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ORIGINAL RESEARCH

CORONARY

Coronary Sinus Narrowing for Treating Refractory Angina

REDUCER-I Multicenter "Real-World" Observational Study Primary Endpoint Analysis

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ABSTRACT

BACKGROUND Patients with refractory angina are often ineligible for revascularization and have poor quality of life despite optimal medical therapy. The coronary sinus (CS) Reducer (Shockwave Medical Inc) was safe and effective in the treatment of refractory angina in the COSIRA (Coronary Sinus Reducer for Treatment of Refractory Angina) randomized sham-controlled trial.

OBJECTIVES This study sought to perform the primary endpoint analysis of the complete REDUCER-I (An Observational Study of the Neovasc Reducer System) study cohort.

METHODS REDUCER-I is a nonrandomized, "real-world" study of patients with refractory angina treated with the CS Reducer conducted at 25 centers from 9 European countries. The primary effectiveness endpoint was an improvement in Canadian Cardiovascular Society (CCS) class at 6 months. The primary safety endpoints were major adverse cardiac events and device- or procedure-related serious adverse events through 30 days. Study follow-up is planned through 5 years with some interim 3-year analyses included here.

RESULTS From 2016 to 2023, 400 patients were enrolled, including 78.0% (312/400) male patients, 54.3% (216/398) with previous myocardial infarction, 73.6% (293/398) with previous revascularization, and 72.0% (280/389) CCS class III/IV. Major adverse cardiac event and serious adverse event rates were 1.6% (95% CI: 0.7-3.6) and 1.1% (4/371), respectively, with no deaths within 30 days. At 6 months, 69.8% (240/344) of patients improved by ≥1 CCS class. Six-minute walk distances improved by 34.1 ± 85.8 m at 6 months ($P < 0.0001$). Interim 3-year results showed CCS class and Seattle Angina Questionnaire quality of life improvements were sustained ($P < 0.0001$).

CONCLUSIONS The complete primary endpoint analysis of the REDUCER-I study shows patients with refractory angina were safely and effectively treated with the CS Reducer. Improvements in angina and quality of life appear sustained through 3 years. (JACC Cardiovasc Interv. 2024;17:2908–2918) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Some of the study results were recently presented at the 2024 American College of Cardiology Annual Meeting, April 6-8, 2024, Atlanta, Georgia, USA, and published in the *Journal of American College of Cardiology* as an abstract.

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Refractory angina is defined by the presence of long-lasting (≥3 months) symptoms caused by reversible ischemia that are not controlled with optimal medical therapy or interventional strategies.[1] Patients with refractory angina have poor quality of life (QOL), limitations in daily physical activities, multiple comorbidities, and poor mental health.[2,3] Up to 150,000 new cases of refractory angina are diagnosed per year in the United States and Europe.[4-6] The numbers of these patients, the amount of medical attention they require, and their modest mortality rate[3,5,7,8] result in a significant strain on the health care system.[9-11] Thus, the primary goal of treating refractory angina is to reduce symptoms of angina, restore QOL, and reduce the need for rehospitalization and health care resource use.[5,9]

Cell therapies,[12-14] enhanced external counterpulsation,[3,13] extracorporeal shockwave therapies,[5] and neuromodulation[15] have been used to treat patients who have refractory angina.[16] However, most of these technologies still require adequately powered randomized evaluation to confirm their safety and effectiveness. By contrast, the coronary sinus (CS) Reducer (Shockwave Medical Inc) is a stainless steel hourglass-shaped mesh that creates a focal narrowing in the CS lumen with the intention of redistributing myocardial blood flow into the subendocardium of ischemic myocardium.[17,18] In randomized placebo-controlled trials, COSIRA and ORBITA-COSMIC (Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance), patients treated with the Reducer device had a significant reduction of angina episodes, improved QOL,[18] and redistribution of blood into subendocardial myocardial layers.[19]

Since receiving the CE mark, the safety and effectiveness of the CS Reducer have been further corroborated in small investigator-led studies.[18,20-23] Larger multicenter studies have also concluded that the CS Reducer is safe and relieves symptoms of angina, but these findings are limited by short follow-ups.[22-24] The REDUCER-I study (NCT02710435) evaluated "real-world" use of the CS Reducer in a large and challenging patient population. Interim results showed a favorable safety profile as well as improvements in QOL and functional capacity.[9] In this analysis,[25] the primary endpoints for the full cohort of the REDUCER-I study along with an interim analysis of changes in Canadian Cardiovascular Society (CCS) class and QOL through 3 years are presented.

