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Coronary sinus reducer for the treatment of refractory angina: a literature review

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Abstract

Background. Refractory angina remains an important health issue despite improvements in coronary artery disease diagnosis and treatment, and its incidence is expected to grow. Although patients with refractory angina exhibit a mortality rate comparable to that of individuals with asymptomatic stable angina, the quality of life is worse and associated healthcare expenditure is higher. After having exhausted all treatment options, coronary sinus reducer (CSR) has recently gained more attention as a non – pharmacological treatment of refractory angina.

Aim. To summarize the current knowledge about CSR for the treatment of refractory angina, its mechanism of action, efficacy, safety and cost-effectiveness.

Materials and methods. A comprehensive literature search was performed on PubMed database using the keywords “coronary sinus reduction” AND “refractory angina”, focusing on articles published in English in the last 5 years.

Results. Implantation of the CSR creates backward pressure in the coronary venous circulation resulting in a redistribution of flow from the subepicardial to the ischaemic subendocardial region. This translates into sustained angina reduction as demonstrated by a significant improvement in Canadian Cardiovascular Society angina class, quality of life, mainly as assessed by the Seattle Angina Questionnaire, increased exercise tolerance as assessed by the 6-minute walk test and improved left ventricular systolic function. Under proper selection, CSR could also be of benefit to patients with right coronary artery disease. The most common complication is haematoma at the vascular access site. Cost-effectiveness is achieved within 2 years.

Conclusions. CSR is an efficient, safe and cost-effective treatment of refractory angina.

Keywords: coronary sinus reducer, coronary sinus reduction, refractory angina, non-pharmacological treatment.

1. Introduction

Refractory angina refers to ≥3 months lasting symptoms of angina due to known reversible ischaemia in the presence of obstructive coronary artery disease (CAD), which cannot be controlled by escalating medical therapy (including second- and third-line pharmacological agents), bypass grafting, or stenting including percutaneous coronary intervention (PCI) of chronic total coronary occlusion; or due to angina / ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) [1]. Refractory angina remains an important issue despite improvements in CAD diagnosis and treatment – it accounts for 30 000 – 50 000 new cases/year in Europe, making up 5-10% of patients with stable angina [2]. The incidence of refractory angina is expected to grow due to population ageing, increasing complexity of CAD and the presence of multiple comorbidities – all factors limiting the spectrum of therapeutic options [3]. Patients with refractory angina exhibit a mortality rate comparable to that of individuals with asymptomatic stable angina, however the quality of life is worse, and healthcare expenditure associated with refractory angina is higher. After having exhausted all options for medical therapy and mechanical revascularization, 2024 European Society of Cardiology Guidelines on chronic coronary syndromes suggest coronary sinus reducer (CSR) as one of the non-pharmacological treatments (class IIb recommendation, level of evidence B) [1]. During this minimally invasive procedure an hourglass-shaped stainless-steel mesh is implanted percutaneously via right internal jugular vein in the coronary sinus, thus narrowing its lumen. This procedure has recently gained more attention as a potentially effective, safe and accessible option for the treatment of refractory angina [3]. This literature review aims to summarize current knowledge about CSR for the treatment of refractory angina, its mechanism of action, efficacy, safety and cost-effectiveness.

2. Materials and methods

A comprehensive literature search was conducted using PubMed database. Articles published in the last 5 years in English were selected for the analysis. Case reports were excluded. The following keywords were used: “coronary sinus reduction” AND “refractory angina”.

