ORIGINAL ARTICLE

Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina

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ABSTRACT

BACKGROUND

Many patients with coronary artery disease who are not candidates for revascularization have refractory angina despite standard medical therapy. The balloon-expandable, stainless steel, hourglass-shaped, coronary-sinus reducing device creates a focal narrowing and increases pressure in the coronary sinus, thus redistributing blood into ischemic myocardium.

METHODS

We randomly assigned 104 patients with Canadian Cardiovascular Society (CCS) class III or IV angina (on a scale from I to IV, with higher classes indicating greater limitations on physical activity owing to angina) and myocardial ischemia, who were not candidates for revascularization, to implantation of the device (treatment group) or to a sham procedure (control group). The primary end point was the proportion of patients with an improvement of at least two CCS angina classes at 6 months.

RESULTS

A total of 35% of the patients in the treatment group (18 of 52 patients), as compared with 15% of those in the control group (8 of 52), had an improvement of at least two CCS angina classes at 6 months (P=0.02). The device was also associated with improvement of at least one CCS angina class in 71% of the patients in the treatment group (37 of 52 patients), as compared with 42% of those in the control group (22 of 52) (P=0.003). Quality of life as assessed with the use of the Seattle Angina Questionnaire was significantly improved in the treatment group, as compared with the control group (improvement on a 100-point scale, 17.6 vs. 7.6 points; P=0.03). There were no significant between-group differences in improvement in exercise time or in the mean change in the wall-motion index as assessed by means of dobutamine echocardiography. At 6 months, 1 patient in the treatment group had had a myocardial infarction; in the control group, 1 patient had died and 3 had had a myocardial infarction.

CONCLUSIONS

In this small clinical trial, implantation of the coronary-sinus reducing device was associated with significant improvement in symptoms and quality of life in patients with refractory angina who were not candidates for revascularization. (Funded by Neovasc; COSIRA ClinicalTrials.gov number, NCT01205893.)

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A GROWING NUMBER OF PATIENTS WITH severe and diffuse obstructive coronary artery disease who are not candidates for revascularization have debilitating angina despite medical therapy.[1-3] The worldwide prevalence of refractory angina is increasing, and new therapeutic options are needed.[4]

An endoluminal, balloon-expandable, stainless steel, hourglass-shaped device designed for percutaneous implantation in the coronary sinus (Reducer, Neovasc) creates a focal narrowing that leads to increased pressure in the coronary sinus, which may relieve angina (Fig. 1). A nonrandomized first-in-human study involving 15 patients with refractory angina who were treated with the device showed significant improvement with respect to angina class.[5] This clinical benefit was maintained at 3 years of follow-up, with patency of all the devices documented by means of computed tomographic (CT) angiography and with no evidence of device migration.[6] Recently, the outcomes in 21 patients who received the device were reported, showing improvement in anginal symptoms and in objective measurements of ischemia.[7]

The development of new therapies for patients with refractory angina should focus not only on reducing the risks of death and myocardial infarction but also on relieving angina and improving quality of life.[8] The Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA) trial examined whether the implantation of the coronary-sinus reducing device could effectively improve angina symptoms in patients with obstructive coronary artery disease who had concomitant evidence of reversible myocardial ischemia and who were not considered to be candidates for revascularization.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted this phase 2, multicenter, randomized, double-blind, sham-controlled clinical trial to test the safety and efficacy of the coronary-sinus reducing device. The trial was conducted at 11 clinical centers and was sponsored by Neovasc. The trial protocol, which is available with the full text of this article at NEJM.org, was designed by the academic authors with input from the sponsor. The data were collected, managed, and analyzed by a contract research organization paid by the sponsor. The academic authors had full access to the data and take full responsibility for the accuracy and completeness of the data and the analyses reported, as well as for the fidelity of this report to the trial protocol. Six of the academic authors wrote the first draft of the manuscript and made the decision to submit the manuscript for publication.

The trial was overseen by an independent coordinating center, steering committee, clinical-events committee, and data and safety monitoring board (see the Supplementary Appendix, available at NEJM.org). The study protocol and amendments, as well as the informed-consent form, were reviewed and approved by the relevant national authority in each country and by the independent ethics committee at each participating center. The study was conducted in compliance with the provisions of the Declaration of Helsinki. All the patients provided written informed consent before enrollment.

