Percutaneous Transvascular Implantation of a Coronary Sinus Reducing Stent

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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.

CONTENT INFORMATION

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Content

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List of abbreviations

ACC.....American College of Cardiology
ADE .....Adverse device effect
AHA .....American Heart Association
AE.....adverse events
AP.....Angina pectoris
CABG.....Coronary-artery bypass grafting
CAD .....Coronary artery disease
CCS .....Canadian Cardiovascular Society
CG .....control group
CHF .....congestive heart failure
CMR.....cardiac magnetic resonance
COPD.....chronic obstructive pulmonary disease
CRT.....cardiac resynchronization therapy
CS .....coronary sinus
CSRS .....coronary sinus reducing stent
ECG.....electrocardiogram
ESC .....European Society of Cardiology
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
IG ..... intervention group
IHE ..... Institute of Health Economics
MI ..... myocardial infarction
MRI..... magnetic resonance imaging
NUB..... neue Untersuchungs- und Behandlungsmethoden
LAO ..... left anterior oblique
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

According to Global Burden of Disease 2015, cardiovascular disease at large causes an estimated 17.92 million deaths per year [1]. Ischemic heart disease (that angina pectoris is part of) was the leading cause of all health loss globally as well as in each world region [1]. 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 [2].

AP is part of ischemic heart disease which is the leading cause of all health loss globally and in each world region

AP refers to long-lasting symptoms due to reversible ischemia despite escalating medical therapy

The risk factors for developing CAD (and eventually refractory AP) are high blood pressure, high blood cholesterol levels, smoking, diabetes, overweight or obesity, lack of physical activity, unhealthy diet, and stress. Those factors that cannot be controlled include: age, sex, family history, and race [3].

numerous risk factors

Description of Technology

Coronary sinus reducing stent (CSRS) is a stainless-steel mesh that is designed to create a focal narrowing in the lumen of the coronary sinus (CS). CSRS is pre-mounted on a customized hourglass shaped balloon catheter inserted into its place via the jugular vein under local anaesthesia [4]. The final expanded diameters are compatible with CS diameters of 9.5-13 mm at the proximal implant site [4].

CSRS is inserted via the jugular vein and creates a focal narrowing in the lumen of the CS

The mechanism of action of CSRS is unclear [5], 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 [6].

mechanism of action is unclear; the principle of a reverse angioplasty is assumed

The CSRS device (Neovasc Reducer™ System) received CE mark authorization in 2011 for the treatment of refractory AP [7]. In January 2020, Neovasc Inc. submitted premarket approval application to the US Food and Drug Administration (FDA) [8].

Neovasc Reducer™ has a CE mark; premarket approval application is submitted to the FDA

Methods

The aim of this systematic review was to investigate the use of CSRS in refractory AP patients when compared to sham CSRS procedure. The question was whether CSRS is more effective and safe or equally effective, but safer with respect to the crucial outcomes of Canadian Cardiovascular Society (CCS) angina score, Seattle Angina Questionnaire (SAQ) for quality of life (QoL) score, and serious adverse device effects (SADEs). The EUnetHTA Core Model for Rapid Assessment of Relative Effectiveness was the main source for selecting relevant assessment elements.

aiming to compare the efficacy and safety of CSRS to sham procedure

systematic search in 4 databases; 363 hits overall

The systematic literature search was conducted on the 10-13th of December 2019 in the following databases (Medline via Ovid, Embase, The Cochrane Library, CRD (DARE, NHS-EED, HTA)). The systematic search was not limited to years of publication, but it was limited to German and English. After deduplication, overall 349 citations were included. Together with additional 14 references found via hand search, the overall number of hits was 363.

search in 3 clinical trial registries, 13 potentially relevant hits; no response from the manufacturer

A search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 29-30.01.2020 resulting in 13 potentially relevant hits. The only known manufacturer Neovasc Inc. was contacted, but did not reply or submit any publications.

Results

Available evidence

1 RCT ("COSIRA", 104 patients) included for assessment of clinical effectiveness

For the assessment of clinical effectiveness, one study met the inclusion criteria. It was a randomized controlled trial (RCT) comparing CSRS with a sham procedure where no stent was implanted (study name COSIRA, NCT01205893). It was conducted in 11 centres in Belgium, Canada, Denmark, the Netherland, Sweden, and the UK between April 2010 and April 2013 and was sponsored by the manufacturer Neovasc Inc. [9]. The RCT included 104 patients, of which 52 were in the intervention group (IG) and 52 in the control group (CG). 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.

7 studies (1 RCT, 4 prospective case series, 2 prospective registries) included for safety assessment: 348 patients in total (+52 in CG)

For the assessment of safety, seven studies met the inclusion criteria. One RCT described above [9], four prospective case series [10-13], and two prospective registries [14, 15]. Together with the RCT [9], the total number of patients receiving the CSRS therapy was 348 (plus 52 patients in CG). The observational studies were conducted in Germany, India, Israel, Italy, and Belgium between October 2004 and April 2017 and none stated the source of funding. The follow-up ranged from four [10] to 24 months [11] and all but one [13] of these observational studies had improvement in CCS angina score as its primary outcome measure.

Clinical effectiveness

statistically significant differences between CSRS and sham procedure shown for: CCS angina score improvement of at ≥ 2 classes and by 1 class; overall mean reduction of CCS class and SAQ QoL score

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 [9]: CCS angina score improvement of at least two classes at six months follow-up (35% of IG as opposed to 15% of CG ($p=0.02$)); CCS angina score improvement by one class (71% of IG and 42% of CG ($p=0.003$)); overall mean reduction of CCS class (1.1 classes in IG and 0.5 classes in CG ($p=0.001$)); and SAQ QoL score improvement in IG by 17.6 points and in CG by 7.6 points ($p=0.048$).

Safety

lower rate of SADEs in the IG than in CG (19% vs. 46%); single case of death in CG

Concerning safety, the sham-controlled trial data indicate that there were less SADEs in the IG (19%) than in CG (46%) [9]. SADEs reported in observation studies remain to be a point of concern as they range from none [10, 13] to 30% [11]. The most frequently reported SADEs were death and stable angina. In the RCT, the only case of death occurred in CG [9]. 8% of observational studies patient died, while 5% of deaths were explicitly claimed not to be related to CSRS [11, 12, 14, 15].

Upcoming evidence

Currently, there are three ongoing studies on CSRS. Two prospective observational studies with 100 (NCT01566175) and 400 (NCT02710435) patients, and one RCT (NCT04121845) with 40 patients. There is also an ongoing ISCHEMIA trial (NCT01471522) that aims to determine the best management strategy for higher-risk patients with stable ischemic heart disease that has the potential to change the guideline for refractory AP patients considerably.

3 ongoing trials, including 1 RCT with 40 patients
one large ISCHEMIA trial to potentially change the guideline

Reimbursement

In Germany, the Institut für das Entgeltsystem im Krankenhaus, (the German Institute for the Hospital Remuneration System), has awarded the Neovasc Reducer™ an NUB Status 1 designation again for 2020 [16]. Neovasc Reducer™ is not known to be reimbursed in any other country. Concerning the costs of Neovasc Reducer™-System, in a 2019 cost-effectiveness analysis, the only manufacturer Neovasc Inc. assigned it the cost of 7,000 Euro [17].

Neovasc Reducer™ reimbursed currently only in Germany (NUB Status 1); according to manufacturer the costs amount to € 7,000

Discussion

Concerning clinical effectiveness (RCT [9]), the RoB was rated to be low and concerning safety, the RoB was rated to range from low [10, 11, 13, 14] to moderate [12, 15]. The main reasons for increased risk was assumed selective outcome reporting [12, 13] and the lack of clarity whether two studies were conducted prospectively [12, 15]. As assessed by GRADE, the overall strength of evidence for effectiveness and safety was moderate.

RoB for clinical effectiveness was low, for safety low to moderate; GRADE: moderate overall strenght of evidence

When interpreting the findings on clinical effectiveness, the issues with mechanism of action, placebo effect, sample size, randomization procedure, inconsistency between outcomes, and inappropriate inclusion criteria should be taken into account. While no study has evaluated the effect of CSRS upon myocardial perfusion and hence there is no clear demonstration of its mechanism of action [18], large placebo effects are associated with novel therapies in this specific patient population [2, 4, 18]. Also, the clinical benefit of CSRS may be overstated because the sample size is too small to reject a true null hypothesis [19] and potential issues with randomization were highlighted in the literature [19]. Furthermore, there was inconsistency between more objective outcomes such as exercise duration and CCS and SAQ QoL scores, and the patient group included in the studies does not fully correspond with the refractory AP definition.

issues with mechanism of action, placebo effect, sample size, randomization procedure, inconsistency between outcomes, and inappropriate inclusion criteria should be considered

Concerning the interpretation of safety findings, issues surrounding potential SADEs (such as device migration [20] or acute myocardial infarction caused by the implantation), obstruction of future therapy (cardiac-resynchronization therapy that refractory AP patients may require later on), and underreporting of complications related to dual antiplatelet therapy should be taken into account.

potential SADEs as well as obstruction of future therapy should be taken into account

In terms of external validity, the data is considered generalizable to other contexts. However, 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. Larger RCTs with longer follow-up are required to define the role of each treatment modality for specific subgroups, to decrease non-responder rates, and ascertain benefit beyond potential placebo effects [2].

data generalizable to other contexts; larger RCTs with longer follow-up required

Recommendation

currently not recommended;

re-evaluation recommended in 2022

The inclusion in the catalogue of benefits is currently not recommended. Even though the current evidence indicates 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, the lacking internal validity of the studies undermines the partially positive results. For the establishment in clinical practice, larger RCTs that can potentially influence the effect estimate are needed.

