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REVIEW

Coronary Sinus Reducing Stent for the Treatment of Refractory Angina Pectoris: A Health Technology Assessment

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Aim: To summarize the evidence on the clinical effectiveness and safety of coronary sinus reducing stent (CSRS) therapy in refractory angina pectoris (AP) patients.

Methods: We performed a systematic literature search in common databases (n=4). The evidence obtained was summarized according to GRADE methodology. A health technology assessment (HTA) was conducted using the HTA Core Model® for Rapid Relative Effectiveness Assessment. Primary outcomes for the clinical effectiveness domain were the proportion of patients with improvement in two or more Canadian Cardiovascular Society (CCS) angina score classes, overall mean reduction of CCS class, and Seattle Angina Questionnaire (SAQ) quality of life (QoL) score improvement. Outcomes for the safety domain were adverse device effects (ADEs) and serious adverse device effects (SADEs).

Results: One randomized controlled trial (RCT) was identified. Outcomes that showed statistically significant differences between CSRS and sham treatment (in favor of CSRS) were CCS angina score improvement of one or two classes, overall mean reduction of CCS class, and SAQ QoL score improvement. Concerning safety, the sham-controlled trial data indicate that there were fewer SADEs in the intervention group (19%) than in the control group (46%). SADEs reported in observation studies ranged from none to 30%. The most frequently reported SADEs were death and stable angina. In the RCT, the only case of death occurred in the control group. Concerning clinical effectiveness, the risk of bias (RoB) was rated to be low, and concerning safety, the RoB was rated to range from low to moderate. As assessed by GRADE, the overall strength of evidence for effectiveness and safety was moderate. Internal and external validity of the evidence base were low.

Conclusion: Even though the current evidence indicates that the assessed technology, CSRS, is potentially more effective than sham intervention for refractory AP patients, the lack of internal validity of the studies undermines the partially positive results.

Keywords: refractory angina pectoris, coronary artery disease, coronary sinus reducing stent, coronary sinus

Introduction

Cardiovascular disease at large is a major cause of health loss across all regions of the world.[1] The Global Burden of Disease project 2015 estimated that 442.7 million prevalent cases of cardiovascular disease were present worldwide, which caused an estimated 17.92 million deaths.[1] Ischemic heart disease was one of the leading causes of all health loss globally.[1] Exact estimates of the incidence and prevalence of refractory angina pectoris (AP) are not available, but a guessed estimate by the 2002 European Society of Cardiology (ESC) Joint Study Group suggests that refractory AP occurs in 5–10% of

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all AP patients.[2] Refractory AP is conventionally defined as a chronic condition (≥3 months in duration) characterized by angina in the setting of ischemic heart disease, which cannot be controlled by a combination of optimal medical therapy, angioplasty, or bypass surgery, and where reversible myocardial ischemia has been clinically established to be the cause of the symptoms.[2] The estimated incidence of newly diagnosed patients with refractory angina in the USA ranges between 50,000 and 100 000 per year, while in Europe, the incidence is estimated to range between 30,000 and 50,000 new cases per year.[3]

The coronary sinus reducing stent (CSRS) aims to treat refractory AP patients and is suggested to be put in place once all the other therapeutic options are exhausted. Except for palliative management, the only alternative option for refractory AP that is based on controlled evidence is external counterpulsation.[4,5]

According to the ESC 2019 guideline, CSRS received the recommendation 2b, which means that the usefulness of CSRS is less well established by evidence/opinion, but that it may be considered for use in clinical practice.[5] There is also limited information on the effectiveness and safety of the CSRS, which would be published in the form of health technology assessment (HTA) reports.[6,7] For our assessment, we used the European Network for Health Technology Assessment (EUnetHTA) Core Model® for rapid Relative Effectiveness Assessment (REA), which is used for assessing the clinical effectiveness and safety of pharmaceuticals, diagnostic technologies, medical and surgical interventions, and screening technologies. We used this model to evaluate the clinical effectiveness and safety of CSRS therapy in refractory AP patients.

Methods

Systematic Literature Search

We conducted a systematic literature search on 10–13 December 2019 in four databases (Medline via Ovid, Embase, The Cochrane Library, and CRD [DARE, NHS-EED, HTA]) without a limit to years of publication, but limited to German and English. We searched for published clinical studies on CSRS in refractory AP patients. The search strategies can be provided upon request. In order to identify ongoing and unpublished studies, we conducted a search in three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP, and EU Clinical Trials) on 29–30 January 2020, resulting in 13 potentially relevant hits.

Study Selection and Internal Validity Assessment

The inclusion criteria for the literature selection were defined using the Population–Intervention–Comparison–Outcome–(Study design) model (PICOs) shown in Table 1. No limit was set on the minimum number of study participants, but individual case reports were excluded. Two researchers selected references for inclusion and systematically extracted relevant studies into data-extraction tables. Internal validity was assessed using the risk of bias (RoB) tool for RCTs of the Cochrane Collaboration,[8] as well as by the checklist for single-arm studies of the Institute of Health Economics (IHE).[9] No cases of disagreement occurred.

Outcome Measures

Outcomes were selected in accordance with EUnetHTA guidelines for rapid REAs, which state that clinical endpoints relevant for patients should be selected whenever possible (mortality, morbidity, health-related quality of life, and treatment satisfaction). Primary outcomes for clinical effectiveness were: Canadian Cardiovascular Society (CCS) angina score improvement of one or two classes, overall mean reduction of CCS class, and Seattle Angina Questionnaire (SAQ) quality of life (QoL) score improvement. For the assessment of safety, adverse device effects (ADEs) and serious adverse device effects (SADEs) were included.

Synthesis of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used for summarizing and evaluating the strength of the evidence.[11] Categories of high, moderate, low, and very low were applied and only critical outcomes were assessed. No meta-analysis was performed as only one prospective controlled trial was identified.

Methodological Framework and Reporting

An adaptation of the EUnetHTA Core Model for REAs was used for this HTA. The generic questions from Core Model (version 4.2) were translated into actual research questions. This analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

Table 1 PICOs Inclusion Criteria

Population	Heavily pretreated adult patients (≥18 years of age) with coronary artery disease (CAD) who are not candidates for revascularization demonstrate reversible ischemia, and have refractory angina pectoris despite standard medical therapy. ICD-10 Code: I20.9 MeSH terms: Heart, Heart Diseases, Myocardial Ischemia, Coronary Artery Disease, Angina Pectoris
Intervention	Coronary-sinus reducing device/stent made of stainless steel is implanted in the coronary sinus and pre-mounted on a customized hourglass-shaped balloon catheter. The catheter is inserted into its place via the jugular vein under local anesthesia Available agent: Neovasc Reducer™ System (Neovasc Inc, British Columbia, Canada) MeSH terms: Percutaneous Coronary Intervention, Stents
Control	Sham procedure MeSH terms: NA
Outcomes	
Efficacy	Clinical endpoints: CCS angina score SAQ for QoL SAQ for treatment satisfaction Surrogate endpoints: Exercise tolerance as assessed with the use of a symptom-limited stress test ST-segment depression during exercise Modified Wall Motion Score Index Antianginal medication intake
Safety	Serious adverse device effects (SADEs) Adverse device effects (ADEs)
Study design	
Efficacy	Randomized controlled trials (RCTs) Prospective non-randomized controlled trials (NRCTs)
Safety	Randomized controlled trials (RCTs) Prospective non-randomized controlled trials (NRCTs) Prospective case series (single-arm studies, registries, etc.) (No minimum number of patients required, but individual case reports excluded)