3. Results

3.1. Mechanism of action

In a healthy heart, exercise induces sympathetic-mediated vasoconstriction of the subepicardial vessels, thus directing more blood flow to the subendocardial layer. With obstructive epicardial coronary disease or microvascular disease, these regulatory mechanisms are compromised: the perfusion is no longer redistributed to the subendocardial layer leading to ischaemia of this region, which reduces contractility; reduced contractility increases left ventricular end-diastolic pressure thus compressing subendocardial coronary vessels and further reducing the perfusion of subendocardial layer. Implantation of coronary sinus narrowing device increases venous pressure in the coronary circulation. Created backward pressure in coronary venules, capillaries and arterioles increases cross-sectional area of these vessels, significantly reducing the resistance in the vascular bed of subendocardial layer. This results in a redistribution of flow from the subepicardial to the ischaemic subendocardial region, thus

bringing the ratio between subepicardial and subendocardial perfusion closer to that observed in physiological conditions [2, 3]. In silico study shows that the mechanism of coronary sinus reducer depends on the severity of coronary stenosis: in the case of moderate coronary stenosis, an increase in capillary transit time is the key mechanism, allowing more time for myocardial oxygenation; with severe coronary stenosis, redistribution of blood from nonischaemic to ischaemic regions predominates [4]. The imaging study using rubidium-82 positron emission tomography supports redistribution of myocardial blood flow from well perfused to hypoperfused myocardium under stress conditions in both the left and right coronary artery distributions [5]. Similar results were demonstrated by quantitative perfusion cardiovascular magnetic resonance study [6].

3.2. Efficacy

Generally, studies show a significant reduction in angina symptoms and number of antianginal drugs, improved quality of life, increased exercise tolerance after the implantation of CSR. A total of 69,8 – 90,9% of patients improved by at least 1 Canadian Cardiovascular Society (CCS) angina class; 24,1 – 50,9% of patients improved by at least 2 CCS classes [7–14]. Some patients improved by 3 CCS classes and some even became asymptomatic [8, 10]. The observed variability in the improvement proportions between studies could be partly explained by differences in sample size and the diversity of study design. Patients after CSR implantation were more likely to have a lower number of daily episodes of angina with odds ratio (OR) of 1,40. Angina reduction with CSR developed gradually over time (an effect detectable at 10 weeks), in contrast to percutaneous coronary intervention, where angina reduction is immediate [15]. The proportion of non-responders in the included studies ranged from 15,8% to 25,0% of patients, which is within the range of previously reported rates in older literature [9]. A modest reduction in the number of anti-anginal drugs was reported [8, 9]. Studies show an improvement in Quality of Life (QoL), mainly as assessed by the Seattle Angina Questionnaire (SAQ); the majority of studies show an improvement in all domains of the SAQ [8, 9, 11–15]. An increase in exercise tolerance, as assessed by the 6-minute walk test (6-MWT), was observed and ranged from 10,45% to 36,07% increase in distance walked, with a tendency for smaller increases with longer follow-up [11–14]. CSR also improved left ventricular (LV) function by increasing ejection fraction (EF); this was more pronounced in patients with baseline EF < 50%, resulting in an 11,3% increase compared with only an 3,8% increase in patients with baseline EF > 50%; a significant improvement of global circumferential and global longitudinal strain was observed; one study showed a reduction in LV volumes, while the other found no significant changes [10, 11]. Although it was previously postulated that the increased venous pressure induced by CSR implantation could cause interstitial oedema with subsequent increase in myocardial stiffness, no detrimental effects on microstructural remodelling and associated diastolic function were found [11]. The duration of follow-up in the included studies ranged from 3 months to 3 years. At 3-year follow-up, CSR was still effective, demonstrating sustainability of performance [12].

It was generally believed that CSR would not be effective in patients with isolated right coronary artery (RCA) disease due to the cardiac venous

anatomy: the inferior and inferoseptal LV wall usually drains to the proximal coronary sinus, whereas CSR is implanted more distally and therefore has no means of generating backward pressure [3, 16]. This group of patients has traditionally been excluded from CSR studies. However, patients with chronic total occlusion (CTO) of the RCA differ from patients with non-occlusive RCA disease by the presence of a developed collateral network, mostly originating from the left anterior descending (LAD) and circumflex (LCX) coronary arteries, thus creating a reason to speculate that even patients with CTO RCA disease could benefit from CSR. Mrak et al. evaluated the efficacy of CSR implantation in refractory angina patients with CTO RCA disease, compared them to CSR recipients with left coronary artery (LCA) ischemia and found that it was comparably effective in alleviating angina and improving QoL: there was no difference in improvement for at least one CCS class between groups and QoL domain of SAQ improved significantly more in CTO RCA group [16]. Although further research is required, current results suggest that, under proper selection, CSR could also be of benefit to patients with RCA disease. A detailed summary of the efficacy of CSR in the included studies is provided in Table 1.