The re-evaluation is recommended in 2022 when results from ISCHEMIA trial might be published because those may change the effect estimate considerably

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

refraktäre Angina pectoris: lang andauernde Symptome durch myokardiale Ischämie welche durch Medikamente, Bypassoperation oder Stentimplanation nicht kontrollierbar sind

Laut Global Burden of Disease 2015 führen kardiovaskuläre Erkrankungen zu einer geschätzten Zahl von 17,92 Millionen Todesfällen weltweit pro Jahr [1]. Die ischämische Herzkrankheit (und damit auch die Angina pectoris) war die führende Ursache für den Verlust der Gesundheit weltweit [1]. Bei dem im vorliegenden Assessment thematisierten Gesundheitsproblem handelt es sich um die refraktäre Angina pectoris (AP). Laut Defintion der Europäischen Gesellschaft für Kardiologie (European Society of Cardiology, ESC) wird die AP durch lange andauernde Symptome (≥3 Monate) definiert, welche 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 [2].

Risikofaktoren nur teilweise beeinflussbar

Risikofaktoren für die Entstehung der KHK (und letztendlich auch der refraktären AP) sind erhöhter Blutdruck, erhöhter Cholesterinspiegel, Rauchen, Diabetes, Übergewicht oder Adipositas, mangelnde körperliche Aktivität, ungesunde Ernährung und Stress. Zu den Risikofaktoren die nicht beeinflussbar sind zählen Alter (ältere Menschen haben ein erhöhtes KHK-Risiko), Geschlecht (Männer haben generell ein höheres KHK-Risiko), Familienanamnese und Ethnizität [3].

Beschreibung der Technologie

CSRS erzeugt fokale Verengung im Koronarsinus

Der Koronarsinus-verengende Stent (Coronary sinus reducing stent, CSRS) ist ein Drahtgeflecht das eine fokale Verengung im Lumen des Koronarsinus (coronary sinus, CS) erzeugen soll. Der CSRS ist auf einem individuell angepassten, sanduhrförmigen Ballonkatheter vormontiert und wird unter Lokalanästhesie über die Jugularvene an seinen Platz gebracht [4]. Zur Gänze erweitert ist der Durchmesser des CSRS kompatibel mit einem Koronarsinus-Durchmesser von 9,5 bis 13 mm am proximalen Ende des Implantats [4].

Wirkungsweise unklar

Die Wirkungsweise des CSRS ist unklar [5], bislang ist die vorherrschende Hypothese, dass der CSRS wie eine reverse Angioplastie funktioniert. Während bei der Angioplastie eine Einschränkung des Blutflusses behoben wird, wird durch den CSRS eine Engstelle im Bereich des Blutabflusses geschaffen. Sobald der Stent mit dem Gewebe verwachsen ist, soll so die Perfusion der ischämischen Bereiche des Myokards gesteigert werden [6].

CE-Kennzeichnung seit 2011

Der CSRS (Neovasc Reducer™ System) erhielt 2011 eine CE-Kennzeichnung für die Behandlung der refraktären AP [7]. Im Januar 2020 wurde von Neovasc Inc. ein Zulassungsantrag an die US-amerikanische Behörde für Lebensmittel- und Arzneimittelsicherheit (US Food and Drug Administration, FDA) gestellt [8].

Methoden

Ist CSRS wirksamer und sicherer als eine entsprechende Scheinprozedur bei PatientInnen mit refraktärer AP?

Das Ziel dieser systematischen Übersichtsarbeit war es, die Anwendung von CSRS mit der Durchführung einer entsprechenden Scheinprozedur bei PatientInnen mit refraktärer AP zu vergleichen. Es sollte festgestellt werden, ob der CSRS wirksamer und sicherer oder gleich wirksam aber sicherer ist, und zwar in Bezug auf entscheidungsrelevante Endpunkte für die Wirksamkeit (mittels Canadian Cardiovascular Society (CCS) Angina Score und Seattle Angina Fragebogen (Seattle Angina Questionnaire, SAQ) zur Lebensqualität (quality of life, QoL)), sowie zu schwerwiegenden Nebenwirkungen. Das EUnetHTA Core Model für Rapid Assessment of Relative Effectiveness diente als Basis für die Auswahl relevanter Elemente für die Bewertung.

systematische Literatursuche in 4 Datenbanken

Gesamtzahl der identifizierten Referenzen: 363

Vom 10. bis 13. Dezember 2019 wurde eine systemische Literatursuche in vier Datenbanken (Medline via Ovid, Embase, The Cochrane Library, CRD (DARE, NHS-EED, HTA)) durchgeführt. Die Suche war nicht auf das Publikationsjahr, aber auf Ergebnisse in deutscher und englischer Sprache beschränkt. Nach erfolgter Deduplikation wurden insgesamt 349 Referenzen in das vorliegende Assessment eingeschlossen. Zusammen mit 14 Referenzen welche im Rahmen der Handsuche gefunden wurden, lag die Gesamtzahl der Treffer bei 363.

Suche in 3 klinischen Studienregistern ergab 13 Treffer

keine Rückmeldung des Herstellers

Eine Suche in drei klinischen Studienregistern (ClinicalTrials.gov, WHO-ICTRP und EU Clinical Trials), durchgeführt am 29./30. Januar 2020, ergab 13 potentiell relevante Treffer. Der einzig bekannte Hersteller Neovasc Inc. wurde kontaktiert, allerdings erfolgte weder eine Rückmeldung noch die Bereitstellung von Publikationen.

Ergebnisse

Verfügbare Evidenz

RCT mit 104 PatientInnen eingeschlossen (52 davon erhielten den CSRS); Follow-up nach 6 Monaten

Anteil der PatientInnen mit Steigerung von ≥2 CCS-Klassen als primärer Endpunkt

Für die Analyse der klinischen Wirksamkeit wurde eine randomisierte, kontrollierte Studie (randomized controlled trial, RCT) eingeschlossen. Im Rahmen dieser Studie („COSIRA“, NCT01205893) wurde der CSRS mit einer Scheinprozedur (ohne Implantation eines Stents) verglichen. Die Studie wurde zwischen April 2010 und April 2013 in 11 Zentren in Belgien, Kanada, Dänemark, den Niederlanden, Schweden und Großbritannien durchgeführt und vom Hersteller Neovasc Inc. gesponsert [9]. An der Studie nahmen 104 PatientInnen teil, 52 davon in der Interventionsgruppe (IG) und 52 in der Kontrollgruppe (CG). Die PatientInnen wurden 6 Monate lang beobachtet, bei allen PatientInnen wurde eine Verlaufskontrolle durchgeführt. Als primärer Endpunkt der COSIRA-Studie wurde der Anteil der PatientInnen mit einer Steigerung von zwei oder mehr CCS-Klassen definiert.

7 Studien mit insgesamt 400 PatientInnen für die Analyse der Sicherheit eingeschlossen

Follow-up zwischen 4 und 24 Monaten

Um die Sicherheit des CSRS zu analysieren wurden sieben Studien eingeschlossen. Darunter der zuvor beschriebene RCT [9], vier prospektive Fallserien [10-13] und zwei prospektive Registerstudien [14, 15]. Von insgesamt 400 PatientInnen (inklusive der RCT-PatientInnen) [9], erhielten 348 PatientInnen einen CSRS. Die Beobachtungsstudien wurden in Deutschland, Indien, Israel, Italien und Belgien zwischen Oktober 2004 und April 2017 durchgeführt, zur Finanzierung dieser Studien sind keine Informationen verfügbar. Das Follow-up wurde in einem Zeitrahmen zwischen vier [10] und 24 Monaten durchgeführt [11] und in allen außer einer [13] der genannten Beobachtungsstudien wurde die Steigerung im CCS Angina Score als primärer Endpunkt angeführt.

Klinische Wirksamkeit

Endpunkte mit statistisch signifikantem Unterschied

Bezüglich der klinischen Wirksamkeit gibt es Ergebnisse des RCT, welche für die PatientInnen potentiell klinisch relevant sind. Endpunkte mit einem statistisch signifikanten Unterschied zwischen dem CSRS und der Scheinprozedur sind [9]:

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

Endpunkte ohne statistische Signifikanz

Bei folgenden Endpunkten konnte keine statistische Signifikanz erreicht werden: SAQ Behandlungszufriedenheit (p=0,981), Gesamtverlängerung der Belastungsdauer (p=0,072) (mittlere Verlängerung der Belastungsdauer (p=0,07)), Steigerung des Wall Motion Index (p=0,20) [9].

Sicherheit

RCT: niedrigere Rate von SADEs bei PatientInnen der IG

Was die Sicherheit betrifft, weisen die kontrollierten Daten des RCT darauf hin, dass in der IG (19 %) weniger schwerwiegende Nebenwirkungen des Produktes (serious adverse device effects, SADEs) auftraten als in der CG (46 %) [9]. Anlass zur Sorge gibt die Rate der SADEs in den Beobachtungsstudien, da diese zwischen 0 [10, 13] und 30 % variiert [11]. Die am häufigsten berichteten SADEs waren Todesfälle und stabile Angina. Im Rahmen des RCT ereignete sich der einzige Todesfall in der CG [9]. 8 % der PatientInnen der Beobachtungsstudien verstarben, 5 % der Todesfälle wurden explizit als nicht in Zusammenhang mit CSRS stehend beschrieben [11, 12, 14, 15].