STUDY PATIENTS

The inclusion and exclusion criteria for the COSIRA trial have been reported in detail previously[9] and are listed in the Supplementary Appendix. Patients were considered for participation in the trial if they were older than 18 years of age and had Canadian Cardiovascular Society (CCS) class III or IV angina (on a scale from I to IV, with higher classes indicating greater limitations on physical activity owing to angina), despite efforts to control symptoms with medical therapy for at least 30 days before screening. Medical therapy included beta-blockers, calcium-channel blockers, nicorandil, ivabradine, and short-acting and long-acting nitrates used at maximum tolerated doses.[10] All the participants were required to have evidence of reversible myocardial ischemia and a left ventricular ejection fraction of more than 25%.

Only patients who were not considered to be candidates for coronary revascularization were eligible to participate in the study, as decided by the heart team at each institution on reviewing the recent coronary angiographic videos, as detailed previously.[11] Patients were excluded if they had undergone a recent revascularization procedure (≤6 months earlier), had had a recent acute coronary syndrome (≤3 months earlier), or
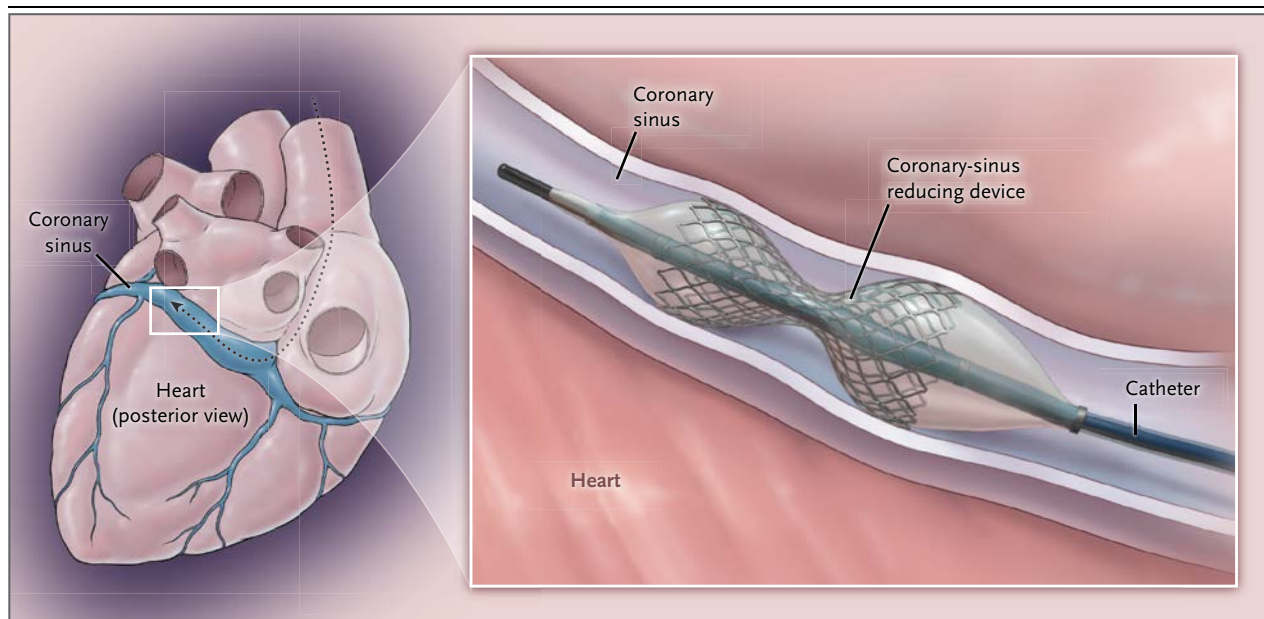
Figure 1. Coronary Sinus Reducer System.