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Results

Search Results

Through a systematic search, we found 349 relevant citations. An additional 14 were found by a hand search, which resulted in overall 363 hits. The specific search strategy employed can be provided by the authors upon request. Concerning clinical effectiveness, one randomized controlled trial (RCT)[13] met the inclusion criteria. Concerning safety, seven studies met the inclusion criteria: one RCT used also in the clinical effectiveness assessment[13] and six prospective observational non-comparative studies.[14–19] No retrospective study was included in the assessment. All the extracted data can be found in Tables 2, 3, and 4.

Study and Patient Characteristics

Study Characteristics

Concerning clinical effectiveness, one controlled trial was found (an RCT) that compared CSRS with a sham procedure (study name COSIRA, NCT01205893) and was sponsored by the manufacturer Neovasc Inc.[13] It was conducted between April 2010 and April 2013 in 11 centers (in Belgium, Canada, Denmark, the Netherlands, Sweden, and the UK). The RCT included 104 patients (52 were in the intervention group [IG] and 52 in the control group [CG]) and the patient population was followed for 6 months. No patient was lost to follow-up.

Concerning safety, seven studies met the inclusion criteria. One RCT, described above,[13] four prospective case series,[14–16,19] and two prospective registries.[17,18] The total number of patients analyzed in safety analysis who received the CSRS therapy was 348 (plus 52 patients in CG). The observational studies were conducted between October 2004 and April 2017 in Germany, India, Israel, Italy, and Belgium. The follow-up ranged from 4[14] to 24 months.[15] No observational study stated the source of funding.

Patient Characteristics

In the RCT included in the assessment of clinical effectiveness analysis, patients were evenly distributed between the IG and CG. All patients belonged to CCS angina class III or IV, despite attempted optimal pharmacological therapy for 30 days prior to screening, and all had evidence of reversible ischemia with limited options for revascularization. Mean left ventricular ejection fraction (LVEF) ranged between 53.5% and 54.8%. Most of the patients had experienced the following conditions or received the following interventions: previous coronary artery bypass grafting (CABG), previous percutaneous coronary intervention (PCI), previous myocardial infarction (MI), current/previous smoking, diabetes mellitus, hypertension,

Table 2 CSRS: Results from RCTs

Authors (Year)	**Verheye et al[13] (2015)**
Country	11 clinical centers (Belgium, Canada, Denmark, Netherlands, Sweden, UK)
Sponsor	Neovasc Inc.
Study design	Multi-center, prospective, double-blinded, randomized, sham-controlled, Phase 2 trial (COSIRA, NCT01205893)
Conducted in	04/2010–04/2013
Indication	Refractory AP despite standard medical therapy (pts with CAD, no candidates for revascularization, reversible ischemia)
Intervention (I)	Coronary-sinus reducing stent (Reducer)
Comparator (C)	Sham procedure: no stent implanted
Number of pts (I vs C)	52[a] vs 52
Inclusion criteria	Pts ≥18 years of age, symptomatic CAD pts with chronic refractory AP grade III or IV (classified by CCS) despite attempted optimal medical therapy for 30 days prior to screening, limited treatment options for revascularization by CABG or PCI, evidence of reversible ischemia attributable to the left coronary arterial system by dobutamine Echo, LVEF >25%, informed consent, compliance with follow-up
Exclusion criteria	Pregnancy, acute coronary syndrome in <3 mos, CABG/PCI in <6 mos, unstable angina (recent-onset angina, crescendo angina, or rest angina with ECG changes) in <1 month prior to screening, decompensated CHF or hospitalization due to CHF during 3 mos prior to screening, lifethreatening rhythm disorders or any rhythm disorders that would require placement of an internal defibrillator and/or pacemaker, severe COPD as indicated by a forced expiratory volume in one second that is less than 55% of the predicted value, pts unable to undergo exercise tolerance test (bicycle) for reasons other than refractory AP, severe valvular heart disease, pacemaker or defibrillator electrode in the right atrium, right ventricle, or coronary sinus, tricuspid valve replacement or repair, chronic renal failure (serum creatinine >2 mg/dL) with patients on chronic hemodialysis, moribund pts, pts with comorbidities limiting life expectancy to <1 yr, contraindication to required study medications that cannot be adequately controlled with pre-medication, allergy to stainless steel or nickel, contraindication to having an MRI performed, enrollment in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints, mean right atrial pressure ≥15 mmHg, anomalous or abnormal CS as demonstrated by angiogram (abnormal CS anatomy – tortuosity, aberrant branch, persistent left SVC) and/or; CS diameter at the site of planned reducer implantation <9.5 mm or >13 mm
Primary outcome measure	Proportion of pts with improvement in 2 or more CCS angina score classes from baseline to 6-mo follow-up
Secondary outcome measure	Technical and procedural success measured at 24 hrs Measured at 30-day follow-up: • Periprocedural AEs and SAEs (death, MI, cardiac tamponade, life-threatening arrhythmia, and respiratory failure)Measured at 6-mo follow-up: • Proportion of pts with improvement of one or more CCS angina score classes • Exercise tolerance assessed with the use of a symptom-limited stress test • SAQ Score • Dobutamine echo WMSI • Major AEs (cardiac death, major stroke, and MI)

(*Continued*)

Table 2 (Continued).