Rate der SADEs in Beobachtungsstudien variiert stark

ADEs: Bedenken hinsichtlich zu geringer Angaben

Dieselben Bedenken hinsichtlich zu geringer Angaben von Komplikationen betrifft auch die unerwünschten Nebenwirkungen des Produktes (adverse device effects, ADEs). Während im Rahmen des RCT 64 % der PatientInnen in der IG und 69 % in der CG ADEs erlitten, reichte die Zahl der ADEs in den Beobachtungsstudien von 0 [10] bis 45 %[15].

Laufende Studien

derzeit 3 laufende Studien, davon 1 RCT mit 40 PatientInnen; Ergebnisse der laufenden ISCHEMIA-Studie könnte Leitlinie für die Behandlung refraktärer AP maßgeblich beeinflussen

Derzeit gibt es drei laufende Studien zum CSRS. Zwei prospektive Beobachtungsstudien mit 100 (NCT01566175) und 400 (NCT02710435) PatientInnen und einen RCT (NCT04121845) mit 40 PatientInnen. Im Rahmen der derzeit laufenden ISCHEMIA-Studie (NCT01471522) soll die bestmögliche Management-Strategie für die Behandlung von PatientInnen mit stabiler ischämischer Herzerkrankung und höherem Risiko ermittelt werden. Die Ergebnisse könnten potenziell die Leitlinie für die Behandlung von PatientInnen mit refraktärer AP maßgeblich beeinflussen.

Kostenerstattung

Kostenerstattung derzeit nur in Deutschland, Kosten laut Hersteller: € 7.000

In Deutschland wurde dem Neovasc Reducer™ vom Institut für das Entgeltsystem im Krankenhaus, für 2020 wieder der NUB Status 1 zuerkannt [16]. Eine Kostenerstattung in anderen Staaten ist nicht bekannt. Im Rahmen einer Kosten-Wirksamkeitsanalyse (2019) wurden die Kosten vom Hersteller Neovasc Inc. mit € 7.000 beziffert [17].

Diskussion

Gesamtstärke der Evidenz nach GRADE: moderat

In Bezug auf die klinische Wirksamkeit (RCT [9]), wurde das Verzerrungspotential (Risk of Bias, RoB) als niedrig und bezüglich der Sicherheit als niedrig [10, 11, 13, 14] bis moderat bewertet [12, 15]. Hauptursachen für das erhöhte Risiko sind die mutmaßlich selektive Berichterstattung [12, 13] und die Unklarheit darüber, ob zwei der Studien prospektiv durchgeführt wurden. Die Gesamtstärke der Evidenz für Wirksamkeit und Sicherheit wurde nach GRADE als moderat bewertet.

relevante Fragestellungen hinsichtlich Wirkmechanismus, Placeboeffekt, Fallzahl, Randomisierung, Inkonsistenz von Ergebnissen sowie inadäquater Einschlusskriterien

Im Rahmen der Interpretation der Ergebnisse zur klinischen Wirksamkeit, sollten die Fragestellungen hinsichtlich Wirkmechanismus, Placeboeffekt, Fallzahl und Randomisierungsprozess, Inkonsistenz zwischen Ergebnissen und inadäquater Einschlusskriterien miteinbezogen werden. So gibt es keine Studie zur Untersuchung der Wirkung von CSRS auf die myokardiale Perfusion und daher auch keinen eindeutigen Nachweis des Wirkmechanismus [18], obwohl gerade in dieser Patientenpopulation neuartige Therapien mit ausgeprägten Placeboeffekten assoziiert sind [2, 4, 18]. Auch könnte eine übersteigerte Einschätzung des klinischen Nutzens des CSRS vorliegen, da die Fallzahl zu niedrig ist um eine wahre Nullhypothese zu verwerfen [19] und in der Literatur potentielle Probleme hinsichtlich der Randomisierung hervorgehoben wurden [19]. Es besteht eine Inkonsistenz zwischen objektiveren Parametern wie der Belastungsdauer einerseits und den CCS- und SAQ QoL Scores andererseits. Eine weitere Unstimmigkeit besteht hinsichtlich der Definition der refraktären AP und den Einschlusskriterien aller prospektiven Studien bezüglich der Dauer der Symptomatik und des Gebrauchs antianginöser Medikamente.

potentielle SADEs, Blockade des CS für zukünftige Therapien und Komplikationen durch DAPT berücksichtigen

Im Rahmen der Interpretation der Sicherheitsergebnisse sollten Fragestellungen zu potentiellen SADEs, die Blockade des CS für zukünftige Therapien und die zu geringen Angaben von Komplikationen in Zusammenhang mit der zweifachen Thrombozytenaggregationshemmung (dual antiplatelet therapy, DAPT) berücksichtigt werden.

anatomische Gegebenheiten zu beachten

Bei etwa 20 % der PatientInnen mit refraktärer AP kann der CSRS aufgrund von Variabilitäten in Anatomie und Größe des CS nicht implantiert werden. Die anatomischen Gegebenheiten sollten auch hinsichtlich der Implantationsprozedur berücksichtigt werden. Dazu zählt die Nähe der Koronararterie, deren Beschädigung einen akuten Myokardinfarkt verursachen würde, sowie das Vorhandensein einer Thebesius-Klappe oder einer Vieussen-Klappe (in bis zu 85 % der PatientInnen), welche die Implantation erschweren könnten [21]. Ein weiteres Problem könnten SADEs, entstanden durch Stentmigration – Fälle von Stentmigration in das rechte Atrium wurden beschrieben – darstellen [20]. Auch sollten, da eine DAPT mit Aspirin und Clopidogrel für 6 Monate nach der CSRS-Implantation empfohlen wird [4], die mit der DAPT in Zusammenhang stehenden Komplikationen – neben den Komplikationen durch CSRS – berücksichtigt werden. Der tatsächliche Gebrauch von DAPT wurde nur in zwei Studien beschrieben [9, 15], in keiner der Studien wurde über Blutungen in Zusammenhang mit DAPT berichtet.

Stentmigration als Problem

Komplikationen durch DAPT

CS durch CSRS für künftige Therapien blockiert

Da die Entstehung einer Herzinsuffizienz bei einem beträchtlichen Anteil der PatientInnen mit refraktärer AP möglich ist, gibt es Bedenken, dass ein im CS implantierter CSRS eine künftige Nutzung des Sinus im Rahmen einer kardialen Resynchronisationstherapie unmöglich machen könnte [19].

Daten nicht generalisierbar

In Bezug auf die externe Validität sind die Daten nicht auf PatientInnen mit refraktärer AP in anderen Kontexten generalisierbar. Obwohl die Studien in Deutschland, Indien, Italien, Israel, Belgien, Kanada, Dänemark, den Niederlanden, Schweden und Großbritannien durchgeführt wurden und diese Kontexte dem österreichischen Kontext ähnlich sind, wird die Generalisierbarkeit der Ergebnisse dadurch unterminiert, dass nicht nur PatientInnen mit refraktärer AP eingeschlossen wurden. Weiters ist fraglich, in welchem Ausmaß die hochspezifischen Ein- und Auschlusskriterien der Studien im „real-world"-Kontext angewandt werden können.

umfangreichere RCTs mit längerem Follow-up sind erforderlich

Die vorhandene Evidenzgrundlage war bei der Beantwortung der Forschungsfrage nur teilweise relevant. Der einzige identifizierte RCT war zwar für das Ausschließen von Placeboeffekten relevant, dieses Ergebnis wurde aber teilweise dadurch unterminiert, dass neuartige Therapien in dieser speziellen Patientenpopulation mit starken Placeboeffekten assoziiert sind [2]. Umfangreichere RCTs – durchgeführt über längere Beobachtungszeiträume – sind erforderlich um Behandlungsmodalitäten für spezielle Teilgruppen zu definieren, um die Anzahl der Non-Responder zu senken und um den Nutzen des CSRS über einen möglichen Placeboeffekt hinaus zu ermitteln [2].

sozio-ökonomische und ethische Aspekte

Bei der Betrachtung sozio-ökonomischer und ethischer Aspekte von CSRS, sollten die Auswirkungen der neuen Intervention im Lichte der Prinzipien Fürsorge, Schadensvermeidung, Autonomie, Gerechtigkeit und Unsicherheit betrachtet werden. Derzeit ist unklar ob CSRS das Potential hat, den CCS Angina Score und die Lebensqualität (gemessen mittels SAQ) zu erhöhen ohne zu einer höheren Rate an SADEs zu führen als die Scheinprozedur (basierend auf einer moderaten Qualität der Evidenz). Die Gründe dafür sind die ungeeigneten Einschlusskriterien der Studien, die unvollständige Verblindung im Rahmen des RCT, inkonsistente Ergebnisse und unvollständige Sicherheitsdaten in Bezug auf DAPT. Auch muss die Tatsache, dass mit dem CSRS eine therapeutische Lücke geschlossen werden kann und die Intervention ein positives Sicherheitsprofil aufweist in Kontext gebracht werden mit dem mangelnden Wissen über den Wirkmechanismus, weitere potentielle SADEs und das Fehlen eines Langzeit-Sicherheitsprofils. Darüberhinaus sollte die Kosteneffektivität des CSRS [17] dem überhöhten Placeboeffekt in dieser speziellen (relativ kleinen) Zielgruppe gegenübergestellt werden. Vor dem Hintergrund dieses komplexen Bildes von CSRS muss festgehalten werden dass, laut ESC 2019 Leitlinien, CSRS mit der Empfehlung 2b versehen wurde – dies bedeutet, dass der Nutzen von CSRS weniger gut durch Evidenz fundiert ist, dass die Intervention aber für die Nutzung in der klinischen Praxis in Betracht gezogen werden kann.

