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Coronary Sinus Reducer Implantation for the Treatment of Chronic Refractory Angina

A Single-Center Experience

Francesco Giannini, MD, Luca Baldetti, MD, Francesco Ponticelli, MD, Neil Ruparelia, MD, Satoru Mitomo, MD, Azeem Latib, MD, Matteo Montorfano, MD, Richard J. Jabbour, MD, Andrea Aurelio, MD, Luca Ferri, MD, Antonio Mangieri, MD, Damiano Regazzoli, MD, Marco Ancona, MD, Matteo Pagnesi, MD, Alessia Faccini, MD, Alaide Chieffo, MD, Lorenzo Azzalini, MD, Mauro Carlino, MD, Antonio Colombo, MD

ABSTRACT

OBJECTIVES The aim of this study was to assess the safety and efficacy of the Reducer in a real-world cohort of patients presenting with refractory angina.

BACKGROUND The coronary sinus Reducer is a novel device to aid in the management of patients with severe angina symptoms refractory to optimal medical therapy and not amenable to further revascularization.

METHODS Fifty patients with refractory angina and objective evidence of myocardial ischemia who were judged unsuitable for revascularization were treated with coronary sinus Reducer implantation at a single center between March 2015 and August 2016. Safety endpoints were procedural success and the absence of device-related adverse events. Efficacy endpoints, assessed at 4- and 12-month follow-up, were a reduction in Canadian Cardiovascular Society angina class, improvement in quality of life assessed using the Seattle Angina Questionnaire, improvement in exercise tolerance assessed using the 6-min walk test, and reduction in pharmacological antianginal therapy.

RESULTS Procedural success was achieved in all patients, with no device-related adverse effects during the procedure or at follow-up. Regarding the efficacy endpoint, 40 patients (80%) had at least 1 reduction in Canadian Cardiovascular Society class, and 20 patients (40%) had at least 2 class reductions, with a mean class reduction to 1.67 ± 0.83 vs. 2.98 ± 0.52 ($p < 0.001$) at 4-month follow-up. All Seattle Angina Questionnaire items improved significantly ($p < 0.001$ for all). A significant increment in 6-min walk distance to 388.6 ± 119.7 m vs. 287.0 ± 138.9 m ($p = 0.004$) was observed. Sixteen patients (32%) and 3 patients (6%) demonstrated reductions of at least 1 or 2 antianginal drugs, respectively. The benefit of Reducer implantation observed at 4-month follow-up was maintained at 1 year.

CONCLUSIONS In this real-world, single-center experience, implantation of the coronary sinus Reducer appeared safe and was associated with reduction in anginal symptoms and improvement in quality of life in patients with refractory angina who were not candidates for further revascularization. (J Am Coll Cardiol Intv 2018;11:784–92) © 2018 by the American College of Cardiology Foundation.

Chronic angina refractory to medical and interventional therapies is a disabling and prevalent condition, predominantly due to severe obstructive coronary artery disease (CAD) (1–3). Although refractory angina does not adversely affect mortality compared with stable, chronic CAD, it is associated with a significant reduction in quality of life and increased cardiovascular hospitalizations, leading to increased health care–associated costs (4–6). Treatment of this population is thus directed primarily at improving quality of life by relieving symptoms (7). However, although a considerable

From the Unit of Cardiovascular Interventions, IRCCS San Raffaele Scientific Institute, Milan, Italy. Dr. Giannini is a consultant for Neovasc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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number of innovative pharmacological and nonpharmacological therapeutic options have been studied in this patient group in recent years, none has demonstrated clear efficacy, leading to a weak recommendation supporting their use in the most recent guidelines (3,8).

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Coronary sinus (CS) Reducer (Neovasc, Richmond, British Columbia, Canada) implantation has emerged as a novel therapeutic treatment for patients with refractory angina (9), with a single randomized clinical trial (10) and 2 observational studies demonstrating safety and efficacy (11,12). The Reducer is a stainless steel, balloon-expandable, hourglass-shaped device that is percutaneously implanted in the CS to create a controlled narrowing of the CS lumen (9,13). This ultimately leads to an increase in coronary venous pressure, capillary and arteriolar dilatation, lower resistance to flow, and restoration of the normal endocardial/epicardial blood flow ratio, which is impaired in the ischemic myocardium.

Currently, there are limited real-world data describing the Reducer's use outside of clinical trials. We therefore report procedural and clinical outcomes of the first 50 consecutive patients who underwent CS Reducer implantation at our center.

METHODS

STUDY DESIGN AND POPULATION SELECTION CRITERIA. This was a single-center, single-arm, prospective, observational study including consecutive patients treated with the CS Reducer at our center between March 2015 and August 2016. Patients were considered eligible for Reducer implantation if they met all of the following criteria: 1) refractory angina of at least Canadian Cardiovascular Society (CCS) class 2, despite optimal or maximally tolerated medical antianginal therapy; 2) objective evidence of inducible myocardial ischemia in the left coronary artery distribution territory (as determined by myocardial perfusion imaging, dobutamine stress echocardiography, or stress perfusion cardiac magnetic resonance imaging); and 3) CAD not amenable to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) because of unsuitable coronary anatomy, diffuse disease, or absence of satisfactory distal graft anastomosis sites, following evaluation by the heart team.