METHODS

Study design details including enrollment, screening, and follow-up protocols have been previously described.[9] Briefly, the REDUCER-I study is a nonrandomized, real-world observational study conducted at 25 medical centers from 9 European countries. Patients with refractory angina despite optimal medical therapy and without revascularization options were eligible for enrollment. Full details on the Reducer device and implantation procedure have been previously published.[26] The majority of the patients were enrolled prospectively (arm 1, n = 350). A total of 50 additional patients were enrolled retrospectively in arm 2; 11 patients were treated as part of the COSIRA randomized controlled trial (RCT)[18] and reconsented for further longer-term follow-up in the REDUCER-I study, and 39 patients were treated after the Reducer device had received the CE mark but before the start of the REDUCER-I study. Notably, CCS class II to IV patients were eligible for this study compared with the COSIRA RCT in which enrollment was restricted to CCS III and IV patients. Full inclusion and exclusion criteria are provided in the Supplemental Methods.

All sites were required to follow local legal and regulatory requirements for ethics committee and Institutional Review Board approvals. The study was conducted in accordance with the Declaration of Helsinki guidelines and good clinical practices. Study follow-up is planned through 5 years, although some interim 3-year data are presented here.

PRIMARY AND SECONDARY ENDPOINTS. The primary effectiveness endpoint of the study was defined as the percentage of patients who experienced a reduction in CCS class at 6 months compared with baseline. The primary safety endpoints were the rate of device- and/or procedure-related periprocedural serious adverse events

ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walk test
CABG = coronary artery bypass graft
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
CS = coronary sinus
EQ-5D-5L = EuroQol-5 Dimension-5 Level
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
QOL = quality of life
RCT = randomized controlled trial
SAE = serious adverse event(s)
SAQ = Seattle Angina Questionnaire

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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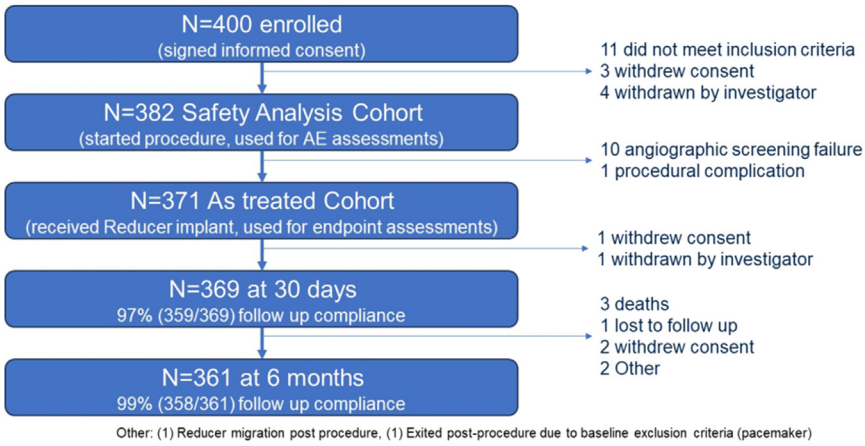
FIGURE 1 **REDUCER-I Patient Enrollment and Follow-Up Through 6 Months**



AE = adverse event(s).

(SAEs) and major adverse cardiac events (MACEs) up to 30 days postimplant. Device- and/or procedure-related periprocedural SAEs were defined as a composite of death, myocardial infarction (MI), cardiac tamponade, clinically driven redilatation of the narrowing created by the CS Reducer, life-threatening arrhythmias (vein thrombosis or ventricular fibrillation), and respiratory failure. Importantly, the definition for MI was based on changes in cardiac biomarkers with thresholds dependent on baseline creatine kinase-myocardial band or cardiac troponin measurements (Supplemental Table 1). MACE was defined as a composite of cardiac death, major stroke, and MI. An independent clinical events committee was responsible for adjudicating the protocol-defined adverse events.

The secondary endpoints included the percentage of patients who experienced a reduction in CCS class compared with baseline and the rate of MACEs at 12 months and then annually. Exercise duration and 6-minute walk tests (6MWTs) were assessed at 6 and 12 months. Patient QOL was evaluated with the Seattle Angina Questionnaire (SAQ)[27] and EuroQol-5 Dimension-5 Level (EQ-5D-5L) test[28] at 6 months, 12 months, and thereafter annually.

STATISTICAL ANALYSIS. Because this was an observational study, there were no prespecified power calculations for the primary endpoints. However, the sample size of 400 patients was chosen to be able to observe adverse events that occur at a population rate of 0.75% or higher with 95% probability. Additionally, 400 subjects would provide a precision of approximately 5% or better for a categorical endpoint and 0.0983 SD units or better for a continuous endpoint.

