a class IIb guideline recommendation for its use.[6] For a procedure with non-negligible risk and significant cost, robust placebo-controlled evidence of its mechanism of action and efficacy is required. The Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (ORBITA-COSMIC) trial used mandatory sedation, mandatory auditory isolation, and quantification of blinding fidelity, coupled with daily symptom reporting and quantitative myocardial perfusion, to investigate the mechanism of action of the CSR and its placebo-controlled impact on myocardial ischaemia and symptoms.

Methods

Study design and participants

ORBITA-COSMIC is an investigator-initiated, randomised, double-blind, placebo-controlled trial conducted at six hospitals in the UK (appendix p 5). The trial protocol has been published[7] and is available in the appendix (p 99). The study was approved by the London Riverside Research Ethics Committee (reference 21/LO/0203). Trial conduct was overseen by a steering committee with an independent chair. The data and safety monitoring board adjudicated all study adverse events. Independent data monitoring was performed by Syntactx, NAMSA. Authors MJF and RKA-L attest to the accuracy and completeness of the data and adherence to the protocol.

See Online for appendix

Patients were eligible to be enrolled in the ORBITA-COSMIC trial if they had angina, epicardial coronary artery disease, ischaemia, and no further options for antianginal therapy (ie, medication, percutaneous coronary intervention, or coronary artery bypass grafting). The details of previous therapies were obtained from the referring physician, patients, and the medical records. Severity of coronary artery disease was defined by use of the British Cardiovascular Intervention Society Jeopardy score. Exclusion criteria were age younger than 18 years (no upper age limit), recent acute coronary syndrome (<3 months) or revascularisation (<6 weeks), permanent pacemaker or defibrillator leads in the right heart, severe left ventricular systolic impairment (ejection fraction <25%), indication for cardiac resynchronisation therapy, right atrial pressure of 15 mm Hg or higher, life expectancy of less than 1 year, severe renal impairment, contraindication to cardiac magnetic resonance or adenosine, ischaemia isolated to the inferior wall, pregnancy, or inability to consent. Sex was patient-reported (male or female options).

After referral to the trial by their local heart team, the eligibility of each participant was rechecked by the ORBITA-COSMIC multidisciplinary team. Only patients with no further antianginal therapy options were randomly assigned to study groups.

At enrolment, eligibility was reconfirmed and written informed consent was obtained. All patients underwent adenosine-stress cardiac magnetic resonance with fully automated quantitative perfusion mapping (appendix pp 9–10).[8,9] This cardiac magnetic resonance sequence quantifies regional blood flow in all 16 myocardial segments, with further stratification into endocardial and epicardial layers.[9] Myocardial blood flow was measured during adenosine stress and at rest. Patients without ischaemia or with ischaemia only in the inferior wall were withdrawn. Three imaging consultant cardiologists with expertise in cardiac magnetic resonance independently double-reported all scans (GDC, JPH, and TK). All three experts were masked to clinical data, randomised treatment allocation, timepoint of the scan, and their own previous opinion. They designated each segment as ischaemic or not ischaemic and categorised the amount of scar in each segment (0%, 1–24%, 25–49%, 50–74%, 75–99%, and 100%). Segments were classified as ischaemic if they were given this categorisation in three or more of the six viewings. The cardiac magnetic resonance protocol and details of analysis are provided in the appendix (pp 9–10).

Patients were instructed in the use of a dedicated smartphone symptom application (ORBITA-app) to record the number of daily angina episodes throughout the trial (appendix pp 11–12). Patients completed the following symptom and quality-of-life questionnaires: the Seattle Angina Questionnaire (SAQ),[10] EQ-5D-5L including the visual analogue scale (EQ VAS),[11] and MacNew Heart Disease Health-Related Quality of Life Questionnaire.[12] Investigators graded participants' angina severity with the Canadian Cardiovascular Society (CCS) angina class. Patients performed a treadmill exercise test with the modified Bruce protocol (appendix pp 10–11).

Dual antiplatelet medications and proton pump inhibitors were started or continued in all enrolled patients. Patients then entered the 2-week, pre-randomisation, symptom assessment phase. Patients were only eligible to progress to randomisation if they reported symptoms during this period. The protocol did not mandate any changes to antianginal medications during the trial, and pre-enrolment medications were continued. The medication management protocol is provided in the appendix (p 23).

Following the symptom assessment phase, patients attended hospital for the research cardiac catheterisation laboratory randomisation procedure. A right internal jugular 9-Fr venous sheath was implanted under ultrasound guidance. Patients wore headphones playing music to establish auditory isolation throughout the procedure. Right atrial pressure was measured and a coronary sinus venogram was obtained with a diagnostic catheter. Intravenous heparin was administered to all patients during the procedure, immediately after the venogram.

Randomisation and masking

After documentation of both appropriate right atrial pressure (<15 mm Hg), measured by invasive cardiac catheterisation of the right atrium, and appropriate coronary sinus anatomy, verified with a coronary sinus venogram, patients were sedated with incremental intravenous doses of opiates and benzodiazepines, to achieve a deep level of conscious sedation. Auditory isolation was continued, and patients were randomly assigned (1:1) to receive either CSR or placebo with a validated, automated, online randomisation platform (Randi, open-source application for randomisation in clinical trials) with a variable block size algorithm (minimum block size 4, maximum block size 12), with no stratification.[13] Patients, recovery staff outside of the catheterisation laboratory, subsequent medical care-givers, and research teams were masked to study group assignment. The study team present during the randomisation procedure had no further contact with the patient. The blinding index for patients and staff at randomisation and follow-up were calculated with published methods.[14]