Exclusion criteria included ischemia related exclusively to the right coronary artery, the presence of a foreign body in the CS (e.g., a left ventricular pacemaker wire for cardiac resynchronization therapy), recent acute coronary syndrome (<3 months), recent coronary revascularization (<6 months), or a mean right atrial pressure higher than 15 mm Hg.

All patients provided informed consent for Reducer implantation after thorough explanation of the procedure, possible complications, and expected clinical benefits. All patients consented to participate in this study.

DEVICE AND IMPLANTATION PROCEDURE. The Reducer is a percutaneous, endoluminal, hourglass-shaped, balloon-expandable, stainless-steel stent that is designed for implantation in the CS to create a focal narrowing. A few weeks following implantation, the Reducer is fully endothelialized, and it is only at this time point that the device establishes a controlled narrowing of the CS. Device characteristics and procedural aspects have been previously described (9,13) and are summarized in the Online Appendix. Online Figure 1A describes the main procedural steps with the use of the 0.035-inch Hi-Torque Supra Core Peripheral Guide Wire (Abbott Laboratories, Abbott Park, Illinois), which, according to our experience, provides adequate support for device delivery and additionally features a soft, shapeable, and radiopaque tip that helps prevent venous vascular injury. Online Figures 1B and 1C illustrate alternative strategies that are sometimes helpful with challenging CS anatomy.

All study patients were pre-treated with aspirin 75 to 100 mg/day for a minimum of 72 h prior to device implantation in addition to clopidogrel (75 mg/day for at least 7 days prior to the procedure or a loading dose of 300 to 600 mg within 24 h prior to the procedure), prasugrel, or ticagrelor. Dual antiplatelet therapy (DAPT) was continued for at least 1 month after implantation.

BASELINE AND FOLLOW-UP EVALUATION. Prior to device implantation, all patients underwent a thorough clinical assessment with evaluation of CCS class, Seattle Angina Questionnaire (SAQ) scores, 6-min walk distance, echocardiography, and stress testing for inducible myocardial ischemia. Follow-up visits were scheduled 4 months after Reducer implantation and were performed by physicians who were not directly involved in the implantation procedure (M.A., D.R., A.M., L.F., M.P.), who evaluated angina status, administered the SAQ, performed the 6-min walk test, performed echocardiographic evaluation, and registered medical therapy and occurrence of

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CCS = Canadian Cardiovascular Society