Authors (Year)	**Verheye et al[13] (2015)**
Baseline patient characteristics (I vs C) (intention-to-treat)	
Mean age, yrs (±SD)	69.6 (8.7) vs 66.0 (9.8)
Sex, female:male, n	8:44 vs 12:40
Previous MI, n (%)	27 (52) vs 30 (58)
Previous CABG, n (%)	42 (81) vs 38 (73)
Previous PCI, n (%)	36 (69) vs 40 (77)
Hypercholesterolemia, n (%)	50 (96) vs 46 (88)
Diabetes mellitus, n (%)	21 (40) vs 25 (48)
Hypertension, n (%)	42 (81) vs 41 (79)
Current or previous smoking, n (%)	27 (52) vs 31 (60)
CCS angina class, n (%)	
Class III	42 (81) vs 45 (87)
Class IV	10 (19) vs 7 (13)
Mean LVEF, n (±SD)	53.5 (10.2) vs 54.8 (11.9)
No. of antianginal medications[b], n (%)	
0	3 (6) vs 4 (8)
1	10 (19) vs 10 (19)
2	23 (44) vs 18 (35)
3	12 (23) vs 18 (35)
>3	4 (8) vs 2 (4)
Follow-up time, mos	6
Loss to follow-up, %	0
Efficacy (I vs C)	
CCS angina score improvement of at least 2 classes at 6 mos, n (%)	18 (35) vs 8 (15) *p*=0.02
CCS angina score improvement of at least 1 class at 6 mos, n (%)	37 (71) vs 22 (42) *p*=0.003
Reduction in CSS class, mean n (SD), (baseline/6 mos)	3.2 (0.4)/2.1 (1.0) vs 3.1 (0.3)/2.6 (0.9)
Difference, n	*p*=0.001 1.1 vs 0.5
SAQ QoL score improvement, n of points	17.6 vs 7.6 *p*=0.048
SAQ treatment satisfaction, mean difference baseline/follow-up (±SD), n of points	2.9 (16.6) vs 2.9 (15.8) *p*=0.981
Total exercise duration improvement, n of seconds (%)	59 (13) vs 4 (1) *p*=0.07
WMSI improvement, %	14 vs 8 *p*=0.20
Safety (I vs C)	
Total SADEs, n	10 vs 24[c]
MI, n (%)	1 (2) vs 3 (6)[d]
Stable angina, n (%)	1 (2) vs 5 (10)
Crohn's disease flare, n (%)	1 (2) vs 0 (0)
Unstable angina, n (%)	1 (2) vs 4 (8)
Epigastric pain, n (%)	0 (0) vs 1 (2)
Atypical chest pain, n (%)	1 (2) vs 6 (12)

(*Continued*)

Table 2 (Continued).

Authors (Year)	Verheye et al[13] (2015)
Acute coronary syndrome, n (%)	0 (0) vs 2 (4)
Arrhythmia, n (%)	0 (0) vs 1 (2)
Multi-system failure/death, n (%)	0 (0) vs 1 (2)
Pulmonary edema, n (%)	0 (0) vs 1 (2)
COPD, n (%)	1 (2) vs 1 (2)
Cough, n (%)	0 (0) vs 1 (2)
Decompensated heart failure, n (%)	1 (2) vs 0 (0)
Gastrointestinal bleeding, n (%)	1 (2) vs 0 (0)
Injury, n (%)	1 (2) vs 0 (0)
Bleeding events associated with dual antiplatelet therapy	NA
ADEs (at least 1 AE in n of pts (%))	32[e] (64) vs 37[f] (69)

Notes: [a]Implantation failed in 2 pts owing to a venous valve in the coronary sinus that could not be crossed with the device; [b]Antianginal medications include beta-blockers, calcium-channel inhibitors, nitrates, nicorandil, ivabradine; [c]Occurred in the total of 17 pts. [d]Unclear as the extracted information comes from the running text, while the Table 5 in Appendix states that one case of MI occurred in IG as well as CG; [e]Out of 50 pts. Total of 76 AEs reported in IG; [f]Out of 54 pts. Total of 93 AEs reported in the control group.

Abbreviations: ADE, adverse device effect; AP, angina pectoris; C, control; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CG, control group; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CS, coronary sinus; ECG, electrocardiogram; hrs, hours; I, intervention; IG, intervention group; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mos, months; n, number; NA, not available; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; pts, patients; QoL, quality of life; SADE, serious adverse device effect; SAQ, Seattle Angina Questionnaire; SD, standard deviation; WMSI, Wall Motion Score Index; yr, year.

hypercholesterolemia, and intake of one or more antianginal medications.[13] Exclusion criteria were highly specific and are presented in detail in Tables 2, 3, and 4.

In the trials included in the assessment of safety, all patients belonged to CCS angina classes II–IV and had an LVEF of more than 25/30%. Inclusion criteria in all prospective observational studies were homogeneous with respect to the definition of severe refractory AP despite pharmacological therapy, ineligibility for CABG and/or PCI, and objective myocardial ischemia. Exclusion criteria were more heterogeneous, as three observational studies excluded patients with MI and CABG/PCI in less than 3 (to 7) months and patients with the presence of life-threatening arrhythmias, decompensated heart failure, and severe valvular heart disease.[16,17,19] While tricuspid valve replacement/repair was an exclusion criterion in two studies,[16,19] presence of a pacemaker lead was an exclusion criterion in four studies,[15,16,18,19] acute coronary syndrome in less than 3 months was an exclusion criterion in three studies,[14,15,18] and right atrial pressure of more than or equal to 15 mmHg was a criterion in all studies.[14–19]

Clinical Effectiveness

Data from the only controlled trial found (an RCT) served as the only source for reporting on clinical effectiveness outcomes and were reported at the 6-month follow-up.[13] No longer-term data were found and so no results on progression and/or recurrence are present. Concerning the outcome of mortality, one case of SADE of death was reported in the RCT. It occurred in the CG, while no cases of death occurred in the IG. Concerning morbidity, the outcome of CCS angina score improvement of at least two classes occurred in 35% of IG and 15% of CG patients (p=0.02). CCS angina score improvement by one class occurred in 71% of IG and 42% of CG patients (p=0.003), and the overall mean reduction of CCS class was 1.1 classes in the IG and 0.5 classes in the CG (p=0.001).

In terms of the effect of CSRS on the patient's body functions, two outcomes were considered relevant: Wall Motion Score Index (WMSI) improvement and total exercise duration improvement. While the WMSI improved by 14% in the IG and 8% in the CG (p=0.20), the total exercise duration improved by 59 seconds (13%) in the IG and by 4 seconds (1%) in the CG (p=0.07).

Disease-specific QoL was reported with respect to improvement in SAQ QoL score, and while IG patients improved by 17.6 points, CG patients improved by 7.6 points (p=0.048). Patient satisfaction was reported with respect to SAQ treatment satisfaction score, which improved by a mean of 2.9 points in both the IG and the CG. See Table 2 for further details.

Safety

Comparative Studies

In the only RCT,[13] 10 (19%) SADEs occurred in the IG as opposed to 24 (46%) in the CG, and no SADEs occurred with more frequency in the IG than the CG. Almost all cases of

Table 3 CSRS: Results from Observational Studies (Part 1)

