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Percutaneous Transvascular Implantation of a Coronary Sinus Reducing Stent

Update 2022
Systematic Review

AIHTA Decision Support Document: 121/1. Update 2022 | ISSN-online: 1998-0469

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Update 2022
Systematic Review

Vienna, March 2022

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This report should be referenced as follows:

Erdos J. Percutaneous Transvascular Implantation of a Coronary Sinus Reducing Stent. AIHTA Decision Support Documents No. 121 Update 1; 2022. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

IMPRINT

Publisher:

HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:

Priv.-Doz. Dr. phil. Claudia Wild, managing director

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AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 121 Update 1

ISSN online 1998-0469

Content

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List of abbreviations

ADE.....Adverse device effect
AE .....adverse events
AP .....Angina pectoris
CABG .....Coronary-artery bypass grafting
CAD .....Coronary artery disease
CCS .....Canadian Cardiovascular Society
CHF .....congestive heart failure
COPD .....chronic obstructive pulmonary disease
CRT .....cardiac resynchronization therapy
CS.....coronary sinus
CSRS .....coronary sinus reducing stent
DAPT .....dual antiplatelet therapy
ESC .....European Society of Cardiology
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
ICTRP.....International Clinical Trials Registry Platform
IHE .....Institute of Health Economics
MI.....myocardial infarction
MRI.....magnetic resonance imaging
NRCT .....non-randomised controlled trial
LVEF .....left ventricular ejection fraction
PAD .....peripheral artery disease
PCI .....percutaneous coronary intervention
QoL.....Quality of life
RAP .....right atrial pressure
RCT .....randomised controlled trial
RoB .....risk of bias
SADE.....serious adverse device effect
SAQ .....Seattle Angina Questionnaire
TAVR..... transcatheter aortic valve replacement
WMSI .....wall motion score index

Executive Summary

Introduction

Health Problem

Refractory angina pectoris (AP) is the health problem at stake in the current assessment. As defined by the European Society of Cardiology (ESC), refractory AP refers to long-lasting symptoms (for ≥3 months) due to established reversible ischemia in the presence of obstructive coronary artery disease (CAD), which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting including percutaneous coronary intervention (PCI) of chronic total coronary occlusion.

indication: refractory AP

Description of Technology

Coronary sinus reducing stent (CSRS) is designed to create a focal narrowing in the lumen of the coronary sinus. The mechanism of action of CSRS is unclear, yet the prevailing hypothesis assumes that CSRS functions as a reverse angioplasty. While in angioplasty, a narrowing on the inflow is being treated, in CSRS, a narrowing on the outflow is being created. This outflow narrowing is intended to improve perfusion to ischaemic territories of the myocardium and hence, it is only at the point when CSRS is covered by tissue ingrowth that the narrowing occurs and the claimed benefit may occur.

technology: CSRS

The CSRS device (Neovasc Reducer™ System) received CE mark authorization in 2011 for the treatment of refractory AP. In January 2020, Neovasc Inc. submitted premarket approval application to the US Food and Drug Administration (FDA), which was declined in 2020 October due to insufficient evidence. The company is conducting a randomized controlled trial (RCT) to secure the approval at a later date.

Neovasc Reducer™ has a CE mark; FDA approval is pending

Methods

The systematic literature search was conducted in December 2021 in four databases. As this is an update of the 2020 Assessment Report, the search considered publications starting from November 2019.

update search

Results

Available evidence

For the analysis of effectiveness no new studies could be identified in the update search. Therefore, the effectiveness results and conclusions rely solely on the evidence presented in the 2020 Assessment Report, which included one RCT comparing CSRS with a sham procedure (study name COSIRA, NCT01205893) with 104 patients (of which 52 received the CSRS treatment) and a follow-up of six months. For the assessment of safety, seven studies were included in the 2020 Assessment Report: one RCT, and six prospective single-arm studies. In the update search three prospective single-arm studies met the inclusion criteria and were included in the present analysis, making up in total nine observational single-arm studies included for the safety analysis besides the RCT.

evidence from 2020 Assessment Report: 1 RCT, 6 single-arm studies,
update report: 3 single-arm studies

Clinical effectiveness

no new evidence for effectiveness, 1 RCT from the 2020 Assessment Report

In the RCT a statistically significant difference in favour of CSRS was shown for:

endpoints with stat. significant difference

- Canadian Cardiovascular Society (CCS) angina score improvement of at least two classes at six months follow-up (35% of the CSRS group and 15% of the sham group (p=0.02));
- CCS angina score improvement by one class (71% of the CSRS group and 42% of the sham group (p=0.003));
- overall mean reduction of CCS class (1.1 classes in the CSRS group and 0.5 classes in the sham group (p=0.001)); and
- Seattle Angina Questionnaire (SAQ) QoL score improvement (in the CSRS group by 17.6 points and in the sham group by 7.6 points (p=0.048)).

The quality of the evidence was moderate for clinical efficacy for all endpoints, mainly due to the small patient number in the included evidence base.

Safety

lower rate of SADEs in the CSRS group than in sham (19% vs. 46%); SADEs in observational studies: death, MI, CAD progression, stroke

Concerning safety, the RCT data indicate that there were less serious adverse device events (SADEs) in the CSRS group (19%) than in sham group (46%). SADEs were reported in all observational studies and they remain to be a point of concern as they range from 0% to 30%. The most frequently reported SADEs were death, myocardial infarction (MI), CAD progression and stroke. In the RCT, the only case of death occurred in the sham group. 65 patients in the observational studies died (range: 4% - 15.1%), while 24 of these were explicitly stated to be of cardiovascular origin (range: 2.6% - 10%).

The strength of evidence of the safety outcomes was rated to be very low (for mortality, MI, CAD progression, stroke, stable and unstable angina) to moderate (for SADEs).

Upcoming evidence

5 ongoing trials

Five studies are currently ongoing, of which three are controlled trials, which have the potential to change the evidence base. Based on the clinicaltrials.gov trial registration information, these trials have an estimated primary completion date in two to three years.

Reimbursement

currently not reimbursed

The intervention is currently not reimbursed in Austria.

Discussion

conclusions of the 2020 Assessment Report remain unchanged

In the absence of new comparative evidence, the conclusion about the effectiveness and safety of CSRS of the 2020 Assessment Report remains unchanged. However, due to some internal validity issues and the small size of a selective sample of patients included in the evidence base, the conclusions about effectiveness and the positive safety profile are considered to be inflated. Results from well-designed, sufficiently large randomized controlled trials are lacking to clarify the role of CSRS in clinical practice. The potential for CSRS to fulfil the therapeutic gap needs to be further put in the context of the paucity of knowledge about its mechanism of action, further potential SADEs, and the lacking long-term safety profile.

RCT data needed from ongoing trials

Conclusion

inclusion not recommended

The current evidence suggests that the assessed technology, CSRS is potentially more effective than sham intervention for refractory AP patients (in terms of CCS and SAQ QoL scores) who have no other alternative interventions available. However, the lacking internal validity of the included study undermines the partially positive results. In terms of safety, the wide variation in SADEs remain to be a point of concern. The inclusion in the catalogue of benefits is currently not recommended.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Indikation: refraktäre AP

Bei dem im vorliegenden Assessment thematisierten Gesundheitsproblem handelt es sich um die refraktäre Angina pectoris (AP). Laut der Europäischen Gesellschaft für Kardiologie (European Society of Cardiology, ESC) definiert sich die AP auf Basis lang andauernder Symptome (≥3 Monate), die durch eine bestehende reversible Ischämie bei Vorliegen einer obstruktiven koronaren Herzkrankheit (KHK) hervorgerufen werden und nicht durch eine medikamentöse Therapie mit Zweit- und Drittlinien-Medikamenten, Bypassoperationen oder Stentimplantation (inklusive perkutaner Koronarintervention bei chronischem vollständigem Koronararterienverschluss) unter Kontrolle gebracht werden können.

Beschreibung der Technologie

Technologie: CSRS

Der Koronarsinus-Reducer (Coronary sinus reducing stent, CSRS) soll eine fokale Verengung im Lumen des Koronarsinus erzeugen. Der Wirkmechanismus des CSRS ist noch unklar, allerdings nimmt die gängige Hypothese an, dass der CSRS wie eine umgekehrte Angioplastie funktioniert: Der CSRS schafft eine Engstelle im Bereich des Blutabflusses. Sobald der Stent mit dem Gewebe verwachsen ist, soll so die Perfusion der ischämischen Bereiche des Myokards gesteigert werden. D.h. während bei der Angioplastie eine Verengung am Zufluss behandelt wird, wird beim CSRS eine Verengung am Abfluss geschaffen. Diese Ausflussverengung soll die Perfusion ischämischer Myokardgebiete verbessern, und daher tritt die Verengung erst dann auf, wenn das CSRS durch das Einwachsen von Gewebe abgedeckt ist und der behauptete Nutzen eintreten kann.

CE-Kennzeichnung seit 2011: ausstehende FDA Zulassung

Der CSRS (Neovasc Reducer™ System) erhielt 2011 eine CE-Kennzeichnung für die Behandlung der refraktären AP. Im Januar 2020 wurde von Neovasc Inc. ein Zulassungsantrag an die US-amerikanische Food and Drug Administration (FDA) gestellt, welcher jedoch aufgrund unzureichender Evidenz abgelehnt wurde. Das Unternehmen führt nun eine randomisierte kontrollierte Studie (RCT) durch, um die Zulassung zu einem späteren Zeitpunkt zu erhalten.

Methoden

Update-Suche

Die systematische Literaturrecherche wurde im Dezember 2021 in vier Datenbanken durchgeführt. Da es sich um ein Update des Reviews aus 2020 handelt, wurden bei der Suche Publikationen ab November 2019 berücksichtigt.

Ergebnisse

Verfügbare Evidenz

Evidenz aus 2020 Review: 1 RCT, 6 Beobachtungsstudien

Update: 3 zusätzliche Beobachtungsstudien

Für die Wirksamkeitsanalyse konnten in der Update-Suche keine neuen Studien identifiziert werden.

Die Evidenz zur vergleichenden Wirksamkeit besteht daher aus einem RCT (n=104), welches im ursprünglichen Assessment eingeschlossen wurde. In dieser Studie wurde CSRS mit einem Scheinverfahren verglichen (Studienname COSIRA, NCT01205893) und die Patient*innen wurden sechs Monate nachbeobachtet. Für die Bewertung der Sicherheit wurden drei prospektive einarmige Studien im Zuge der Update-Suche neu identifiziert. Die derzeitig verfügbare Evidenz zur Sicherheit des CSRS besteht damit aus der COSIRA Studie und weiteren neun Beobachtungsstudien.

Die Qualität der Evidenz - die klinische Wirksamkeit betreffend – gestaltete sich moderat für alle Endpunkte, was vor allem auf die kleine Patient*innenanzahl zurückzuführen ist.