The interim analysis of the REDUCER-I study presented the prospectively enrolled patients separate from the entire cohort and concluded that patient outcomes between the prospectively (arm 1) and retrospectively (arm 2) enrolled patients were not different.[9] In the complete primary endpoint analysis, outcomes were reported for the whole REDUCER-I cohort where data were available. Continuous variables are shown as mean ± SD and categoric variables expressed as percentages. Patient responses to the EQ-5D-5L subcategories were dichotomized into "problem" and "no problem" groups, and the Bowker test of symmetry was used to analyze changes in CCS class from baseline as well as the subcategories for EQ-5D-5L questionnaires. Kaplan-Meier time-to-event estimates were used for analysis of freedom from MACEs. Paired *t*-tests were used to analyze changes from baseline in 6MWT distance, exercise tolerance parameters, and SAQ domains. All analyses were performed using SAS 9.4 (SAS Institute Inc).

RESULTS

A total of 400 patients (350 patients in arm 1 and 50 patients in arm 2) consented between 2016 and 2023 (**Figure 1**). Of these, 382 patients began the procedure (defined as the safety cohort). Ten of the 382 patients did not meet the angiographic screening criteria, and 1 patient had a CS dissection leading to the Reducer

TABLE 1 Baseline Patient Demographics (N = 400)

Age, y	68.8 ± 9.7 (398)
Male	78.0 (312/400)
Previous myocardial infarction	54.3 (216/398)
Previous CABG	73.6 (293/398)
Previous PCI	73.6 (293/398)
Hypercholesterolemia	89.2 (355/398)
Diabetes mellitus	46.5 (185/398)
Hypertension	84.7 (337/398)
Current or previous smoking	60.3 (240/398)
Coronary artery disease[a]	100.0 (350/350)
Obstructive CAD	79.5 (264/332)
Nonobstructive CAD	20.5 (68/332)
CCS angina class	
I	0.5 (2/389)[b]
II	27.5 (107/389)
III	63.5 (247/389)
IV	8.5 (33/389)
Number of anginal medications[c,d]	
0	1.6 (6/386)
1	9.8 (38/386)
2	22.5 (87/386)
3	28.8 (111/386)
>3	37.3 (144/386)

Values are mean ± SD (n) or % (n/N). [a]Obstructive vs nonobstructive was not collected in arm 1 until 2021; therefore, some subjects did not provide this information (n = 18). [b]Some baseline screen failure subjects in arm 1 did not provide CCS class (n = 3); retrospective data were not available for some arm 2 subjects (n = 8). [c]Includes antianginal drugs, beta-blockers, calcium-channel blockers, and vasodilators. [d]3 subjects (104-023, 114-026, and 131-001) exited as screen failures before entering medication data, and 11 are from arm 2, resulting in the denominator of 386.

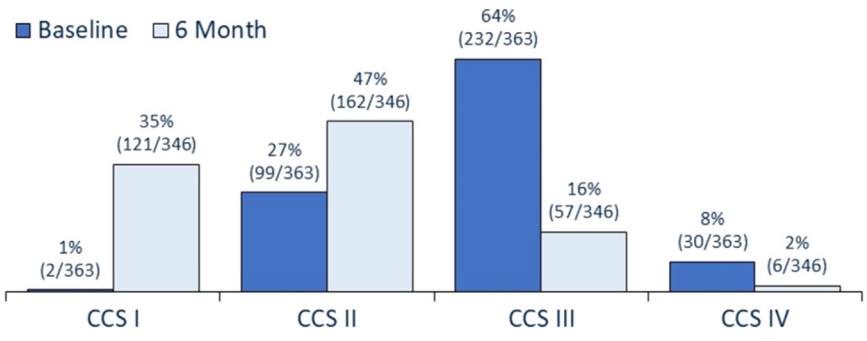
CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; PCI = percutaneous coronary intervention.

implant not being attempted. A total of 371 patients received a Reducer device (defined as the as-treated cohort), of whom 7 required a second attempt at implantation. Therefore, of the 382 patients who started the procedure, 95.3% (364/382) patients were implanted on the first attempt, and 97.1% (371/382) were ultimately implanted in total. For the complete primary safety endpoint analysis at 6 months, 361 patients were eligible; data were available in 99% (358/361).

Patient baseline characteristics revealed high rates of cardiovascular risk factors and comorbidities (Table 1). Most patients had a history of MI, had undergone previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and had diabetes mellitus. In this observational (real-world) registry that did not have inclusion criteria specifying a minimal number of antianginal medications to be enrolled, two-thirds of the patients were on 3 or more medications, and one-third of the patients were on <3 medications. All patients had coronary artery disease (CAD); 20.5% (68/332) were reported as nonobstructive. Despite prior revascularizations and optimal medical therapy, 72.0% (280/389) were assessed as CCS class III or IV at the start of the study.