Authors (Year)	**Banai et al[19] (2007)**	**Giannini et al[20] (2018)**	**Konigstein et al[16] (2014)**
Country	Germany, India, Israel	Italy, Israel, Belgium	Israel, Belgium
Sponsor	Neovasc Inc.	Neovasc Inc.	Neovasc Inc.
Study design	Multicenter, open-label, prospective, safety and feasibility, first-in-man case series	Multicenter, prospective[a], single-arm, non-blinded registry study	Multicenter, prospective case series
Conducted in	10/2004–07/2005	09/2010–04/2017	NA
Indication	Refractory AP despite standard medical therapy (pts with CAD, reversible ischemia, no candidates for revascularization)	Refractory AP despite standard medical therapy (pts with CAD, reversible ischemia, no candidates for revascularization)	Refractory AP despite standard medical therapy (pts with CAD, reversible ischemia, no candidates for revascularization)
Intervention	Coronary-sinus reducing stent (Reducer)	Coronary-sinus reducing stent (Reducer)	Coronary-sinus reducing stent (Reducer)
Comparator	None	None	None
Number of pts	15[b]	141	23[c]
Inclusion criteria	Symptomatic CAD, refractory angina – CCS class II–IV despite medical therapy, pts not eligible for CABG or PCI, reversible myocardial ischemia (determined by perfusion scan and/or by dobutamine ECG), LVEF ≥30%	Obstructive CAD, chronic disabling AP (CCS class II–IV) despite maximally tolerated medical therapy, pts not eligible for CABG or PCI, objective demonstration of ischemia with either treadmill/pharmacological stress test, myocardial stress scintigraphy, stress ECG, or MI, consent	Obstructive CAD, severe AP (CCS class II–IV) despite optimal medical therapy, objective evidence of myocardial ischemia and LVEF ≥25%, non-candidates for PCI, pre-screened pts passing the treadmill exercise test, echo dobutamine test, and radionuclide perfusion scan
Exclusion criteria	MI within 3 mos, PCI or CABG within 7 mos, severe arrhythmias, decompensated heart failure, severe valvular heart disease, pacemaker or other CS electrode, mean RAP ≥15 mmHg, pts who had undergone tricuspid valve replacement or repair	Ischemia related exclusively to right coronary artery, presence of a pacemaker lead in CS, acute coronary syndrome in <3 mos, coronary revascularization in <6 mos, mean right atrial pressure >15 mmHg	MI in <3 mos, PCI/CABG <3 mos, life-threatening rhythm disorders or those requiring ICD or pacemaker (or other CS electrode), decompensated heart failure, severe valvular heart disease, tricuspid valve replacement/repair pts, pts with mean RAP >15 mmHg
Primary outcome measure	Efficacy: NA Safety: Absence of procedure-related SAEs (death, MI, perforation of CS, CS occlusion), need for urgent dilation of the Reducer	Efficacy: Change in AP severity assessed by CCS and SAQ, Six-Minute Walk Test Safety: Successful delivery and deployment of the Reducer in the CS (assessed by angiogram and/or CT angiography), AEs and SAEs (death, MI, cardiac tamponade), clinically driven revision of an implanted device (eg due to embolization or suboptimal implantation position), life-threatening arrhythmias, respiratory failure needing invasive ventilation, access site complications, CS dissection	Efficacy: Change in AP severity assessed by CSS class Safety: NA

(*Continued*)

Table 3 (Continued).

Authors (Year)	Banai et al[19] (2007)	Giannini et al[20] (2018)	Konigstein et al[16] (2014)
Secondary outcome measure	Successful delivery and deployment of the Reducer in the CS (assessed by angiogram and/or CT angiography)	Exercise stress test, myocardial scintigraphy with technetium-99, dobutamine stress test, WMSI	NA
Baseline patient characteristics			
Mean age, yrs (±SD)	65 (range 50–80)	69.4 (10.7)	71.4 (9.8)
Sex, female:male, n	3:12	74:67	7:16
Previous MI, n (%)	4 (27)	76 (54)	19 (83)
Previous CABG, n (%)	3 (20)	107 (76)	17 (74)
Previous PCI, n (%)	6 (40)	116 (82)	Unclear[d]
Previous stroke, n (%)	NA	13 (9)	4 (17)[e]
Previous PAD, n (%)	NA	31 (22)	5 (22)
Previous pacemaker, n (%)	NA	13 (9)	NA
Hypercholesterolemia, n (%)	NA	NA	NA
Diabetes mellitus, n (%)	1 (7)	63 (45)	13 (56.5)
Hypertension, n (%)	10 (67)	118 (84)	18 (78)
Hyperlipidemia, n (%)	5 (33)	45 (32)[f]	20 (87)
Current/previous smoking, n (%)	NA	52 (37)	10 (43.5)
CSS angina class, n (%)			
Class II	1 (7)	19 (13)	NA
Class III	12 (80)	99 (70)	NA
Class IV	2 (13)	23 (16)	NA
LVEF, n (±SD)	NA	Mean 53.0 (8.7)	NA
No. of antianginal medications, n	NA	Mean 2.33±0.97[g]	NA
Follow-up, mos	6	6[h]	6
Loss to follow-up, n (%)	0	2 (1)[i]	3
Efficacy			
CCS angina score reduction of at least 2 classes at follow-up, n (%)	NA	63 (45)[j]	NA
CCS angina score reduction of at least 1 class at follow-up, n (%)	NA	113 (81)	NA
Reduction in CSS class, n (baseline/follow-up)	Average 1.43 (3.07/1.64) $p<0.0001$	Mean 1.42 (3.05±0.53/1.63±0.98) $p<0.001$	Mean 1.35[k] (3.35±0.6/2.0±1) $p<0.001$
SAQ QoL score improvement, n of points (baseline/follow-up)	NA	25.6l (26.6±16.5/52.2±19.9) $p<0.001$	NA
Exercise treadmill stress test, mean n of min, (baseline/follow-up)	NA	6:15±2.49/6:28±3.44[m] NA	3:16±1.48/5:16±1.14 $p=0.05$
WMSI improvement, %, (baseline/follow-up)			
At rest	NA	1.34±0.42/1.31±0.40 $p=0.662$	1.5±0.3/1.3±0.4 $p=0.34$
At stress	NA	1.46±0.40/1.46±0.28 $p=0.982$	1.9±0.4/1.4±0.4 $p=0.046$
ST-segment depression during exercise, n of mm (at mean heart rate beats/min) (baseline/follow-up)	2 (117)/1.22 (124) $p=0.047$	NA	NA
Antianginal medication intake, median n (baseline/follow-up)	NA	NA	NA

(*Continued*)

Table 3 (Continued).