Klinische Wirksamkeit

keine neue Evidenz, 1 RCT aus dem 2020 Review

Endpunkte mit statistisch signifikantem Unterschied

Bezüglich der klinischen Wirksamkeit zeigten die Ergebnisse des RCT einen statistisch signifikanten Unterschied zwischen dem CSRS und der Scheinverfahren in den folgenden Endpunkten:

- eine Steigerung des CCS Angina Score von mindestens zwei Klassen nach sechs Monaten (35 % der CSRS Patient*innen verglichen mit 15 % der Patient*innen der Scheinprozedur (p=0,02)),
- eine Steigerung des CCS Angina Score um eine Klasse (71 % der CSRS Patient*innen und 42 % der Patient*innen der Scheinprozedur (p=0,003)),
- eine gesamte mittlere Reduktion der CCS Klasse (1,1 Klassen in der CSRS Patient*innen und 0,5 Klassen in Patient*innen der Scheinprozedur (p=0,001)), und
- eine Steigerung des Seattle Angina Questionnaire Lebensqualität-Score (SAQ QoL Score) bei CSRS Patient*innen von 17,6 Punkten und Patient*innen der Scheinprozedur von 7,6 Punkten (p=0,048).

Sicherheit

RCT: niedrigere Rate von SADEs in der CSRS Gruppe

Rate der SADEs in Beobachtungsstudien variiert stark

In Bezug auf die Sicherheit deuten die RCT-Daten darauf hin, dass es in der CSRS-Gruppe (19 %) zu weniger schwerwiegenden Nebenwirkungen des Produktes (serious adverse device effects, SADEs) kam als in der Scheingruppe (46 %). SADEs wurden in allen Beobachtungsstudien berichtet und reichten von 0 % bis 30 %. Die am häufigsten berichteten SADEs waren Tod, Myokardinfarkt (MI), KHK-Progression und Schlaganfall. Im RCT trat der einzige Todesfall in der Scheingruppe auf. 65 Patient*innen in den Beobachtungsstudien starben (Range: 4 % - 15,1 %), während 24 Todesfälle davon explizit als kardiovaskulär bedingt angegeben wurden (Range: 2,6 % - 10 %).

Das GRADE Assessment zur Qualität der Evidenz zu Sicherheit bescheinigte den einzelnen Endpunkten nur sehr niedrige (Mortalität, MI, KHK-Progression, Schlaganfall, stabile und instabile Angina) bis moderate (SADEs) Sicherheit.

Laufende Studien

5 laufende Studien

Die Suche ergab fünf laufende Studien (3 davon RTCs), welche die Evidenzlage verändern könnten. Laut Informationen aus clinicaltrials.gov sollten diese Studien innerhalb der nächsten zwei bis drei Jahre abgeschlossen sein.

Kostenerstattung

Derzeit in Ö nicht erstattet

Derzeit wird CSRS vom österreichischen Gesundheitssystem nicht erstattet.

Diskussion

Schlussfolgerungen des ursprünglichen Berichts unverändert

In Ermangelung neuer vergleichender Studien bleibt die Schlussfolgerung des Reviews aus 2020 zur Wirksamkeit und Sicherheit von CSRS weitgehend unverändert. Es fehlen Ergebnisse aus gut konzipierten, randomisierten Kontrollstudien, um die Rolle von CSRS in der klinischen Praxis klären zu können.

RCT-Daten aus laufenden Studien erforderlich

Es ist ausreichend darauf hinzuweisen, dass Ergebnisse aus derzeit laufenden Studien abgewartet werden müssen. CSRS hat das Potenzial, eine therapeutische Lücke zu schließen und weist nach derzeitigem Wissen ein positives Sicherheitsprofil auf. Es besteht jedoch mangelndes Wissen über den genauen Wirkmechanismus und es fehlt ein Langzeit-Sicherheitsprofil.

Empfehlung

Aufnahme derzeit nicht empfohlen

Die vorhandene Evidenz weist zwar darauf hin, dass der CSRS – bei Patient*innen mit refraktärer AP, für die keine andere Behandlungsmöglichkeit verfügbar ist – potenziell wirksamer ist (hinsichtlich CCS und SAQ QoL Scores) als die entsprechende Scheinprozedur, allerdings werden diese teilweise positiven Ergebnisse durch die fehlende innere Validität der Studien unterminiert. Um den CSRS in der klinischen Routine zu etablieren, werden umfangreichere RCTs, welche potenziell den Effektschätzer beeinflussen könnten, benötigt. Eine Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen.

Summary of previous assessment(s) 2020

This chapter summarizes the results of the previous assessment published in 2020 [1]. The reader is referred to this report for a nuanced description regarding the health problem and current use as well as the technological characteristics. Information was checked for accuracy and updated in case changes occurred within the past years.

Health problem and characteristics of the technology

Overview of the disease, health condition and target population

Indikation: refraktäre Angina pectoris

Refractory angina pectoris (AP) refers to long-lasting symptoms (for ≥3 months) due to established reversible ischemia in the presence of obstructive coronary artery disease (CAD), which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting [2].

Current clinical practice

konservative Therapien

Angina is conventionally treated with antianginal drugs, percutaneous coronary interventions (PCI), and/or coronary artery bypass grafting (CABG) [3].

Features of the intervention

CSRS erzeugt fokale Verengung im Koronarsinus

Coronary sinus reducing stent (CSRS) (Neovasc Reducer™ System) is a stainless-steel mesh that is designed to create a focal narrowing in the lumen of the coronary sinus. It is pre-mounted on a customized balloon catheter inserted via the jugular vein under local anaesthesia [4]. Neovasc Reducer™ System received CE mark in 2011 for the treatment of refractory AP [5].

CE-Kennzeichnung seit 2011

Results

RCT mit 104 Patient*innen für die Analyse der Wirksamkeit, 7 Studien mit insg. 400 Patient*innen für die Analyse der Sicherheit eingeschlossen

For the assessment of clinical effectiveness, one randomized controlled trial (RCT) met the inclusion criteria (COSIRA, NCT01205893), comparing CSRS with a sham procedure, including 104 patients (of which 52 received the CSRS treatment) with a follow-up of six months [6].

For the assessment of safety, seven studies met the inclusion criteria. One RCT described above [6], four prospective case series [7-10], and two prospective registries [11, 12]. Together with the RCT, the total number of patients receiving the CSRS therapy was 348 (and the total number of included patients was 400). The follow-up ranged from four to 24 months.

statistisch signifikanter Unterschied in 4 Endpunkten

Concerning clinical effectiveness, results from the RCT [6] showed a statistically significant difference in favour of CSRS in:

- Canadian Cardiovascular Society (CCS) angina score improvement of at least two classes at six months follow-up (35% of the CSRS group as opposed to 15% of the sham group (p=0.02));
- CCS angina score improvement by one class (71% of the CSRS group and 42% of the sham group (p=0.003));

- overall mean reduction of CCS class (1.1 classes in the CSRS group and 0.5 classes in the sham group (p=0.001)); and
- Seattle Angina Questionnaire (SAQ) QoL score improvement in the CSRS group by 17.6 points and in the sham group by 7.6 points (p=0.048).

RCT: niedrigere Rate von SADEs bei CSRS Patient*innengruppe, Rate der SADEs in Beobachtungsstudien variiert stark

Concerning safety, the RCT data indicated less serious adverse device effects (SADEs) in the CSRS group (19%) than in the sham group (46%) [6]. Most of the SADEs occurred in no more than two patients in the CSRS group or sham group (4%) except for stable angina (CSRS=1, sham=5), unstable angina (CSRS=1, sham=4), and atypical chest pain (CSRS=1, sham=6). No SADE occurred more frequently in the CSRS group than in the sham group. SADEs reported in observational studies ranged from 0% [7, 10] to 30% [9]. While two studies reported none [7, 10], the remaining four studies reported 14 (10%), 5 (22%), 6 (13%), and 15 (30 %) patients suffering from SADEs, respectively [8, 9, 11, 12]. The most frequently reported SADEs were death and stable angina. In the RCT, the only case of death occurred in the sham group [6]. 8% of patients in the observational studies died, while 5% of deaths were explicitly claimed not to be related to CSRS [8, 9, 11, 12].

Gesamtstärke der Evidenz nach GRADE: moderat

Concerning clinical effectiveness (RCT [6]), the RoB was rated to be low and concerning safety, the RoB was rated to range from low [7, 9, 10, 12] to moderate [8, 11]. The main reasons for increased risk was assumed selective outcome reporting [7, 8] and the lack of clarity whether two studies were conducted prospectively [8, 11]. As assessed by GRADE, the overall strength of evidence for effectiveness and safety was moderate.

Recommendation

Aufnahme nicht empfohlen

The inclusion in the catalogue of benefits was not recommended in 2020. Even though the evidence indicated that the assessed technology CSRS was potentially more effective than sham intervention for refractory AP patients (in terms of CCS and SAQ QoL scores) who have no other alternative interventions available, the lacking internal validity of the studies undermined the partially positive results. It was concluded that for the establishment in clinical practice, larger RCTs that could potentially influence the effect estimate were needed.

UPDATE 2022

1 Objectives and Scope

1.1 PICO question

PIKO-Frage

Is percutaneous transvascular implantation of a coronary sinus reducing stent (CSRS) in comparison to sham intervention in patients with refractory angina pectoris (AP) despite standard medical therapy more effective and safe concerning Canadian Cardiovascular Society (CCS) angina score, Seattle Angina Questionnaire (SAQ) for quality of life (QoL) score, and serious adverse device effects (SADEs)?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: 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 anaesthesia. Available agents: ■ 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 excercise ■ Modified wall motion index ■ Antianginal medications intake
Safety	Serious adverse device effects (SADEs) Adverse device effects (ADEs)
Study design	
Efficacy	Randomised controlled trials (RCTs) Prospective non-randomised controlled trials (NRCTs)
Safety	Randomised controlled trials (RCTs) Prospective non-randomised controlled trials (NRCTs) Prospective case-series (single arm studies, registries ... etc.) (No minimum number of patients required, but individual case report excluded)

2 Methods

2.1 Systematic literature search

systematische Literatursuche in vier Datenbanken

The systematic literature search was conducted on the 26.11.2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA Database

The systematic search was limited from November 2019 onwards, and to articles published in English or German. After deduplication, overall 53 citations were screened for eligibility. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 29.11.2021 resulting in 6 potential relevant hits.

2.2 Flow chart of study selection

Literaturauswahl

Overall 53 hits were identified in the update search. The references were screened by one researcher. The selection process is displayed in Figure 2-1.