CS = coronary sinus

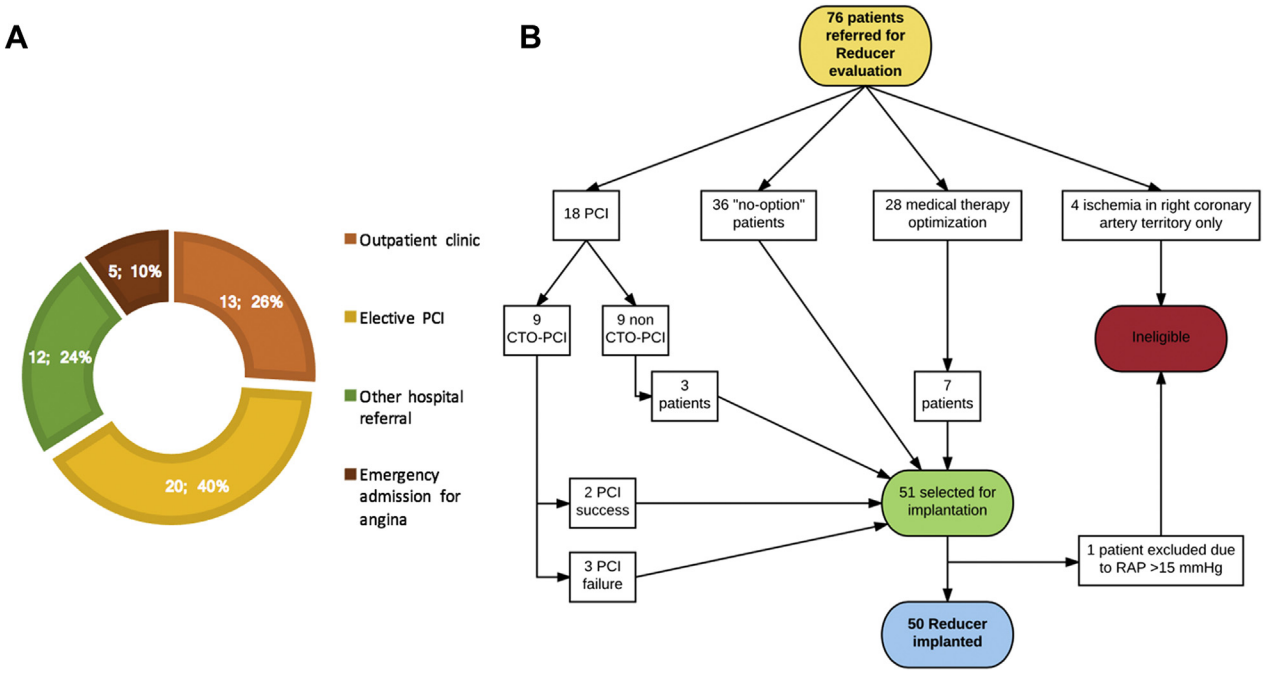
DAPT = dual antiplatelet therapy

IQR = interquartile range

PCI = percutaneous coronary intervention

SAQ = Seattle Angina Questionnaire

FIGURE 1 Patient Screening and Selection



All patients were reassessed by our team in terms of severity of symptoms, objective evidence of inducible ischemia, current medical therapy, coronary angiography, potential epicardial coronary artery revascularization options, and eligibility for Reducer implantation. Of 50 patients, 20 (40%) were selected following successful elective percutaneous coronary intervention (PCI) with residual symptoms, 13 (26%) from an outpatient clinic, 12 (24%) from other hospitals, and 5 (10%) following emergency admissions with symptoms of angina **(A)**. Of the screened patients, 18 patients underwent PCI (9 chronic total occlusion [CTO] PCI and 9 non-CTO PCI). Of these, 3 patients with failed CTO PCI, 2 with successful CTO PCI, and 3 with non-CTO PCI subsequently underwent Reducer implantation for ongoing symptoms. Twenty-eight patients were treated with further optimization of medical therapy; 7 subsequently underwent Reducer implantation for persistent symptoms. Thirty-six patients directly underwent Reducer implantation as judged "no-option" patients following heart team discussion. Four patients were deemed ineligible for Reducer implantation because of ischemia in only the right coronary artery territory. One Reducer procedure was aborted because of right atrial pressure (RAP) >15 mm Hg **(B)**.

adverse clinical events. Telephone contact was made at 1-year follow-up to evaluate angina status, complete a further SAQ, update currently administered medical therapy, and record any adverse clinical events.

ENDPOINTS. The procedural safety and efficacy endpoints were defined as successful device delivery and deployment to the intended site in the absence of any adverse or serious adverse device-related events prior to hospital discharge and during follow-up. Serious adverse events included death, myocardial infarction, cardiac tamponade, clinically driven dilation of an implanted device, life-threatening arrhythmias, respiratory failure needing invasive ventilation, access site complications, and CS dissection.

The clinical efficacy endpoint included the evaluation of 4-month and 1-year clinical outcomes as death, cardiac death, rehospitalization for angina, PCI, CABG, escalation of antianginal therapy at follow-up, reduction in CCS class, and changes in 6-min walk distance and SAQ score.

STATISTICAL ANALYSIS. Continuous variables are described as mean ± SD or as median (interquartile range [IQR]), as appropriate. Normality was checked using the Kolmogorov-Smirnov test. Categorical variables are expressed as proportions. The baseline and follow-up measurements were compared using a paired Student's *t*-test or the 1-sided Wilcoxon signed rank test, as appropriate. For comparisons between means of independent samples, a Student's *t*-test was used. A p value <0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION. Between March 2015 and August 2016, 76 patients with severe refractory

TABLE 1 Baseline Clinical Characteristics (N = 50)

Patient characteristics	
Age, yrs	68 ± 9
Male	41 (82)
Body mass index, kg/m^2	29 ± 5
Arterial hypertension	43 (86)
Diabetes mellitus	22 (44)
Dyslipidemia	45 (90)
Current or previous smoking	32 (64)
Familial coronary artery disease	38 (76)
Atrial fibrillation	6 (12)
Glomerular filtration rate, ml/min	62 ± 22
Coronary artery disease	50 (100)
3-vessel coronary artery disease	41 (82)
Previous MI	33 (66)
Previous PCI	38 (76)
Previous CABG and PCI	28 (56)
NYHA functional class	1.69 ± 0.68
Left ventricular ejection fraction, %	52 ± 11
Canadian Cardiovascular Society angina class	
II	7 (14)
III	36 (72)
IV	7 (14)
Mean Canadian Cardiovascular Society angina class	2.98 ± 0.52
Location of myocardial ischemia	
Anterior	36 (72)
Lateral	18 (36)
Septal	18 (36)
Apical	11 (22)
Inferior	19 (38)
Seattle Angina Questionnaire scores	
Physical limitation	47.8 ± 15.1
Angina stability	40.2 ± 11.9
Angina frequency	45.0 ± 19.1
Treatment satisfaction	38.3 ± 14.8
Quality of life	25.7 ± 12.6
6-min walk test	
Distance walked, m	287 ± 139
Borg dyspnea scale score	4.5 (3-5)

Values are mean ± SD, n (%), or median (interquartile range).
CABG = coronary artery bypass grafting; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