3.3. Safety

The most common complication was hematoma at the vascular access site with an incidence rate of 8,9% [14]. The second most common - periprocedural CSR embolization / dislocation with an incidence rate ranging from 0,5% to 8,0% [8, 9, 12, 13, 15]. Other less common complications included inability to deploy CSR, failure to cannulate the coronary sinus (CS), dissection or perforation of CS, cardiac tamponade requiring pericardiocentesis and myocardial infarction, possibly related to the procedure and device [8, 9, 12, 15]. A detailed summary of the safety of CSR in the included studies is provided in Table 2.

3.4. Cost-effectiveness

Budget impact analysis revealed incremental resource savings beginning in the third year after the CSR implantation, which translated into a total of 59 772,44 € saved over the time horizon of 5 years. This resulted from the reduction in consumed healthcare resources: hospitalizations, specialist visits, emergency room accesses, coronary examinations, and percutaneous coronary interventions [17]. Cost-utility analysis showed that even under both the assumptions of a reducer effect duration for 2 and 3 years from implant with a 30%-year efficacy decrease, the Incremental Cost-Effectiveness Ratio (ICER) (€/quality-adjusted life year (QALY)) became dominant (meaning that the reducer device turned out to be less expensive and more effective than the Standard of Care (SoC)) starting from year 3 onward [17, 18]. Starting from year 2, device implantation was cost-effective as resulting ICERs were well below both World Health Organization (WHO) (defined as three times the national annual GDP per capita) and 50 000 €/QALY thresholds [18].

4. Conclusions

Coronary sinus reducer is an efficient, safe and cost-effective treatment of refractory angina. It is associated with a significant reduction in angina symptoms, an improvement in left ventricular function, exercise tolerance and quality of life. Redistribution of perfusion from subepicardial to subendocardial myocardium in ischaemic segments and improvement in coronary

microcirculatory function parameters after device implantation may underlie these effects. The incidence of complications is modest, the effect of the device is durable, and cost-effectiveness is achieved within 2 years.

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Table 1. Summary of the efficacy of CSR in the included studies

Authors / date	n	Type of study / paper	Inclusion criteria	Relevant outcomes	Results
Foley et al. (ORBITA-COSMIC) (2024) [15]	50	Multicentre, randomised, double-blind, placebo-controlled trial.	≥ 18 years old patients with angina, epicardial coronary artery disease, ischaemia, and no further options for antianginal therapy	1. Myocardial blood flow on adenosine-stress cardiac magnetic resonance in myocardial segments designated as ischaemic at enrolment (excluding transmurally infarcted segments). 2. The number of daily episodes of angina. 3. SAQ, MacNew Heart Disease Health-Related Quality of Life, EQ-5D-5L index values; CCS class.	At 6 - month follow-up: 1. No benefit of CSR over placebo was detected in stress myocardial blood flow in segments designated ischaemic at enrolment (difference for CSR vs placebo 0,06 mL/min per g [95% CrI –0,09 to 0,20]). 2. Patients in the CSR group were more likely to have a lower number of daily episodes of angina (OR 1,40 [95% CrI 1,08 to 1,83]). 3. Both SAQ angina frequency and MacNew Heart Disease Health-Related Quality of Life scores improved in the CSR group compared with the placebo group; no difference between the groups was seen in any other SAQ domains, EQ-5D-5L index value, CCS class.
Tebaldi et al. (INROAD) (2024) [7]	24	Multicentre, single-cohort, investigator-driven study.	≥ 18 years old patients with the diagnosis of refractory angina having at least 1 open coronary artery (excluded right coronary artery) where to perform invasive coronary physiological assessment	1. Change of index of microcirculation resistance (IMR) values from baseline to follow-up. 2. Variation from baseline to follow-up of coronary flow reserve (CFR). 3. Variation from baseline to follow-up of resistive resistance ratio (RRR). 4. CCS class, SAQ changes from baseline, The Beck Depression Inventory.	At 4 - month follow-up: 1. A significant (≥20% from baseline) reduction of IMR was observed in 71,4% [95% CI, 47,8%–88,7%]) patients. 2. CFR values did not change significantly. 3. RRR values did not change significantly. 4. A total of 42,8% and 76,1 % patients had an improvement of at least 2 or 1 CCS class, respectively; SAQ summary score increased by 4 points in the IMR responders, whereas it remained unchanged in the IMR nonresponders; no significant changes in Beck Depression