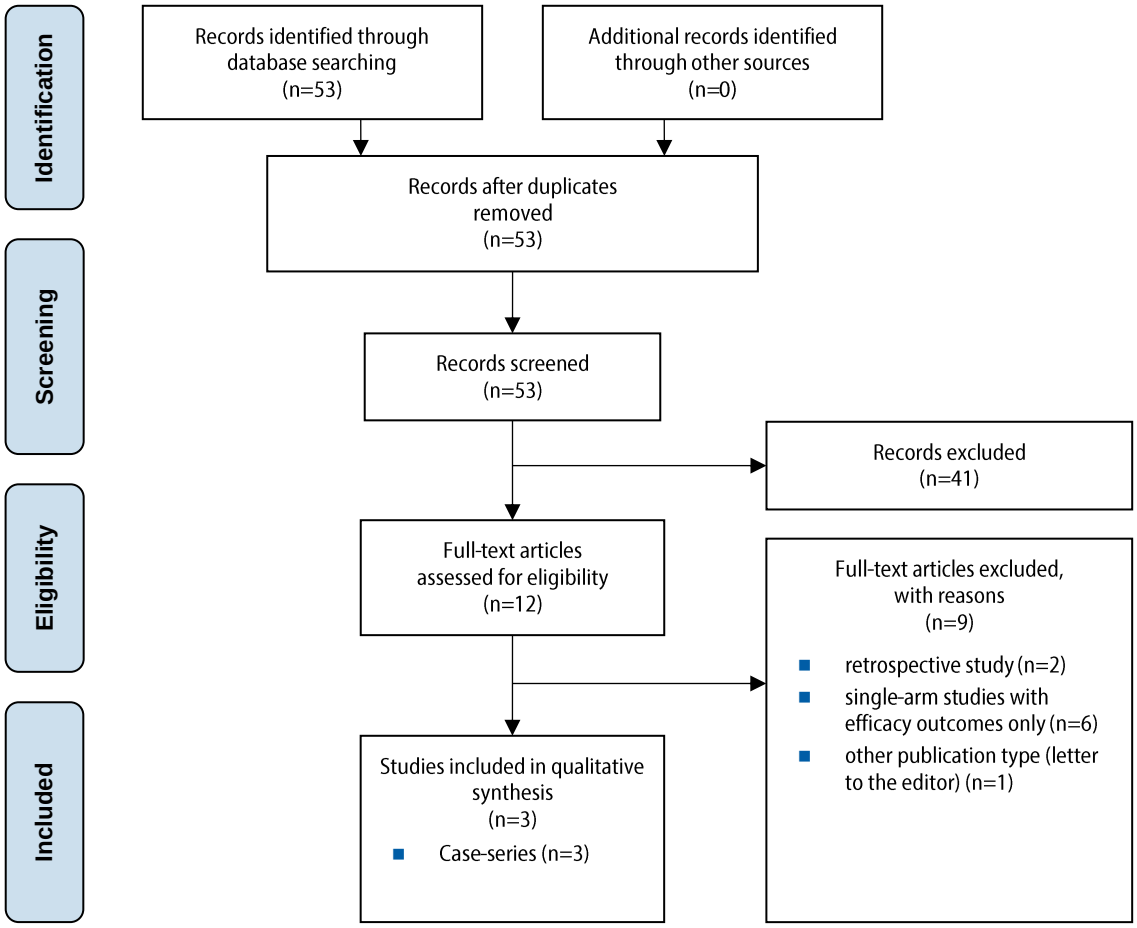

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.3 Analysis and synthesis of the evidence

Datenextraktion

The data retrieved from the selected studies were systematically extracted into a data-extraction-tables (see Table A - 1 -Table A - 4). No further data processing (e.g. indirect comparison) was applied. One researcher systematically assessed the risk of bias (RoB) of observational studies using the IHE-20 checklist [13], which is presented in Table A - 6 and Table A - 7. The RCT was assessed with the Cochrane Collaboration's tool for randomised trials [20] and is presented in Table A - 5.

Qualitätsbeurteilung der Studien mit IHE-20 Checkliste

qualitative Synthese der Evidenz

Based on the data-extraction-table (Table A - 1 - Table A - 4), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [14] (see Table 4-1).

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

entscheidungsrelevante Endpunkte für die Wirksamkeit

For the evaluation of the clinical effectiveness, the following outcomes were defined as crucial to derive a recommendation:

- CCS angina score
- SAQ for QoL
- SAQ treatment satisfaction

CCS Angina Score: AP in 4 Kategorien unterteilt

CCS score classifies AP in four categories (see Table 3-1). Patients with refractory AP belong mainly to Grade III and IV.

Table 3-1: CCS angina score [15]

Grade	Description	Example
Grade I	AP symptoms with strenuous exertion	e.g. no symptoms during walking or climbing stairs
Grade II	AP symptoms with moderate exertion	e.g. symptoms when walking or climbing stairs rapidly
Grade III	AP symptoms with mild exertion	e.g. symptoms when walking or climbing stairs
Grade IV	AP symptoms at rest	e.g. discomfort with any physical activity

Fragebogen zur Lebensqualität

SAQ for QoL is a validated, self-administered, disease-specific measure for patients with coronary artery disease. The QoL section uses the following classification: excellent (75-100), good (50-74), fair (2-49), and poor (0-24) [16].

Fragebogen zur Behandlungszufriedenheit

SAQ treatment satisfaction reports on the mean difference in percentage of patients satisfied with the intervention between baseline and follow-up.

entscheidungsrelevante Endpunkte für die Sicherheit: SADEs

For the evaluation of safety, the following outcomes were defined as crucial to derive a recommendation:

- SADEs (including the following conditions/interventions)
  - Death
  - Myocardial infarction (MI)
  - Stable angina
  - Crohn's disease flare
  - Unstable angina
  - Epigastric pain
  - Atypical chest pain
  - Acute coronary syndrome
  - Arrhythmia
  - Multi-system failure
  - Pulmonary edema
  - Chronic obstructive pulmonary disease (COPD)
  - Cough
  - Decompensated heart failure
  - Gastrointestinal bleeding

- Injury
- Coronary artery disease (CAD) progression
- Bleeding events associated with dual antiplatelet therapy (DAPT)

weiters berücksichtigt: ADEs

Further outcomes considered include:

- ADEs (including the following interventions)
  - Hospitalization
  - Coronary angiogram
  - Revascularization
  - Device migration

3.2 Included studies

3.2.1 Clinical effectiveness

keine neue Studie für die Analyse der Wirksamkeit gefunden, 1 RCT aus 2020 Review

In the update search no new studies for the assessment of clinical effectiveness could be identified. Therefore, the effectiveness results rely solely on the evidence included in the 2020 Assessment Report, which included one RCT comparing CSRS with a sham procedure where no stent was implanted (study name COSIRA, NCT01205893) [6].

Study characteristics

RCT (04/2010-04/2013) gesponsert vom Hersteller

The RCT was conducted in 11 centres in Belgium, Canada, Denmark, the Netherland, Sweden, and the UK between April 2010 and April 2013. It was sponsored by the manufacturer Neovasc Inc. [6].

Patient characteristics

104 Patient*innen, 52 davon erhielten CSRS

The RCT included 104 patients, of which 52 were in the intervention group (CSRS group) and 52 in the control group (sham treatment). Implantation procedure failed in two patients due to a venous valve in the coronary sinus that could not be crossed with the device. Mean age in the CSRS group was 69.6±8.7 and 85% of the population was male while mean age in the sham group was 66±9.8 and 77% of the population was male [6]. The patient population was followed for six months and no patient was lost to follow-up. The primary outcome was proportion of patients with improvement in two or more CCS angina classes.

primärer Endpunkt: Anteil der Patient*innen mit Steigerung um ≥2 CCS-Klassen

stark vorbehandelte Patient*innen

As the target patient group are refractory AP patients, the population was heavily pre-treated. All the patients belonged to CCS angina class III or IV and had mean left ventricular ejection-fraction (LVEF) between 53.5-54.8%. Majority of patients received the following interventions or experienced the following conditions: previous MI, previous CABG, previous PCI, hypercholesterolemia, diabetes mellitus, hypertension, current/previous smoking, and intake of one or more antianginal medication [6].

Einschluss: ≥18 Jahre, refraktäre AP trotz Therapie, reversible Ischämie

In terms of inclusion criteria, patients were required to be of 18 years of age and more with symptomatic CAD and refractory AP (CCS class II and IV) despite medical therapy for 30 days prior to screening. Patients were further

required to have evidence of reversible ischemia attributable to left coronary arterial system and LVEF of at least 25% [6].

hochspezifische Ausschlusskriterien

Exclusion criteria were highly specific and included acute coronary syndrome in less than three months, CABG/PCI in less than six months, unstable angina in one month prior to screening, de-compensated congestive heart failure (CHF) or hospitalization due to CHF during three months prior to screening. Further exclusion criteria included life threatening rhythm disorders, the use of defibrillator or pacemaker in right atrium, right ventricle, or coronary sinus, severe chronic obstructive pulmonary disease (COPD), inability to undergo exercise tolerance tests for reasons other than AP, sinus, tricuspid valve replacement or repair, chronic renal failure with patients on chronic hemodialysis, moribund patients, patients with comorbidities limiting life expectancy to less than one year, pregnancy, allergy to stainless steel or nickel, contraindication to having an magnetic resonance imaging (MRI) performed, enrollment in another investigational device or drug trial, mean right atrial pressure of less or equal to 15 mmHg, anomalous or abnormal CS as demonstrated by angiogram, and coronary sinus diameter at the site of planned CSRS implantation of less than 9.5 mm or more than 13 mm [6].

Detailed study characteristics and results are displayed in Table A - 1 and in the summary of findings table in Table 4-1.

3.2.2 Safety

Sicherheit: 1 RCT und 9 prospektive einarmige Studien (3 aus der Update-Suche)

In the update search, three observational studies [17-19] were identified and included for the safety analysis. The 2020 Assessment report included besides the RCT [6] already included for effectiveness analysis, six observational studies [7-12].

Study characteristics

6 der Beobachtungsstudien wurden in mehr als einem Zentrum durchgeführt, Finanzierung bei fast allen Beobachtungsstudien unklar

The RCT [6] study and patient characteristics are described in 3.2.1 Clinical effectiveness. Additionally, nine observational studies were included (three of which were identified in the update search). Six observational studies were conducted in more than one centre in countries of Germany, India, Israel, Italy, and Belgium [7, 8, 11, 17-19] and the remaining three observational studies were all conducted in single centres in Italy [9, 10, 12]. Funding was unclear in all but one study [19] and all of the studies were published by authors who declared financial interests to the manufacturer Neovasc Inc. The studies were conducted between October 2004 and March 2020. One study had two study arms, one prospective and a retrospective [19], the latter being a long-term follow-up of the COSIRA study, which was included in the 2020 Assessment Report [1].

Patient characteristics

Insg. 914 Patient*innen in den Studien Follow-up zwischen 4 Monaten und 3.38 Jahren

The nine observational studies included in total 810 patients. Hence, together with the RCT [6], the total number of patients receiving the CSRS therapy was 862 and the total number of patients included in the studies was 914. The follow-up ranged from four [10] months to 3.38 years, while five studies had six months follow-up [6-8, 11, 12]. The mean age varied between 65 to 71.4 years.

Loss to Follow-up variiert stark

Loss to follow-up was reported differently in the studies, therefore the comparability is seriously hindered. One study [18] included patients who completed the two-year follow-up and did not consider those who were lost-to follow-up or died before that and stated that no patient was lost to follow-up after the two years. In the other studies, the loss to follow-up varied greatly from 0% [10] to 61.1 % [19] (whereby the low losses to follow-up could be observed in the studies with shorter follow-up periods).

Mehrheit der Patient*innen stark vorbehandelt und CCS-Klasse III oder IV

As the target patient group are refractory AP patients, the population was heavily pre-treated in all but one study [10]. 68-98% of patients in each study belonged to CCS angina class III or IV and had mean LVEF between 52-61%. A large proportion of patients received the following interventions or experienced the following conditions (while some studies did not report on this baseline information) [6-12, 17-19]: previous MI (27-95%), previous CABG (20-81%), previous PCI (40-100%), previous stroke (4.3-17%), hypercholesterolemia (0-100%), diabetes mellitus (7-64%), hypertension (67-86%), current/previous smoking (37-64%). The number of antianginal medications was not comparable in the studies due to different reporting format.

schwere refraktäre AP trotz medikamentöser Therapie als Einschlusskriterium in allen Studien

The inclusion criteria were, in general, homogenous. Severe refractory AP despite medical therapy was a criterion in all studies, however, CCS classes II-IV were sufficient for inclusion in [7-11, 17, 19] and CCS classes III-IV in [6, 12]. The inclusion criteria in one study were unclear with regard to CCS class [18]. All studies included only those patients who were not eligible for CABG and/or PCI [7-12, 17-19], had objective myocardial ischemia (determined by perfusion scan and/or by dobutamine ECG) [6-12], and in most cases had LVEF as low as 25-30% [7, 8, 12].