The complete system for the coronary-sinus reducing device we evaluated comprises a metal mesh device that is premounted on a balloon catheter and is shaped like an hourglass when expanded. After the device is implanted in the coronary sinus, local flow disruption and vascular reaction lead to a hyperplastic response in the vessel wall, with occlusion of the fenestrations in the metal mesh. The central orifice of the device remains patent and becomes the sole path for blood flow through the coronary sinus, leading to the development of an upstream pressure gradient that results in the redistribution of blood from the less ischemic epicardium to the ischemic endocardium.

had undergone placement of permanent pacemaker or defibrillator leads in the right heart.

RANDOMIZATION AND INTERVENTION

Candidates meeting the inclusion criteria underwent right heart catheterization with angiography of the coronary sinus before the planned intervention. Only patients with coronary-sinus anatomy that was suitable for implantation of the device were eligible to undergo randomization (for a list of anatomical features that were criteria for exclusion, see the Supplementary Appendix).

Participants were randomly assigned in a 1:1 ratio, with the use of a computer-generated random allocation sequence, to undergo either implantation of the device (treatment group) or the sham procedure (control group). Study assignments were concealed in opaque numbered, sealed envelopes. The allocation sequence remained concealed until the study groups were assigned.[9]

All the participants were unaware of the study assignment throughout the 6-month study period. Although the physicians performing the implan-

tation were aware of the study assignments, the investigators responsible for assessing the angina class at follow-up, all core laboratory staff, the biostatisticians performing the analysis, and the members of the clinical-events committee were not.

DEVICE DESIGN AND IMPLANTATION

The coronary-sinus reducing device that we evaluated is made of stainless steel and is available in a single model designed to fit a range of anatomies. Its diameter expands with the inflation pressure of the semicompliant balloon, which has an hourglass shape, and the device conforms to the tapering anatomy of the coronary sinus (Fig. 1).

Dual antiplatelet therapy was given for at least 1 week before the procedure and for 6 months after the procedure in the two study groups. Patients randomly assigned to the treatment group were treated with intravenous heparin at the time of implantation. Participants were offered either headsets playing music or conscious sedation to mask the conversation in the room regarding the

randomization and the procedure. The physicians performing the implantation were instructed to behave similarly during device implantation and the sham procedure, including spending a similar amount of procedure time per patient, regardless of the patient's study assignment.

A 6-French diagnostic catheter was introduced into the right atrium. Right atrial pressure was measured and recorded. The catheter was then introduced into the coronary sinus, and an angiogram was obtained with 30-degree left anterior oblique angulation. The implantation site was determined according to the vessel diameter; side-branch bifurcation was avoided.

In participants assigned to the control group, no additional invasive manipulation was performed. In participants assigned to the treatment group, a preshaped 9-French guiding catheter was introduced into the coronary sinus, and the device was implanted at the chosen site with the use of a 1.1:1.0 ratio of the expanded device diameter to the coronary-sinus diameter. Postimplantation angiography was performed to ensure appropriate implantation.

STUDY END POINTS

The prespecified primary end point was the proportion of patients with an improvement of two or more CCS angina classes from baseline to 6 months after the procedure. Secondary end points included the proportion of patients with an improvement of one or more CCS classes from baseline to 6 months and exercise tolerance as assessed with the use of a symptom-limited stress test.[12,13]

Cardiac regional wall motion during stress and at rest was assessed by means of dobutamine echocardiography at baseline and at 6 months. The motion of each of 16 wall segments at rest and during peak dobutamine infusion was quantified (with a score of 1 indicating normal, 2 hypokinetic, 3 akinetic, 4 dyskinetic, and 5 aneurysmal),[14] and the sum of the wall-motion scores for the myocardial segments was divided by the number of segments to provide a wall-motion index. A modified wall-motion index for the left coronary artery was also calculated, with the use of 11 segments attributed to the left-coronary-artery territory.

Angina-related quality of life was assessed with the use of the Seattle Angina Questionnaire, which is a 19-item questionnaire that measures five domains of health status related to coronary artery disease: angina stability, angina frequency, physical limitation, treatment satisfaction, and quality of life. Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status.[15]

Technical and procedural success was evaluated, and periprocedural and nonprocedural adverse events were recorded. Details of the end-point assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

An independent data and safety monitoring board was chartered to monitor and evaluate patient safety in order to identify any clinically relevant trends and advise the steering committee accordingly. Interim analyses, provided to the data and safety monitoring board by the contract research organization, took place after 30 patients had completed 30 days of follow-up and after 50% of the originally planned cohort had completed 6 months of follow-up.