					Inventory values were observed.
Ferreira Reis et al. (2023) [8]	26	Multicentre, prospective, single-arm, non-blinded study.	Angina (at least CCS class 2) no further options for antianginal therapy, and ischaemia documented by myocardial stress single-photon emission computed tomography (SPECT) or myocardial stress magnetic resonance imaging (MRI) attributable to the left coronary artery regardless of the presence of obstructive epicardial CAD.	1. CCS class change. 2. Improvement in QoL assessed by SAQ-7. 3. Reduction in number of antianginal drugs.	At 6 - month follow-up: 1. A total of 42,0% and 75,0% patients had an improvement of at least 2 or 1 CCS class, respectively; 16,7% became asymptomatic. 2. All scales of the SAQ-7 showed a significant improvement: the QoL score improved by 20,2 points and summary score improved by 16,6 points. 3. 54,0% discontinued or had the dose reduced of at least one anti-ischemic drug.
D'Amico et al. (2020) [9]	187	Multicentre, observational, national, single arm, non-blinded study.	Patients suffering from chronic disabling angina pectoris (CCS classes 2 to 4) and no further options for antianginal therapy	1. CSS class change. 2. Physical limitation, angina stability and frequency, treatment satisfaction and quality of life assessed by SAQ. 3. Reduction in number of antianginal drugs.	At median follow-up of 18,4 months: 1. A total of 49,0% and 82,0% patients had an improvement of at least 2 or 1 CCS class, respectively. 2. Physical limitation scores improved by 20,1 points, angina stability scores improved by 21,5 points, angina frequency scores improved by 25,5 points, treatment satisfaction scores improved by 27,8 points and quality of life scores improved by 30,8 points. 3. Significant reduction of anti-ischemic drugs (mean number 2,77±1,04 vs 2,00±1,2, $p < 0,001$). Detailed distribution of changes in number of antianginal drugs was not provided.
Tzanis et al. (2020) [10]	19	Single-centre, prospective, non-blinded study.	Refractory angina of at least CCS class 2, despite optimal medical	1. CCS class change. 2. Change in LV ejection fraction (LVEF), LV end-diastolic volume	At 4 - month follow-up: 1. A total of 37,0% and 84,0% patients had an improvement of at least