TABLE 2 Baseline Medical Therapy (N = 50)

Antithrombotic therapy	
Acetylsalicylic acid	35 (70)
Clopidogrel	41 (82)
Ticagrelor	6 (12)
Prasugrel	2 (4)
Direct oral anticoagulants	3 (6)
Vitamin K antagonists	3 (6)
Anti-ischemic therapy	
Beta-blockers	46 (92)
Calcium-channel antagonists	26 (52)
Long-acting nitrates	28 (56)
Ivabradine	18 (36)
Ranolazine	33 (66)
Number of anti-ischemic drugs	3 (1-5)

Values are n (%) or median (interquartile range).

angina who met all of the inclusion criteria were screened for Reducer implantation. Details of to patient screening and selection are illustrated in Figure 1. Following clinical evaluation, 50 patients proceeded to Reducer implantation. Baseline clinical characteristics of the study population are summarized in Table 1. Mean CCS angina class at baseline was 2.98 ± 0.52. All patients reported a high anginal burden associated with impaired quality of life, as highlighted by low scores on the SAQ, poor exercise tolerance with a mean distance walked of 287 ± 139 m, and a median grade of 4.5 (IQR: 3.0 to 5.0) on the Borg dyspnea scale after exercise. All patients had objective noninvasive evidence of myocardial ischemia in the left coronary artery vascular territory, as documented by myocardial single-photon emission computed tomography, dobutamine stress echocardiography, or perfusion cardiac magnetic resonance imaging. Not unexpectedly, there was a high prevalence of previous myocardial infarction among the study population (n = 33 [66%]). Most of the patients exhibited complex coronary anatomy: 38 patients (76%) had histories of PCI, 39 (78%) of CABG, and 28 (56%) of CABG and PCI. In our population, there was a high prevalence of 3-vessel CAD (n = 41 [82%]). Mean age at the time of implantation was 68.1 ± 8.9 years. Forty-one patients (80%) were male, the mean ejection fraction was 52.36 ± 10.7%, the mean New York Heart Association class was 1.69 ± 0.68, and 22 patients (44%) had diabetes. The median number of antianginal drugs used was 3 (range 1 to 5). Details of antianginal medications are summarized in Table 2.

TECHNICAL ASPECTS AND PROCEDURAL SAFETY. All 50 patients underwent successful Reducer implantation. Table 3 summarizes procedural data. No cases of death, cardiac tamponade, access-site complication, CS perforation, or device embolization were observed. Right jugular venous access was used in 47 patients, and 3 patients had their procedures performed via left jugular venous access. The majority of CS ostia were engaged with a 5-F multipurpose diagnostic catheter (n = 40), while different catheters were required in 10 patients (Amplatz Left 1 in 6 patients, Amplatz Left 2 in 1 patient, and Josephson electrophysiology catheter in 3 patients). In the majority of cases, the standard technique with the 0.035-inch Hi-Torque Supra Core Peripheral Guide Wire was used for Reducer implantation.

TABLE 3 Periprocedural Data (N = 50)

Access site	
Left jugular vein	47 (94)
Right jugular vein	3 (6)
Catheter used for coronary sinus engagement	
Multipurpose	40 (80)
Amplatz Left 1	6 (12)
Amplatz Left 2	1 (2)
Josephson catheter	3 (6)
Device implantation technique	
Standard technique	43 (86)
Mother-and-child technique	4 (8)
Josephson technique	3 (6)
Right atrial pressure and balloon inflation pressure	
Baseline right atrial pressure, mm Hg	5.4 ± 2.9
Balloon inflation pressure, atm	4.0 ± 0.7
Procedural length and contrast volume	
Procedural time, min	58.2 ± 25.5
Contrast volume, ml	28.3 ± 12.7
Fluoroscopy time, min	18.8 ± 16.9
Procedural complications	
Access-site complications	0 (0)
Device embolization	0 (0)
Cardiac tamponade	0 (0)
Procedural death	0 (0)
Safety endpoint	0 (0)

Values are n (%) or mean ± SD.

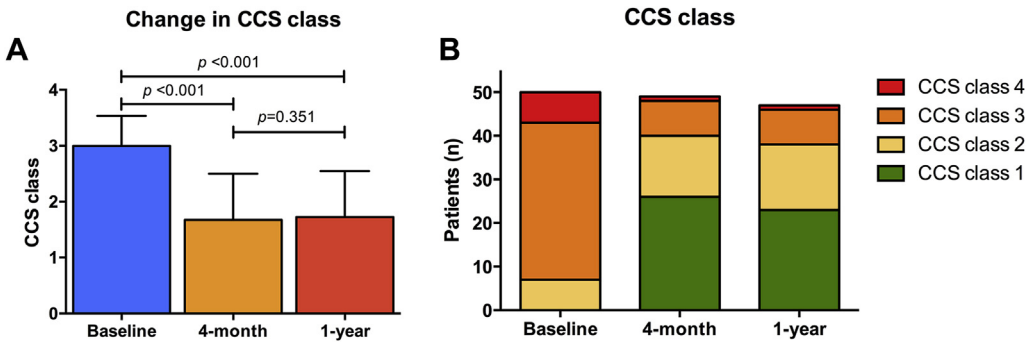
In 7 patients with challenging CS anatomy (sharp CS takeoff, ostial valve, vessel tortuosity, CS tortuosity, or severe right atrial dilatation resulting in lack of adequate support), alternative strategies for device delivery were successfully used (mother-and-child technique in 4 patients and Josephson catheter technique in 3 patients), with none of these patients experiencing procedural complications.