The study was designed to have 80% power to test the two-sided hypothesis, at a type I error level of 0.05, that 40% of the participants assigned to the treatment group would have an improvement of two or more CCS angina classes, as compared with 15% of the participants assigned to the control group. A 10% rate of study withdrawal or loss to follow-up was assumed because of uncertainties about deliverability of the device. On the basis of these assumptions, we calculated that we would need to enroll 124 participants in the study. Owing to the longer-than-expected time to complete enrollment and the lower-than-expected rate of withdrawal or loss to follow-up, the sponsor elected to stop enrollment after 104 patients had undergone randomization. The sponsor had no knowledge of the unblinded end-point data when the decision to stop enrollment was made; the randomization code was held by the contract research organization.

Continuous variables are described as means and standard deviations or as medians and interquartile ranges, as appropriate. Between-group differences in means were compared with the use of paired Student's t-tests. Categorical variables are expressed as proportions and were

compared with the use of Pearson's chi-square test or Fisher's exact test, as appropriate. For continuous variables in the secondary end points, analysis of covariance was used to compare the variation in the change from baseline to 6 months between the patients in the treatment group and those in the control group, after adjustment for baseline differences. All the efficacy analyses were performed according to the intention-to-treat principle. The safety analysis, which included all the patients who underwent randomization, was performed according to the actual treatment received. P values of less than 0.05 were considered to indicate statistical significance. No type I error adjustment for multiple comparisons was planned. All the analyses were performed with the use of SPSS software, version 21 (IBM).

RESULTS

CHARACTERISTICS AT BASELINE

From April 2010 through April 2013, a total of 104 patients were enrolled in the trial; 52 patients were assigned to the treatment group and 52 to the control group. The mean (±SD) age of the patients was 67.8±9.4 years (range, 35 to 87), and 81% of the patients were men. The study population was characterized by high rates of risk factors and coexisting conditions (Table 1).

The device was successfully implanted in 50 of the 52 patients (96%) randomly assigned to the treatment group. In 2 patients, the implantation failed owing to a venous valve in the coronary sinus that could not be crossed with the device.

EFFICACY END POINTS

Baseline and follow-up information regarding CCS angina class was available for all 104 patients. A total of 18 of 52 patients in the treatment group and 8 of 52 in the control group had an improvement of at least two CCS classes (35% vs. 15%, P=0.02) (Fig. 2A). The mean CCS class was reduced from 3.2±0.4 at baseline to 2.1±1.0 at 6 months of follow-up in the treatment group, as compared with a reduction from 3.1±0.3 to 2.6±0.9 in the control group (P=0.001) (Fig. 2B). In the treatment group, 71% of the patients (37 of 52 patients) had an improvement of at least one CCS class, as compared with 42% (22 of 52) in the control group (P=0.003) (Fig. 2A and 3).

Quality of life as measured by the score on the Seattle Angina Questionnaire improved by 17.6 points in the treatment group, as compared with 7.6 points in the control group (P=0.048). There were no significant differences between the two groups with respect to improvement in angina stability (18.1 vs. 8.3 points, P=0.16) or angina frequency (15.3 vs. 11.0 points, P=0.44) (Table S1 in the Supplementary Appendix).

Table 1. Characteristics of the Patients.*

Characteristic	Control Group (N=52)	Treatment Group (N=52)
Age — yr	66.0±9.8	69.6±8.7
Male sex — no. (%)	40 (77)	44 (85)
Previous myocardial infarction — no. (%)	30 (58)	27 (52)
Previous CABG — no. (%)	38 (73)	42 (81)
Previous PCI — no. (%)	40 (77)	36 (69)
Hypercholesterolemia — no. (%)	46 (88)	50 (96)
Diabetes mellitus — no. (%)	25 (48)	21 (40)
Hypertension — no. (%)	41 (79)	42 (81)
Current or previous smoking — no. (%)	31 (60)	27 (52)
CCS angina class — no. (%)†		
I	0	0
II	0	0
III	45 (87)	42 (81)
IV	7 (13)	10 (19)
Left ventricular ejection fraction	54.8±11.9	53.5±10.2
Antianginal medication — no. (%)		
Beta-blocker	40 (77)	40 (77)
Calcium-channel blocker	26 (50)	29 (56)
Nitrates	32 (62)	29 (56)
Nicorandil	6 (12)	7 (13)
Ivabradine	5 (10)	4 (8)
No. of antianginal medications — no. (%)		
0	4 (8)	3 (6)
1	10 (19)	10 (19)
2	18 (35)	23 (44)
3	18 (35)	12 (23)
>3	2 (4)	4 (8)