Empfehlung

Aufnahme derzeit nicht empfohlen

Eine Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen. Die vorhandene Evidenz weist zwar darauf hin, dass der CSRS – bei PatientInnen 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.

Re-Evaluierung für 2022 empfohlen

Um den CSRS in der klinischen Routine zu etablieren werden umfangreichere RCTs, welche potenziell den Effektschätzer beeinflussen könnten, benötigt. Eine Re-Evaluierung wird für 2022 empfohlen wenn die Ergebnisse der ISCHEMIA-Studie publiziert worden sind, da diese den Effektschätzer maßgeblich beeinflussen könnten.

1 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 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is CSRS and the comparator(s)?
A0020	For which indications has CSRS received marketing authorisation or CE marking?
B0002	What is the claimed benefit of CSRS in relation to the comparators?
B0003	What is the phase of development and implementation of CSRS?
B0004	Who administers CSRS and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use CSRS?
B0009	What supplies are needed to use CSRS?
A0021	What is the reimbursement status of CSRS?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is CSRS used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is CSRS utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of CSRS on mortality?
D0003	What is the effect of CSRS on the mortality due to causes other than the target disease?
D0005	How does CSRS affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does CSRS affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of CSRS on patients' body functions?
D0016	How does the use of CSRS affect activities of daily living?
D0012	What is the effect of CSRS on generic health-related quality of life?
D0013	What is the effect of CSRS on disease-specific quality of life?
D0017	Was the use of CSRS worthwhile?

Safety	
Element ID	Research question
C0008	How safe is CSRS in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying CSRS?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of CSRS?
C0007	Are CSRS and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of CSRS and the comparator?

2.2 Sources

Quellen: Handsuche, systematische Suche sowie Informationen des einreichenden Krankenhauses

Description of the technology

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospitals

For the domains clinical effectiveness and safety a systematic literature search and hand search was conducted, as described in detail in the following chapter.

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 10-13th of December 2019 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was not limited to years of publication, but it was limited to German and English. After deduplication, overall 349 citations were included. The specific search strategy employed can be found in the Appendix.

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 29-30.01.2020 resulting in 13 potentially relevant hits.

Suche nach laufenden Studien

The only known manufacturer Neovasc Inc. was contacted, but did not reply or submit any publications.

keine Rückmeldung des Herstellers

By hand-search, an additional 14 references were found, resulting in overall 363 hits.

insgesamt wurden 363 Publikationen identifiziert

2.4 Flow chart of study selection

Overall 363 hits were identified. The references were screened by two independent researchers (MS, ER) and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl

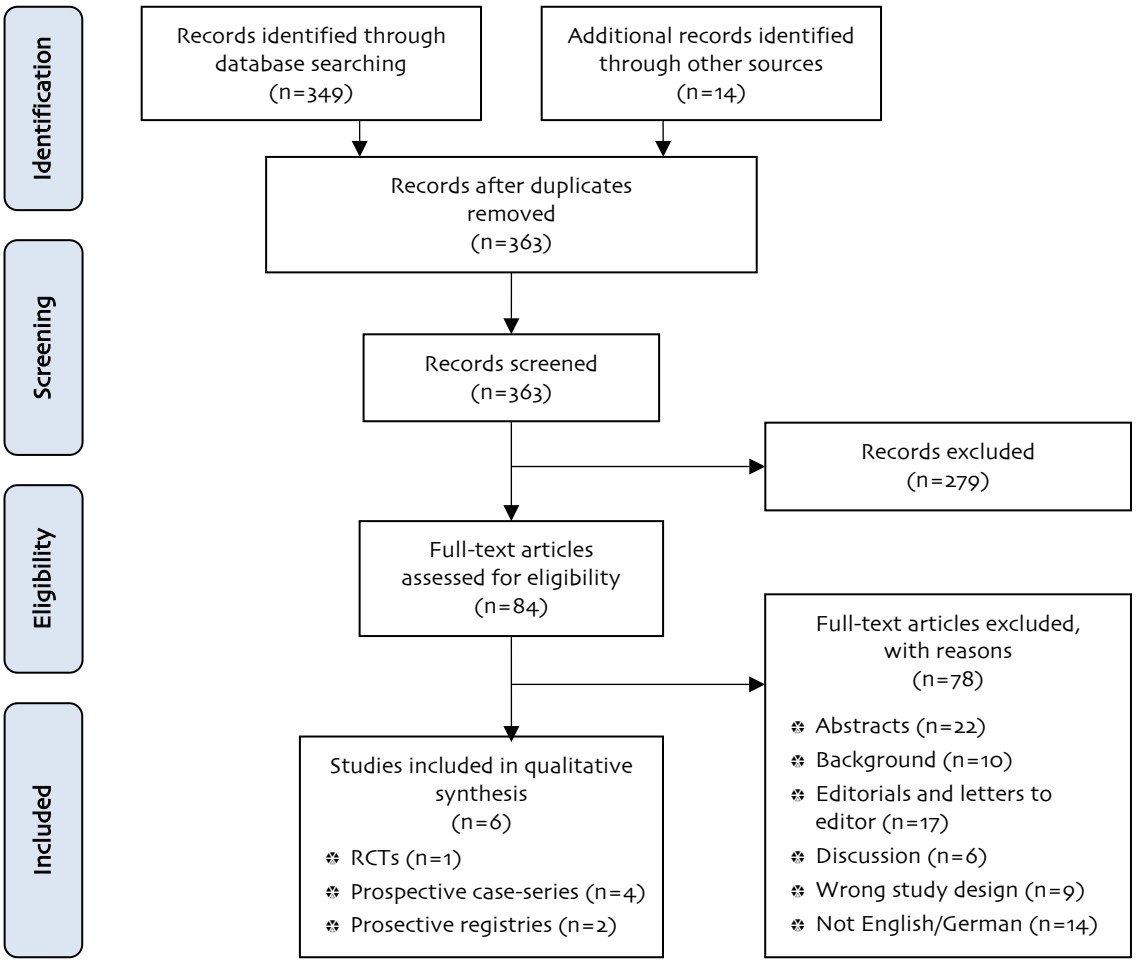

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion, Bewertung der Qualität der Evidenz und des Biasrisikos

The data retrieved from the selected studies were systematically extracted into a data-extraction-table (see Table A-1). No further data processing (e.g. indirect comparison) was applied. Two independent researchers (MS, ER) systematically assessed the quality of evidence. No cases of disagreement occurred (see Table 7-1). The risk of bias (RoB) was assessed using the checklists presented in Table A-3 and Table A-4.

2.6 Synthesis

Evidenzsynthese mittels GRADE

Based on the data-extraction-table (see Table A-1), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [22]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 7-1).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is CSRS and the comparators?

CSRS description

Coronary sinus reducing stent (CSRS) is a stainless-steel mesh that is designed to create a focal narrowing in the lumen of the coronary sinus (CS) (see Figure 3-1). Within four to six weeks after implantation – once the device is covered by tissue ingrowth – CSRS claims to create a pressure gradient across the CS that aims to improve the symptoms of patients with refractory angina pectoris (AP). The balloon is available in one single size and once inflated, the expanded balloon gives the metal mesh its hourglass configuration [4]. The final expanded diameters are dependent on the inflation pressure and CSRS is compatible with CS diameters of 9.5-13 mm at the proximal implant site [4]. The proximal and distal portions of the device are configured to different diameters (based on balloon expansion), which allows the device to conform to the tapered configuration of the individual patient's anatomy of the CS, with the centre narrowing being consistently 3 mm in diameter [4].

CSRS erzeugt eine fokale Verengung des Koronarsinus

durch den entstehenden Druckgradienten sollen die Symptome der refraktären AP verbessert werden

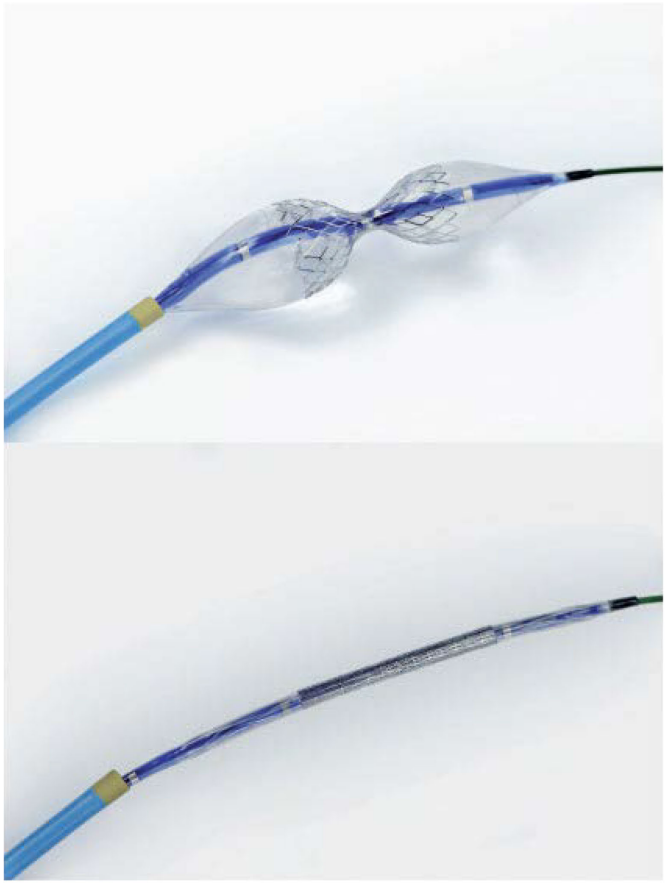

Figure 3-1: CSRS stainless steel balloon expandable mesh [4]

die Verengung kann nach der Implantation jederzeit erweitert werden

During implantation, both wide ends of CSRS are oversized by 10-20% with the purpose of: (1) anchoring CSRS into the elastic vessel wall to help prevent migration and (2) to trigger a process of injury-induced tissue proliferation [4]. The central narrowing can be easily dilated if needed with the use of a 5-8 mm balloon at any time after implantation [4].