Procedures

Auditory isolation and a deep level of conscious sedation were maintained throughout the procedure, with assessment throughout the procedure by an investigator. Patients in the intervention group had CSR (Neovasc Reducer, Shockwave Medical, Santa Clara, CA, USA) implantation according to standard techniques, utilising a 9-Fr guiding catheter and the Neovasc Reducer System (appendix pp 24–25). Patients assigned to the placebo group were kept sedated on the cardiac catheterisation laboratory table for at least 15 min (the approximate amount of time necessary to implant a CSR), but without further intervention. At the end of the procedure, protamine 50 mg was administered intravenously, and the venous sheath was removed. Standardised handover was performed from the catheterisation laboratory team to the masked ward recovery team, with no information transfer regarding treatment allocation. Participants were discharged with 6 months of dual antiplatelet medication and standardised documentation. Before discharge, fidelity of blinding was assessed for all patients and recovery ward staff by means of previously described methods.[14]

Patients entered a 6-month, blinded, follow-up phase, in which they recorded their daily angina symptoms using the ORBITA-app. Any changes to antianginal medication during this phase were patient-initiated and made by the masked research team according to a prespecified protocol (appendix p 23). At 6 months, all patients repeated stress cardiac magnetic resonance, symptom and quality-of-life

questionnaires, CCS class assessment, and treadmill exercise testing. The blinding index was reassessed for patients and the research team. Patients, research, and clinical teams were then unmasked, and routine clinical care resumed. The patients in the placebo group were offered CSR implantation. No actions that occurred after the scheduled unblinding affected trial outcomes. The trial was overseen by a steering committee and all adverse events were discussed with an independent data and safety monitoring board (appendix p 7).

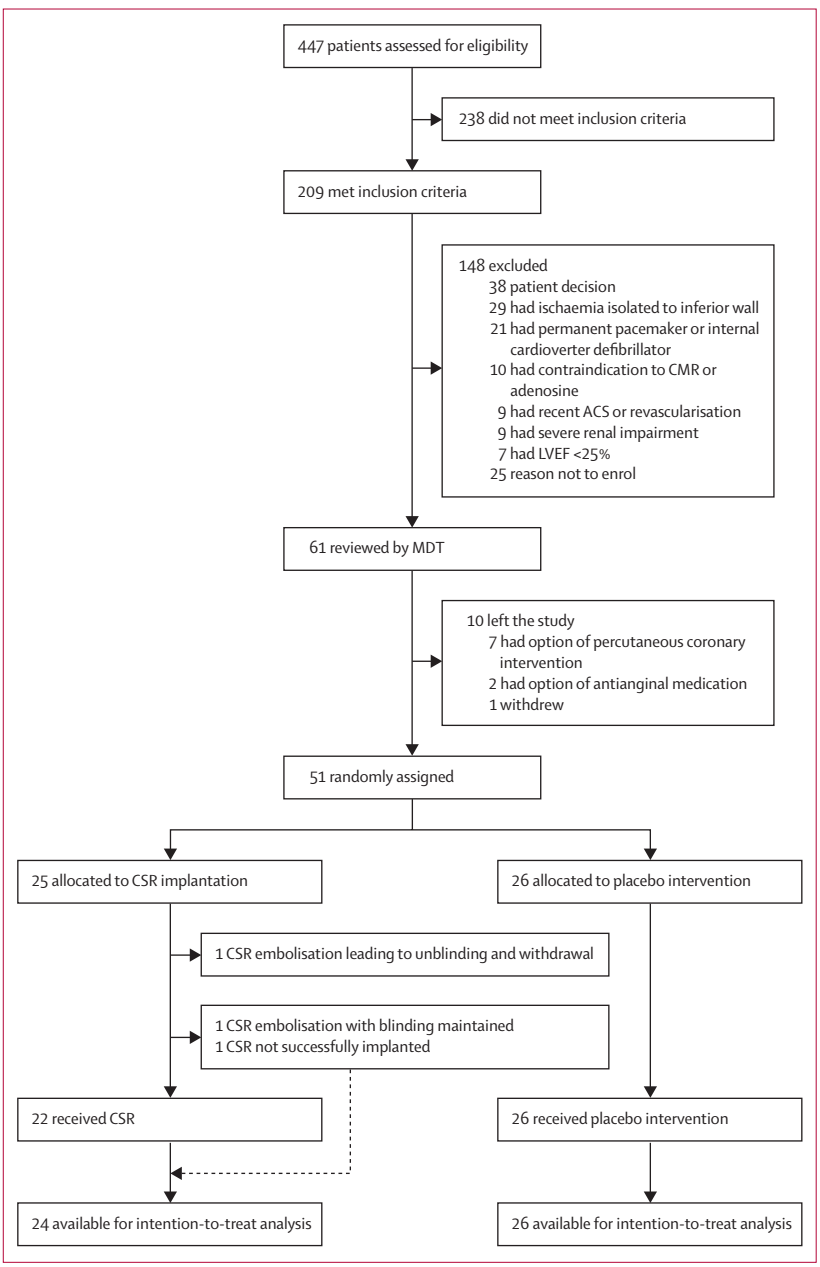


Figure 1: **Trial profile**
ACS=acute coronary syndrome. CMR=cardiac magnetic resonance scan. CSR=coronary sinus reducer. LVEF=left ventricular ejection fraction. MDT=ORBITA-COSMIC multidisciplinary team.

Outcomes

The primary outcome was myocardial blood flow on adenosine-stress cardiac magnetic resonance in myocardial segments designated as ischaemic at enrolment (excluding transmurally infarcted segments). The primary symptom outcome was the number of daily episodes of angina recorded on the ORBITA-app. Both prespecified primary outcomes were centrally assessed.