Ausschlusskriterien der Studien uneinheitlich

Exclusion criteria were more heterogeneous. Five observational studies excluded patients with MI and CABG/PCI in less than three (to seven) months [7, 8, 12, 17, 19], patients with decompensated heart failure [7, 8, 12, 17, 19], the presence of life threatening arrhythmias [7, 8, 12, 17, 19], and severe valvular heart disease [7, 8, 12, 17, 19]. Tricuspid valve replacement or repair was an exclusion criterion in two studies [7, 8], acute coronary syndrome in less than three months in five studies [9-11, 17, 19], presence of a pacemaker lead was an exclusion criterion in six studies [7-9, 11, 17, 19], and right atrial pressure of more or equal to 15 mm Hg was a criterion in all but one studies [7-12, 17, 19].

Study characteristics and results of included studies are displayed in Table A - 2 - Table A - 4 and in the summary of findings table in Table 4-1.

3.3 Results

3.3.1 Clinical effectiveness

keine neue Evidenz, 1 RCT aus dem 2020 Review

No new evidence could be identified for the evaluation of effectiveness, hence the effectiveness evidence base comprises exclusively the RCT [6] analysed in the 2020 Assessment Report.

Concerning the primary outcome of **CCS angina score improvement** of at least two classes at six months follow-up, 35% of the CSRS group as opposed to 15% of sham group patients improved (p=0.02) [6]. CCS angina score improvement by one class was observed in 71% of CSRS group and 42% of sham group patients (p=0.003) [6]. Overall, mean reduction of CCS class from baseline to six months follow-up was 1.1 classes in the CSRS group and 0.5 classes in the sham group (p=0.001) [6].

Steigerung von mind. 2 CCS-Klassen bei 35 % der Patient*innen in der CSRS Gruppe

Disease specific QoL was measured by improvement in SAQ QoL score. While patients in the CSRS group improved their SAQ QoL score by 17.6 points, patients in the sham group improved by 7.6 points (p=0.048) [6].

Lebensqualität höher bei Patient*innen der CSRS Gruppe

SAQ treatment satisfaction outcome showed the same mean improvement of 2.9 points both in the CSRS and in the sham group [6].

Behandlungszufriedenheit in beiden Gruppen gleich

Two surrogate endpoints were reported on in the RCT: **total exercise duration** improved by 59 seconds (13%) in the CSRS group and by 4 seconds (1%) in the sham group (p=0.07) [6]. **Wall motion index** improved by 14% in the CSRS group and 8% in the sham group (p=0.20) [6].

Belastungsdauer und Wall Motion Index in der CSRS Gruppe gesteigert

3.3.2 Safety

SADES

The only controlled data come from the sham-controlled RCT in which there was a total of 10 (19%) SADEs in the CSRS group and 24 (46%) in the sham group [6]. Most of the SADEs occurred in no more than two patients in the CSRS group or sham group (4%) except for stable angina (CSRS=1, sham=5), unstable angina (SCRS=1, sham=4), and atypical chest pain (CSRS=1, sham=6). No SADE occurred more frequently in the CSRS group than in the sham group.

RCT:
19 % SADEs in der CSRS Gruppe verglichen mit 46 % in der Kontrollgruppe

SADEs were reported in all of the included studies, ranging 0% to 30%. While two studies reported none [7, 10], the remaining seven studies reported various types and rate of SADEs: death, MI, CAD progression, major stroke, stable and unstable angina were the most frequently reported. Seven observational studies reported in total 65 deaths (14 (10%) [11], 1 (4%) [8], 3 (6%) [12], 5 (10%) [9], 14 (7.9%) [17], 13 (5.7%) [19], and 15 patients (15.1%) [18]). Six of the seven studies also reported death of cardiovascular origin separately: 24 of the 65 deaths had a cardiovascular origin (4 (3%) [11], 1 (4%) [8], 1 (2%) [12], 5 (10%) [9], 7 (6%) [17] and 6 patients (2.6%) [19]). MI occurred in four studies in 3 (6%) [9], 14 (7.9%) [17], 16 (7%) [19] and 9 (9%) [18] patients, and stable angina in two studies [8, 12] in 4 (17%) and 2 (4%) patients, respectively. Furthermore, unstable angina occurred in 1 (2%) patient [12], and CAD progression in 7 (14%) [9] and 21 (11.2%) patients [17]. Major stroke was reported by 7 patients in two studies (range 1.8% - 3%) [18, 19].

Beobachtungsstudien:
0 bis 30 % SADEs berichtet

Concerning non-serious ADEs, the RCT reported that 32 (64%) patients in the CSRS group and 37 (69%) in the sham group experienced ADEs. In observational evidence, ADEs were either not reported [7, 8], or reported to occur in 0-45% of patients. No ADEs (0%) we reported in [10], and they occurred in 64 (45%) patients in [11], 4 (8%) patients in [12], and 13 (26%) patients in [9]. The newly included three observational studies [17-19] did not report the total number of patients experiencing any ADEs. The ADEs reported were

RCT: ADEs in 64 % der CSRS Gruppe und 69% der Kontrollgruppe
Beobachstungsstudien: ADEs bei 0 bis 45 % der Patient*innen

hospitalization, coronary angiogram, revascularization, and device migration.

ADEs: Hospitalisierung, Angiographie, PCI, Device Migration

Three studies reported that 66 patients were hospitalized during follow-up (15 (13.3%) [19], 28 (28.2%) [18] and 23 (17%) [11], respectively). Four studies [9, 11, 17, 18] reported that 61 patients underwent repeat angiography (30 (16.9%) [17], 31 (31.3%) [18], 26 (19%) [11] and 13 (26%) [9] patients, respectively). Five studies reported revascularization (PCI): 44 patients underwent repeat PCI during follow-up (23 (12.9%) [17], 21 (21.2%) [18], 3 (6%) [12], 15 (11%) [11] and 0 (%) [10] patients). Device migration was reported in three studies [10, 12, 18] and it occurred in two patients.

Technical and procedural failures

Anatomische Variabilität die Implantation kann zu Komplikationen beim Eingriff führen

Other events, not classified as ADEs or SADEs, were considered technical and procedural failure. Four studies reported on implantation failures [8, 12, 17, 19]. In one study [19] device implantation was not successful in two patients, in other three patients the first implantation attempt failed but successful implantation was accomplished at second attempt. One peri-procedural MACE (an MI event) occurred less than 3 weeks post implant. It was adjudicated as unknown if device or procedure-related, hence it was not reported in the safety results of the study. In another study [17], device implantation was not possible in two patients because of unfavorable anatomy of the CS or venous anomaly and there were two device failures (one due to a CS dissection treated conservatively, and the second due to a device embolization). Two patients experienced CS perforation. The device dislocated during balloon retrieval in four patients and a second device was successfully implanted in all of them. In two other studies failure to implant CSRS occurred in two patients due to unsuitable anatomy of the CS in each study [8, 12].

4 Quality of evidence

RoB: RCT: niedrig, Beobachtungsstudien: niedrig bis hoch

RoB for individual studies was assessed with IHE-20 checklist [13] for single-arm studies and is presented in Table A - 6 and Table A - 7 in the Appendix. The RCT was assessed with the Cochrane Collaboration's tool for randomised trials [20] and is presented in Table A - 5. The RCT [6] was rated with a low RoB. The RoB for the observational studies varied greatly: low RoB in four studies [7, 9, 10, 12], moderate in three studies [8, 11, 17], and high RoB in two studies [18, 19].

Eight of the nine case series did not state the source of financial support, there was assumed selective outcome reporting of ADEs in [7, 8], outcome assessors were either not blinded [7-12] or there were uncertainties about the lack of blinding of outcome assessors [17-19], the sample size and event sizes were small in all of the studies, the distribution of data was not reported, and estimates of random variability in the data analysis of relevant outcomes were not reported either. Additionally, it was unclear if two studies were conducted prospectively [8, 11] and two other studies [18, 19] reported partially retrospectively collected data.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE [14] for each endpoint individually.

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = 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** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table in Table 4-1.

Gesamtstärke der Evidenz für Wirksamkeit: moderat, für Sicherheit: sehr niedrig bis moderat

For the comparison of CSRS and sham procedure no new evidence is available. The newly identified single-arm studies did not change the evidence considerably. Overall the strength of evidence for the effectiveness of CSRS is moderate. The evidence on safety is slightly enriched by the three new single-arm studies, however the overall strength of the evidence for safety is rated to be very low to moderate.

Table 4-1: Summary of findings table of CSRS

Certainty assessment							Impact			
							Anticipated absolute effects (95% CI)			Certainty (importance)
Number of studies (pts)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	with sham	with CSRS	Difference	
Efficacy										
CCS angina score improvement of at least 2 classes at 6 mos follow-up, %										
1 (104)	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	15	35	20% more in CSRS group than in sham group Statistically significant (P=0.02)	⨁⨁⨁◯ moderate (crucial)
SAQ QoL score improvement at 6 mos follow-up, n of points										
1 (104)	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	7.6	17.6	10 points more in CSRS group than in sham group Statistically significant (P=0.048)	⨁⨁⨁◯ moderate (crucial)
Total exercise duration improvement at 6 most follow-up, n of seconds										
1 (104)	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	4	59	55 sec more in CSRS group than in sham group Statistically not significant (P=0.07)	⨁⨁⨁◯ moderate (crucial)
Safety										
SADEs at 6 mos follow-up, n of events										
1 (104)	Randomised trial	Not serious	Not serious	Not serious	Serious[a]	None	24	10	27% fewer in CSRS group than in sham group	⨁⨁⨁◯ moderate (crucial)
Death, n of pts										
7 (776)	Single-arm observational studies	Very serious[b, c]	Serious[d]	Not serious	Serious[e]	Reporting bias strongly suspected[f]	Death across studies: 65 (range: 4% - 15.1%) Cardiovascular death: 24 (range: 2.6% - 10%) in six studies			⨁◯◯◯ very low (crucial)
MI, n of pts										
4 (564)	Single-arm observational studies	Very serious[b, g]	Not serious	Not serious	Serious[e]	Reporting bias strongly suspected[f]	MI across studies: 42 (range: 6% - 9%)			⨁◯◯◯ very low (crucial)
CAD progression, n of pts										
2 (237)	Single-arm observational studies	Very serious[b]	Not serious	Not serious	Serious[e]	None	CAD progression: 28 (11.2%-14%)			⨁◯◯◯ very low (crucial)

Certainty assessment							Impact			
							Anticipated absolute effects (95% CI)			Certainty (importance)
Number of studies (pts)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	with sham	with CSRS	Difference	
(Major) stroke, n of pts										
2 (327)	Single-arm observational studies	Very serious[b, g]	Not serious	Not serious	Serious[e]	Reporting bias strongly suspected[f]	Major stroke across studies: 7 (range: 1.8% - 3%)			⨁◯◯◯ very low (crucial)
Stable angina, n of pts										
2 (71)	Single-arm observational studies	Very serious[b, h]	Serious[i]	Not serious	Serious[e]	None	Stable angina across studies: 6 (4% - 17%)			⨁◯◯◯ very low (crucial)
Unstable angina, n of pts										
1 (48)	Single-arm observational studies	Serious[b]	Not serious	Not serious	Serious[e]	None	Unstable angina: 1 (2%)			⨁◯◯◯ very low (crucial)

Comments:

a Optimal information size is not met and the sample size is small

b Only single-arm observational studies form the body of evidence.

c Two studies report partially retrospectively collected data and it was unclear in two other studies if retrospective (creating a survival bias for the outcome mortality).

d Rate of mortality varied across the included studies between 5.7 % and 15.1%.

e Small event size. No confidence interval reported in the studies.

f Reporting bias/underreporting: one study included only patients who had at least the two year follow-up data and therefore the outcomes before the two year were not considered (16 patients died and 33 pts were lost to follow-up before the two years and hence not included in the analysis)

g Two studies report partially retrospectively collected data.

h In one study it was unclear if study retrospective, no consecutive patient recruitment. In the same study AEs are not reported (and most presumably occurred). Both studies are unclear about financial support.

i Rate of stable angina across the included studies varied between 4% and 17%.