Implantation

Vorbehandlung mit Aspirin und Clopidogrel

Zugang über die rechte Vena jugularis interna

Before the implantation of CSRS, patients are pre-treated with aspirin and clopidogrel and under local anaesthesia and ultrasound guidance, a 9 F introducer sheath is inserted into the right internal jugular vein [4]. In a left anterior oblique (30 degree) angulation, the CS is engaged with a diagnostic multipurpose catheter. After confirming that the catheter tip is in the lumen of the main vessel, venography is performed to size the CS, locate side branches, and identify the preferred site for device implantation. The ideal location for implantation is usually about 2-4 cm distal to the CS ostium, where the CS diameter is between 7-13 mm, avoiding side branches.

der Stent wird mittels Katheter im Koronarsinus platziert

dann erfolgt die Aufdehnung

abschließende Venographie

Aspirin und Clopidogrel für 6 Monate empfohlen

The selected site for implantation is landmarked by bony markers (vertebrae, inter-vertebral space). A wire is then advanced within the multipurpose catheter deep into the CS, and the diagnostic catheter is removed. After intravenous administration of 70 u/kg of unfractionated heparin, the CSRS inside a 9 F guiding catheter is advanced over the guide wire into the CS. The guiding catheter is withdrawn, exposing the CSRS, which is held in the landing zone previously identified. While the balloon is fully inflated, a small amount of contrast is injected through the guiding catheter to verify sufficient oversizing [4]. The final venography is then conducted to confirm the correct position of the scaffold and exclude complications. After the CSRS implantation, a dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended for 6 months [4].

Mechanism of action

Wirkmechanismus unklar, Funktionsweise wird als retrograde Angioplastie betrachtet

The mechanism of action of CSRS is unclear [5], 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. As coronary veins provide a direct retrograde access route to the ischemic myocardium, in case of myocardial ischaemia, this outflow narrowing is intended to improve perfusion to ischaemic territories of the myocardium [6]. It claims to do so by forcing redistribution of blood from the less ischaemic subepicardium to the more ischaemic subendocardium, thus alleviating the symptoms of angina. By elevating the backward pressure in the coronary venous system, a slight dilatation of the diameter of arterioles is created, which may lead to a reduction to vascular resistance in the subendocardium. Consequently, blood flow in the ischaemic subendocardial layers of the myocardium may be enhanced, contractility improved, and left ventricular end diastolic pressure decreased. Thus, the result of the decreased subendocardial vascular resistance may be the redistribution of blood from the less ischaemic subepicardium to the more ischaemic subendocardium, which may lead to symptom relief [4]. The neovascularisation created by CSRS is thus expected to take a few weeks and hence also clinical improvement is, in most cases, reported to have started a few weeks following the procedure [23].

Comparators to CSRS

weitere Behandlungsmöglichkeiten für PatientInnen mit refraktärer AP

The use of CSRS is suggested to be put in place once all the other therapeutic options are exhausted. The alternative options for refractory angina patients (of which none, except for external counterpulsation, is based on controlled evidence) include the following interventions [2, 24]:

- **External counterpulsation** – also referred to as enhanced external counterpulsation – is a technique that increases arterial blood pressure and retrograde aortic blood flow during diastole. Cuffs are wrapped around the patient's calves, thighs, and pelvis and, using compressed air, sequential pressure (up to 300 mmHg) is applied in early diastole to propel blood back to the heart.
- **Neuromodulation** includes a spectrum of therapies that aim at altering the relationship between the heart, its autonomic innervation, and the central nervous system with the purpose of reducing the ischaemic burden and diminishing the perception of angina. The neuromodulation therapies include spinal cord stimulation, transcutaneous electrical neural stimulation, subcutaneous electrical neural stimulation, and sympathectomy.
- **Transmyocardial laser revascularization** is a procedure that uses laser ablation to create transmural channels in the ischemic myocardium in order to restore myocardial perfusion.
- **Apheresis** is an extracorporeal medical therapy in which the blood of a person is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. For refractory angina patients and raised levels of lipoprotein(a), apheresis aims to improve the myocardial blood flow.
- **Extracorporeal shockwave therapy** is used routinely in the orthopedic setting, as well as for the treatment of renal stones by urologists in the form of lithotripsy. Its aim is to alleviate symptoms of refractory angina through improvement of myocardial perfusion by inducing shear stress and myocardial angiogenesis.
- **Gene therapy**, in particular the adenovirus fibroblast growth factor 5 therapy, aims at promoting new blood vessel formation in the heart, which is believed to provide enhanced cardiac perfusion and the related symptom relief. Adenovirus fibroblast growth factor 5 is a replication-deficient serotype 5 adenovirus encoding the gene for fibroblast growth factor-4 (FGF-4) driven by a cytomegalovirus promoter.
- **Autologous cell therapy**, in particular the mononuclear bone marrow-derived haematopoietic stem cell therapy, aims to improve angina symptoms through haematopoietic stem cells undergoing metamorfosis into cardiac myocytes thus in effect improving the regional blood flow (where injected).
- **Palliative management** includes the alleviation of symptoms (pain, breathlessness, persistent cough, fatigue, and limitation in physical activity, anxiety, depression, sleeping problems, nausea, and constipation) as well as psychological and spiritual support [25].

A0020 – For which indications has CSRS received marketing authorisation or CE marking?

CE-Kennzeichnung seit 2011

The CSRS device (Neovasc Reducer™ System) received CE mark authorization in 2011 for the treatment of refractory angina [7]. In January 2020, Neovasc Inc. submitted premarket approval application to the US Food and Drug Administration (FDA) [8].

B0002 – What is the claimed benefit of CSRS in relation to the comparators?

CSRS soll die Perfusion ischämischer Areale steigern und so Symptome lindern

In the absence of current treatment options for refractory angina patients, CSRS aims to meet this unmet need. It claims to reduce the extent and severity of ischemia by improving perfusion to ischemic territories of the myocardium [4]. Through this mechanism of action, it claims to improve QoL and alleviate symptoms of angina of patients with obstructive CAD who are not candidates for revascularization [4]. CSRS further claims to fit a range anatomies of CS by being compatible with CS diameters of 9.5-13 mm at the proximal implant site [4].

kein direkter Vergleich von CSRS mit externer Gegenpulsation verfügbar

As recognized by the European Society of Cardiology (ESC) 2019 guideline, the only other intervention (apart from CSRS) with other than observational evidence is external counterpulsation [2]. Based on a sham-controlled study with 139 patients, it is claimed that active counterpulsation patients demonstrated significant improvement in QoL, bodily pain, and social functioning at 12 months follow-up as compared to sham [26]. There are no controlled trials comparing the two interventions head to head.

B0003 – What is the phase of development and implementation of CSRS?

CSRS ist keine Standardtherapie, kann aber laut ESC Leitlinie 2019 für die Behandlung der refraktären AP in Betracht gezogen werden

CSRS is a novel technology that is in its emerging phase with its first prospective case series (first-in-human study) published in 2007 [13] and first RCT in 2015 [9]. It is not established as part of standard practice, however, it is part of the 2019 ESC guideline for the diagnosis and management of chronic coronary syndromes where it received the status of IIb (intervention that is less well established by evidence/opinion, yet its use *may be considered* for refractory angina patients) [2].

By 2020, four prospective case-series, two prospective registries, and one RCT have been published. No information was found concerning different generations of the device.

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers CSRS and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use CSRS?