Mean baseline right atrial pressure was 5.4 ± 2.9 mm Hg, and mean balloon inflation pressure was 4.0 ± 0.7 atm. Mean total procedural time was 58.2 ± 25.5 min, and mean fluoroscopy time was 18.8 ± 16.9 min. The mean iodine contrast volume used was 28.3 ± 12.7 ml.

LEARNING CURVE. To explore the feasibility and the learning curve of the procedure, characteristics and outcomes in the first 25 patients and subsequent 25 patients were compared. No differences in procedural and clinical outcomes were observed between the 2 groups. Of note, although total procedural time (54.1 ± 22.9 min vs. 62.4 ± 22.9 min; p = 0.12) or mean iodine contrast volume used (26.2 ± 17.2 ml vs. 33.2 ± 18.2 ml; p = 0.10) did not significantly differ, the implantation procedure lasted significantly less time in the latter 25 patients (fluoroscopy time 13.7 ± 7.6 min vs. 21.8 ± 16.6 min; p = 0.034), suggesting a learning curve with regard to CS ostia engagement and device delivery that did not, however, negatively affect ultimate procedural success.

EARLY OUTCOMES. A total of 40 patients (80%) improved by at least 1 CCS class with regard to symptoms following Reducer implantation: 20 patients (40%) demonstrated a 1 CCS class reduction, 16 patients (32%) a 2 CCS class reduction, and 4 patients (8%) a 3 CCS class reduction. A significant reduction in mean CCS anginal class was seen at 4-month follow-up with respect to baseline: 1.67 ± 0.83 vs. 2.98 ± 0.52 (p < 0.001) (Figure 2). Of note, a reduction in mean New York Heart Association functional class

FIGURE 2 Canadian Cardiovascular Society Class Variation After Reducer Implantation



A significant benefit in terms of angina symptoms was observed at 4 months and 1 year after Reducer implantation, as highlighted by a significantly lower mean Canadian Cardiovascular Society (CCS) class of the study population **(A)** and a higher proportion of patients in lower CCS classes after Reducer implantation **(B)**.

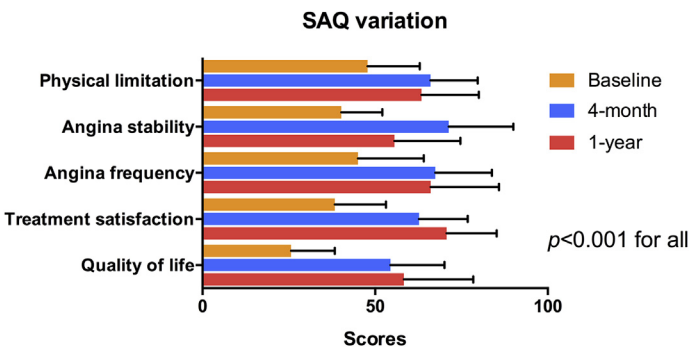
to 1.35 ± 0.60 vs. 1.69 ± 0.68 ($p < 0.001$) was also observed. At 4-month follow-up, significant improvements in mean SAQ scores were observed in terms of physical limitation (66.0 ± 13.7 points vs. 47.8 ± 15.1 points; $p < 0.001$), angina stability (71.3 ± 18.7 points vs. 40.2 ± 11.9 points; $p < 0.001$), angina frequency (67.4 ± 16.4 points vs. 45.0 ± 19.1 points; $p < 0.001$), treatment satisfaction (62.7 ± 14.1 points vs. 38.3 ± 14.8 points; $p < 0.001$), and quality of life (54.4 ± 15.7 points vs. 25.7 ± 12.6 points; $p < 0.001$) (Figure 3). Exercise tolerance significantly increased, as evidenced by the increment in the 6-min walk distance 388.6 ± 119.7 m vs. 287 ± 139 m ($p = 0.004$) and by the reduction in median dyspnea severity score on the Borg scale after exercise to 1 (IQR: 0.5 to 2.5) vs. 4.5 (IQR: 3 to 5) ($p = 0.009$) (Figure 4).

These benefits enabled a reduction in pharmacotherapy in 19 patients (38%): the median number of antianginal drugs at follow-up was 3 (IQR: 2 to 3) vs. 3 (IQR: 2 to 4) ($p = 0.001$) (Figure 5). Reductions in a single drug were possible in 16 patients and of 2 drugs in 3 patients compared with baseline. Table 4 shows the number of patients with SAQ score improvement and reductions in the number of antianginal drugs at 4-month follow-up according to the observed CCS class change.