***Abbreviations**: **CAD** – coronary artery disease, **CCS** – Canadian Cardiovascular Society, **CI** –confidence interval, **CSRS** – coronary sinus reducing stent, **MI** – myocardial infarction, **mos** – months, **n** – number, **pts** – patients, **QoL** – quality of life, **SADE** – serious adverse device effect, **SAQ** – Seattle Angina Questionnaire*

5 Discussion

The aim of this systematic review was to update the 2020 Assessment Report, which investigated the use of CSRS in refractory AP patients when compared to sham CSRS procedure. This update report comprises new information from three single-arm observational studies on CSRS available since the previous report was published in March 2020. No new RCTs could be identified to evaluate the effectiveness of CSRS compared to sham procedure.

keine neue direkte Evidenz: Schlussfolgerungen zu Wirksamkeit und Sicherheit unverändert

In the absence of new comparative evidence, the conclusion about the effectiveness of CSRS remains unchanged compared to the 2020 Assessment Report. Concerning clinical effectiveness, results from the RCT report on patient relevant outcomes that are of potential clinical relevance. Outcomes that show statistically significant difference between CSRS and sham treatment are [6]:

- Canadian Cardiovascular Society (CCS) angina score improvement of at least two classes at six months follow-up (35% of the CSRS group as opposed to 15% of the sham group (p=0.02));
- CCS angina score improvement by one class (71% of the CSRS group and 42% of the sham group (p=0.003));
- overall mean reduction of CCS class (1.1 classes in the CSRS group and 0.5 classes in the sham group (p=0.001)); and
- Seattle Angina Questionnaire (SAQ) QoL score improvement in the CSRS group by 17.6 points and in the sham group by 7.6 points (p=0.048).

statistisch signifikante Ergebnisse: Steigerung des CCS Angina Score (von ≥ 2 Klassen, um 1 Klasse); gesamte mittlere Reduktion der CCS-Klasse; Steigerung des SAQ QoL Score

The improvement reported in the remaining outcomes analysed did not reach statistical significance: SAQ treatment satisfaction (p=0.981), total exercise duration improvement (p=0.07) (mean exercise duration improvement (p=0.07)), wall motion index improvement (p=0.20) [6].

Concerning safety, the sham-controlled trial data indicate that there were less SADEs in the CSRS group (19%) than in the sham group (46%) [9]. The evidence base from observational studies is only slightly enriched by the three new studies identified in this update report. The total mortality rate both in the 2020 Assessment Report and the update report has a wide range (0% - 10% and 4% - 15.1%, respectively) and the wide variation in other SADEs also remains to be a point of concern.

RCT: niedrigere Rate von SADEs bei CSRS Patient*innen

Rate der SADEs in Beobachtungsstudien variiert stark

Internal and external validity

When interpreting the findings on clinical effectiveness, the issues with mechanism of action, placebo effect, sample size, randomization procedure, and inconsistency between outcomes should be taken into account. First, the mechanism of action of CSRS is unclear. It is it is also unclear why there remains to be a 15-30% rate of non-responders [21]. Second, a repeated concern in the academic literature highlights that CSRS implantation may be associated with a large placebo effect that is reported to be related to novel therapies in this specific patient population [2, 4, 22]. Thirdly, the evidence base still consist of only a small size of selective sample of patients, hence the clinical benefit of CSRS may be overstated. Fourth, concerns about the randomization process (of the only RCT [6]) were highlighted. Fifth, there is inconsistency between more objective parameters such as total exercise duration improvement, mean exercise duration improvement, or wall motion index improvement (that did not improve in statistically significant ways) and CCS and SAQ QoL scores (that did) [6].

Wirkmechanismus unklar, mögliche Placebo-Effekt, kleine Fallzahl im RCT, Bedenken hinsichtlich des Randomisierung, und Inkonsistenzen von Ergebnissen

potentielle SADEs, anatomische Gegebenheiten und potentielle Hindernisse der künftigen Therapien zu berücksichtigen

Concerning the interpretation of safety findings, issues surrounding potential SADEs, obstruction of future therapy, and underreporting of complications related to dual antiplatelet therapy (DAPT) should be taken into account. Not only that approx. 20% of refractory AP patients are not eligible to receive CSRS implantation due to high variability in CS anatomy and size, but also other relevant anatomical considerations during implantation should be considered. Also, because heart failure will eventually develop in a substantial proportion of patients with refractory AP, there remains a concern that CSRS implanted in the CS may preclude the future use of the coronary sinus for implantation of a left ventricular pacing lead for the therapy established to treat heart failure, cardiac-resynchronization therapy (CRT) [23]. As DAPT with aspirin and clopidogrel is recommended for 6 months after the CSRS implantation [4], the complications related to DAPT need to be considered alongside complication with CSRS. The actual use of DAPT was reported only in two studies [6, 11] and none of the studies reported on bleeding events associated with DAPT.

Daten nicht generalisierbar, da nicht nur Patient*innen in CCS Klasse III-IV inkludiert

The generalizability of the results are undermined by the fact that the CSRS patient population does not include only refractory AP patients. It thus remains to be a question to what extent can the highly specific inclusion and exclusion criteria from the studies be applied in the real world context.

überzogene Schlussfolgerungen zu Wirksamkeit und Sicherheit

Given the small size of the selective sample of patients included in the evidence base, the conclusions about effectiveness and the positive safety profile are considered to be inflated.

Einbettung in bestehendes Wissen: NICE: potentieller Nutzen, aber niedrige Qualität der Evidenz; Norweger Mini-Review: positive Schlussfolgerungen ohne Reflektion an Evidenzqualität

This systematic review is mostly aligned with other recent reviews. The evidence-based recommendations published by the National Institute for Health and Care Excellence (NICE) in 2021 [24] highlighted that evidence on the safety of CSRS for refractory angina showed well-recognised complications and that evidence on efficacy is limited in quantity and quality. Therefore, the CSRS procedure should only be done in specialist centres by interventional cardiologists with specific training in the technique, with special arrangements for clinical governance, consent, and audit or research. Another recent review, a Norwegian mini-review from 2020 [25], based on the single RCT data, concluded that CSRS had a good level of efficacy and safety in comparison with the current treatments and it was recommended that it should be introduced as part of the clinical routine in Norwegian hospitals. It was also recommended that the method and clinical effect should be followed up over several years. However, the review failed to address evidence quality considerations.

Limitations

keine neue RCTs

No new controlled trials were identified, therefore even though the 2020 Assessment Report concluded that CSRS is a potentially effective and safe technology, evidence is still limited. Excluding retrospective may have led to not capturing studies with a bigger sample size. However, retrospective studies are prone to internal validity concerns and, hence, the interpretation of the evidence would have not changed by including these studies. Abstract-and full-text screening and data extraction was conducted by one person. However, the likelihood of error (e.g., not identifying relevant studies) is still small.

Ausschluss von retrospektiven Studien

Ongoing studies

Five studies investigating CSRS for the treatment of refractory AP are currently ongoing. Three of these studies were already identified in the 2020 Assessment Report (including one RCT). The two newly identified ongoing trials are RCTs (COSIRA-II, ORBITA-COSMIC) and they investigate CSRS compared to sham procedure. COSIRA-II started in 2022 and will include 380 patients. It aims to demonstrate the safety and effectiveness of the CSRS compared to sham. ORBITA-COSMIC started in 2021 and aims to compare the effects of CSRS and sham procedure on myocardial perfusion, exercise time and symptoms in 40 participants. Study results are expected from both studies in 2024.Detailed description of the ongoing studies can be found in Table A - 8.

5 laufende Studien, 3 davon RCTs, Studienergebnisse frühestens 2024 publiziert

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

The current evidence suggests that the assessed technology, CSRS is potentially more effective than sham intervention for refractory AP patients (in terms of CCS and SAQ QoL scores) who have no other alternative interventions available. However, the lacking internal validity of the studies undermines the partially positive results. In terms of safety, the wide variation in SADEs remain to be a point of concern. New study results will potentially influence the effect estimate considerably.

The re-evaluation is recommended in 2025, when the COSIRA-II study results will be published.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A - 1: CSRS: Results from RCTs

Author, year	Verheye et al. [6] (2015)
Country	11 clinical centers (Belgium, Canada, Denmark, Netherland, Sweden, UK)
Sponsor	Neovasc Inc.
Study design	Multi-centre, prospective, double-blinded, randomised, 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[1] vs. 52
Inclusion criteria	Pts ≥ 18 years of age, symptomatic CAD pts with chronic refractory AP grades III or IV (classified by CCS) despite attempted optimal medical therapy for thirty 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, de-compensated CHF or hospitalization due to CHF during 3 mos prior to screening, life threatening 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 two or more CCS angina score classes from baseline to 6 mos follow-up
Secondary outcome measure	Technical and procedural success measured at 24 hrs *Measured at 30 days follow-up:* ■ Periprocedural AEs and SAEs (death, MI, cardiac tamponade, life-threatening arrhythmia, and respiratory failure). *Measured at 6 mos 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 Wall Motion Score Index, ■ Major AEs (cardiac death, major stroke, and MI).

[1] Implantation failed in 2 pts due to a venous valve in the coronary sinus that could not be crossed with the device.

Author, year	Verheye et al. [6] (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 Class IV	 42 (81) vs. 45 (87) 10 (19) vs. 7 (13)
Mean LVEF, n (±SD)	53.5 (10.2) vs. 54.8 (11.9)
No. of antianginal medication[2], n (%) 0 1 2 3 >3	 3 (6) vs. 4 (8) 10 (19) vs. 10 (19) 23 (44) vs. 18 (35) 12 (23) vs. 18 (35) 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) **Difference, n**	3.2 (0.4)/2.1 (1.0) vs. 3.1 (0.3)/2.6 (0.9) 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
Wall motion index improvement, %	14 vs. 8 p=0.20
Safety (I vs. C)	
Total SADEs, n	10 vs. 24[3]
MI, n (%)	1 (2) vs.3 (6)[4]
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)

[2] Antianginal medications include: betablockers, calcium-channel inhibitors, nitrates, nicorandil, ivabradine.