Behandlung durch erfahrenes, multidisziplinäres Team empfohlen

According to the above mentioned ESC guideline, patients with refractory angina are best treated in dedicated tertiary 'angina clinics' by multidisciplinary teams experienced in selecting the most suitable therapeutic approach in the individual patient based on an accurate diagnosis of the mechanisms of the pain syndrome [2].

spezielle Anordung im OP empfohlen

Because the delivery system is designed to use the right internal jugular vein, a specific operating room set up is recommended (Figure 3-2) [6]:

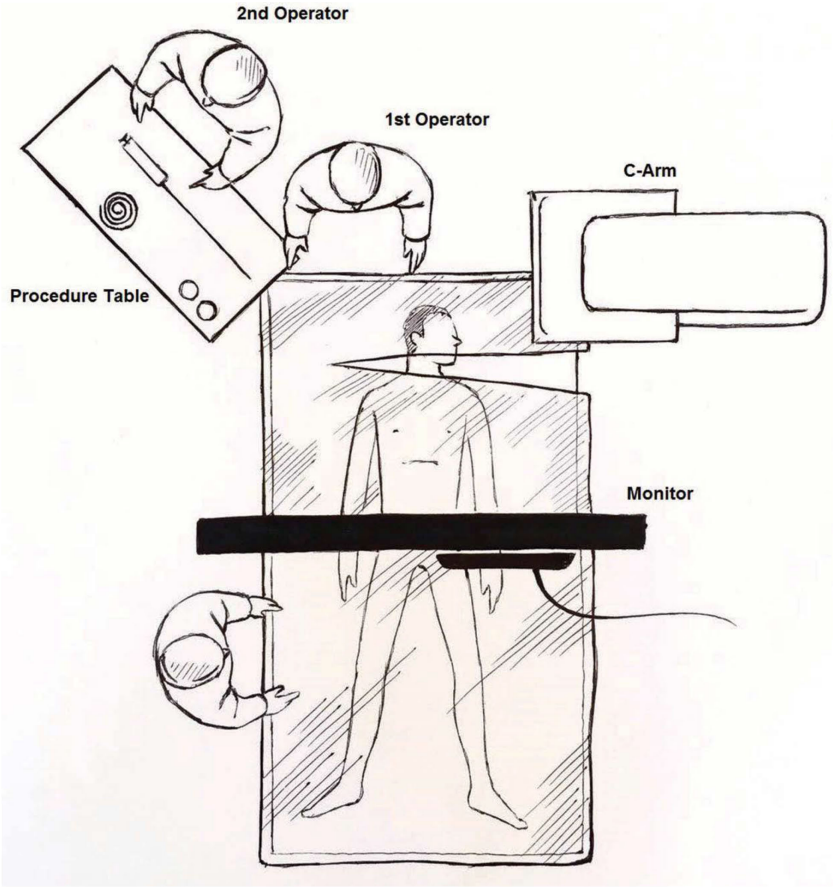

Figure 3-2: Recommended operating room set-up [6]

1. Physicians should operate cranially to the patient: the primary operator should stand just behind the head of the patient, with the second operator to the right of the first operator with the sterile trolley placed at 45° to the operating table, at the level of patient's shoulders. This position allows the operators to maintain catheters horizontally and preventing kinking.
2. The C-arm should be placed at 90° to the patient, in order to provide adequate space for the first operator; throughout the implantation procedure, the C-arm angulation is kept at 30 degrees flat left anterior oblique (LAO).
3. The monitors are turned perpendicularly to the usual position, crossing the operating table at the level of patient's waist.

B0009 – What supplies are needed to use CSRS and the comparator(s)?

CSRS System Kit erforderlich

Apart from supplies needed for any cardiac catheterization, the CSRS system kit is required. It contains [6]:

1. The pre-mounted CSRS on a balloon catheter.
2. A 9Fr Straight guide-catheter (Cordis Vista Brite Tip 55 cm, n.rif.598-943p).
3. (A rotating hemostatic valve (MEDEX Inc., MX336LBP1)

Regulatory & reimbursement status

A0021 – What is the reimbursement status of CSRS?

CE-Kennzeichen vorhanden, Neovasc Reducer™ nur in der EU erhältlich; Deutschland: NUB-Status1

Neovasc Reducer™-System is currently CE marked and only available in the EU [8]. In Germany, the Institut für das Entgeltsystem im Krankenhaus, (the German Institute for the Hospital Remuneration System), has awarded the Neovasc Reducer™ an NUB Status 1 designation again for 2020 [16]. The new examination and treatment methods (NUB) status allows novel medicines to be utilized by the hospitals before reaching full reimbursement eligibility [16].

Kosten vom Hersteller mit € 7.000 beziffert

Concerning the costs of Neovasc Reducer™-System, in a 2019 cost-effectiveness analysis, the only manufacturer Neovasc Inc. assigned it the cost of 7,000 Euro [17]. In the analysis, the cost of the procedure of Neovasc Reducer™-System implantation was estimated as the cost of the diagnosis-related group (DRG) for an elective PCI procedure [17]. See Table 3-1 for the list of angina related health care resources for from Belgium, the Netherlands, and Italy.

Table 3-1: List of angina related health care resources in Belgium, Netherlands, and Italy [17]

Angina-related healthcare resources	Belgium	the Netherlands	Italy
Reducer Implant (€)	12,735.00	8,031.48	13,434.00
Hospitalization (€)	-	-	1,8700.00
Hospitalization days (€)	560.00	602.68	-
Outpatient visit (€)	152.69	55.81	88.06
ED admission (€)	92.81	166.25	193.00
Coronarography (€)	1,920.00	1,185.57	2,142.00
Elective PCI (€)	5,735.00	1,157.46	6,434.00

Abbreviation: *PCI – percutaneous coronary intervention*

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is CSRS used?

A0002 – What is the disease or health condition in the scope of this assessment?

CSRS is the last line of therapy for patients with CAD who are not candidates for revascularization, demonstrate reversible ischemia, and have refractory AP despite standard medical therapy. CAD is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive [2]. One set of clinical presentations of CAD are chronic coronary syndromes where refractory AP belongs to as well. AP refers to chest pain caused by CAD that occurs when the heart muscle does not get as much blood as required, usually, due to ischemia cause by blockage in one or more heart arteries. The symptoms of AP are usually associated with uncomfortable pressure, fullness, squeezing or pain in the centre of the chest. They may further include discomfort in the neck, jaw, shoulder, back, or arm [27].

Zielgruppe für die CSRS-Therapie: PatientInnen mit refraktärer AP trotz Standardtherapie

Refractory AP – the condition at stake in the present assessment – as defined by the ESC, refers to long-lasting symptoms (for ≥3 months) due to established reversible ischemia in the presence of obstructive CAD, which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, bypass grafting, or stenting including percutaneous coronary intervention (PCI) of chronic total coronary occlusion [2].

refraktäre AP: anhaltende Symptome durch myokardiale Ischämie die durch Medikamente, Bypassoperation oder Stentimplanation nicht kontrollierbar sind

A0003 – What are the known risk factors for the disease or health condition?

Concerning risk factors for CAD, those that can be controlled include high blood pressure, high blood cholesterol levels, smoking, diabetes, overweight or obesity, lack of physical activity, unhealthy diet, and stress. Those that cannot be controlled include: age (elderly have a higher chance for CAD), sex (men are generally at greater risk of CAD), family history, and race [3].

Risikofaktoren nur teilweise beeinflussbar

A0004 What is the natural course of the disease or health condition?

CAD can have long, stable periods, but can become unstable at any time, for instance, due to an acute atherothrombotic event caused by plaque rupture or erosion [2]. Once myocardial ischemia is present, it first leads to diastolic dysfunction, then systolic wall motion abnormalities, and progressive left ventricular dysfunction. AP is usually the last manifestation of myocardial ischemia [28]. In terms of refractory AP, patients are either unsuitable for revascularization or continue to suffer from angina revascularization procedures that are successful in eliminating symptoms in about two-thirds of patients with stable CAD [4]. The natural course of refractory AP is thus high incidence of hospitalization, considerable psychological morbidity and depression, and death [4].

Verlauf der AP: hohe Rate an Klinikaufenthalten, psychische Erkrankungen und Depression, Todesfälle

Effects of the disease or health condition on the individual and society

17,92 Millionen Todesfälle weltweit durch kardiovaskuläre Erkrankungen

A0005 – What is the burden of disease for patients with the disease or health condition?

The burden of disease for cardiovascular disease at large is a major cause of health loss across all the regions of the world [1]. According to Global Burden of Disease 2015, an estimated 442.7 million prevalent cases of cardiovascular disease were present worldwide causing estimated 17.92 million deaths [1]. Ischemic heart disease (that AP is part of) was the leading cause of all health loss globally as well as in each world region [1].

Österreich: Inzidenz von 17.000 Erkrankungen/Jahr (2011)

Precise estimates of the prevalence and incidence of refractory AP are not available. European estimates from 2002/2004 expect 30,000-50,000 new cases per year [27]. And with respect to Austrian statistics in 2011, the incidence rate of AP is estimated to be 17,000. Regional comparisons show that the incidence rates are highest in Carinthia and Upper Austria, and lowest in the federal states of Salzburg, Burgenland, Styria and Tyrol [29].

A0006 – What are the consequences of the disease or health condition for the society?

Inzidenz refraktärer AP steigt mit fortgeschrittener koronarer Herzerkrankung, mehreren Komorbiditäten und Alter der Bevölkerung

The incidence of refractory AP is growing with more advanced CAD, multiple comorbidities, and ageing of the population. Due to the gradual deterioration of physical as well as psychological symptoms, the QoL of patients with refractory angina is poor [27]. It leads to frequent hospitalization and high level of resource utilization that is depicted on the higher number of sick leaves among patients who are still actively working [4]. An increase in the prevalence of angina is expected as the population continues to age, with no discrimination between males and females [2]. The American College of Cardiology (AAC) and the American Heart Association (AHA) estimate that refractory AP amounts to annual costs in tens of billions of dollars due to high cost to society, both in terms of healthcare expenditure and lost productivity [30].

Current clinical management of the disease or health condition

A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

Diagnostik bei PatientInnen mit AP und Verdacht auf koronare Herzerkrankung: 6 Schritte

According to the 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes, the general approach for the initial diagnostic management of patients with angina and suspected obstructive CAD includes the following six steps (outlined in Table 4-1) [2].