One patient died 1 month after the procedure because of ischemic stroke. One patient had a non-ST-segment elevation acute coronary syndrome and required PCI 3 months after the procedure.

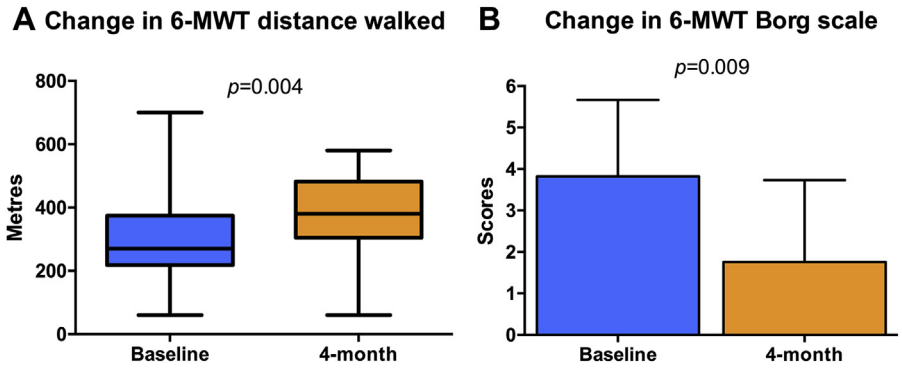
LATE OUTCOMES. In all patients, 12-month follow-up was available. Overall, the significant benefit with regard to angina symptoms was maintained in terms of mean CCS class with respect to baseline: 1.72 ± 0.83 vs. 2.98 ± 0.53 ($p < 0.001$) (Figure 2). Of note, no significant change in CCS class was observed between 4-month and 1-year follow-up: 1.64 ± 0.82 vs. 1.72 ± 0.83 ($p = 0.351$). The benefit achieved with regard to mean New York Heart Association functional class at 4-month follow-up was maintained at 1 year: 1.23 ± 0.63 vs. 1.68 ± 0.70 ($p < 0.001$). All SAQ scores remained significantly higher than baseline: physical limitation, 63.4 ± 16.6 points vs. 47.9 ± 15.2 points ($p < 0.001$); angina stability, 55.6 ± 19.0 points vs. 40.7 ± 11.5 points ($p < 0.001$); angina frequency, 66.1 ± 19.8 points vs. 45.0 ± 19.1 points ($p < 0.001$); treatment satisfaction, 70.7 ± 14.5 points vs. 38.2 ± 14.9 points ($p < 0.001$); and quality of life, 58.3 ± 20.1 points vs. 26.0 ± 12.5 points ($p < 0.001$) (Figure 3).

FIGURE 3 Seattle Angina Questionnaire Score Variation After Reducer Implantation



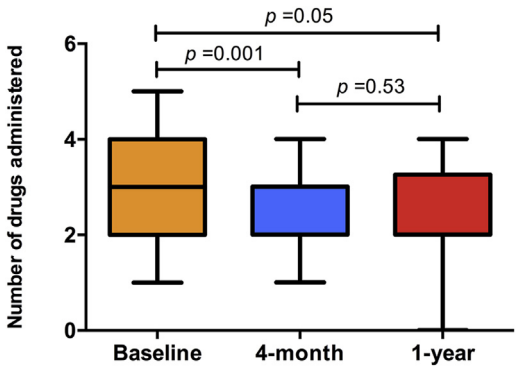
Reducer implantation significantly reduced angina symptoms and improved quality of life, as shown by higher Seattle Angina Questionnaire (SAQ) scores at 4 months after Reducer implantation. This benefit was maintained at 1-year follow-up.

FIGURE 4 Changes in 6-Min Walk Distance



Reducer implantation significantly improved exercise tolerance, as demonstrated by a longer distance walked in the 6-min walk test (6-MWT) **(A)**. Device implantation translated also to lower Borg dyspnea scores after exercise **(B)**.

FIGURE 5 Change in Administered Antianginal Drugs



Reducer implantation significantly reduced the requirement of antianginal drugs at 4-month follow-up. A tendency toward this benefit was maintained at 1 year, and no difference was noted in the median number of drugs used at 1 year compared with 4-month follow-up.

The median number of antianginal drugs required at 1-year follow-up remained lower compared with baseline and was 2 (IQR: 2 to 3.25) vs. 3 (IQR: 2 to 4) (p = 0.05). Of note, no significant change in the number of drugs used was seen between 4-month and 1-year follow-up: 3 (IQR: 2 to 3) vs. 2 (IQR: 2 to 3.25) (p = 0.53) (Figure 5). Table 5 shows the number of patients with SAQ score improvement and reductions in the number of antianginal drugs at 1-year follow-up according to the observed CCS class change.