Secondary imaging outcomes were myocardial perfusion reserve, myocardial blood flow at rest, myocardial blood flow at stress, myocardial blood flow at rest and myocardial perfusion reserve with inferior and inferoseptal segments excluded, endocardial to epicardial ratio of myocardial blood flow at stress, endocardial to epicardial ratio of myocardial blood flow at rest, endocardial to epicardial ratio of myocardial perfusion reserve, myocardial strain, and myocardial scar. Secondary symptom outcomes were CCS class, angina symptom score (a daily score incorporating angina episodes, standardised units of antianginal medication [appendix pp 23–24], unblinding due to intolerable angina, acute coronary syndrome, and death), SAQ angina frequency, SAQ physical limitation, SAQ quality of life, SAQ treatment satisfaction, SAQ angina stability, EQ-5D-5L index value, EQ VAS, and MacNew Heart Disease Health-Related Quality of Life questionnaire scores, and treadmill exercise time. Invasive coronary physiology outcomes[7] were assessed before randomisation and at 6-month follow-up in a small subgroup of 15 patients. These patients were identified as suitable by the COSMIC-MDT if they had at least one native coronary artery that could be safely investigated with a pressure wire. The results are not reported in this primary manuscript because this element of the research protocol was designed as a secondary substudy, which will be reported elsewhere.

The primary timepoint for analysis was set at 6 months because clinical experience with the CSR and data from the only previous randomised controlled trial (COSIRA) indicated that this was a reasonable timepoint for the hypothesised physiological effects of the CSR to have taken place and symptom benefit to be measurable.

Statistical analysis

The sample size was calculated to detect a change in the primary outcome (between-group difference in myocardial blood flow on stress cardiac magnetic resonance at 6 months). 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 the only study of perfusion change with the CSR, which was unblinded and single-arm and reported a variable effect (8% difference from baseline to follow-up in global perfusion and a 35% difference in ischaemic segments),[3] and by a reproducibility standard deviation of stress myocardial blood flow of 17%.[8] This effect size is approximately half of that seen with unblinded percutaneous coronary intervention.[15] Conservatively, to

detect a change in the ischaemic segments of 17% (half the published unblinded CSR effect size) with a 17% reproducibility standard deviation, with 90% power at the 5% significance level, the study would require 44 patients. We estimated a crossover and dropout rate of 10% and, therefore, planned to randomly assign 50 patients.

The primary outcome was stress myocardial blood flow at follow-up in segments that were designated ischaemic at enrolment, with transmurally infarcted segments excluded. This outcome was designed to allow the possibility that flow might be redistributed from non-ischaemic to ischaemic segments without changing global myocardial blood flow, and that quantification of myocardial perfusion might be unreliable in transmurally infarcted segments. The original protocol specified myocardial perfusion reserve as the primary outcome, which is the ratio of myocardial blood flow at stress to myocardial blood flow at rest. Before final data lock, advice from the statistical and CMR working groups was that outcomes based on absolute values rather than a ratio would have better statistical properties. Therefore, the primary outcome was changed from ratio of myocardial blood flow at stress to myocardial blood flow at rest, to myocardial blood flow at stress only.

The primary outcome was analysed by means of a proportional odds ordinal logistic model fitted by means of the R rmsb package.[16] The perfusion data from every segment were included in this model, in which the stress myocardial blood flow at follow-up was conditioned on the stress myocardial blood flow at enrolment and the randomisation group (CSR or placebo), which was allowed to interact with an indicator variable coded for whether the segment was ischaemic (on the basis of blinded expert consensus) and clustered by participant. This model produced odds ratio (OR) that was transformed to the original scale through a weighted mean of the possible response levels with weights equal to the cell probabilities estimated from the proportional odds model. We present associated 95% credible intervals (CrI), constructed from the highest posterior density interval, and the probability of benefit (Pr(Benefit)) or interaction (Pr(Interaction)).

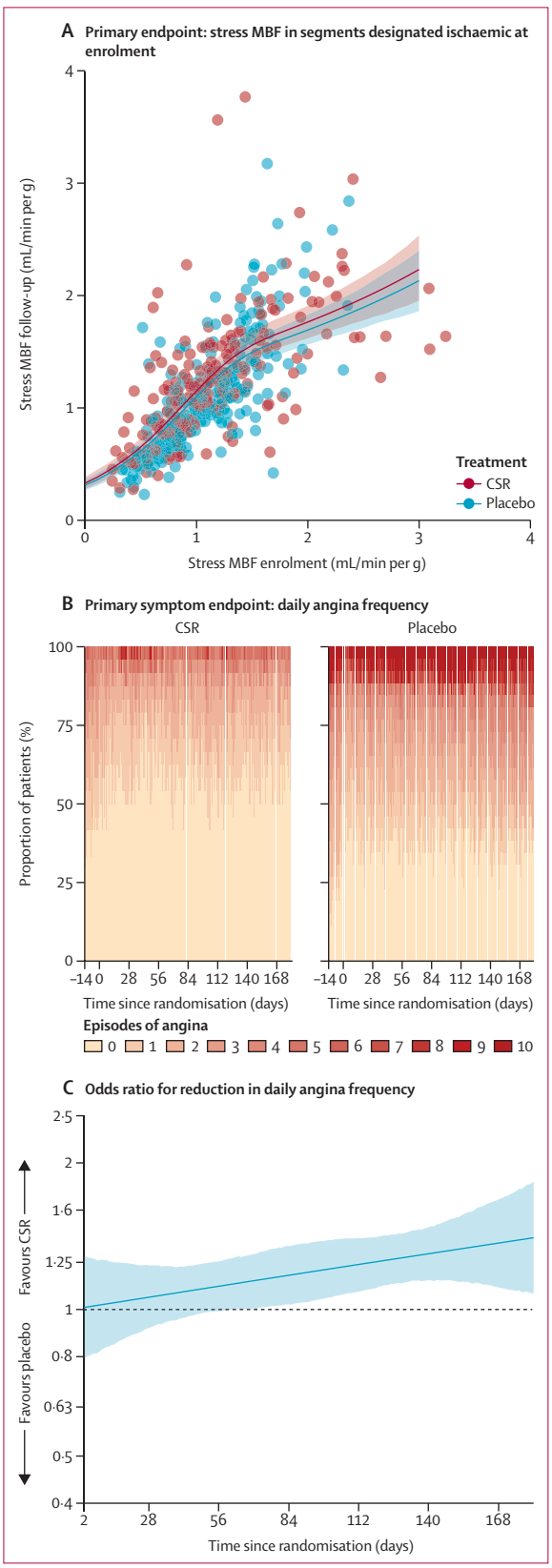
The primary symptom endpoint was the daily OR of transitioning to fewer daily episodes of angina reported using the ORBITA-app. ORs were constructed such that an OR higher than 1 reflected a reduction in the number of episodes of angina. The OR was derived by constructing a Bayesian Markov longitudinal ordinal model, which maximises power by using the daily episodes of angina. The model included the previous day's number of episodes (a first order Markov model), mean daily angina episodes during the pre-randomisation period, trial day number, and randomisation group. The trial day number was allowed to interact with the treatment group to allow the model to detect variation in treatment effect with time. Effects were allowed to be non-linear with restricted cubic splines, and partial proportional odds with constraints with respect to time. In addition to the daily OR, clinically relevant estimates and contrasts could be drawn from the model (eg, by derivation of the mean daily angina episodes or the number of days in a state [eg, no angina], for an exemplar patient, from the daily transition probabilities).