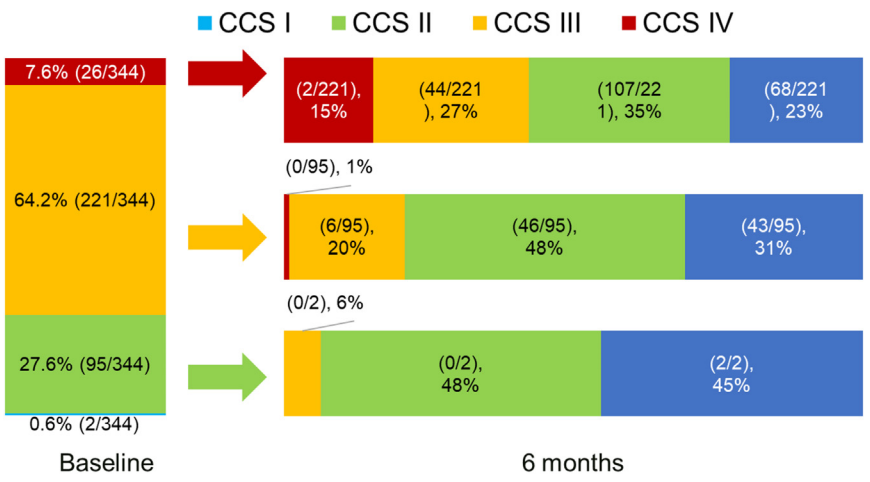
PRIMARY EFFECTIVENESS ENDPOINT. At baseline, patients had a mean CCS class of 2.8 ± 0.6 (n = 363), which improved to 1.8 ± 0.8 (n = 346) at 6 months. The mean change in CCS class at 6 months compared with baseline was −0.9 ± 0.8 (n = 344; $P < 0.0001$), and the median CCS class change was a decrease of

FIGURE 2 Distribution of CCS Class at Baseline and 6 Months



Paired analysis for those with both baseline and 6-month CCS class assessment. CCS = Canadian Cardiovascular Society.

FIGURE 3 6-Month Changes in CCS Class Stratified by Starting Baseline CCS Class



*2 patients enrolled as CCS class I remained CCS class I at their 6-month follow-up. Paired analysis for those with both baseline and 6-month CCS class assessment. CCS = Canadian Cardiovascular Society.

1 grade (Q1-Q3: 0-1). Figure 2 shows the distribution of CCS class at baseline and 6 months. At baseline, 72.2% (280/389) of patients suffered from severe disabling angina at rest or minimal effort (CCS class III or IV). At the 6-month follow-up, only 18.2% (63/346) of patients remained CCS class III or IV. Overall, 69.8% (240/344) of patients improved by ≥1 CCS class, and 24.1% (83/344) improved by ≥2 CCS classes.

For patients with both baseline and 6-month CCS class measurements, there were different degrees of improvement based on their preprocedure CCS class (Figure 3). Of the 26 patients who began the study in CCS class IV, 84.6% (22/26) improved at 6 months. Similarly, 79.2% (175/221) of patients who started the study as CCS class III improved to CCS classes I or II at 6 months. Baseline CCS class II patients also improved; 45.2% (45/95) were CCS class I 6 months after Reducer implantation. There were 2 patients who were retrospectively enrolled (arm 2) despite being CCS class I at baseline (Table 1, Figure 3). These 2 patients did not have room for improvement but were noted to have remained CCS class I at their 6-month follow-up.

PRIMARY SAFETY ENDPOINT. The Kaplan-Meier estimate of MACEs through 30 days was 1.6% (95% CI: 0.7%-3.6%) (Table 2). There were 6 patients who experienced 7 MI events in the first 30 days. Six of the MIs were adjudicated as unrelated to the procedure, having occurred 9 to 29 days after the Reducer implant. Of the 7 MIs, 2 required no specific treatment, 3 had a medication change, 1 patient underwent PCI to the circumflex artery 9 days after onset, and 1 patient underwent stenting of the right coronary artery 3 days after onset (adjudicated as possibly related the

TABLE 2 Primary Safety Endpoint: MACE Through 30 Days

Event	30-Day Kaplan-Meier Event Rate % [95% CI] (Number of Subjects With Event)
MACE[a]	1.6% [0.7-3.6] (6)
Cardiac death	0.0% [0.0-0.0] (0)
Major stroke	0.0% [0.0-0.0] (0)
Myocardial infarction[a]	1.6% [0.7-3.6] (6)