* Plus–minus values are means ±SD. There were no significant differences between the study groups at baseline. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† Canadian Cardiovascular Society (CCS) angina classes range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.
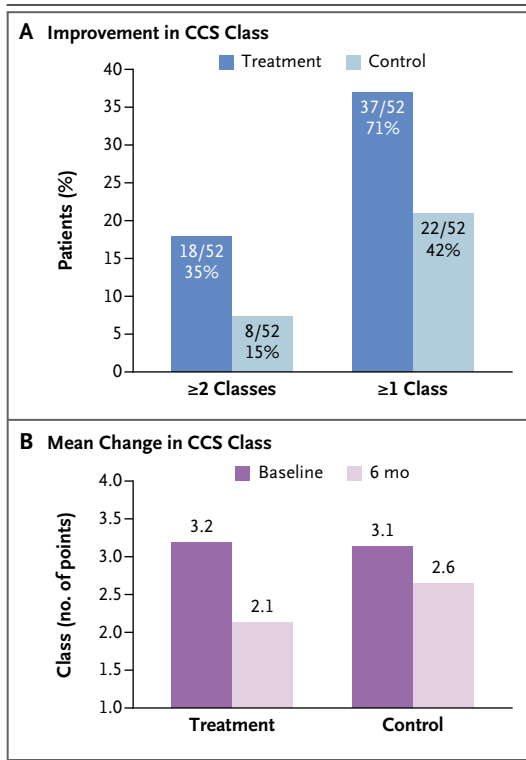
Figure 2. Change in Canadian Cardiovascular Society (CCS) Angina Class, According to Study Group.

The proportion of patients with improvement of at least two CCS angina classes (primary end point) and the proportion with improvement of at least one CCS class were significantly higher in the group that received the active treatment than in the group that underwent the sham procedure (at least two CCS classes, P=0.02; at least one CCS class, P=0.003) (Panel A). CCS classes range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina. The mean (±SD) CCS class was reduced from 3.2±0.4 at baseline to 2.1±1.0 at 6 months of follow-up in the treatment group, as compared with a reduction from 3.1±0.3 to 2.6±0.9 in the control group (P=0.001) (Panel B).

by 18 seconds (4%) in the control group (P=0.41) (Table S2 in the Supplementary Appendix).

The change from baseline to 6 months in the wall-motion index as assessed by means of dobutamine stress echocardiography and in the modified stress wall-motion index of the left coronary artery did not differ significantly between the two groups. The wall-motion index improved by 14% in the treatment group and by 8% in the control group (P=0.20). The modified stress wall-motion index of the left coronary artery improved by 13% in the treatment group and by 3% in the control group (P=0.06) (Table S3 in the Supplementary Appendix).

SAFETY END POINTS

A periprocedural myocardial infarction occurred in one patient in the treatment group. Other periprocedural serious adverse events included un-