The secondary outcomes were measured at pre-randomisation and at 6 months' follow-up. For both continuous and categorical outcome variables, a Bayesian ordinal proportional odds model was used. The follow-up value was conditioned on the pre-randomisation value (transformed by a restricted cubic spline with three knots) and randomisation group. No interactions were

	CSR group (n=25)	Placebo group (n=26)
Median age, years	72 (63–74)	67 (61–72)
Sex		
Male	21 (84%)	23 (88%)
Female	4 (16%)	3 (12%)
Ethnic origin		
White	13 (52%)	12 (46%)
Asian	9 (36%)	9 (35%)
Arab	3 (12%)	4 (15%)
Afro-Caribbean	0	1 (4%)
Hypertension	17 (68%)	23 (88%)
Diabetes		
Non-insulin dependent	13 (52%)	17 (65%)
Insulin-dependent	2 (8%)	2 (8%)
Hyperlipidaemia	16 (64%)	18 (69%)
Previous CABG	21 (84%)	23 (88%)
Previous PCI	14 (56%)	14 (54%)
Smoking status		
Never smoked	18 (72%)	17 (65%)
Ex-smoker*	5 (20%)	7 (27%)
Current smoker	2 (8%)	2 (8%)
Left ventricular systolic function		
Normal	19 (76%)	23 (88%)
Mild impairment	4 (16%)	0
Moderate impairment	2 (8%)	3 (12%)
Canadian Cardiovascular Society class		
II	2 (8%)	1 (4%)
III	19 (76%)	17 (65%)
IV	4 (16%)	8 (31%)
Median angina duration, months	60·0 (22·0–96·0)	36·0 (18·0–60·0)
Median number of antianginal medications	4·0 (3·0–4·0)	3·0 (3·0–4·0)
Median British Cardiovascular Intervention Society Jeopardy	7·0 (6·0–9·0)	5·0 (4·0–6·0)

Data are median (IQR) or n (%). Left ventricular systolic function was defined as normal (≥55%), mildly impaired (45–54%), or moderately impaired (35–44%). CSR=coronary sinus reducer. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. *Ex-smoker was defined by the patient reporting that they had stopped smoking more than 6 months previously.

Table 1: **Baseline characteristics of study participants**



specified. For clinical interpretation, the contrast between the CSR and placebo groups are presented for a typical patient with the median pre-randomisation value, transformed to the original scale, along with the probability of benefit (Pr(Benefit)). Further details including priors are provided in the appendix (p 28).

The EQ-5D-5L score was converted to the index value via the UK value set from the EuroQol crosswalk calculator spreadsheet.[17] The distribution of raw responses across the EQ-5D-5L domains are presented in the appendix (pp 61–63).

All analyses were conducted with R software, package rmsb for Bayesian modelling,[16] and package BI for the blinding index. Analysis was conducted according to the intention-to-treat principle. The study statistician was masked to treatment allocation until final data lock. The study is registered with ClinicalTrials.gov, NCT04892537, and is completed.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 26, 2021, and June 28, 2023, 447 patients were assessed for eligibility and 209 patients met the trial inclusion criteria. Of these, 61 were assessed by the ORBITA-COSMIC multidisciplinary team, and 51 progressed to random assignment to either CSR (25 patients) or placebo (26 patients; figure 1). One patient in the CSR group was withdrawn during the randomisation procedure, because of a device embolisation event that required unblinding for adequate management. Therefore, the final number of patients included in the intention-to-treat analysis was 24 in the CSR group and 26 in the placebo group. The median follow-up was 184 days (IQR 177–196).

Baseline characteristics are described in table 1. Most patients were male (44 [86%] male; seven [14%] female). The median age was 67 years (IQR 61–74) and most patients had had previous coronary artery bypass grafting (44 patients [86%]) or previous percutaneous coronary intervention (28 patients [55%]). Most patients (48 [94%]) were in CCS class III or IV. Median LDL before randomisation was 1·47 mmol/L (IQR 1·01–2·05) and median HbA_{1c} before randomisation was 51·0 mmol/mol (41·0–56·5; appendix p 30). The median number of

Figure 2: **Primary outcomes**
(A) Individual patient data for the primary endpoint (stress MBF) in segments designated ischaemic at enrolment. (B) Individual patient data for the primary symptom endpoint (daily angina episodes), reported via the ORBITA smartphone symptom application. (C) Odds ratio for reduction in daily angina episodes for CSR versus placebo. CSR=coronary sinus reducer. MBF=myocardial blood flow.

antianginal drugs at enrolment was 3 (3–4). Median British Cardiovascular Intervention Society Jeopardy score was 6·0 (4·5–8·0). Enrolment and follow-up scans were available for all 50 patients included in the intention-to-treat analysis. Due to technical issues, two baseline scans could not be processed for quantitative perfusion analysis but were available for expert qualitative analysis. The number of ischaemic segments at enrolment was 454 (57%) of 800 segments, and the median stress myocardial blood flow in these segments was 1·08 mL/min per g (IQR 0·77–1·41). Global stress myocardial blood flow at enrolment was 1·33 mL/min per g (IQR 1·03–1·51), and myocardial perfusion reserve was 1·76 (IQR 1·52–2·10). The number of segments with any scar was 176 (22%) of 800, and no patients had full thickness infarction. The median left ventricular ejection fraction was 62·0% (IQR 57·0–67·0).