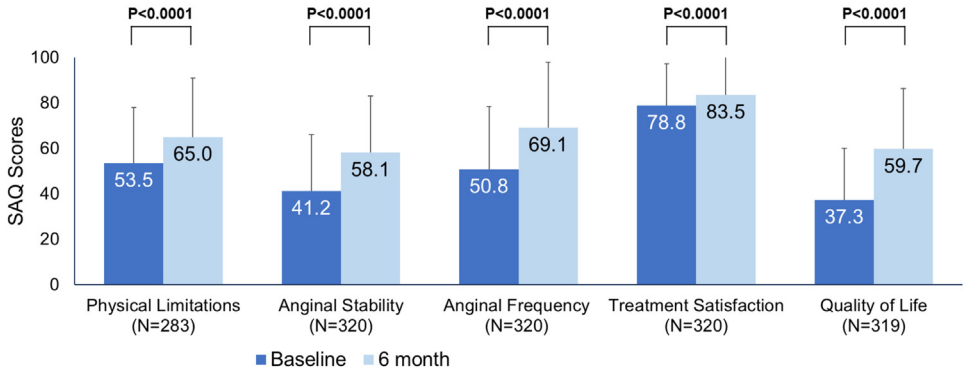
[a]1 subject had 2 myocardial infarctions within 30 days; only the first event is counted in the Kaplan-Meier estimate.
MACE = major adverse cardiac event(s).

TABLE 3 Primary Safety Endpoint: Device- or Procedure-Related SAEs Within 30 Days

Complications	No. of Events	Subjects With Event
Device or procedure SAE within 30 days	4	1.1 (4/371)
All-cause death	0	0.0 (0/371)
Myocardial infarction	3	0.8 (3/371)
Cardiac tamponade	1	0.3 (1/371)
Clinically driven redilatation of a Reducer	0	0.0 (0/371)
Life-threatening arrhythmias	0	0.0 (0/371)
Respiratory failure	0	0.0 (0/371)

Values are % (n/N) unless otherwise indicated.
SAE = serious adverse event(s).

FIGURE 4 SAQ Assessments at Baseline and 6 Months

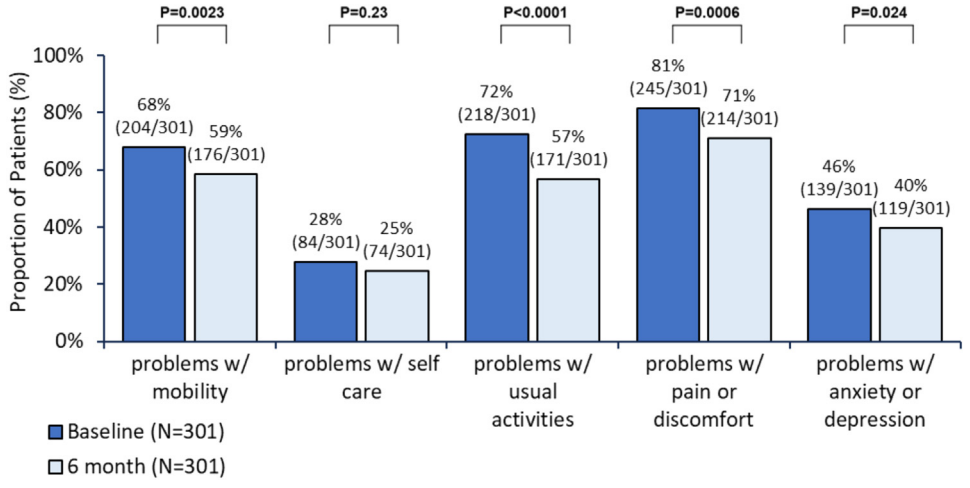


Paired analysis for those with both baseline and 6-month SAQ assessment. SAQ = Seattle Angina Questionnaire.

procedure and device). Total device- or procedure-related SAEs within 30 days were 1.1% (4/371) (Table 3). Details of the MI events were previously described. One patient had a postinterventional pericardial effusion and became hypotensive; transthoracic echocardiography showed pericardial tamponade, which was adjudicated as related to the device/procedure. The patient was treated with pericardiocentesis and became hemodynamically stable; the event was considered resolved 2 days after onset. Three subjects experienced device migrations (0.8%, 3/371), but the devices were left in place and did not require further reinterventions.