Table 4-1: Approach for the initial diagnostic management of patients with angina and suspected CAD

1	**Assess symptoms and perform clinical investigations**
	The assessment of patient history is key in diagnosing angina. It is possible to achieve a high degree of certainty on a diagnosis based on history alone, although physical examination and objective tests are most often necessary to confirm the diagnosis, exclude alternative diagnoses, and assess the severity of underlying disease. The history should include any manifestation of cardiovascular disease and risk factors (outlined above).
2	**Consider comorbidities and quality of life**
	Before any testing is considered, an assessment of the patient's general health, comorbidities, and QoL is required. If revascularization is unlikely to be an acceptable option, further testing may be reduced to a clinically indicated minimum and appropriate therapy should be instituted. Non-invasive functional imaging for ischemia may be an option if there is need to verify the diagnosis.
3	**Perform basic (first-line) testing**
	Basic (first-line) testing in patients with suspected CAD includes standard laboratory biochemical testing, a resting ECG, possible ambulatory ECG monitoring, resting echocardiography, and, in selected patients, a chest X-ray. Such testing can be done on an outpatient basis.
4	**Assess pre-test probability and clinical likelihood of CAD**
	The performance of the available methods in diagnosing obstructive CAD depends on the prevalence of disease in the population studied. Diagnostic testing is most useful when the likelihood is intermediate. When likelihood is high, a large number of patients need to be studied to identify the few patients that do not have disease, and a negative test result can seldom rule out the presence of obstructive CAD. When the likelihood is low, a negative test can rule out the disease, but the lower the likelihood, the higher the likelihood of a false positive test. In patients at the extreme ends of the probability range, it is therefore reasonable to refrain from diagnostic testing, and assume that the patient does or does not have obstructive CAD based on clinical evaluation alone.
5	**Offer diagnostic testing**
	In patients in whom revascularization is futile due to comorbidities and overall QoL, the diagnosis of CAD can be made clinically and only medical therapy is required. If the diagnosis of CAD is uncertain, establishing a diagnosis using non-invasive functional imaging for myocardial ischemia before treatment is reasonable. In a patient with a high clinical likelihood of CAD, symptoms unresponsive to medical therapy or typical angina at a low level of exercise, and an initial clinical evaluation (including echocardiogram and, in selected patients, exercise ECG) that indicates a high event risk, proceeding directly to ICA without further diagnostic testing is a reasonable option. In other patients in whom CAD cannot be excluded by clinical assessment alone, non-invasive diagnostic tests are recommended to establish the diagnosis and assess the event risk. The current recommended imaging techniques include *noninvasive functional imaging of ischemia* or *anatomical imaging using coronary CT angiography* as the initial test for diagnosing CAD.
6	**Choose appropriate therapy based on symptoms and event risk**
	The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms. Event risk stratification is usually based on the assessments used to make a diagnosis of CAD. All patients should undergo cardiovascular event risk stratification using clinical evaluation, the assessment of left ventricular function by resting echocardiography, and, in the majority of cases, non-invasive assessment of ischemia or coronary anatomy. Although the diagnostic value of an exercise ECG is limited, the occurrence of ST segment depression at a low workload combined with exertional symptoms (angina or dyspnea), low exercise capacity, complex ventricular ectopy, arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality.

Abbreviations: ***BP*** *– blood pressure*, ***CAD*** *– coronary artery disease*, ***CT*** *– computed tomography*, ***ECG*** *– electrocardiogram*, ***ICA*** *– invasive coronary angiography*, ***QoL*** *– quality of life*

A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?

Optionen für PatientInnen mit koronarer Herzerkrankung:

The current management options of general CAD patients include lifestyle, pharmacological, as well as surgical management options.

Lifestyle management

Änderung des Lebensstils

The implementation of healthy lifestyle behaviours decreases the risk of subsequent cardiovascular events and mortality. The key lifestyle interventions include [2]:

- smoking cessation,
- healthy diet (high in vegetables, fruits, and wholegrains, saturated fat <10% of total intake, and alcohol intake of <100g/week),
- physical activity (30-60 min of moderate activity in most days),
- healthy weight (<25km/m2).

Pharmacological management

medikamentöse Therapie

The aim of pharmacological management is the reduction of angina symptoms, exercise-induced ischemia, and the prevention of cardiovascular events [2]. Prevention of cardiovascular events targets myocardial infarction (MI) and death associated with CAD, and focuses primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction [2]. Immediate relief of anginal symptoms is usually obtained with rapidly acting formulations of nitroglycerin. Anti-ischemic drugs play a role in minimizing or eradicating symptoms over the long-term, while preventing the occurrence of cardiac events [2].

antiischämische medikamentöse Therapie muss individuell angepasst warden

Appropriate anti-ischemic therapy, however, needs to be tailored to individual patients. By and large, initial drug therapy consists of one or two antianginal drugs, plus drugs for secondary prevention of cardiovascular disease. The initial choice of antianginal drug(s) depends on the expected tolerance related to the individual patient's profile and comorbidities, potential drug interactions with co-administered therapies, the patient's preferences after being informed of potential adverse effects, and drug availability [2]. These are the recommended lines of interventions [2]:

- First-line therapy usually includes beta-blockers and/or calcium channel blockers. If those do not manage to control angina symptoms, the combination of beta-blocker with a dihydropyridine calcium channel blocker is recommended.
- Second line of therapy includes long-acting nitrates or (if not contradicted) the following interventions are recommended: nicorandil, ranolazine, ivabradin, or trimetazidine.

Surgical management

operative Therapie: Revaskularisierung mettels PCI oder CABG

PCI: klinisch beobachtete Wirksamkeit versus fehlende Evidenz aus RCTs

On top of pharmacological therapy, myocardial revascularization plays a central role in the management CAD is patients who continue to be symptomatic. The two objectives of revascularization are symptom relief in patients with angina and/or improvement of prognosis. Revascularization by PCI or coronary-artery bypass grafting (CABG) have the potential to relieve angina, reduce the use of antianginal drugs, and improve exercise capacity and quality of life compared with a strategy of medical therapy alone [2]. It is important, however, to put the clinically observed efficacy of PCI (in terms of symptomatic relief) into context with the missing evidence from blinded, placebo-

controlled randomized trials [25]. While the ISCHEMIA trial (NCT01471522-ongoing) points to no advantage of revascularization over conservative management on prognosis, the ORBITA trial (NCT02062593) points to no advantage of revascularization over conservative management concerning symptoms [25].

Target population

A0007 – What is the target population in this assessment?

The target population of this assessment are adult patients of more than 18 years of age who are not candidates for revascularization, demonstrate reversible ischemia, and have refractory AP despite standard medical therapy.

≥18 Jahre, refraktäre AP trotz Standardtherapie, reversible Ischämie, ungeeignet für Revaskularisations-therapie

A0023 – How many people belong to the target population?

As outlined in A0005, the gross estimate of annual incidence of refractory AP in Europe is estimated at 30,000-50,000 new cases per year [27]. In 2011 in Austria, around 17,000 people had AP as such (while no data was found specifically on refractory AP) [29]. Men had an incidence rate that was around 1.7 times higher than that of women, and the rate was higher in the elderly. A time comparison shows that the AP incidence rate – after a period of stability – fell significantly between 2007 and 2011 (by an average of 9.7% annually). A sudden increase in the incidence rate can be seen from the age of 50 and while 53% of AP cases were in people 70+, 8% of people were under 50 years of age [29].

17.000 Fälle von AP in Österreich (2011)

höhere Inzidenz bei Männern

53 % der AP-Fälle bei Personen 70+

A0011 – How much is CSRS utilised?

The manufacturer Neovasc Inc. provided no data with respect to the rate of utilization of CSRS.

keine Daten zu Häufigkeit der Anwendung

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidungsrelevante Endpunkte für die Wirksamkeit

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

Further outcomes considered were

weitere berücksichtigte Endpunkte

- Exercise tolerance as assessed with the use of a symptom-limited stress test
  - ST-segment depression during exercise
- Modified wall motion index
- Antianginal medications intake

CCS score classifies AP in four categories (see Table 5-1). Patients with refractory AP belong mainly to Grade III and IV.

CCS Angina Score: AP in 4 Kategorien unterteilt

Table 5-1: CCS angina score [31]

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

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) [32].

Fragebogen zur Lebensqualität

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

Fragebogen zur Behandlungszufriedenheit

Exercise tolerance assessed with symptom-limited stress test is a non-invasive screening test for CAD. It aims to determine how well the patient's heart works under exercise induced stress. Typically, the patient exercises on a treadmill while connected to an electrocardiogram (ECG) machine [33].

Belastungstoleranztest

ST-segment depression is used as a marker for adverse cardiac events. 2 mm of additional exercise-induced ST-segment depression or downsloping depression of 1 mm or more in recovery are potential markers for CAD [33]. Improvement in ST-segment depression thus potentially implies improvement in CAD.

ST-Senkung als Marker für kardiale Komplikationen

Cardiac regional wall motion during stress and at rest assessed by dobutamine stress ECG is a surrogate marker of ischemia. It is due to the fact that ischemia typically manifests itself via new or worsening wall motion abnormalities, delayed contraction, the development of left ventricular enlargement, or a decrease in ejection fraction [34]. The motion of each of 16 wall segments at rest and during peak dobutamine infusion was quantified (with a score of

Wall-motion-Index

1 indicating normal, 2 hypokinetic, 3 akinetic, 4 dyskinetic, and 5 aneurysmal), and the sum of the wall-motion scores for the myocardial segments was divided by the number of segments to provide a **wall-motion index** [9].