At baseline, the mean total exercise duration was 441±191 seconds in the treatment group and 464±257 seconds in the control group. At 6 months of follow-up, the mean exercise duration had improved by 59 seconds (13%) in the treatment group and by 4 seconds (1%) in the control group (P=0.07). The mean time to ST-segment depression of 1 mm was prolonged by 49 seconds (13%) in the treatment group and
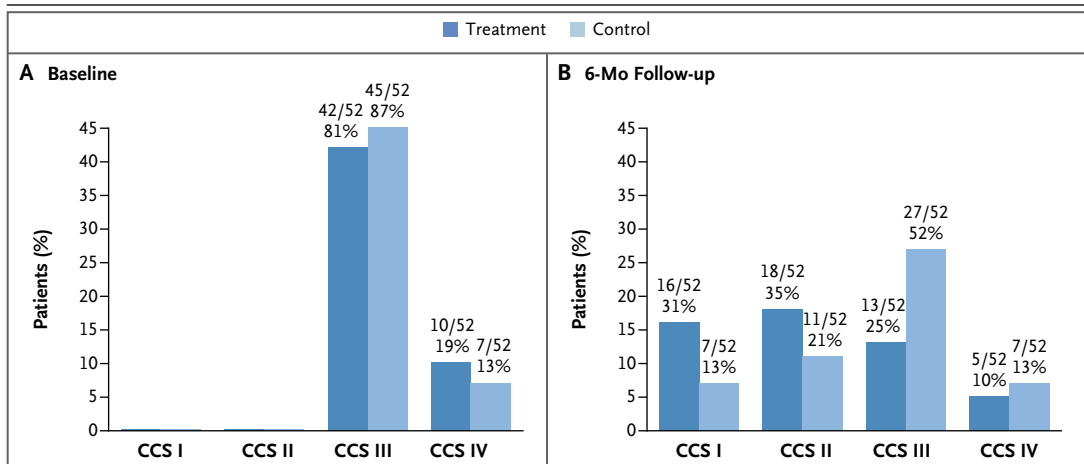
Figure 3. CCS Angina Class at Baseline and 6 Months after Randomization, According to Study Group.

At baseline, no patient in either study group had a CCS angina class of I or II, according to the inclusion criteria for the trial.

stable angina and Crohn's disease flare (in one patient each) in the treatment group and unstable angina and epigastric pain (in one patient each) in the control group.

At least one adverse event was reported in 32 of 50 patients (64%) who received the device and in 37 of 54 patients (69%) who did not receive the device (P=0.68). Overall, 76 adverse events were reported in the treatment group, and 93 in the control group.

There were three myocardial infarctions and one death (due to multiorgan failure at day 118) in the control group, and there was one periprocedural myocardial infarction and no deaths in the treatment group. There were 34 serious adverse events in the trial (10 events in the treatment group and 24 in the control group). The full lists of periprocedural serious adverse events and of other serious adverse events are shown in Tables S4 and S5, respectively, in the Supplementary Appendix.

CT angiography was performed in 36 of 50 patients who received the implant, with no evidence of device migration or occlusion in any of the patients. Figure 4 shows a longitudinal view and a series of cross-sectional views from a representative CT angiographic study performed 6 months after implantation of the device.