Authors (Year)	Banai et al[19] (2007)	Giannini et al[20] (2018)	Konigstein et al[16] (2014)
Safety			
SADEs, n (%)	0 (0)	14 (10)	5 (22)
Death, n (%)	NA	14 (10)[n]	1 (4)[o]
MI, n (%)	NA	NA	NA
Stable angina, n (%)	NA	NA	4 (17)[p]
Crohn's disease flare, n (%)	NA	NA	NA
Unstable angina, n (%)	NA	NA	NA
Epigastric pain, n (%)	NA	NA	NA
Atypical chest pain, n (%)	NA	NA	NA
Acute coronary syndrome, n (%)	NA	NA	NA
Arrhythmia, n (%)	NA	NA	NA
Multi-system failure/death, n (%)	NA	NA	NA
Pulmonary edema,n (%)	NA	NA	NA
COPD, n (%)	NA	NA	NA
Cough, n (%)	NA	NA	NA
Decompensated heart failure, n (%)	NA	NA	NA
Gastrointestinal bleeding, n (%)	NA	NA	NA
Injury, n (%)	NA	NA	NA
CAD progression, n (%)	NA	NA	NA
Bleeding events associated with dual antiplatelet therapy, n (%)	NA	NA	NA
ADEs (at least 1 ADE in n of pts (%))	NA	64 (45)	NA[t]
Hospitalization, n (%)	NA	23 (17)[q]	NA
Coronary angiogram, n (%)	NA	26 (19)[r]	NA
Revascularization, n (%)	NA	15 (11)[s]	NA
Device migration, n (%)	NA	NA	NA

Notes: [a]In study limitations, it is stated that the present study is retrospective, while in the methods section, it is stated that the study is prospective; [b]QoL measure (CCS score) reported on 14/15 pts. ST-segment depression during exercise stress test reported in 9/15 pts; [c]Failure to implant CSRS in 2 pts owing to unsuitable CS anatomy, and 1 pt lost to follow-up; [d]Number of pts having undergone PCI us not stated. It is only stated that mean number of PCIs was 4.8±4.2; [e]Stroke or transient ischemic event; [f]Dyslipidemia; [g]Mean number of antianginal medications, including anti-ischemic and acetylsalicylic acid therapy; [h]Follow-up was performed either by telephone or at a face-to-face clinic visit; [i]Lost to follow-up due to failed CSRS implantation; [j]Of which 20 pts (14%) demonstrated reduction of 3 CCS classes; [k]Results on 20 pts; [l]Other SAQ score results were: physical limitation scores improved from 43.9±17.6 to 62.2±20.7 points (p<0.001); angina stability scores from 36.9±20.4 to 66.6±27.0 points (p<0.001); angina frequency scores from 45.6±22.1 to 66.7±20.8 points (p<0.001); treatment satisfaction scores from 51.9±22.0 to 68.4±17.6 points (p<0.001); [m]Results on 51 pts; [n]2 deaths due to fatal MI, 1 due to advanced heart failure, 1 due to refractory angina leading to anorexia and decubitus. The remaining 10 deaths are claimed not to be of cardiovascular origin; [o]1 pt died 1 year after the procedure. The implantation of CSRS was not successful in this pt and this pt died of heart failure; [p]It is unclear whether the angina was stable or unstable. 2 of these pts we treated by PCI, 1 by CABG, and 1 pharmacologically; [q]Due to recurrent angina; [r]7 pts underwent 2 angiograms, 1 pt 3, and another 5; [s]Further revascularizations due to de novo lesions; [t]No information is stated concerning AEs; however, based on results from the rest of the studies, it is assumed that AEs occurred, but were not reported.

Abbreviations: ADE, adverse device effect; AP, angina pectoris; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CMR, cardiac magnetic resonance; CS, coronary sinus; CSRS, coronary sinus reducing stent; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CS, coronary sinus; ECG, electrocardiogram; hrs, hours; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mos, months; MRI, magnetic resonance imaging; n, number; NA, not available; p, p-value; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; pts, patients; QoL, quality of life; RAP, right atrial pressure; SADE, serious adverse device effect; SAQ, Seattle Angina Questionnaire; SD, standard deviation; TAVR, transcatheter aortic valve replacement; WMSI, Wall Motion Score Index; yr, year.

SADEs occurred in no more than two patients in the IG or CG, with the exception of the following: atypical chest pain (IG=1, CG=6), unstable angina (IG=1, CG=4), and stable angina (IG=1, CG=5). With respect to ADEs, they were reported in 32 patients (64%) in the IG and 37 (69%) in the CG.

Prospective Observational Non-Comparative Studies

All of the observational evidence reported SADEs and ADEs at 4–6 months of follow-up, except for one study with the longest follow-up (which reported results at 24 months).[15] This was also the study with the highest number of SADEs (30%).

While two observational studies reported no SADEs,[14,19] the remaining four studies reported 14 (10%), five (22%), six (13%), and 15 patients (30%) suffering from SADEs, respectively.[15–18] The SADE of death occurred in 14 patients (10%),[18] in one patient (4%),[16] in three patients (6%),[17] and in five patients (10%).[15] MI occurred in one study[15] in three

Table 4 CSRS: Results from Observational Studies (Part 2)

Authors (Year)	Konigstein et al[17] (2018)	Ponticelli et al[15] (2019)	Tzanis et al[14] (2019)
Country	Israel	Italy	Italy
Sponsor	Neovasc Inc.	Neovasc Inc.	Neovasc Inc.
Study design	Single-center, open-label, prospective registry	Single-center, prospective case series	Single-center, prospective case series
Conducted in	08/2011–11/2017	03/2015–08/2016	NA
Indication	Refractory AP despite standard medical therapy (pts with CAD, reversible ischemia, no candidates for revascularization)	Refractory AP despite standard medical therapy (pts with CAD, reversible ischemia, no candidates for revascularization)	Refractory AP despite standard medical therapy
Intervention	Coronary-sinus reducing stent (Reducer)	Coronary-sinus reducing stent (Reducer)	Coronary-sinus reducing stent (Reducer)
Comparator	None	None	None
Number of pts	48[a]	50	19
Inclusion criteria	Severe AP (CCS class III or IV) despite optimal medical therapy, objective evidence of myocardial ischemia of left coronary arteries territory by perfusion scan and/or by dobutamine ECG, LVEF ≥30%, non-candidates for surgical PCI	Severe AP (CCS class II–IV) despite optimal medical therapy, objective evidence of myocardial ischemia of left coronary arteries territory by perfusion scan and/or by dobutamine ECG or stress perfusion cardiac MRI, CAD not amenable to PCI/CABG due to unsuitable coronary anatomy, diffuse disease, or absence of satisfactory distal graft anastomosis sites[b]	Severe AP (CCS class II–IV) despite optimal medical therapy, objective evidence of inducible myocardial ischemia involving at least one myocardial segment at dipyridamole stress cardiac MRI, coronary artery disease not amenable to further revascularization with PCI/CABG
Exclusion criteria	MI, PCI, CABG in <3 mos, life-threatening rhythm disorders, decompensated heart failure, severe valvular heart disease, LVEF <30% who may require CRT, mean RAP >15 mmHg	Ischemia related exclusively to right coronary artery, presence of a foreign body in the CS (eg a left ventricular pacemaker wire for cardiac resynchronization therapy), acute coronary syndrome in <3 mos, coronary revascularization in <6 mos, mean RAP >15 mmHg	Acute coronary syndrome in <3 mos, coronary revascularization in <6 months, mean RAP >15 mmHg and CMR or dipyridamole contraindications
Primary outcome measure	Efficacy: Change in AP severity assessed by CSS class, SAQ, treadmill stress test, echo dobutamine Safety: NA	Efficacy: Change in AP severity assessed by CSS class, SAQ, improvement in exercise tolerance assessed using the Six-Minute Walk Test, and reduction in pharmacological antianginal therapy Safety: procedural success and absence of device-related AEs	Efficacy: CCS class improvement, Six-Minute Walk Test, and reduction in pharmacological antianginal therapy Safety: SAEs and AEs
Secondary outcome measure	NA	NA	NA

(*Continued*)

Table 4 (Continued).