[3] Occurred in the total of 17 pts.

[4] Unclear as the extracted information comes from the running text, while the table 5S in Appendix states that one case of MI occurred in IG as well as CG.

Author, year	Verheye et al. [6] (2015)
Epigastric pain, n (%)	0 (0) vs. 1 (2)
Atypical chest pain, n (%)	1 (2) vs. 6 (12)
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[5] (64) vs. 37[6] (69)

Abbreviations: ***ADE*** *– adverse device effect,* ***AP*** *– angina pectoris,* ***C*** *– control,* ***CABG*** *– coronary artery bypass grafting,* ***CAD*** *– coronary artery disease,* ***CCS*** *– Canadian Cardiovascular Society,* ***CHF*** *– congestive heart failure,* ***COPD*** *– chronic obstructive pulmonary disease,* ***CS*** *– coronary sinus,* ***ECG*** *– electrocardiogram,* ***I*** *– intervention,* ***LVEF*** *– left ventricular ejection fraction,* ***MI*** *– myocardial infarction,* ***mos*** *– months,* ***n*** *– number,* ***NA*** *– not available,* ***hrs*** *– hours,* ***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,* ***yr*** *– year*

[5] Out of 50 pts. Total of 76 AEs reported in the intervention group.

[6] Out of 54 pts. Total of 93 AEs reported in the control group.

Table A - 2: CSRS: Results from observational studies (part 1, 2020 Assessment Report)

Author, year	Banai et al. [7] (2007)	Giannini and Baldetti et al. [11] (2018)	Königstein et al. [8] (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[7], 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[8]	141	23[9]
Inclusion criteria	Symptomatic CAD, refractory angina – CCS class II to 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 classes 2-4) despite maximally tolerated medical therapy, pts not eligible for CABG or PCI, objective demonstration of ischemia with either treadmill/pharmacologic 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 ischaemia 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 mm Hg, pts who had undergone tricuspid valve replacement or repair	Ischemia related exclusively to the right coronary artery, the presence of a pacemaker lead in the CS, acute coronary syndrome in <3 mos, coronary revascularization in <6 mos, mean right atrial pressure >15 mm Hg	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 higher than 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, 6 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 (e.g. due to embolization or sub-optimal 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

[7] 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.

[8] QoL measure (CCS score) reported on 14/15 pts. ST-segment depression during exercise stress test reported in 9/15 pts.

[9] Failure to implant CSRS in 2 pts due to unsuitable CS anatomy, and 1 pt loss to follow-up.

Author, year	Banai et al. [7] (2007)	Giannini and Baldetti et al. [11] (2018)	Königstein et al. [8] (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[10]
Previous stroke, n (%)	NA	13 (9)	4 (17)[11]
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)[12]	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 medication, n	NA	Mean 2.33±0.97[13]	NA
Follow-up, mos	6	6[14]	6
Loss to follow-up, n (%)	0	2 (1)[15]	3

[10] Number of pts having undergone PCI us not stated. It is only stated that mean number of PCI's was 4.8±4.2.

[11] Stroke or transient ischaemic event.

[12] Dislipidemia.

[13] Mean number of antianginal medications including anti-ischaemic and acetylsalicylic acid therapy.

[14] Follow-up was performed either by telephone or a face-to-face clinic visit.

[15] Loss to follow-up due to failed CSRS implantation.

Author, year	Banai et al. [7] (2007)	Giannini and Baldetti et al. [11] (2018)	Königstein et al. [8] (2014)
Efficacy			
CCS angina score reduction of at least 2 classes at follow-up, n (%)	NA	63 (45)[16]	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[17] (3.35±0.6/2.0±1) p<0.001
SAQ QoL score improvement, n of points, (baseline/follow-up)	NA	25.6[18] (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[19] NA	3:16±1.48/5:16±1.14 p=0.05
Wall motion index 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 medications intake, median n (baseline/follow-up)	NA	NA	NA
Safety			
SADEs, n (%)	0 (0)	14 (10)	5 (22)
Death, n (%)	NA	14 (10)[20]	1 (4) [21]
MI, n (%)	NA	NA	NA
Stable angina, n (%)	NA	NA	4 (17)[22]

[16] Of which 20 pts (14%) demonstrated reduction of 3 CCS classes.

[17] Results on 20 pts.

[18] 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)

[19] Results on 51 pts.

[20] 2 deaths due to fatal MI, 1 due to advanced heart failure, 1 due to refractory angina leading to anorexia and decubitus. The remained 10 deaths are claimed not to be of cardiovascular origin.

[21] 1 pt died one year after the procedure. The implantation of CSRS was not successful in this pt and this pt died of heart failure.

[22] It is unclear if the angina was stable or unstable. 2 of these pts we treated by PCI, one by CABG, and one pharmacologically.

Author, year	Banai et al. [7] (2007)	Giannini and Baldetti et al. [11] (2018)	Königstein et al. [8] (2014)
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[26]
Hospitalization, n (%)	NA	23 (17)[23]	NA
Coronary angiogram, n (%)	NA	26 (19)[24]	NA
Revascularization, n (%)	NA	15 (11)[25]	NA
Device migration, n (%)	NA	NA	NA

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 resynchronisation therapy,* ***CS*** *– coronary sinus,* ***ECG*** *– electrocardiogram,* ***ICD*** *– implantable cardioverter defibrillator,* ***LVEF*** *– left ventricular ejection fraction,* ***MI*** *– myocardial infarction, mos – months,* ***hrs*** *– hours,* ***n*** *– number,* ***MRI*** *– magnetic resonance imaging,* ***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 effects,* ***SAQ*** *– Seattle Angina Questionnaire,* ***SD*** *– standard deviation,* ***TAVR*** *– Transcatheter aortic valve replacement,* ***WMSI*** *– wall motion score index,* ***yr*** *– year*

[23] Due to recurrent angina.

[24] 7 pts underwent 2 angiograms, 1 pt 3, and another 5.

[25] Further revascularizations due to de novo lesions.

[26] 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.

Table A - 3: CSRS: Results from observational studies (part 2, 2020 Assessment Report)

Author, year	Königstein et al. [12] (2018)	Ponticelli et al. [9] (2019)	Tzanis et al. [10] (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[27]	50	19
Inclusion criteria	Severe AP (CCS class 3 or 4) despite optimal medical therapy, objective evidence of myocardial ischaemia of the left coronary arteries territory by perfusion scan and/or by dobutamine ECG, LVEF ≥30%, non-candidates for surgical PCI	Severe AP (CCS class 2 or 4) despite optimal medical therapy, objective evidence of myocardial ischaemia of the 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[28]	Severe AP (CCS II to 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 the right coronary artery, the presence of a foreign body in the CS (e.g., a left ventricular pacemaker wire for cardiac resynchronization therapy), acute coronary syndrome in <3 mos, coronary revascularization in <6 mos), mean RAP higher than 15 mm Hg	Acute coronary syndrome in <3 months, 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 6-min walk test, and reduction in pharmacological antianginal therapy *Safety:* procedural success and absence of device-related AEs	*Efficacy:* CCS class improvement, 6 minute walk test, and reduction in pharmacological antianginal therapy *Safety:* SAEs and AEs
Secondary outcome measure	NA	NA	NA

[27] Failure to implant CSRS in 2 pts dies to unsuitable CS anatomy.

[28] Inclusion and exclusion criteria come from the 12 mos publication from Giannini 2018 [7] Banai S, Ben Muvhar S, Parikh KH, et al. Coronary sinus reducer stent for the treatment of chronic refractory angina pectoris: a prospective, open-label, multicenter, safety feasibility first-in-man study. J Am Coll Cardiol 2007;49:1783-9..

Author, year	Königstein et al. [12] (2018)	Ponticelli et al. [9] (2019)	Tzanis et al. [10] (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)[29]	18 (95)
Previous CABG, n (%)	39 (81)	28 (56)[30]	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)[31]	NA
Current/previous smoking, n (%)	27 (56)	32 (64)	NA
CSS angina class, n (%)			
Class II	1 (2)	7 (14)	NA[32]
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 medication, n	NA[33]	Median 3 (range 1-5)[34]	Median 3 (range 1-5)[35]
Follow-up, mos	6	24	4

[29] All baseline criteria reported from the 12 mos publication from Giannini 2018 [7]ibid..

[30] CABG and PCI reported as one.

[31] Dislipidemia reported.

[32] Baseline information only on pooled CSS class: 3 (IQR 3-3).

[33] Antianginal medications including: beta-blockers, calcium channel blockers, ACE/ARB inhibitors, nitrates, diuretics, aspirin, clopidogrel, warfarin, statins ivabradine.

[34] Antianginal medication includes: beta-blockers, calcium-channel antagonists, long-acting nitrates, ivabradine, ranolazine.

[35] Antianginal medication includes: beta-blockers, calcium-channel antagonists, nitrates, ranolazine, ivabradine, aspirin, clopidogrel.

Author, year	Königstein et al. [12] (2018)	Ponticelli et al. [9] (2019)	Tzanis et al. [10] (2019)
Loss to follow-up, n (%)	3[36]	8[37]	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[38] (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[39] (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)[40] p=0.002
Wall motion index 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 medications 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
Safety			
SADEs, n (%)	6 (13)	15 (30)	0
Death, n (%)	3 (6)[41]	5 (10)[42]	NA
MI, n (%)	NA	3 (6)	NA

[36] 3 lost to follow-up and 4 other patients not yet completed the 6 mos evaluation and hence not part of the analysis.

[37] 5 pts died and 3 were not reachable by telephone calls or emails.

[38] Results on 39 pts.

[39] Results on 23 pts.

[40] Results on 6 minutes walk test.

[41] 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.

[42] 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.

Author, year	Königstein et al. [12] (2018)	Ponticelli et al. [9] (2019)	Tzanis et al. [10] (2019)
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)[43]	NA
Revascularization, n (%)	3 (6)	NA	0
Device migration, n (%)	1 (2)	NA	0[44]

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 resynchronisation therapy,* ***CS*** *– coronary sinus,* ***ECG*** *– electrocardiogram,* ***ICD*** *– implantable cardioverter defibrillator,* ***LVEF*** *– left ventricular ejection fraction,* ***MI*** *– myocardial infarction, mos – months,* ***hrs*** *– hours,* ***n*** *– number,* ***MRI*** *– magnetic resonance imaging,* ***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 effects,* ***SAQ*** *– Seattle Angina Questionnaire,* ***SD*** *– standard deviation,* ***TAVR*** *– Transcatheter aortic valve replacement,* ***WMSI*** *– wall motion score index,* ***yr*** *– year*

[43] Angiography.

[44] Results on device embolization.