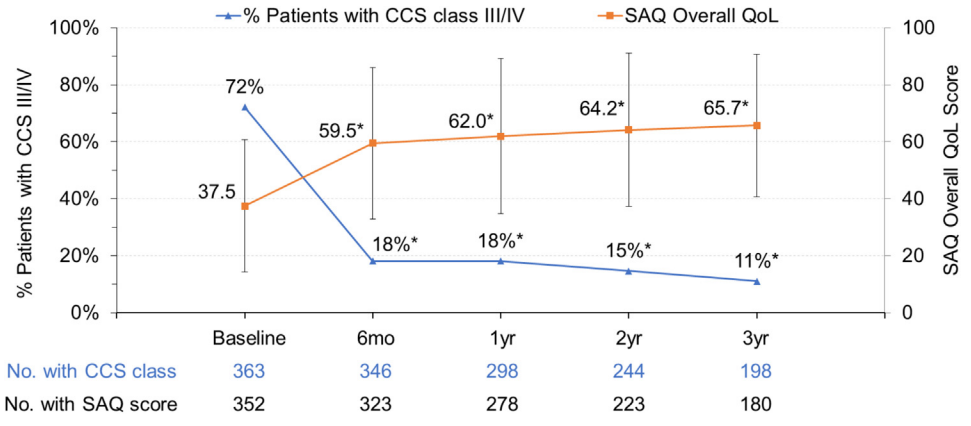
QOL AND FUNCTIONAL CAPACITY ASSESSMENTS. Comparisons of SAQ scores at baseline and 6 months are shown in Figure 4. Notably, the overall SAQ QOL score and subcategories of anginal stability and anginal frequency were all significantly improved from baseline ($P < 0.0001$). Similarly, comparisons of EQ-5D-5L in patients with both baseline and 6-month measurements are shown in Figure 5 with a significant decrease in the proportion of patients with limited mobility ($P = 0.0023$), with limitations in their usual activities ($P < 0.0001$), having pain or discomfort ($P = 0.0006$), and having anxiety or depression ($P = 0.024$). Overall, the EuroQol Visual Analogue

FIGURE 5 EQ-5D-5L Assessment at Baseline and 6 Months



Paired analysis for those with both baseline and 6-month EQ-5D-5L assessment. EQ-5D-5L = EuroQol 5 Dimension 5 Level.

FIGURE 6 Sustained Improvement in CCS Class and SAQ Overall QoL Through 3 Years



*$P < 0.0001$ for comparisons to baseline results. QoL = quality of life; other abbreviations as in Figures 2 and 4.

Scale (EQ-VAS) score improved from 56.4 ± 20.2 (300) at baseline to 64.8 ± 18.4 (300) at 6 months ($P < 0.0001$).

Assessment of changes in functional capacity was performed for prospectively enrolled patients as well as the few retrospectively enrolled patients who had a 6MWT captured at baseline. This subset of patients walked 325.2 ± 116.6 (263) m at baseline and 359.0 ± 110.9 (268) m at 6 months ($P < 0.0001$) in the 6MWT. The mean change in 6MWT at 6 months was 34.1 ± 85.8 (263) m. Exercise duration also increased from 355.7 ± 150.7 (244) seconds at baseline to 387.0 ± 162.1 (244) at 6 months ($P < 0.0001$).

INTERIM 3-YEAR ANALYSIS. In a preliminary analysis of patients who reached at least 3 years of follow-up, there were 198 patients with CCS measurements and 180 patients with SAQ measurements at 3 years and at baseline. The decrease in the proportion of patients with CCS class III or IV at 6 months was sustained through 3 years, with the proportion of CCS class III/IV patients remaining below 20% (Figure 6) ($P < 0.0001$ for differences between all time points and baseline). Similarly, SAQ overall QOL was significantly increased at 6 months, and these scores also remained above 60% for the following 3 years (Figure 6) ($P < 0.0001$ for all comparisons to baseline).

DISCUSSION

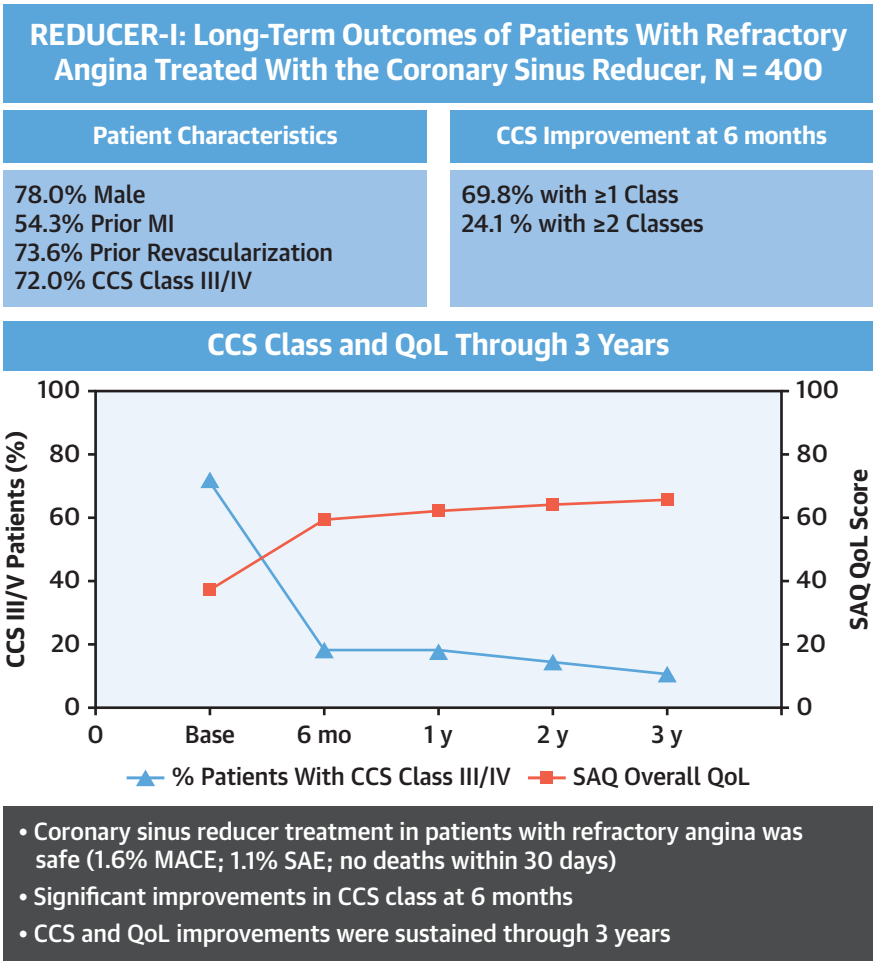
The REDUCER-I cohort consisted of a large and challenging patient population suffering from chronic effort angina (CCS class II-IV) with multiple comorbidities in which optimal medical therapy or prior PCI or CABG had not been effective. These patients exhibited persistent chest pain that resulted in daily physical activity limitations, depression, and overall poor QOL. In this primary endpoint analysis of the full cohort, the main findings are as follows (Central Illustration):