DISCUSSION

We evaluated a coronary-sinus reducing device as a new therapy for patients with refractory angina. Implantation of the device was significantly better than a sham intervention in improving angina symptoms in patients with advanced coronary artery disease who were not candidates for revascularization and whose disease was refractory to standard medical therapy. A reduction of at least two CCS angina classes at 6 months (the primary end point) occurred 2.4 times as frequently in the treatment group as in the control group. Although underpowered for the prespecified secondary end points, the trial nonetheless showed a greater proportion of patients with improvement of at least one CCS class and greater improvement in quality of life in the treatment group than in the control group. Significant differences were not seen between the two groups with respect to changes in the other secondary end points, such as exercise duration, the change in the time to ST-segment depression of 1 mm, or the change in the wall-motion index.
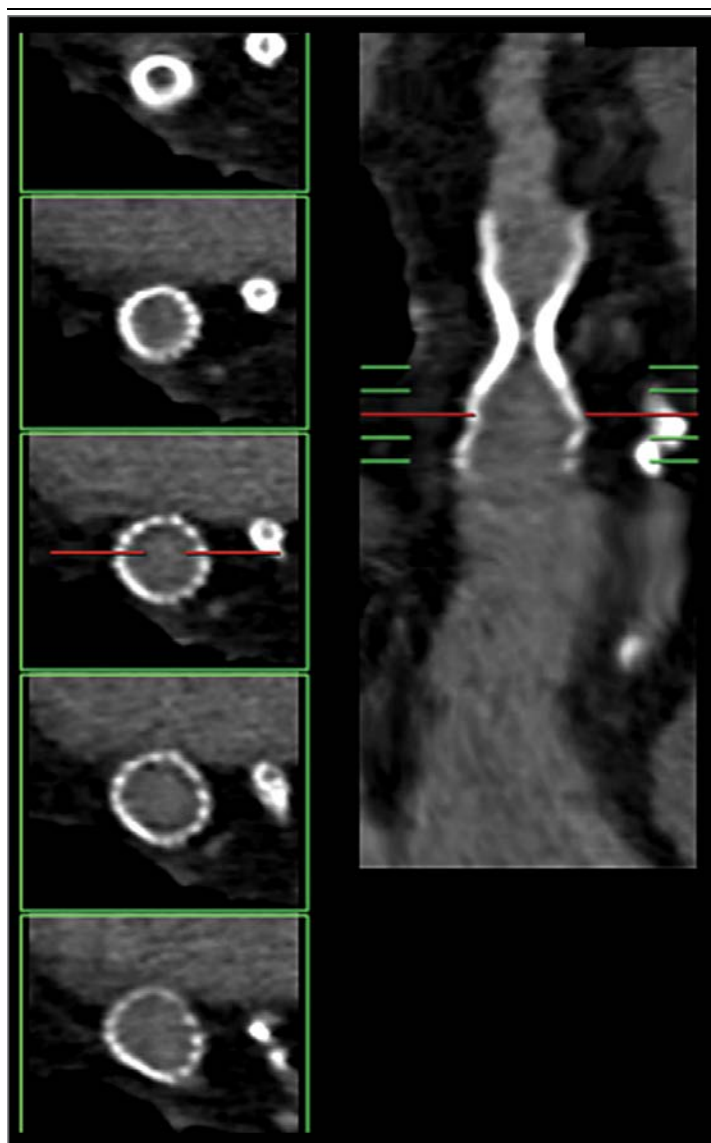
Figure 4. Representative CT Angiogram of the Device in the Coronary Sinus at 6 Months.

Cross-sectional and longitudinal CT angiographic views of the device in the coronary sinus show the flow of contrast material, indicating continued patency 6 months after implantation. The green and red bars in the longitudinal image, on the right, mark the positions of the cross-sectional images shown on the left. The red bars that appear in the third cross-sectional image and in the longitudinal image are in the same relative position in the two images and mark the positions of the opposing walls of the implant.

The prevalence of refractory angina continues to increase, owing to its association with aging of the population in Western industrialized countries and to the increase in the life expectancy of patients with ischemic heart disease. Therapeutic options that focus on angina relief and improved quality of life are needed for this group of patients.[4,8,11,16]

The physiological rationale for a beneficial effect of increased coronary sinus pressure in angina pectoris remains unclear. In 1954, Beck and Leighninger described a surgical procedure for partial occlusion of the coronary sinus, which was associated with relief of angina, an improvement in functional class, and a reduction in mortality.[17-21] The most commonly proposed mechanism of benefit is recruitment of coronary collateral flow, with redistribution from the less-ischemic epicardium to the ischemic endocardium.[22-26]

Our sham-controlled clinical trial was designed to control for both patient and investigator biases in the interpretation of the end points. A placebo intervention alone can lead to a substantial improvement in angina symptoms and exercise duration.[27-32] In a study of transmyocardial laser revascularization for the treatment of angina, a pronounced placebo effect was noted, with a 30% improvement in exercise duration and angina symptoms in the control group of patients.[33] Consequently, in our trial, extensive precautions were taken so that the patients and the investigators performing the follow-up would be unaware of the study assignments.

Our study was not statistically powered to detect an improvement in ischemia by means of objective measures such as stress testing or wall-motion index. A larger trial would be necessary to show such a benefit. Since the planning of this study, tools with better fidelity to detect improvement in myocardial ischemia, such as magnetic resonance imaging and positron-emission tomography, have become more commonplace and would be attractive methods to use in phase 3 studies of the coronary-sinus reducing device.

In conclusion, this small, double-blind, randomized, sham-controlled trial showed that the coronary-sinus reducing device led to a reduction in symptoms and improved quality of life in patients with disabling angina pectoris.

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