For the primary study outcome, no benefit of CSR over placebo was detected in stress myocardial blood flow in segments designated ischaemic at enrolment (0·06 mL/min per g [95% CrI –0·09 to 0·20]; Pr(Benefit)=78·8%, figure 2; table 2).

In ischaemic segments, the endocardial to epicardial ratio of stress myocardial blood flow improved in the CSR group (0·09 [95% CrI 0·00 to 0·17]; Pr(Benefit)=98·2%), and we found evidence of a difference in this effect between ischaemic and non-ischaemic segments (0·10 [0·02 to 0·19]; Pr(Interaction)=99·2%). We found no difference in the other secondary imaging outcomes (table 2; appendix pp 74, 94–96).

For the primary symptom outcome, data were available for 8717 (99·8%) of 8732 patient-days. At 6-month follow-up, patients in the CSR group were more likely to have a lower number of daily episodes of angina recorded on the ORBITA-app (OR 1·40 [95% CrI 1·08 to 1·83]; Pr(Benefit)=99·4%; table 3). This benefit was not apparent at day 2 after intervention (OR 1·01 [95% CrI 0·80 to 1·28]; Pr(Benefit)=53·1%), but slowly developed throughout the follow-up period, with evidence of benefit by day 70 (1·15 [1·00 to 1·30]; 98·1%; figure 2; table 3). Many other effect estimands can be derived from the primary model; for example, a patient reporting a median of two episodes of angina each day pre-randomisation would be expected to report 1·1 episodes in the CSR group and 1·5 episodes in the placebo group after 6 months (difference –0·5 episodes [95% CrI –0·8 to –0·1]; Pr(Benefit)=99·6%). Alternatively, over 6 months, this patient would be expected to have 84·5 days (95% CrI 79·0 to 90·4) free from angina in the CSR group or 71·5 days (66·0 to 76·7) free from angina in the placebo group (difference 13·1 days [6·4 to 19·8]; Pr(Benefit)=99·9%).

Both SAQ angina frequency and MacNew Heart Disease Health-Related Quality of Life scores improved in the CSR group compared with the placebo group; no difference between the groups was seen in any other SAQ domains, CCS class, EQ-5D-5L index value, EQ VAS, or treadmill exercise time (table 4). Very few patients in either group became free from angina, with no evidence of difference between the groups (two [8%] of 24 patients in the CSR group and none of the 26 patients in the placebo group).

	Difference at 6-month follow-up for CSR *vs* placebo	Probability of benefit with CSR *vs* placebo*
Quantitative perfusion, stress MBF, mL/min per g		
In ischaemic segments, mL/min per g (primary outcome)	0·06 (–0·09 to 0·20)	78·8%
In non-ischaemic segments, mL/min per g	–0·00 (–0·14 to 0·13)	48·7%
Difference between ischaemic and non-ischaemic segments	0·06 (–0·03 to 0·15)	90·8%
Quantitative perfusion (secondary imaging outcomes)		
Rest MBF, mL/min per g		
In ischaemic segments	0·01 (–0·05 to 0·07)	58·0%
In non-ischaemic segments	–0·01 (–0·07 to 0·05)	33·6%
Difference between ischaemic and non-ischaemic segments	0·02 (–0·01 to 0·05)	89·0%
MPR		
In ischaemic segments	0·06 (–0·17 to 0·27)	69·1%
In non-ischaemic segments	0·06 (–0·15 to 0·27)	72·7%
Difference between ischaemic and non-ischaemic segments	–0·01 (–0·13 to 0·12)	44·1%
Quantitative perfusion, inferior and inferoseptal segments excluded (secondary imaging outcomes)		
Stress MBF, mL/min per g		
In ischaemic segments	0·08 (–0·07 to 0·24)	85·6%
In non-ischaemic segments	–0·00 (–0·14 to 0·13)	47·6%
Difference between ischaemic and non-ischaemic segments	0·09 (–0·03 to 0·19)	93·9%
Rest MBF, mL/min per g		
In ischaemic segments	0·02 (–0·05 to 0·09)	71·2%
In non-ischaemic segments	–0·01 (–0·07 to 0·05)	31·9%
Difference between ischaemic and non-ischaemic segments	0·03 (–0·01 to 0·07)	94·4%
MPR		
In ischaemic segments	0·07 (–0·15 to 0·30)	74·4%
In non-ischaemic segments	0·05 (–0·16 to 0·25)	67·3%
Difference between ischaemic and non-ischaemic segments	0·03 (–0·12 to 0·18)	63·7%
Quantitative perfusion, endocardial to epicardial ratio (secondary imaging outcomes)		
Endocardial to epicardial ratio of stress MBF		
In ischaemic segments	0·09 (0·00 to 0·17)	98·2%
In non-ischaemic segments	–0·02 (–0·10 to 0·07)	35·1%
Difference between ischaemic and non-ischaemic segments	0·10 (0·02 to 0·19)	99·2%
Endocardial to epicardial ratio of rest MBF		
In ischaemic segments	0·03 (–0·04 to 0·10)	81·6%
In non-ischaemic segments	0·10 (0·03 to 0·17)	99·7%
Difference between ischaemic and non-ischaemic segments	–0·07 (–0·13 to –0·01)	1·8%
Endocardial to epicardial ratio of MPR		
In ischaemic segments	0·07 (–0·11 to 0·24)	77·2%
In non-ischaemic segments	–0·13 (–0·33 to 0·06)	8·3%
Difference between ischaemic and non-ischaemic segments	0·20 (0·02 to 0·37)	98·9%

Data are difference (95% credible interval) and percentage. The follow-up and increment values are model-based estimates (to avoid floor and ceiling effects), for an exemplar patient, conditional on the median pre-randomisation value. CSR=coronary sinus reducer. MBF=myocardial blood flow. MPR=myocardial perfusion reserve. *Differences between ischaemic and non-ischaemic segments are shown with an associated probability of interaction (Pr(Interaction)). The secondary outcomes of global MPR, global MBF, and myocardial strain and myocardial scar are shown in the appendix (pp 74, 94–97).