Table A - 4: CSRS: Results from observational studies (part 3, update evidence)

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Country	16 clinical centres (Italy)	20 clinical centres (Belgium, UK, Germany, Switzerland, Netherland, Italy)	3 clinical centres (Belgium, Italy, Isreal)
Sponsor	NA	Neovasc Inc.	NA
Study design	Multi-centre, national, single-arm observational study	Multi-centre, prospective, non-randomized, open-label observational study (REDUCER-I, NCT02710435) with a prospective study arm (Arm 1) and a retrospective study arm (Arm 2, long-term follow-up of the intervention arm from the COSIRA study)	Prospective, single-arm registry study
Conducted in	03/2015 – 07/2019	03/2016 – 03/2020	09/2010 – 10/2017
Indication	Chronic disabling angina pectoris (CCS class II - IV) refractory to maximally toleradted medical therapy not amenable to revascularization	Chonic angina pectoris, CCS class II - IV with no or limited revascularization option	CAD and chronic angina pectoris, CCS class II - IV despite maximally tolerated medical therapy not amenable to further revascularization
Intervention	Coronary-sinus reducing stent (Reducer System)	Coronary-sinus reducing stent (Reducer System)	Coronary-sinus reducing stent (Reducer System)
Comparator	None	None	None
Number of pts	187	Arm 1: 180 Arm 2: 48	99[45]
Inclusion criteria	Chronic disabling angina pectoris (CCS class II to IV) refractory to medication with no revascularization option	Symptomatic CAD with chronic refractory angina pectoris (CCS class II to IV despite medical therapy, pts have limited treatment options for CABG or PCI, reversible myocardial ischemia (determined by perfusion MRI or MIBI SPECT or DSE or ETT), LVEF ≥30%, male or non-pregnant female	Patients with severe angina who underwent Reducer implantation and completed 2 years follow-up
Exclusion criteria	Ischemia related mainly to the right coronary artery, pacemaker, acute CS within 3 mos, PCI or CABG withion 6 mos, RAP ≥15 mm Hg	Acute CS within 3 mos, PCI or CABG within 6 mos, unstable angina, severe arrhythmias, decompensated heart failure, severe COPD, severe valvular heart disease, pacemaker or other CS electrode, pts who had undergone tricuspid valve replacement or repair, pts who cannot undergo ETT or 6MWT for other reasons than refractory angina, chronic renal failure, moribund pts, contraindication to required medications, allergy to stainless steel or nickel, pts enrolled in another trial that has not completed the primary endpoint/interferes with the current study, mean RAP ≥15 mm Hg, abnormal CS, CS diameter < 9.5 mm or > 13 mm	Procedure <2 years prior to study

[45] 197 pts were treated but only 99 included in the analysis because they completed the 2 year follow-up.

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Primary outcome measure	*Efficacy:* NA *Safety:* procedure or device-related AEs (death, MI, cardiac tamponade, device revision, life-threatening arrhythmias, respiratory failure, access site complications, CS dissection	*Efficacy:* percentage of pts who experience improvement in their angina symptoms (defined a s reduction in CCS grade at 6-month as compared to baseline) *Safety:* SAEs, MACE at 30 days post implant, 12 and 24 ms	*Efficacy:* CCS class improvement *Safety:* SAEs (mortality, MI, stroke, repeat angiography, repeat PCI, hospitalization)
Secondary outcome measure	Successful delivery and deployment of the Reducer in the CS, absence of acute need for intervention to address any ADEs before hospital discharge	Percentage of pts who experience a reduction in CCS grade and the rate of MACE at 12-month and annually through 5 years post implant compared to baseline	NA
	Baseline patient characteristics		
Mean age, yrs (±SD)	69.9 (8.8)	Arm 1: 68.7 (9.5) Arm 2: NA[46] Overall: 68.3 (9.6)	69.8 (9.4)
Sex, male/female, n (%)	155: 32 (82.9: 17.1)	Arm 1: 148:32 (82.2: 17.8) Arm 2: NA Overall: 184: 44 (80.7:19.3)	76: 23 (76.8: 23.2)
Previous MI, n (%)	122 (65.2)	Arm 1: 94 (52.2) Arm 2: NA Overall: 117 (51.3)	51 (51.5)
Previous CABG, n (%)	134 (71.7)[47]	Arm 1: 143 (79.4) Arm 2: NA Overall: 180 (78.9)	78 (78.8)
Previous PCI, n (%)	158 (84.5)	Arm 1: 129 (71.7) Arm 2: NA Overall: 161 (70.6)	83 (83.3)
Previous stroke, n (%)	8 (4.3)	NA	11 (11.1)
Previous PAD, n (%)	58 (31.0)	NA	NA
Previous pacemaker, n (%)	13 (7.0)	NA	6 (6.1)
Hypercholesterolemia, n (%)	NA	Arm 1: 155 (86.1) Arm 2: NA Overall: (87.3)	97 (98)

[46] Data for Arm 2 is included elsewhere [6] Verheye S, Jolicoeur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. N Engl J Med 2015;372:519-27.

[47] 60% of pts were treated by both PCI and CABG before CSRS

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]		Konigstein et al. 2021 [18]
Diabetes mellitus, n (%)	89 (47.6)	Arm 1: 79 (43.9) Arm 2: NA Overall: (44.7)		44 (44.4)
Hypertension, n (%)	163 (87.9)	Arm 1: 146 (81.1) Arm 2: NA Overall: (82.0)		82 (82.8)
Hyperlipidemia, n (%)	174 (93.0)	NA		NA
Current/previous smoking, n (%)	102 (54.5)	Arm 1: 113 (62.8) Arm 2: NA Overall: (61.4)		44 (44.2)
CSS angina class, n (%) Class II Class III Class IV	 13 (7.0) 134 (71.7) 40 (21.4)	Arm 1: 58 (32.4) 112 (62.6) 9 (5.0)	Overall: (29.0) (63.8) (6.3)	 9 (9.1) 72 (72.7) 18 (18.2)
LVEF, n (±SD)	51.7 (9.1)	NA		NA
No. of antianginal medication, n (%)	2.77 (± 1.04)	Arm 1: 3.1 (± 1.3) 0: 14 (7.8) 1: 37 (20.6) 2: 50 (27.8) 3: 49 (27.2) >3: 30 (16.7)	Overall: 0: 20 (8.8) 1: 49 (21.7) 2: 63 (27.6) 3: 58 (25.3) >3: 38 (16.6)	NA Beta blocker: 81 (81.8) Calcium channel blocker: 43 (43.4) Nitrates: 61 (61.6) Ivabradine: 19 (19.2) Ranolazine: 25 (25.3)
Follow-up	18.4 mos	Arm 1: 666 days (range: 0.0 – 1386.0) Arm 2: NA		3.38 yrs

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Loss to follow-up, n (%)	10 (5.3)	Arm 1: At 1 year: 65 (36.1) At 2 year: 110 (61.1) Arm 2: At 1 year: 5 (10.4) At 2 year: 7 (14.6) Overall: At 1 year:70 (30.7) At 2 year: 117 (51.3)	0[48]
	Efficacy		
CCS angina score reduction of at least 2 classes at follow-up, n (%)	80/163 (49)	Overall: At 1 year: 36/140 (25.7) At 2 year: 30/98 (30.6)	NA
CCS angina score reduction of at least 1 class at follow-up, n (%)	135/163 (82.8)	Overall: At 1 year: 104/140 (74.3) At 2 year: 80/98 (81.6)	NA
Reduction in CSS class, n (±SD), (baseline/follow-up)	3.2 (0.5)/ 1.8 (0.9)	Arm 1: At 1 year (n=114): 2.7 (0.5)/ 1.8 (0.8) At 2 year (n=69): 2.7 (0.5)/ 1.8 (0.7) Arm 2: NA Overall: At 1 year (n=145): 2.8 (0.6)/ 1.7 (0.7) At 2 year (n=105): 2.8 (0.6)/ 1.8 (0.7)	3.1 (0.5)/ 1.72 (0.8)
SAQ QoL score improvement, n of points (±SD), (baseline/follow-up)	+30.8	Arm 1: At 1 year: 37.4 (22.6)/ 65.6 (26.0) At 2 year: 37.4 (22.6)/ 62.7 (28.1) Arm 2: NA Overall: At 1 year: 36.9 (22.3)/ 64.2 (26.7) At 2 year: 36.9 (22.3)/ 62.5 (27.9)	NA

[48] 197 pts were treated but only 99 included in the analysis because they completed the 2 year follow-up. 45 pts were excluded because they underwent the procedure less than 2 years prior to the study, 16 pts died, 33 pts were lost to follow-up.

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Exercise treadmill stress test, mean n of sec (±SD), (baseline/follow-up)	NA	Arm 1 at 1 year: 370 (165.5)/ 415.7 (168.7) Overall at 1 year: 359.9 (165.1)/ 409.4 (165.0)	NA
Wall motion index improvement, %, (baseline/follow-up) At rest At stress	NA	NA	NA
ST-segment depression during exercise, n of mm (at mean heart rate beats/min), (baseline/follow-up)	NA	No change from baseline.	NA
Antianginal medications intake, median n (±SD), (baseline/follow-up)	2.77 (1.04)/ 2.00 (1.2)	At 1 year: 3.1 (1.3)/ 3.0 (1.3) (n=117) At 2 year: 3.1 (1.3)/ 3.0 (1.5) (n=71)	NA
	Safety		
SADEs, n (%)	NA	23/228 (10.1) pts (32 events)	NA
Death, n (%)	Total mortality: 14/177 (7.9) pts Cardiovascular death: 7/177 (4) pts	Total mortality: 13/228 (5.7) pts Cardiovascular death: 6/228 (2.6) pts	Total mortality: 15/99 (15.1)[49] pts
MI, n (%)	14 (7.9) pts	16/228 (7.0) pts (21 events)	9 (9) pts
Major stroke, n (%)	NA	4/228 (1.8) pts (5 events)	3/99 (3.0) pts
Stable angina, n (%)	NA	NA	NA
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

[49] Among patients which were enrolled in the clinical study but did not reach the 2 year follow-up the mortality rate was 31/197 (15.7) with a mean time to death of 3.2 (SD 2.3) years. Cause of death were not available for all patients therefore only the total mortality was reported.

Author, year	D'Amico et al. 2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Decompensated heart failure, n (%)	NA	NA	NA
Gastrointestinal bleeding, n (%)	NA	NA	NA
Injury, n (%)	NA	NA	NA
CAD progression, n (%)	21 (11.9)	NA	NA
Bleeding events associated with dual antiplatelet therapy, n (%)	NA	NA	NA
ADEs (at least 1 ADE in n of pts (%))	NA	NA	NA
Hospitalization, n (%)	NA	15 (13.3) pts (22 events)[50]	28 (28.2) pts
Coronary angiogram, n (%)	New angiography: 30 (16.9) pts	NA	Repeat angiography: 31 (31.3) pts
Revascularization, n (%)	Repeat PCI: 23 (12.9) pts	NA	Repeat PCI: 21 (21.2) pts
Device migration, n (%)	NA	NA	1 (1) pts

***Abbreviations: 6MWT** – 6 minute walk test**, AE – adverse event, ADE** – adverse device effect, **AP** – angina pectoris, **CABG** – coronary artery bypass grafting, **CAD** – coronary artery disease, **CCS** – Canadian Cardiovascular Society, **CS** – coronary sinus, **CSRS** – coronary sinus reducing stent, **COPD** -chronic obstructive pulmonary disease, **CS** – coronary sinus, **DSE** - Dobutamine Stress Echocardiogram, **ETT** - exercise tolerance test, **LVEF** – left ventricular ejection fraction, **MACE** – major adverse cardiovascular events, **MI** – myocardial infarction, **MIBI SPECT** – myocardial perfusion imaging/single-photon emission computed tomography, **mos** – months, **n** – number, **MRI** – magnetic resonance imaging, **NA** – not available, **PAD** – peripheral artery disease, **PCI** – percutaneous coronary intervention, **pts** – patients, **QoL** – quality of life, **RAP** – right atrial pressure, **SADE** – serious adverse device effects, **SAQ** – Seattle Angina Questionnaire, **SD** – standard deviation*

[50] The average number of visits per patient was 0.19 (0.6) (range: 0-4) ($p<0.0001$)

Risk of bias tables and GRADE evidence profile

Table A - 5: Risk of bias – study level (RCTs) of the 2020 Assessment Report

Trial	Adequate generation of randomisation 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, [6]	Yes	Yes	Yes	No	No	Yes	Low

Table A - 6: Risk of bias – study level (case series) of the 2020 Assessment Report

Study reference/ID	Banai et al., 2007, [7]	Giannini & Baldetti et al., 2018, [11]	Konigstein et al., 2014, [8]	Konigstein et al., 2018, [12]	Ponticelli et al., 2019, [9]	Tzanis et al., 2019, [10]
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[51]	Unclear[52]	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	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[53]	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[54]
Intervention and co-intervention						
8. Was the intervention clearly described?	Yes	Partial[55]	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes

[51] While it is stated in the methods that this study was conducted prospectively, the limitations section states that it was retrospective.