1. Implantation of the Reducer was effective in reducing symptoms of angina; nearly 70% of patients improved by ≥1 CCS classes, and QOL measures were significantly improved at 6 months.
2. The CS Reducer device was safe; patients had low rates of device- or procedure-related SAEs and MACEs through 30 days at 1.1% (4/371) and 1.6% (95% CI: 0.7-3.6), respectively.
3. The treatment effect was durable; interim analysis showed improvements in CCS class and QOL were sustained through 3 years.

The CS Reducer was shown to improve angina severity, QOL, and functional capacity in this otherwise "no option" patient population. A similar beneficial symptomatic effect was reported by 2 randomized sham-controlled trials,[18,19] and improvements in CCS class have been reported by other investigator-initiated studies.[18,20-24] Although the REDUCER-I study included a real-world population, such as those with CCS class II and nonobstructive CAD, patients still experienced CCS improvements similar to those observed in the COSIRA and ORBITA-COSMIC randomized clinical trials.[18,19]

Notably, of the most disabled patients, those with CCS class III or IV, 4 of every 5 patients improved

CENTRAL ILLUSTRATION **REDUCER-I Study Outcomes**



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Patients in the REDUCER-I study experienced significant improvements in their Canadian Cardiovascular Society (CCS) class at 6 months, and the CCS and quality of life (QoL) improvements were sustained through 3 years. MACE = major adverse cardiac event(s); MI = myocardial infarction; SAE = serious adverse event(s); REDUCER-I = An Observational Study of the Neovasc Reducer System; SAQ = Seattle Angina Questionnaire.

6 months after Reducer implantation. Nearly one-half of the CCS class II patients in the REDUCER-I study also improved, suggesting that this device can also provide benefit to those with less severe symptoms of angina, although further studies are needed to confirm this signal. Other investigators have proposed that patient selection, device sizing, CAD phenotype and progression, limited baseline ischemia, or alternative drainage systems are potential predictors of response to Reducer implantation.[29,30] In this analysis, the patients with severe angina benefitted the most, possibly because they had the most room for improvement, as was seen in the (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) ISCHEMIA trial.[31] Further analyses into predictors of responders and nonresponders in the REDUCER-I study are planned.

Furthermore, the interim analysis through 3 years suggests durable improvements in CCS and QOL, adding to the prior evidence of a sustained benefit of Reducer.[32,33] An increase in 6MWT of more than 25 to 60 m or reaching a threshold of approximately 350 m is considered clinically significant.[30-33] REDUCER-I

patients walked an average of 360 m at their 6-month test, 34 m further than at baseline. The improvement in 6MWT concurred with other measurements of improved functional capacity, including EQ5D-5L mobility and SAQ physical limitation scores.[34]

The Reducer device and implantation procedure were also shown to be safe; there were no deaths, life-threatening arrhythmias, or respiratory failure. The low SAE rate of 1.1% (4/371) was primarily caused by the occurrence of MI, of which half were adjudicated as unrelated to the device, and most resolved spontaneously or with a simple change in medication. MIs are common in patients with obstructive CAD and no revascularization options, and aligning MI causality to the Reducer implant can be difficult because the device is implanted in the venous circulation, whereas MIs originate from the arterial side. In this study, MI events were based on changes in the creatine kinase-myocardial band, and prior literature has shown rates of MI after PCI or CABG can vary greatly depending on the definitions and thresholds chosen.[35,36] Despite the conservative biomarker threshold used in this study, the 1.6% (95% CI: 0.7%-3.6%) MI rate after Reducer implantation compares favorably with the reported 4% rates for MI after PCI or CABG.[36-38] Furthermore, the REDUCER-I population likely had more advanced disease progression because they were judged to be ineligible for either PCI or CABG.