Authors (Year)	Konigstein et al[17] (2018)	Ponticelli et al[15] (2019)	Tzanis et al[14] (2019)
Baseline patient characteristics			
Mean age, yrs (±SD)	66.8 (8.9)	68 (9)	66 (IQR 56–77)
Sex, female:male, n	8:40	9:41	1:18
Previous MI, n (%)	25 (52)	33 (66)[c]	18 (95)
Previous CABG, n (%)	39 (81)	28 (56)[d]	11 (58)
Previous PCI, n (%)	48 (100)	38 (76)	NA
Previous stroke, n (%)	7 (14.5)	NA	NA
Previous PAD, n (%)	10 (21)	NA	NA
Previous pacemaker, n (%)	NA	NA	NA
Hypercholesterolemia, n (%)	48 (100)	NA	NA
Diabetes mellitus, n (%)	31 (64)	22 (44)	NA
Hypertension, n (%)	41 (85)	43 (86)	NA
Hyperlipidemia, n (%)	NA	45 (90)[e]	NA
Current/previous smoking, n (%)	27 (56)	32 (64)	NA
CSS angina class, n (%)			
Class II	1 (2)	7 (14)	NA[f]
Class III	19 (49)	36 (72)	NA
Class IV	19 (49)	7 (14)	NA
LVEF, n (±SD)	NA	Mean 52 (11)	Median 61 (IQR 47–71)
No. of antianginal medications, n	NA[g]	Median 3 (range 1–5)[h]	Median 3 (range 1–5)[i]
Follow-up, mos	6	24	4
Loss to follow-up, n (%)	3[j]	8[k]	0
Efficacy			
CCS angina score reduction of at least 2 classes at follow-up, n (%)	19 (40)	NA	7 (37)
CCS angina score reduction of at least 1 class at follow-up, n (%)	33 (69)	NA	16 (84)
Reduction in CSS class, n (baseline/follow-up)	Mean 1.4[l] (3.4±0.5/2.0±1) $p<0.001$	Mean 1.26 (1.74±0.86/3.0±0.51) $p<0.001$	Median 2 (3 IQR 3–3/1 (IQR 1–2)
SAQ QoL score improvement, n of points (baseline/follow-up)	23.9[m] (23.2±17.5/47.1±26.0) $p<0.001$	(58.76±18.08/25.67±12.35)	NA
Exercise treadmill stress test, mean n of min (baseline/follow-up)	3:43±1:30/4:35±2:18 $p=0.025$	NA	300 (IQR 240–382)/420 (IQR 353–515)[n] $p=0.002$
WMSI improvement, % (baseline/follow-up)			
At rest	1.46±0.42/1.43±0.44 $p=0.89$	NA	NA
At stress	1.58±0.37/1.37±0.36 $p=0.004$	NA	NA
ST-segment depression during exercise, n of mm (at mean heart rate beats/min) (baseline/follow-up)	299.9±97.9/352.9±75.3 $p=0.002$	NA	NA
Antianginal medication intake, median n (baseline/follow-up)	NA	3 (IQR 2–4)/3 (IQR 2–4) $p=0.101$	3 (IQR 2–3)/3 (IQR 2–3) $p=0.296$

(*Continued*)

Table 4 (Continued).

Authors (Year)	Konigstein et al[17] (2018)	Ponticelli et al[15] (2019)	Tzanis et al[14] (2019)
Safety			
SADEs, n (%)	6 (13)	15 (30)	0
Death, n (%)	3 (6)[o]	5 (10)[p]	NA
MI, n (%)	NA	3 (6)	NA
Stable angina, n (%)	2 (4)	NA	NA
Crohn's disease flare, n (%)	NA	NA	NA
Unstable angina, n (%)	1 (2)	NA	NA
Epigastric pain, n (%)	NA	NA	NA
Atypical chest pain, n (%)	NA	NA	NA
Acute coronary syndrome, n (%)	NA	NA	NA
Arrhythmia, n (%)	NA	NA	NA
Multi-system failure/death, n (%)	NA	NA	NA
Pulmonary edema,n (%)	NA	NA	NA
COPD, n (%)	NA	NA	NA
Cough, n (%)	NA	NA	NA
Decompensated heart failure, n (%)	NA	NA	NA
Gastrointestinal bleeding, n (%)	NA	NA	NA
Injury, n (%)	NA	NA	NA
CAD progression, n (%)	NA	7 (14)	NA
Bleeding events associated with dual antiplatelet therapy, n (%)	NA	NA	NA
ADEs (at least 1 ADE in n of pts (%))	4 (8)	13 (26)	0
Hospitalization, n (%)	NA	NA	NA
Coronary angiogram, n (%)	NA	13 (26)[q]	NA
Revascularization, n (%)	3 (6)	NA	0
Device migration, n (%)	1 (2)	NA	0[r]

Notes: [a]Failure to implant CSRS in 2 pts owing to unsuitable CS anatomy; [b]Inclusion and exclusion criteria come from the 12-mo publication from Giannini et al (2018);[17] [c]All baseline criteria reported from the 12-mo publication from Giannini et al (2018);[17] [d]CABG and PCI one; [e]Dyslipidemia reported; [f]Baseline information only on pooled CSS class: 3 (IQR 3–3); [g]Antianginal medications include beta-blockers, calcium-channel blockers, ACE/ARB inhibitors, nitrates, diuretics, aspirin, clopidogrel, warfarin, statins, ivabradine; [h]Antianginal medications include beta-blockers, calcium-channel antagonists, long-acting nitrates, ivabradine, ranolazine; [i]Antianginal medications include beta-blockers, calcium-channel antagonists, nitrates, ranolazine, ivabradine, aspirin, clopidogrel; [j]3 lost to follow-up and 4 other pts not yet completed the 6-mo evaluation and hence not part of the analysis; [k]5 pts died and 3 were not reachable by telephone calls or emails; [l]Results on 39 pts; [m]Results on 23 pts; [n]Results on Six-Minute Walk Test; [o]None is claimed to be related to CSRS. 1 death due to gradual general physical deterioration, 1 sudden death without explanation for its cause, and 1 patient diagnosed with severe aortic stenosis underwent TAVR and died after the procedure; [p]2 pts died during the first 12 mos due to an ischemic stroke and a urological malignancy, and 3 pts died because of out-of-hospital cardiac arrest, pulmonary malignancy, and nosocomial infection during a hospitalization for heart failure; [q]Angiography; [r]Results on device embolization.