			treatment (OMT) with evidence of inducible myocardial ischemia at dipyridamole stress cardiac magnetic resonance (CMR) and no further options for antianginal therapy.	(LVEDV), LVEDV/body surface area (BSA), LV end-systolic volume (LVESV) and LVESV/BSA measured using CMR. 3. Change in transmural myocardial perfusion reserve index (MPRI).	2 or 1 CCS class, respectively; An improvement of 3 CSS class was observed in 5,3% of patients. 2. A significant improvement was observed in: LVEF (61 [IQR 47–71] to 66 [IQR 57–72] %; p = 0,009). Improvement was more pronounced in patients with EF < 50% (11,3 [IQR 6,5–54,5] vs. 3,8 [IQR 0,6–9,1] %; p = 0,028) LVEDV (132,1 [IQR 118,0–173,6] to 123,0 [IQR 99,7–158,2] mL; p = 0,033) LVEDV/BSA (65,7 [IQR 57,4–89,6] to 64,7 [IQR 53,7–74,1] mL/m^2; p = 0,036) LVESV (55,1 [IQR 37,7–75,3] to 41,2 [IQR 30,7–70,0] mL; p = 0,007) LVESV/BSA (28,7 [IQR 18,6–38,8] to 20 [IQR 15,0–31,4] mL/m^2; p = 0,007). 3. A significant increase in transmural MPRI was observed (p < 0,011). LVEDV decrease was more pronounced in patients that improved the MPRI values (p = 0,054).
Palmisano et al. (2020) [11]	20	Single-centre, single-arm, prospective observational study.	Patients suffering from refractory angina (classified at least as CCS class 2 despite OMT) with evidence of CAD not amenable to revascularization and having inducible myocardial ischemia involving at least one myocardial segment at	1. Change in LVEF, LVEDV, LVESV and indexed LV mass measured using CMR. 2. Change in global circumferential (GCS), longitudinal (GLS) and radial strain (GRS) measured using CMR. 3. Modification of peak diastolic strain rate in circumferential, radial, and longitudinal directions. 4. Changes in myocardial structural remodelling	At 4 - month follow-up: 1. Significant improvement in median LVEF (from 61,0% to 67,0%; p = 0,0079) was observed. There were no significant changes in LVEDV, LVESV and indexed LV mass observed. 2. A significant improvement of GCS and GLS was observed (GCS: − 18,0% vs – 21,0%; p = 0,0017; GLS: − 16,0% vs –

			baseline stress-CMR	parameters (native T1, ECV, cellular and matrix volume). 5. Changes of the ischemic burden and MPRI. 6. CCS class change. 7. SAQ score change. 8. Exercise tolerance assessed by 6 minute walk test (6 - MWT).	19,0%; p = 0,0192). GRS slightly improved without reaching statistical significance (GRS: 43,0% vs 48,0%, p = 0,0897). 3. No significant modification of peak diastolic strain rate was observed in any evaluated directions. 4. Structural remodelling parameters did not change significantly. 5. Reduction of the ischemic burden (13,0–11,0%; p = 0,0135) and improvement of the MPRI (1,10 vs 1.30; p = 0,0085) were observed. MPRR endo/epi ratio increased significantly in the ischaemic segments. 6. A total of 35,0 % and 85,0 % patients had an improvement of at least 2 or 1 CCS class, respectively. 7. Significant improvement in all domains of SAQ was observed. 8. Exercise tolerance significantly improved as assessed by 6 - MWT: 305 [IQR 240–386] vs 415 [IQR 322–495] metres; p = 0,0372
Mrak et al. (2021) [16]	46	Multicentre, prospective, observational study.	Patients ≥ 18 years, refractory angina with CCS class 2 – 4 despite OMT at maximally tolerated doses, obstructive CAD without further revascularization options, and objective evidence of reversible ischemia as assessed by SPECT or CMR.	1. CCS class change: difference between patients with chronic total occlusion (CTO) of right coronary artery (RCA) and obstructive coronary artery disease (CAD) of left coronary artery (LCA). 2. Improvement of SAQ scores. 3. Reduction of segments with inducible ischemia in patients with CTO RCA.	At 12 - month follow-up: 1. There was no difference in CSS class change comparing patients with CTO of RCA and obstructive CAD of LAD: improvement for at least one CCS class was noted in 77,2% CTO RCA and 70,2% LCA patients (p = 0,62). In a subgroup of 12 patients with isolated CTO RCA CCS class improvement was

					comparable to CCS class improvement in the LCA group (p = 0,65); improvement for at least one CCS class was noted in 66,7% patients. 2. All 5 SAQ domains improved in all groups, physical limitations and QoL improved significantly more in the CTO RCA group (p = 0,001 for both domains). 3. The reduction of segments with inducible ischemia observed in the CTO RCA patients was not significant (43 vs. 39 segments, p = 0,29). There was, however, a significant improvement in both the transmurality index and the MPRI.
Verheye et al. (REDUCER-I) (2025) [12]	361	Multicentre, nonrandomized, real-world observational study.	Patients with refractory angina despite OMT and without revascularization options.	1. CCS class change. 2. QoL assessed by SAQ, EQ-5D-5L and EQ-VAS. 3. Changes in functional capacity assessed by 6 - MWT. 4. Treatment durability assessed by sustainability of improvements in CCS class and QoL through 3 years.	At 6 - month follow-up: 1. A total of 24,1% and 69,8% patients had an improvement of at least 2 or 1 CCS class, respectively. 2. Significant improvements in all SAQ domains and in overall EQ-VAS score were observed; similarly, assessed by EQ-5D-5L, a significant decrease in the proportion of patients with limited mobility, with limitations in their usual activities, having pain or discomfort, and having anxiety or depression was observed. 3. Exercise tolerance significantly improved as assessed by 6 - MWT: 325,2 ± 116,6 (263) m vs 359,0 ± 110,9 (268) m (p < 0,0001)