Table 2: **Cardiac magnetic resonance scan primary and secondary endpoints**

	Odds ratio of transition to fewer angina episodes each day with CSR *vs* placebo	Probability of benefit with CSR *vs* placebo
Day 2 of follow-up	1·01 (0·80–1·28)	53·1%
Day 70 of follow-up	1·15 (1·00–1·30)	98·1%
Day 182 of follow-up	1·40 (1·08–1·83)	99·4%

Data are odds ratio (95% credible interval) or percentage. Results are reported for both the start of the follow-up period (day 2), day 70, and the end (day 182). CSR=coronary sinus reducer.

Table 3: **Primary symptom endpoint (angina episodes)**

	n	Score increment	Score at 6-month follow-up	Benefit from baseline to follow-up	Probability of benefit with CSR *vs* placebo
SAQ angina frequency (baseline median 40·0)					
CSR	24	22·7 (10·6 to 34·6)	62·7 (50·6 to 74·6)	16·0 (5·1 to 27·3)	99·7%
Placebo	26	6·5 (–3·5 to 16·6)	46·5 (36·5 to 56·6)	..	..
SAQ physical limitation (baseline median 44·4)					
CSR	24	10·2 (–0·3 to 21·1)	54·6 (44·1 to 65·5)	4·9 (–5·3 to 15·0)	83·3%
Placebo	26	5·3 (–3·0 to 13·8)	49·7 (41·4 to 58·2)	..	..
SAQ angina stability (baseline median 25·0)					
CSR	24	29·4 (15·4 to 43·2)	54·4 (40·4 to 68·2)	9·2 (–7·0 to 24·7)	86·8%
Placebo	26	20·2 (8·1 to 32·4)	45·2 (33·1 to 57·4)	..	..
SAQ quality of life (baseline median 33·3)					
CSR	24	14·1 (2·1 to 26·2)	47·4 (35·5 to 59·6)	6·1 (–6·1 to 18·5)	83·5%
Placebo	26	7·9 (–1·4 to 18·0)	41·2 (31·9 to 51·4)	..	..
SAQ treatment satisfaction (baseline median 75·0)					
CSR	24	0·6 (–10·3 to 10·1)	75·6 (64·7 to 85·1)	5·7 (–4·2 to 16·2)	86·8%
Placebo	26	–5·0 (–16·7 to 5·0)	69·9 (58·4 to 80·0)	..	..
Treadmill exercise time, s (baseline median 366·8)					
CSR	24	61·4 (–18·1 to 141·8)	428·2 (348·6 to 508·6)	40·7 (–36·1 to 120·2)	84·8%
Placebo	26	20·4 (–58·6 to 104·3)	387·1 (308·2 to 471·1)	..	..
Canadian Cardiovascular Society class (baseline median 3·0)					
CSR	24	–0·8 (–1·1 to –0·4)	2·3 (1·9 to 2·6)	–0·3 (–0·7 to 0·1)	92·3%
Placebo	26	–0·4 (–0·8 to –0·1)	2·6 (2·2 to 2·9)	..	..
EQ-5D-5L index value (baseline median 0·6)					
CSR	24	0·0 (–0·1 to 0·1)	0·6 (0·5 to 0·7)	–0·0 (–0·1 to 0·1)	42·0%
Placebo	26	0·0 (–0·1 to 0·1)	0·6 (0·5 to 0·7)	..	..
EuroQol visual analogue scale (baseline median 55·0)					
CSR	24	4·4 (–4·1 to 12·4)	59·4 (51·0 to 67·4)	7·3 (–2·0 to 17·2)	93·3%
Placebo	26	–3·1 (–12·5 to 5·8)	52·0 (42·5 to 60·8)	..	..
MacNew Heart Disease Health-Related Quality of Life questionnaire (baseline median 3·8)					
CSR	24	0·5 (–0·0 to 1·0)	4·3 (3·8 to 4·8)	0·6 (0·2 to 1·1)	99·4%
Placebo	26	–0·1 (–0·6 to 0·3)	3·7 (3·3 to 4·1)	..	..

Data are score values (95% credible interval) and percentages. Treadmill exercise is presented for the patients who had both enrolment and follow-up scores. The follow-up and increment values are model based estimates (to avoid floor and ceiling effects), for an exemplar patient, conditional on the median pre-randomisation value. CSR=coronary sinus reducer. SAQ=Seattle Angina Questionnaire.

Table 4: **Secondary symptom endpoints**

Patients entered the trial on maximally tolerated antianginal therapy. The median number of antianginal agents taken was 3 (IQR 3 to 4), which equated to 6 standardised antianginal units (IQR 4–8). Throughout the 8732 patient-days of follow-up, only eight antianginal medication changes occurred (four in the CSR group and four in the placebo group, appendix p 40). No deaths or acute coronary syndromes occurred, and no patients were unmasked because of intolerable angina. Consequently, changes in the angina symptom score mirror those of daily episodes of angina.

Periprocedural and other serious adverse events are described in table 5, with further details in the appendix (pp 41–42).