The proposed mechanism of action of the Reducer is that narrowing of the CS causes an increase in backward venous pressure, which creates microvasculature dilatation and a reduction of subendocardial microvascular resistance. These changes lead to redistribution of blood flow to the subendocardium and angina relief. Early animal studies demonstrated that CS pressure elevation decrease subendocardial intramyocardial pressure with redistribution of blood flow into the subendocardium of ischemic myocardium with normalization of endocardial/epicardial blood flow ratio.[39,40] The primary outcomes of the ORBITA-COSMIC trial showed a significant reduction in angina episodes in patients treated with the Reducer compared with placebo but did not show an overall increase in stress myocardial blood flow in ischemic segments.[19] However, a prespecified secondary endpoint demonstrated redistribution of blood flow into the subendocardial layers of the ischemic segments of the myocardium.[19] Other improvements in ischemic burden, myocardial perfusion reserve index, and coronary flow reserve after Reducer implantation have also been reported in studies including imaging and invasive physiology.[41-43] Redistribution of myocardial blood flow after Reducer implantation may suggest a rationale for potential clinical benefit not only in patients with obstructive CAD but also in patients with angina caused by microvascular disease, cardiomyopathies, and/or diastolic dysfunction. Assessments of microvascular function in future trials such as the COSIRA II (Efficacy of the COronary SInus Reducer in Patients With Refractory Angina II; NCT05102019) RCT and the REMEDY-PILOT (Coronary Sinus Reducer Implantation in Patients With Ischaemia and Non-obstructed Coronary Arteries and Coronary Microvascular Dysfunction; NCT05492110) will provide further insights.

STUDY LIMITATIONS. The REDUCER-I cohort included patients enrolled prospectively (arm 1) and retrospectively (arm 2). Although the prior interim results noted no differences between the outcomes in the 2 arms of the study,[9] the potential bias with retrospective enrollment should be noted. Because this was a single-arm registry, patients and the technicians performing the functional capacity and quality of life tests were not blinded, which could add to sources of bias. The lack of a comparator arm in the single-arm registry is also important because the COSIRA RCT noted a significant placebo effect.[18] These limitations will be addressed through the COSIRA II trial, a randomized, sham-controlled clinical trial that includes a robust blinding procedure and postassessment of blinding of the patients and the clinical and research teams. Although these are the combined results of patients with obstructive and nonobstructive CAD, it is recognized that the different causes for angina may lead to different results after CS reduction. Future subanalyses are planned to assess potential differences and interactions between the type of CAD and outcomes. Finally, as an observational study, there were some differences from what would be expected in a refractory angina cohort, including one-third of the patients were on <3 medications, which would typically be standard for refractory angina, and there were 2 patients who received PCI (as a result of MIs), although the inclusion criteria specified patients should have limited treatment options for revascularization.

CONCLUSIONS

This primary endpoint analysis of the REDUCER-I study confirms the favorable safety and effectiveness profile of the CS Reducer in a large and clinically challenging real-world patient cohort. The patients in REDUCER-I experienced significant improvements in

their CCS class and other QOL and functional capacity measures at 6 months, and the persistence of these improvements through 3 years is promising. The ongoing COSIRA II RCT trial (NCT05102019) will provide further insights on the performance of the CS Reducer as a treatment option for patients with refractory angina.

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PERSPECTIVES

WHAT IS KNOWN? Patients with refractory angina experience poor quality of life despite optimal medical and interventional therapies.

WHAT IS NEW? In this primary endpoint analysis of the full cohort of the REDUCER-1 study, the coronary sinus reducer had a favorable safety and efficacy profile. Patients had significant improvements in angina symptoms, and their functional capacity and quality of life improvements were maintained through 3 years.

WHAT IS NEXT? Data from completed (ORBITA COSMIC) and ongoing (COSIRA II and REMEDY-PILOT) randomized trials will provide further information on the benefits of treatment with the Reducer over optimal medical therapy alone and may also provide critical mechanistic insights.

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KEY WORDS coronary sinus, functional capacity, quality of life, refractory angina, stent(s)

APPENDIX For an expanded Methods section and a supplemental table, please see the online version of this paper.