					At 3 - year follow-up: 4. The proportion of CCS class III/IV patients remained below 20,0% ($p < 0,0001$). Similarly, SAQ overall scores remained above 60% ($p < 0,0001$).
Włodarczak et al. (2024) [13]	55	Single centre, non-blinded, real-life cohort study.	Diagnosis of chronic refractory angina CCS classes 2–4 for at least 3 months before the procedure in spite of maximum tolerable medical therapy for angina.	1. CCS class change. 2. Improvement of QoL assessed by SAQ-7. 3. Changes in functional capacity assessed by 6 - MWT.	At 3 - month follow-up: 1. A total of 50,9 % and 90,9 % patients had an improvement of at least 2 or 1 CCS class, respectively; 9,1% patients had an improvement of 3 CCS classes. 2. There was a significant improvement in SAQ-7 total ($39,2 \pm 15,8$ vs. $50,4 \pm 20,5$; $p < 0,0001$). 3. Exercise tolerance significantly improved as assessed by 6 - MWT: $233,3 \pm 107,1$ m vs. $305,2 \pm 126,8$ m; $p < 0,0001$.
Włodarczak et al. (2025) [14]	67	Single-centre, single-arm registry analysis	All consecutive patients diagnosed with refractory angina CCS classes 2-4 despite OMT, who underwent implantation of the CSR in the Department of Cardiology of the Copper Health Center in Lubin, Poland.	1. CCS class change. 2. Improvement of QOL assessed by SAQ-7. 3. Changes in functional capacity assessed by 6-MWT.	At 12 - month follow-up: 1. A total of 86,6 % patients had an improvement of at least 1 CCS class. 2. There was a significant improvement in SAQ-7 total score (39,9 [15,2] vs 54,6 [19,7], $p < 0,001$). 3. A significant improvement in functional capacity was observed as assessed by 6 - MWT: (265,9 [136,9] vs. 234,9 [109,1], $p = 0,03$)

Table 2. Summary of the safety of CSR in the included studies

Authors / date	**n**	**Type of adverse event**	**n (incidence)**
Foley et al. (ORBITA-COSMIC) (2024) [15]	25	CSR embolization	2 (8,0%)
		Inability to deploy CSR	1 (4,0%)
Ferreira Reis et al. (2023) [8]	26	Failure to cannulate the CS	1 (3,8%)
		Periprocedural CSR migration to the superior vena cava requiring surgical retrieval	1 (3,8%)
		Perforation of the CS with cardiac tamponade requiring pericardiocentesis	1 (3,8%)
D'Amico et al. (2020) [9]	187	CSR embolization	1 (0,5%)
		CSR dislocation	4 (2,1%)
		Coronary sinus dissection	1 (0,5%)
		Coronary sinus perforation	2 (1,1%)
		Inability to deploy CSR	2 (1,1%)
Verheye et al. (REDUCER-I) (2025) [12]	371 (for safety endpoints assessment)	CSR migration	3 (0,8%)
		Cardiac tamponade treated with pericardiocentesis	1 (0,3%)
		Myocardial infarction (adjudicated as possibly related the procedure and device)	1 (0,3%)
Włodarczak et al. (2024) [13]	55	Migration of the CSR into the pulmonary arteries	1 (1,8%)
Włodarczak et al. (2025) [14]	67	Hematoma at the vascular access site	6 (8,9%)