Blinding was assessed at two timepoints. The primary assessment of blinding before discharge after the randomisation procedure found that the blinding index was 0 in the CSR group (ie, all patients felt unable to guess treatment allocation) and –0·04 (95% CI –0·11 to 0·04) in the placebo group (only one patient felt able to guess treatment allocation and they were incorrect). For medical teams, the blinding index was 0 in both groups (all medical teams felt unable to guess treatment allocation). The blinding index at follow-up is provided in the appendix (pp 97–98).

Discussion

In ORBITA-COSMIC, CSR was not superior to a placebo procedure in improving the primary outcome of stress myocardial blood flow in ischaemic segments in patients with angina, stable coronary artery disease, ischaemia, and no options for further antianginal therapy. However, CSR gradually improved the primary symptom outcome of daily angina episodes as reported on the ORBITA-app, with an effect detectable at 10 weeks and sustained to 6 months. This reduction in angina was seen despite a background of intensive antianginal medication, with patients taking a median of three antianginal drugs during the trial.

For the past 50 years, placebo-controlled data have shown the efficacy of antianginal medications in relieving symptoms in patients with stable coronary artery disease.[18–21] In 2023, placebo-controlled evidence of the efficacy of percutaneous coronary intervention as an antianginal monotherapy procedure was provided.[22] We believe the data from this study provide placebo-controlled evidence of the value of CSR as a third antianginal therapy.

The only previous randomised controlled trial of CSR is the COSIRA trial,[4] which showed no improvement in angina directly reported by the patients, although it did record an improvement in the primary endpoint of physician-assessed severity of angina (CCS class). The magnitude of this effect was similar to that seen in unblinded, single-arm studies—a concordance that is rare for procedural interventions for symptom relief. It is possible that this reflects ineffective blinding.[23]

Building on previous experience of placebo-controlled trials,[22,24] ORBITA-COSMIC was designed to achieve high blinding fidelity, with both intervention and control groups being exposed to identical procedural steps, and only the therapeutic component (device implantation)

removed from the placebo procedure.[25] First, all patients were sedated to a deep level of conscious sedation. Second, all patients received auditory isolation throughout the procedure. Third, intraprocedural medications, including anticoagulation, were identical between groups. Fourth, randomisation was only conducted once each patient was sedated in the cardiac catheterisation laboratory. Fifth, a standardised handover was performed between the catheterisation laboratory and clinical teams on the ward, with no transfer of information that might inform knowledge of treatment allocation. Finally, the efficacy of blinding was tested and reported for both the patients and staff, before discharge and at the 6-month follow-up timepoint.[14]

The original concept of angina improvement from coronary sinus narrowing was described in the pre-coronary artery bypass grafting era.[26] In animal studies, coronary sinus ligation in the setting of coronary artery occlusion led to increased backflow through the distal coronary artery, suggesting an increased flow to the distal vessel through the coronary collateral circulation. Later experiments, in dogs, of coronary sinus obstruction and acute left anterior descending artery ligation showed improvement in subendocardial perfusion and improved perfusion of ischaemic myocardial segments.[2,27] Translation of these animal models to human experience has limitations. Single-arm data in humans have suggested that blood flow might improve in ischaemic myocardial segments following CSR implantation, with less ischaemic segments showing no change.[3] This effect was not replicated in the present study, which used a control group, randomisation, placebo subtraction, blinded reporting, and quantitative assessment of myocardial blood flow. In view of the detectable placebo-controlled improvement in angina seen the CSR group, another mechanism of action of the device might exist. Notably, in the present study, we found evidence of redistribution of perfusion from subepicardial to subendocardial myocardium in ischaemic segments, and this redistribution might underlie the improvement in angina.[2] Other proposed mechanisms have also been suggested and should be tested in randomised controlled trials.[28,29] Understanding this underlying mechanism may influence subjective belief in the therapy.[30]

The population of patients studied in ORBITA-COSMIC had specific characteristics. They were described as having refractory angina with no further options for antianginal therapy, and despite previous coronary artery bypass grafting in 44 (86%) of 51 patients, previous percutaneous coronary intervention in 28 (55%), and a median of three antianginal agents at baseline, almost all patients (48 [94%]) were in CCS class III or IV.

The CSR might have a role in patients with so-called refractory angina. However, this definition is not biological, but rather the consequence of a complex interplay between the nature of the anatomical disease, the tolerability of medications, and the availability, acceptability, and risk of procedures. These considerations will vary between patients, sites, and physicians, and will evolve over time. The CSR might be potentially attractive in the setting of chronic total occlusions, recurrent in-stent restenosis, or complex multivessel disease, where the alternative would be revascularisation for symptom relief with high procedural, short-term, and long-term risks.

	CSR group (n=25)	Placebo group (n=26)
Death	0	0
Myocardial infarction	0	0
Stroke	0	0
Bleeding	0	0
CSR embolisation	2 (8%)	0
Inability to deploy CSR	1 (4%)	0

Data are number of events (%). CSR=coronary sinus reducer.

Table 5: **Adverse events**

One advantage of collecting daily angina frequency data in this trial is that it permitted analysis in the Bayesian longitudinal framework, which detected the time course of progression of angina relief; ORBITA-COSMIC showed that angina reduction with CSR developed gradually over time, in contrast to percutaneous coronary intervention, where angina reduction is immediate.[22]

Our trial had limitations. The definitions of refractory angina and no further options for treatment are challenging. However, all patients were reviewed in the dedicated ORBITA-COSMIC multidisciplinary team to standardise enrolment within the trial, and coronary anatomy was described by means of the British Cardiovascular Intervention Society Jeopardy score. Patients with pacemakers and internal cardioverter defibrillators were excluded from the trial due to the risk of cardiac magnetic resonance artefact. The sample size calculation was based on the available literature at the time of study design. Reassuringly, the credible interval for the primary endpoint was narrow and reflects the reproducibility of quantitative assessment of stress myocardial blood flow. Device embolisation rates in this randomised controlled trial with a data and safety monitoring board were higher than in previously published data from registries. The blinded follow-up phase lasted for 6 months to allow detection of efficacy in the short-to-medium term and ensure that this blinded trial was ethical and acceptable to patients. The efficacy of the device beyond 6 months was not studied. The cardiac magnetic resonance protocol used adenosine-induced hyperaemia, which has some biological variability, however, this variability should have been equally distributed between the groups with randomisation and placebo control.