At longer term follow-up, 1 patient died 11 months after Reducer implantation because of urogenital malignancy. One patient reporting recurrent angina was investigated with computed tomographic coronary angiography, with evidence of progression of coronary disease, and treated with subsequent PCI. No cases of cardiac mortality were recorded.

TABLE 4 Patients With Seattle Angina Questionnaire Score Improvement and Reductions in the Number of Antianginal Drugs at 4-Month Follow-Up According to Observed Canadian Cardiovascular Society Class Change

CCS Class Improvement	Physical Limitation	Angina Stability	Angina Frequency	Treatment Satisfaction	Quality of Life	Reduction in Antianginal Drugs ≥1
0 (n = 10)	2 (20.0)	2 (20.0)	3 (30.0)	1 (10.0)	3 (30.0)	2 (20.0)
1 (n = 20)	7 (35.0)	7 (35.0)	10 (50.0)	10 (50.0)	3 (15.0)	8 (40.0)
>2 (n = 20)	11 (55.0)	14 (70.0)	13 (65.0)	11 (55.0)	13 (65.0)	9 (45.0)

Values are n (%). To define the cutoff points evaluating binary improvement regarding each domain in the SAQ, we calculated Δ of each value between baseline and follow-up and %Δ as the ratio between Δ and the value at baseline. We defined improvement in SAQ score when %Δ was ≥50%.

CCS = Canadian Cardiovascular Society; SAQ = Seattle Angina Questionnaire.

DISCUSSION

The principal findings of this study are the following: 1) in a real-world group of patients with refractory angina without a further coronary revascularization option, CS Reducer implantation was feasible and safe; 2) no periprocedural or midterm device-related complications were observed; and 3) the clinical effectiveness of this therapy was documented by the reduction of disabling angina symptoms, quality of life improvement, improvement in exercise tolerance, and reduction in the requirement of antianginal drug treatment.

Physicians are commonly faced with patients presenting with chronic stable angina that is refractory to traditional medical management. When further revascularization options are limited and symptoms persist despite maximal medical therapy, patients are frequently labeled as having "no option" (1-3). Refractory angina is often disabling and is associated with poor quality of life, chronic pain, frequent hospitalizations, and resultant high level of health care resource utilization (4-6). There is clearly a need for novel therapies to further alleviate symptoms and improve the quality of life in this group of patients. Elevation of coronary venous pressures, achieved by narrowing of the CS as a therapeutic surgical approach for these patients, was first described by Beck and Leighninger in 1955 (14,15). Although associated with significant improvement in symptoms and reduced 5-year mortality rates, the early enthusiasm for this intervention was lost because of the contemporary widespread adoption of cardiac bypass surgery. On the basis of the principle of Beck's procedure, the CS Reducer was designed by Paz and Shinfield using swine models in the mid-1990s, with the first-in-human study demonstrating feasibility and safety 10 years ago (16).

To date, there are limited data relating to the safety and efficacy of this intervention in real-world patients. Evidence is currently limited to the randomized, double-blind COSIRA (Coronary Sinus Reducer for Treatment of Refractory Angina) trial (10) and 2 recent observational studies encompassing only a small number of patients (11,12).

The present study is the largest reported experience of Reducer implantation in a real-world consecutive patient group presenting with chronic refractory angina. Among the 50 consecutive patients treated at our center, all CS anatomy types were suitable for Reducer implantation, suggesting that the device (available in 1 size compatible with CS diameters of 9.5 to 13 mm at the proximal implant site) is suitable for the management of the full range

of CS sizes encountered. Accordingly, in the COSIRA trial (10), a 96% device implantation success rate was reported among the 52 patients randomized to device treatment, with 2 failures due to unsuitable CS anatomy. In an observational study involving 23 patients, Konigstein et al. (11) reported a 91% success rate of Reducer implantation, with 2 failures due to unsuitable CS anatomy. In our experience, we achieved successful device implantation in all patients. No periprocedural complications or device-related adverse events were observed at short-term or midterm follow-up, confirming the safety of the procedure. The high device success rate observed in our study includes the first cases performed at our institution during the operator's learning curve and is therefore suggestive of a good safety profile. From a technical point of view, we have noted that adequate support is required for the advancement of the Reducer system, particularly when crossing the CS ostium, and we therefore routinely use the 0.035-inch Hi-Torque Supra Core Peripheral Guide Wire, which provides greater support and features a soft, shapeable, and radiopaque tip that helps prevent venous vascular injury. Moreover, although in most of the cases the standard technique described here was used, in 7 cases with more challenging anatomy, alternative approaches, including the mother-and-child technique or the use of a Josephson electrophysiology catheter, were required to enable procedural success.

Strict evidence regarding the duration of DAPT after Reducer implantation is lacking, and the 6-month duration is inspired by the COSIRA trial design (17). With this premise and based on the current recommendations with regard to DAPT duration following the implantation of coronary bare-metal stents, we recommended a strict minimum of 1 month of DAPT after Reducer implantation. This is another interesting observation of this study: that 1-month DAPT is safe and efficacious, with no reported device-related complications in the follow-up period.