Abbreviations: ADE, adverse device effect; AP, angina pectoris; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CS, coronary sinus; CSRS, coronary sinus reducing stent; ECG, electrocardiogram; hrs, hours; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mos, months; MRI, magnetic resonance imaging; n, number; NA, not available; *p*, *p*-value; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; pts, patients; QoL, quality of life; RAP, right atrial pressure; SADE, serious adverse device effect; SAQ, Seattle Angina Questionnaire; SD, standard deviation; TAVR, transcatheter aortic valve replacement; WMSI, Wall Motion Score Index; yr, year.

patients (6%), and stable angina in two studies[16,17] in four (17%) and two patients (4%), respectively. Coronary artery disease (CAD) progression further occurred in seven patients (14%)[15] and unstable angina in one patient (2%).[17] With respect to ADEs, those reported were hospitalization, coronary angiogram, revascularization, and device migration. They were not reported in two studies[16,19] and were reported to be none in another study.[14] Furthermore, they were reported to occur in 64 patients (45%),[18] four patients (8%),[17] and 13 patients (26%).[15] See Tables 2, 3, and 4 for further details.

RoB and Quality of Evidence

The RoB of the RCT was rated to be low, the RoB of observational studies was rated to range from low[14,15,17,19] to moderate[16,18] (Tables 5 and 6), and the strength of evidence assessed by GRADE was rated moderate (Table 7).

Table 5 Risk of Bias – Study Level (RCT)[5]

Trial	Adequate Generation of Randomization Sequence	Adequate Allocation Concealment	Blinding		Selective Outcome Reporting Unlikely	No Other Aspects Which Increase the Risk of Bias	Risk of Bias – Study Level
			Patient	Treating Physician			
COSIRA[13]	Yes	Yes	Yes	No	No	Yes	Low

Discussion

For the analysis of clinical effectiveness, one RCT with 104 patients was included,[13] indicating a statistically significant improvement in two crucial outcomes (CCS angina score improvement by one/two classes and SAQ QoL score). The third crucial outcome (SAQ treatment satisfaction) did not improve in a statistically significant way (p=0.981), neither did the more objective outcomes (total exercise duration or WMSI). For the analysis of safety, additional six prospective observational studies with 296 patients were included as well. In total, 348 patients received the CSRS therapy. Based on the RCT data, there were fewer SADEs associated with CSRS compared to the CG and the only case of death occurred in the CG. With respect to observational evidence, there remains a point of concern as the SADEs range from none[14,19] to 30%[15] (with the highest number of SADEs occurring in the study with the longest follow-up). Furthermore, 8% of patients from observational studies died, while 5% of deaths were explicitly claimed not to be related to the CSRS.[15–18]

In our systematic search, we found only one other HTA on the CSRS therapy, which, however, included both prospective and retrospective evidence and arrived at a positive conclusion toward the CSRS therapy.[7] Our HTA is solely based on prospective evidence and our conclusion is more reserved. Also, even though CSRS therapy seems to be a promising treatment for refractory AP patients (with respect to two crucial outcomes and a relatively positive safety profile), the internal and external validity of the studies in the present evidence base is uncertain.

Internal Validity

Regardless of the relatively positive assessment of the evidence quality (low to moderate RoB and moderate strength of evidence), the following issues need to be considered when interpreting the findings on both clinical effectiveness and safety.

Clinical Effectiveness

When interpreting the clinical effectiveness findings, issues with inappropriate inclusion criteria, mechanism of action, placebo effect, sample size, and the randomization procedure should be considered.

First, the main point of concern is the discrepancy between the inclusion criteria in all the studies included in the analysis and the definition of refractory AP (as defined by the ESC[5]). The ESC defines refractory AP as long-lasting symptoms (for ≥3 months) due to established reversible ischemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting, including PCI of chronic total coronary occlusion.[5] Contrary to the definition, none of the studies included patients with symptoms lasting for more or equal to 3 months and, furthermore, while three studies did not report on previous pharmacological therapy,[16,17,19] patients with one to five courses of pharmacological treatment were included in two studies,[14,15] 1.34–3.3 courses in one study,[18] and in the RCT, 25% of patients had zero or one course of medication and 31% had at least three courses.[13]

Second, there is a lack of clarity behind the mechanism of action of the CSRS. The main hypothesis is that the CSRS alleviates symptoms by improving perfusion in ischemic myocardial territories, but no study has evaluated the effect of the CSRS on myocardial perfusion to demonstrate its mechanism of action.[20] One of the potential issues is related to the claimed beneficial hemodynamic changes, which are at odds with one of the principles of use of intermittent and pressure-controlled increase in coronary sinus pressure – a release of obstruction[22] resulting in rapid reduction of coronary sinus pressure after the prolongedplateau phase, which may induce a sort of aspirating effect on fluids and toxic metabolites that have accumulated in the ischemic segment.[23] It is further known that coronary sinus flow at rest and hyperemic states are in agreement with myocardial blood flow values, and reduced coronary flow reserve measured at the coronary sinus level may have an association with adverse outcome.[24]

Table 6 Risk of Bias – Study Level (Case Series)[21]

(Year)Authors	Banai et al (2007)[19]	Giannini et al (2018)[20]	Konigstein et al (2014)[16]	Konigstein et al (2018)[17]	Ponticelli et al (2019)[15]	Tzanis et al (2019)[14]
Study objective						
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	No	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	Yes	Unclear[a]	Unclear[b]	Yes	Yes	Yes
3. Were the cases collected in more than one center?	Yes	Yes	Yes	No	No	No
4. Were patients recruited consecutively?	No	Yes	No	Yes	Yes	No
Study population						
5. Were the characteristics of the participants included in the study described?	Yes	Yes	Yes[c]	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
7. Did participants enter the study at similar point in the disease?	Yes	Yes	Yes	Yes	Yes	Unclear[d]
Intervention and co-intervention						
8. Was the intervention clearly described?	Yes	Partial[e]	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measure						
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial[f]	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No[g]	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes
Statistical analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Results and conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Unclear[h]
16. Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	Yes	Yes	Yes	Yes	Yes
18. Were adverse events reported?	Partial[i]	Yes	Partial[i]	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	No[j]	Yes	No[j]	No[j]	No[j]

(*Continued*)

Table 6 (Continued).

(Year)Authors	Banai et al (2007)[19]	Giannini et al (2018)[20]	Konigstein et al (2014)[16]	Konigstein et al (2018)[17]	Ponticelli et al (2019)[15]	Tzanis et al (2019)[14]
Competing interest and source of support						
20. Were both competing interest and source of support for the study reported?	Partial[k]	Partial[k]	Partial[k]	Partial[k]	Partial[k]	Partial[k]
Overall risk of bias	Low	Moderate	Moderate	Low	Low	Low

Notes: [a]While it is stated in the methods that this study was conducted prospectively, the limitations section states that it was retrospective; [b]It is assumed that the study was conducted prospectively; however, it is unclear at times as some baseline data are missing; [c]However, baseline CCS score was not described; [d]Insufficient baseline information provided; [e]The process of CSRS implantation was not clearly described; [f]Only efficacy measure was clearly established; [g]The two cardiologists performing the intervention were not blinded to therapy, but outcome assessment (of treadmill test and ECG) was conducted by technicians and cardiologists blinded to the time point of the test, in relation to treatment; [h]The length of follow-up was shorter – compared to the rest of the prospective studies – and so it is unclear whether further SAEs/AEs would show up at longer follow-up; [i]It was reported that no SAEs occurred in the study population, yet AEs are not reported (and most presumably occurred); [j]The study design cannot meet the conclusions about effectiveness; [k]The source of financial support is not clearly stated in the publication.