ORBITA-COSMIC did not confirm the prespecified hypothesis that the mechanism of action of CSR consists of an increase of perfusion in ischaemic myocardial segments. However, the imaging data suggested a possible

redistribution of perfusion towards the subendocardium in ischaemic segments. Nevertheless, the CSR produced a clear reduction in angina frequency reported by patients, which developed gradually over a period of weeks. These data provide evidence for the use of CSR as an antianginal therapeutic option for patients with refractory angina, stable coronary artery disease, and myocardial ischaemia.

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Contributors
MJF, JRD, TK, PDO'K, JCS, GDC, JMH, RKA-L (principal investigator), Gerald Clesham (independent chairman), and Tom Johnson (co-chairman) were members of the steering committee. MJF, MJS-S, DPF, and RKA-L were on the writing committee. MJF, GDC, JPH, MJS-S, and RKA-L were responsible for the conception and design of the study. CAR, FA-J, FAS, SC, RHP, MM, AS, DW, and PD were responsible for symptom data acquisition. JRD, CC, JCS, PDO'K, JMH, and TK were principal investigators at individual trial sites. SSN, SS, RP, RDS, TRK, GWM, and RK were responsible for invasive data collection and randomisation. GDC, JPH, PK, and TK were responsible for cardiac magnetic resonance data analysis. MJS-S and FEH were the study statisticians. MJF, MJS-S, FEH, DPF, and RKA-L were responsible for the data interpretation and writing of the report. MJF, MJS-S, and RKA-L directly assessed and verified the data reported in this manuscript. All authors had access to all the included data. MJF and RKA-L were responsible for the decision to submit for publication.

Declaration of interests
MJF reports speaker's fees from Menarini and Philips. CAR reports consulting fees from Philips and speaker's fees from Menarini. FAS reports speaker's fees and travel support from Servier pharmaceuticals. JRD reports grants from Medtronic and Abbott; sponsorship from Vascular Perspectives, Boston Scientific, Medtronic, and Abbott; and speaker's honoraria from AstraZeneca, Pfizer, Bristol Myers Squibb, and Novartis. TRK reports being on an advisory board for Abbott Vascular and SMT; institutional research funding from Terumo, Medtronic, Boston Scientific, Abbott Vascular, Philips Volcano, and Cardionovum; and travel support from Neovasc. CC reports grant support, honoraria, and travel support from Shockwave and Boston Scientific. JCS reports speaker's fees from Boston Scientific, Shockwave, and Medtronic; and institutional research funding from Boston Scientific and Shockwave. PDO'K reports speaker's fees from Abbott Vascular, Biosensors, Boston Scientific, Philips, Shockwave, and Terumo; and advisory boards for Shockwave Medical, Abbott Vascular, and Philips. RDS reports consulting and advisory fees, institutional research support, and speaking fees for Shockwave; and speaking fees and institutional research support from Abbott Vascular. JMH reports speaker's fees, honoraria, and research support from Abbott Vascular, Abiomed, Boston Scientific, Medtronic, and Shockwave; and equity in Shockwave. SSN reports speaker fees from Philips, Pfizer, Bayer, AstraZeneca, Boehringer Ingelheim, and Amarin; and leadership or board roles in the British Cardiac Intervention Society and the Royal Society of Medicine. SS reports speaker's and consultancy fees from Philips, Medtronic, Recor, and AstraZeneca. RP reports consultant fees from Philips and Abbott. GWM reports honoraria from Medtronic and directorship of the Imperial Valve and Cardiovascular Course. RK reports speaker's fees from Medtronic; and consultancy for Novartis, Amgen, and Cryotherapeutics. TK reports honoraria from Bayer and Jansen and travel support from Jansen. GDC reports shares in Mycardium AI. JPH reports shares in Mycardium AI and grant support from the British Heart Foundation. MJS-S reports consulting fees from Mycardium AI and Medtronic. RKA-L reports being on a trial steering committee for Janssen Pharmaceuticals; being on an advisory board for Abbot and Philips; speaker's honoraria for Abbott, Philips, Medtronic, Servier, Omniprex, and Menarini; and grant support from the British Heart Foundation. All other authors declare no competing interests.

Data sharing
The study protocol and statistical analysis plan are available in the appendix. Individual patient data will not be made available.

Acknowledgments
ORBITA-COSMIC was an investigator-led trial sponsored by Imperial College London and funded by grants from the Medical Research Council, Imperial College Healthcare Charity, UK National Institute for Health and Care Research Imperial Biomedical Research Centre, St Mary's Coronary Flow Trust, and the British Heart Foundation. Peter Kellman is employed by the US National Institutes of Health. We thank the data and safety monitoring board members Jason Dungu and Denise Braganza and the independent study monitor for their support. We thank Ken Bowen, our patient representative on the trial steering committee. We thank Raquel Trujillo, Katherine March, Craig Robertson, and Juliet Holmes for their hard work throughout the trial. We thank the research and administrative teams at Imperial College Healthcare NHS Trust, Mid and South Essex NHS Foundation Trust, St George's NHS Foundation Trust, The Royal Free NHS Foundation Trust, University Hospitals Dorset NHS Foundation Trust, The Royal Brompton Hospital, and Guy's and St Thomas' NHS Foundation Trust. We thank the UK National Health Service for funding and facilitating novel and innovative clinical research. Most of all, we thank the ORBITA-COSMIC patients, who volunteered for a demanding placebo-controlled research trial, of a procedure with uncertain personal benefit, with 6 months of blinded follow-up, to help improve the care of patients with coronary artery disease.

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