The implantation of the Reducer was associated with good efficacy, with the majority of patients (80%) demonstrating symptomatic alleviation and angina reduction, with a mean 1.3 ± 0.9 CCS class reduction at 4-month follow-up. The global improvement observed in this real-world population is in line with that of prior nonrandomized studies showing a rate of response of about 85% compared with the 71% recorded in the treatment arm of the COSIRA trial. The magnitude of angina alleviation is comparable with that seen in previous studies; of note, symptom reduction of ≥2 CCS classes occurred in 40% of patients, in line with the 35% observed in the COSIRA trial (10). Moreover, our study shows for the first time that the benefit observed in the short follow-up period after Reducer implantation is maintained at 1-year follow-up.

TABLE 5 Patients With Seattle Angina Questionnaire Score Improvement and Reductions in the Number of Antianginal Drugs at 1-Year Follow-Up According to Observed Canadian Cardiovascular Society Class Change

CCS Class Improvement	Physical Limitation	Angina Stability	Angina Frequency	Treatment Satisfaction	Quality of Life	Reduction in Antianginal Drugs ≥1
0 (n = 10)	1 (9.1)	1 (9.1)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
1 (n = 20)	6 (30.0)	6 (30.0)	12 (60.0)	11 (55.0)	7 (35.0)	8 (40.0)
>2 (n = 20)	15 (78.9)	9 (47.4)	13 (68.4)	12 (63.2)	10 (52.6)	9 (42.1)

Values are n (%). To define the cutoff points evaluating binary improvement regarding each domain in the SAQ, we calculated Δ of each value between baseline and follow-up and %Δ as the ratio between Δ and the value at baseline. We defined improvement in SAQ score when %Δ was ≥50%.

CCS = Canadian Cardiovascular Society; SAQ = Seattle Angina Questionnaire.

The clinical benefit suggested by the reduction in mean CCS class after Reducer implantation is confirmed by the higher scores on the SAQ recorded at 4 months and maintained at 1-year follow-up and by the significant increase in exercise tolerance and in dyspnea severity scores on the Borg scale as evidenced by the 6-min walk test. Furthermore, the reduction in symptoms resulted in reductions in the requirement of antianginal therapy in 19 patients and may have further contributed to the improvement in the quality of life.

Two patients developed acute coronary syndromes requiring PCI during 1-year follow-up after Reducer implantation (1 non-ST-segment elevation myocardial infarction and 1 unstable angina). Although these coronary events were unrelated to the Reducer procedure, it is important to note that Reducer therapy does not have an effect on CAD progression, and further investigation is warranted in the presence of de novo symptoms. Remarkably, no cases of cardiac mortality were recorded. Despite these encouraging results, studies are needed to ascertain the longer term safety and efficacy of the Reducer.

It is also important to note that 20% of patients in our study population were nonresponders, which is consistent with that of previously published studies showing a 15% to 30% rate of nonresponse, highlighting the need for improved screening tools prior to device implantation to identify patients likely to benefit from this intervention. Moreover, it is worth noting that in the COSIRA trial (10), up to 42% of patients in the sham control group reported a reduction in CCS class at 6-month follow-up due to the placebo effect. The placebo effect is reported to be very strong in patients with refractory angina. Therefore, subjective endpoints such as anginal pain

and self-reported questionnaires may be misleading, and more objective methods of determining myocardial ischemia (noninvasive imaging) may be more suitable to assess device efficacy.

STUDY LIMITATIONS. The main limitations of our study are the absence of a control group and the small number of patients enrolled. Another limitation is the absence of an objective measurement of myocardial ischemia reduction following Reducer implantation. To this end, very preliminary data with the use of stress perfusion cardiac magnetic resonance before and after Reducer implantation have recently been reported (18). Despite these limitations, this study includes the largest number of patients treated in a single-center, real-world setting.

CONCLUSIONS

In our real-world, single-center experience, the implantation of the CS Reducer is safe and associated with alleviation of angina symptoms and improvements in objective measures of quality of life in patients with refractory angina who are not candidates for further revascularization. Our results support the use of CS Reducer implantation as an adjunctive therapy in the management of patients presenting with chronic refractory angina.

ADDRESS FOR CORRESPONDENCE: Dr. Francesco Giannini, Interventional Cardiology Unit, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. E-mail: giannini_fra@yahoo.it.

PERSPECTIVES

WHAT IS KNOWN? The CS Reducer is a novel therapeutic treatment for patients with refractory angina, with limited real-world data describing its use outside of clinical trials.

WHAT IS NEW? In our real-world, single-center experience with 50 patients, Reducer implantation appeared safe and was associated with reduction of angina symptoms and improvement in quality of life.

WHAT IS NEXT? Studies on myocardial ischemia reduction following Reducer implantation will improve knowledge of device efficacy.

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KEY WORDS chronic refractory angina, coronary sinus reducer, optimal medical therapy

APPENDIX For supplemental methods and figures, please see the online version of this paper.