Moreover, it is unclear why there remains a 15–30% rate of non-responders.[25] One assumption is that the lack of endothelialization may be at stake, ie that the surface of the device may not be completely covered by endothelium (the vein's inner lining) and thus may not create the pressure gradient.[26] Another assumption is that anatomic variants of the cardiac venous system of individual patients may lead to insufficient pressure gradient across the device.[25]

Third, there is an echoing concern in the academic literature over the potential large placebo effect associated with novel therapies in this specific patient group.[5,20,27] It is further highlighted that such a placebo effect may not result in steady long-term benefit[20] and the short-term follow-up (6 months) of the only RCT[13] does not prove otherwise.

Fourth, the clinical benefit caused by the CSRS may be overstated as the sample size in the RCT is not big enough to reject a true null hypothesis.[28]

Fifth, there is a concern in the literature over the randomization process in the RCT.[13] It was highlighted that intravenous heparin was used only in IG patients and hence post-procedural laboratory testing may have revealed to the patients who belonged to the IG and who to the CG.[28]

Safety

With regard to interpreting safety findings, underreporting of complications, obstruction of future therapy, and further potential SADEs need to be considered.

First, dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is recommended for 6 months after the implantation of a CSRS.[27] The complications related to DAPT are, however, not reported in the studies, even though they should be considered along with CSRS complications. While only two studies reported the use of DAPT,[13,18] no studies reported on the SADE of bleeding events associated with DAPT.

Second, because heart failure may eventually develop in a large proportion of refractory AP patients, there is a concern that the CSRS may preclude the future use of the coronary sinus for implantation of the left ventricular pacing lead necessary for cardiac resynchronization therapy (CRT) (the established heart failure therapy).[28]

Third, potential SADEs related to individual anatomic considerations during implantation should be taken into account. The potential SADEs are related to the close proximity of the circumflex coronary artery, which may provoke an acute MI (if damaged), and the presence of a Thebesian valve or a valve of Vieussens, which could hamper device implantation in up to 85% of patients.[29]

External Validity

In terms of external validity, the data are considered not to be generalizable to other contexts as the CSRS patient population did not actually include refractory AP patients. Application of the highly specific inclusion and exclusion criteria in the real-world context also remains in question. Hence, in the light of the small population size and the selective sample of included patients, the conclusions about effectiveness and safety are considered inflated.

Limitations of Evidence

Owing to the limitations concerning the internal as well as external validity of the evidence base, it remains a question to what extent the RCT identified by our systematic literature

Table 7 Evidence Profile: Efficacy and Safety of CSRS in Patients with Angina Pectoris

Quality Assessment							Summary of Findings				
							Number of Patients		Effect		Quality
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Impression	Other Considerations	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)	
CCS angina score improvement of at least 2 classes at 6-mo follow-up, %											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	–	52	52	–	20% more in IG than CG pts	⊕⊕⊕◯ moderate
SAQ QoL score improvement at 6-mo follow-up, n of points											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	–	52	52	–	10 points more in IG than CG pts	⊕⊕⊕◯ moderate
Total exercise duration improvement at 6-mo follow-up, n of seconds											
1	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	–	52	52	–	55 sec more in IG than CG pts	⊕⊕⊕◯ moderate
SADEs at 6-mo follow-up, n of events											
6	Randomized trial and case series	Serious[b,c]	Not serious	Not serious	Not serious	–	348	52	–	8% fewer in IG than CG	⊕⊕⊕◯ moderate

Notes: [a]Optimal information size is not met and the sample size is small; [b]Source of financial support is unclear; [c]One case series study unclear whether retrospective. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CCS, Canadian Cardiovascular Society; CG, control group; CI, confidence interval; CSRS, coronary sinus reducing stent; IG, intervention group; mo, month; n, number; QoL, quality of life; SADE, serious adverse device effect; SAQ, Seattle Angina Questionnaire; sec, seconds.

search is relevant for excluding placebo effects. Moreover, this result is further undermined by the large placebo effect associated with novel therapies in this specific patient population.[5] Better powered RCTs with longer follow-up are needed for the sake of defining the role of treatment modalities for specific subgroups, for decreasing non-responder rates, and for ascertaining benefits beyond placebo effects.[5]

Socio-Economic and Ethical Considerations

When taking into consideration socio-economic and ethical aspects of the CSRS, the effects have to be reflected against the backdrop of principles of distributive justice, beneficence, non-maleficence, autonomy, and uncertainty. On the one hand, the CSRS is claimed to reduce healthcare spending as it decreased healthcare resource use and related costs in a 1-year timeframe under a spectrum of cost-effectiveness thresholds.[30] Moreover, the CSRS targets a patient population where there is a therapeutic gap[5] and so, if proven to be effective, the CSRS may secure the principles of medical beneficence and patient autonomy.

On the other hand, though, there is a lack of clarity behind the mechanism of action and there are no long-term data.[20] There are further concerns of additional SADEs highlighted above that can, for instance, impede the use of CRT for future heart failure patients.[28] For that reason, as stated above, to prevent breaching the principle of non-maleficence, better powered controlled trials are required. At this point in time, there is no larger RCT in the pipeline. The only RCT that is currently recruiting includes 40 patients and aims to measure the impact of the CSRS on exertional capacity measured by maximal oxygen consumption (VO_2) during cardiopulmonary exercise testing; it aims to be completed by December 2021 (NCT04121845). Important to note is that there is an ongoing ISCHEMIA trial (NCT01471522) that may potentially determine the best management strategy for higher-risk patients with stable ischemic heart disease, and may change the guideline for refractory AP patients considerably.

Conclusion

It is not clear whether the CSRS can improve CCS angina score and QoL without causing more SADEs than the sham intervention (based on moderate quality of evidence). This is because of inconsistent results, incomplete safety data with regard to DAPT, inappropriate inclusion criteria in the studies, insufficient sample size, and incomplete blinding in the RCT. The potential of the CSRS to fulfill the therapeutic gap ought to be considered against the backdrop of its unclear mechanism of action, the lack of a long-term safety profile, and additional potential SADEs. Furthermore, the cost-effectiveness of the CSRS can only be established once the effectiveness of CSRS is established. In that respect, owing to the inconsistencies with internal and external validity of the evidence base, even the conclusions about placebo effects cannot be taken for granted.

Disclosure

Piotr Szymanski reports personal fees from Abbott Laboratories as a speaker, not related to coronary stenting. The authors report no other conflicts of interest in this work.

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