[52] It is assumed that the study was conducted prospectively, however, it is unclear at times as some baseline data is missing.

[53] However, baseline CCS score was not described.

[54] Insufficient baseline information provided.

[55] The process of CSRS implantation was not clearly described.

Study reference/ID	Banai et al., 2007, [7]	Giannini & Baldetti et al., 2018, [11]	Konigstein et al., 2014, [8]	Konigstein et al., 2018, [12]	Ponticelli et al., 2019, [9]	Tzanis et al., 2019, [10]
Outcome measure						
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial[56]	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No[57]	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[58]
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[59]	Yes	Partial[59]	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	No[60]	Yes	No[60]	No[60]	No[60]
Competing interest and source of support						
20. Were both competing interest and source of support for the study reported?	Partial[61]	Partial[61]	Partial[61]	Partial[61]	Partial[61]	Partial[61]
Overall Risk of bias	Low	Moderate	Moderate	Low	Low	Low

[56] Only efficacy measure was clearly established.

[57] The 2 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.

[58] The length of follow-up was shorter – as compared to the rest of prospective studies – and so it is unclear if further SAEs/AEs would show up at longer follow-up.

[59] It was reported that no SAEs occurred in the study population, yet AEs are not reported (and most presumably occurred).

[60] The study design cannot meet the conclusions about effectiveness.

[61] The source of financial support is nor clearly stated in the publication.

Table A - 7: Risk of bias – study level (case series), update evidence

Study reference/ID	D'Amico et al.2021 [17]	Verheye et al. 2020 [19]	Konigstein et al. 2021 [18]
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Yes	Partial[62]	Partial[63]
3. Were the cases collected in more than one centre?	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Yes
Study population			
5. Were the characteristics of the participants included in the study described?	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Partial[64]
7. Did participants enter the study at similar point in the disease?	Yes	Yes	Yes
Intervention and co-intervention			
8. Was the intervention clearly described?	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes
Outcome measure			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	No[65]
13. Were the relevant outcomes measured before and after intervention?	Yes	Yes	Yes
Statistical Analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	No[66]	Yes
Results and Conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes

[62] The study had two study arms of which one arm was part of a retrospective analysis.

[63] Authors report that adverse events were partially collected retrospectively, from clinical documents and patient interviews.

[64] Only the inclusion criteria were clearly stated.

[65] Authors report that differences in the data collection and event definitions could exist between centres, which might have influenced the results.

[66] Adverse events are analysed for the overall cohort, no detailed analysis for Arm 1 (prospective arm) and Arm 2 (retrospective arm).

16. Was the loss to follow-up reported?	Yes	Yes	Yes[67]
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No[68]	No[68]	No[68]
18. Were adverse events reported?	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes
Competing interest and source of support			
20. Were both competing interest and source of support for the study reported?	Partial[69]	Yes	Partial[69]
Overall Risk of bias	Moderate	High	High

[67] Although it was reported but the patients who did not complete the 2 year follow-up were excluded from the analysis resulting in a serious selection bias.

[68] The study did not report estimates of random variability for safety outcomes, which are considered in the present assessment.

[69] Information on funding is not given.

List of ongoing trials

Table A - 8: List of ongoing trials of CSRS for refractory AP

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02710435/ REDUCER-I	400	Reducer™ System (Neovasc)	No comparator	CCS angina score reduction at 6 months, SADEs within 30 days post impant, MACEs within 30 days post implant	Dec 31, 2022	Neovasc
NCT01566175	100	Reducer™ System (Neovasc)	No comparator	CCS angina score at 6 months	Dec 31, 2030	Neovasc
NCT04121845	40	Reducer™ System (Neovasc)	Placabo procedure	Impact of CSRS on exertional capacity measured by maximal oxygen consumption (VO2) during cardio-pulmonary exercise testing	Dec 31, 2021	University Medical Centre Ljubljana
NCT05102019/ COSIRA-II	380	Reducer™ System (Neovasc)	Implantation procedure with no device implanted	Exercise treadmill stress test at 6 months, death, MI, pericardial effusion requiring surgical or percutaneous intervention, device embolization, or BARC 3 or 5 bleeding	June 2024	Neovasc
NCT04892537/ORBITA-COSMIC	40	Reducer™ System (Neovasc)	Pacebo procedure	Change in myocardial perfusion reserve	Jan 2024	Imperial College London

Abbreviations: BARC *- Bleeding Academic Research Consortium,* ***CSRS*** *– coronary sinus reducing stent,* ***CCS*** *– Canadian Cardiovascular Society,* ***MACE*** *– major adverse cardiovascular events,* ***MI*** *– myocardial infarction,* ***NA*** *– not available,* ***SADE*** *– serious adverse device effect*

Literature search strategies

Search strategy for Cochrane

ID	Search
#1	MeSH descriptor: [Coronary Artery Disease] explode all trees
#2	(Corona* Arter*) (Word variations have been searched)
#3	(CAD):ti,ab,kw (Word variations have been searched)
#4	#1 OR #2 OR #3 (Word variations have been searched)
#5	MeSH descriptor: [Angina Pectoris] explode all trees
#6	(Angina*) (Word variations have been searched)
#7	(angor pectoris) (Word variations have been searched)
#8	(stenocardia*) (Word variations have been searched)
#9	(steno-cardia*) (Word variations have been searched)
#10	#5 OR #6 OR #7 OR #8 OR #9 (Word variations have been searched)
#11	#4 OR #10 (Word variations have been searched)
#12	MeSH descriptor: [Coronary Sinus] explode all trees
#13	(Sinus) (Word variations have been searched)
#14	#12 OR #13 (Word variations have been searched)
#15	#11 AND #14 (Word variations have been searched)
#16	(corona* sinus NEAR (reduc* or narrow*)) (Word variations have been searched)
#17	(reducer*) (Word variations have been searched)
#18	(neovasc)
#19	#16 OR #17 OR #18 (Word variations have been searched)
#20	#15 AND #19 with Cochrane Library publication date Between Dec 2019 and Nov 2021 (Word variations have been searched)
#21	#15 AND #19 with Publication Year from 2019 to 2021, in Trials (Word variations have been searched)
#22	#20 OR #21 (Word variations have been searched)
#23	(conference abstract):pt
#24	(abstract):so
#25	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#26	#23 OR #24 OR #25
#27	#22 NOT #26
3 Hits	

Search strategy for Embase

	No. Query Results	Results
#24	#22 NOT #23	24
#23	#22 AND 'Conference Abstract'/it	8
#22	#15 AND #20 AND [13-12-2019]/sd NOT [27-11-2020]/sd	32
#21	#21. #15 AND #20	319
#20	#16 OR #17 OR #18 OR #19	3,313
#19	neovasc*:df	105
#18	reducer*:ti,ab,de,kw,dn	2,960
#17	corona*:ti,ab,de,kw AND ((sinus NEAR/4 (reduc* OR narrow*)):ti,ab,de,kw)	412
#16	'coronary sinus reducer'/exp	48
#15	AND #14	21,638
#11	#14. #12 OR #13	243,444
#13.	sinus:ti,ab,de,kw	243,444
#12	'coronary sinus'/exp	11,917
#11	#4 OR #10	668,367
#10	. #5 OR #6 OR #7 OR #8 OR #9	130,046
#9	'steno cardia*':ti,ab,de,kw	1
#8	stenocardia*:ti,ab,de,kw	940
#7	'angor pectoris':ti,ab,de,kw	73
#6	angina*:ti,ab,de,kw	123,842
#5	'angina pectoris'/exp	108,339
#4	#1 OR #2 OR #3	608,535
#3	cad:ti,ab	74,961
#2	'corona* arter*':ti,ab,de,kw	538,634
#1	'coronary artery disease'/exp	369,898
Date: 26 Nov 2021		

Search strategy Medline

1	exp Coronary Artery Disease/ (85874)
2	Corona* Arter*.mp. (321939)
3	CAD.ti,ab. (59524)
4	1 or 2 or 3 (344103)
5	exp Angina Pectoris/ (46299)
6	Angina*.mp. (82849)
7	angor pectoris.mp. (59)
8	stenocardia*.mp. (969)
9	5 or 6 or 7 or 8 (83021)
10	4 or 9 (394575)
11	exp Coronary Sinus/ (2273)
12	Sinus.mp. (173023)
13	11 or 12 (173023)
14	10 and 13 (9416)
15	(corona* sinus adj5 (reduc* or narrow*)).mp. (334)
16	reducer*.mp. (3368)
17	neovasc.mp. (21)
18	15 or 16 or 17 (3548)
19	14 and 18 (255)
20	limit 19 to dt=20191213-20211126 (73)
21	remove duplicates from 20 (37)

Search strategy HTA-INAHTA database

	Search step # Search query,"Hits","Searched At"
#10	(((corona* sinus) OR ((reduc*) AND ((Sinus) OR ("Coronary Sinus"[mhe])))) FROM 2019 TO 2021) AND (English OR German)[Language],"1","2021-11-26T22:17:16.000000Z"
#9	(((corona* sinus) OR ((reduc*) AND ((Sinus) OR ("Coronary Sinus"[mhe])))) FROM 2019 TO 2021) AND (English OR German)[Language],"1","2021-11-26T22:16:41.000000Z"
#8	((corona* sinus) OR ((reduc*) AND ((Sinus) OR ("Coronary Sinus"[mhe])))) FROM 2019 TO 2021,"1","2021-11-26T22:15:59.000000Z"
#7	(corona* sinus) OR ((reduc*) AND ((Sinus) OR ("Coronary Sinus"[mhe]))),"18","2021-11 26T22:15:27.000000Z"
#6	corona* sinus,"2","2021-11-26T22:14:42.000000Z"
#5	(reduc*) AND ((Sinus) OR ("Coronary Sinus"[mhe])),"17","2021-11-26T22:12:00.000000Z"
#4	reduc*,"3125","2021-11-26T22:11:49.000000Z"
#3	(Sinus) OR ("Coronary Sinus"[mhe]),"55","2021-11-26T22:11:37.000000Z"
#2	Sinus,"55","2021-11-26T22:11:14.000000Z"
#1	"Coronary Sinus"[mhe],"2","2021-11-26T22:10:19.000000Z"
Total hits: 1	

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