Antianginal medications intake refers the increase/decrease of the use of antianginal medication at last follow-up as compared to baseline.

5.2 Included studies

1 RCT ("COSIRA") zur Analyse der Wirksamkeit eingeschlossen

For the assessment of clinical effectiveness, one study met the inclusion criteria. It was a RCT comparing CSRS with a sham procedure where no stent was implanted (study name COSIRA, NCT01205893) [9].

Study characteristics

multizentrischer 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. [9].

Patient characteristics

104 PatientInnen, 52 davon erhielten CSRS

The RCT included 104 patients, of which 52 were in the intervention group (IG) and 52 in the control group (CG). 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 IG was 69.6±8.7 and 85% of the population was male while mean age in CG was 66±9.8 and 77% of the population was male [9]. 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 PatientInnen mit Steigerung um ≥2 CCS-Klassen

stark vorbehandelte PatientInnen

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 [9].

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% [9].

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, con-

traindication 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 [9].

Detailed study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of CSRS on mortality?

Concerning the SADE of death as reported in the RCT, one case of death occurred in CG, while no cases of death occurred in IG [9].

1 Todesfall in der Kontrollgruppe

D0003 – What is the effect of CSRS on the mortality due to causes other than the target disease?

No evidence was found to answer this research question.

keine Evidenz

Morbidity

D0005 – How does CSRS affect symptoms and findings (severity, frequency) of the disease or health condition?

D0016 – How does the use of CSRS affect activities of daily living?

Concerning the primary outcome of CCS angina score improvement of at least two classes at six months follow-up, 35% of IG as opposed to 15% of CG patients improved (p=0.02) [9]. CCS angina score improvement by one class was observed in 71% of IG and 42% of CG patients (p=0.003) [9]. Overall, mean reduction of CCS class from baseline to six months follow-up was 1.1 classes in IG and 0.5 classes in CG (p=0.001) [9].

Steigerung von mind. 2 CCS-Klassen bei 35 % der PatientInnen in der IG

D0006 – How does CSRS affect progression (or recurrence) of the disease or health condition?

No longer-term data (longer than six months) were found and hence no answer can be provided on progression/recurrence of AP post CSRS therapy. Improvement in CCS angina score at six months is reported above.

keine Langzeitdaten verfügbar

Function

D0011 – What is the effect of CSRS on patients' body functions?

Effect on patients' bodily functions can be reported in relation to two outcomes: total exercise duration improvement and wall motion index improvement. Total exercise duration improved by 59 seconds (13%) in IG and by 4 seconds (1%) in CG (p=0.07) [9]. Wall motion index improved by 14% in IG and 8% in CG (p=0.20) [9].

Belastungsdauer und Wall Motion Index in IG gesteigert

Health-related quality of life

D0012 – What is the effect of CSRS on generic health-related quality of life?

keine Evidenz

No evidence was found to answer the research questions as none of the included studies reported on generic health-related QoL.

D0013 – What is the effect of CSRS on disease-specific quality of life?

Lebensqualität höher bei PatientInnen der IG

Disease specific QoL was measured by improvement in SAQ QoL score. While patients in IG improved their SAQ QoL score by 17.6 points, patients in CG improved by 7.6 points (p=0.048) [9].

Patient satisfaction

D0017 – Was the use of CSRS worthwhile?

Behandlungs-zufriedenheit in beiden Gruppen gleich

SAQ treatment satisfaction outcome provides an answer as to whether the treatment with CSRS was worthwhile (from patients' perspective). Patients in both IG and CG report the same mean improvement of 2.9 points [9].

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

endscheidungsrelevante Endpunkte für die Sicherheit: SADEs

- 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)

Further outcomes considered include:

weiters berücksichtigt: ADEs

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

6.2 Included Studies

For the assessment of safety, seven studies met the inclusion criteria. One RCT described in the section on clinical effectiveness above [9], four prospective case series [10-13], and two prospective registries [14, 15]. Study and patient characteristics of the prospective observational studies are described below.

7 Studien wurden zur Beurteilung der Sicherheit inkludiert

Study characteristics

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

Three observational studies were conducted in more than one centre in countries of Germany, India, Israel, Italy, and Belgium [12, 13, 15] and the remaining three observational studies were all conducted in single centres in Italy [10, 11, 14]. Funding was unclear in all the observational studies, but each study included an author with conflict of interest. The studies were conducted between October 2004 and April 2017.

Patient characteristics

insgesamt 400 Patienten

Follow-up zwischen 4 und 24 Monaten

The four case series included 15, 23, 50, and 19 patients respectively [10-13], while the registries included 141 and 48 patients respectively [14, 15]. Hence, together with the RCT [9], the total number of patients receiving the CSRS therapy was 348. Together with the CG patients (n=52), out of the total of 400 patients, 31% were women and a total of 16 (4%) patients were lost to follow-up. The follow-up ranged from four [10] to 24 months [11], while five studies had six months follow-up [9, 12-15]. The mean age varied between 65 to 71.4 years and all but one [13] of these observational studies had improvement in CCS angina score as its primary outcome measure.

Mehrheit der PatientInnen 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]. From 86-98% 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) [9-15]: previous MI (27-95%), previous CABG (20-81%), previous PCI (40-100), previous stroke (9-17%), hypercholesterolemia (0-100%), diabetes mellitus (7-64%), hypertension (67-86%), current/previous smoking (37-64%), and intake of antianginal medications (median 2.33-3).

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 [10-13, 15] and CCS classes III-IV in [9, 14]. All studies included only those patients who were not eligible for CABG and/or PCI [9-15], had objective myocardial ischemia (determined by perfusion scan and/or by dobutamine ECG) [9-15], and in most cases had LVEF as low as 25-30% [12-14].

Ausschlusskriterien der Studien uneinheitlich

Exclusion criteria were more heterogeneous. Three observational studies excluded patients with MI and CABG/PCI in less than three (to seven) months, patients with decompensated heart failure, the presence of life threatening arrhythmias, and severe valvular heart disease [12-14]. Tricuspid valve replacement or repair was an exclusion criterion in two studies [12, 13], acute coronary syndrome in less than three months in three studies [10, 11, 15], presence of a pacemaker lead was an exclusion criterion in four studies [11-13, 15], and right atrial pressure of more or equal to 15 mm Hg was a criterion in all studies [10-15].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

6.3 Results

Patient safety

C0008 – How safe is CSRS in comparison to the comparator(s)?

Sicherheit: kein direkter Vergleich von CSRS mit anderen Interventionen

No statement on the safety profile of CSRS as compared to best practice comparators can be made. The reason is that there is a lack of established best practice interventions for this target patient group of refractory AP patients, no head to head comparisons with the novel interventions such as external counterpulsation, or a network meta-analysis comparing these two novel interventions. The only controlled data come from the sham-controlled RCT in which there was a total of 10 (19%) SADEs in IG and 24 (46%) in CG [9]. Most of the SADEs occurred in no more than two patients in IG or CG (4%) except for stable angina (IG=1, CG=5), unstable angina (IG=1, CG=4), and atypical chest pain (IG=1, CG=6). No SADE occurred more frequently in IG than CG.

RCT: 19 % SADEs in der IG verglichen mit 46 % in der CG

The observational studies reported 0-30% of SADEs. While two studies reported none [10, 13], the remaining four studies reported 14 (10%), 5 (22%), 6 (13%), and 15 (30%) patients suffering from SADEs respectively [11, 12, 14, 15]. The SADEs that occurred were death in 14 (10%) patients in [15], 1 (4%) in [12], 3 (6%) in [14], and 5 (10%) in [11]. MI occurred only in [11] in 3 (6%) patients, stable angina in two studies [12, 14] in 4 (17%) and 2 (4%) patients, respectively. Furthermore, unstable angina occurred in [14] in 1 (2%) patient, and CAD progression in 7 (14%) patients in [11].

Beobachtungsstudien: 0 bis 30 % SADEs berichtet

Concerning ADEs, 32 (64%) patients in IG and 37 (69%) in CG experienced ADEs. In observational evidence, ADEs were either not reported [12, 13], or reported to occur in 0-45% of patients. No ADEs we reported in [10], and they occurred in 64 (45%) patients in [15], 4 (8%) patients in [14], and 13 (26%) patients in [11]. The ADEs reported were hospitalization, coronary angiogram, revascularization, and device migration.

RCT: ADEs in 64 % der IG und 69% der CG

Beobachstungsstudien: ADEs bei 0 bis 45 % der PatientInnen

C0002 – Are the harms related to dosage or frequency of applying CSRS?

keine Evidenz

No evidence was found to answer the research questions as none of the included studies reported on differences in application of CSRS.

C0004 – How does the frequency or severity of harms change over time or in different settings?

nur 1 Studie mit Follow-up nach 24 Monaten: SADEs bei 30 % der PatientInnen

While six studies had the length of follow-up no longer than 6 months [9, 10, 12-15], this research question can be answered only in light of the sixth study with longest follow-up that reports results at 24 months [11]. In this study, 30% of patients experienced SADE's, which is the highest number of SADE's out of all studies with 22% of SADEs occurring in [12], 19% in IG in [9], 13% in [14], 10% in [15], and 0% in [10, 13].

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of CSRS?

stark vorbehandelte und ältere PatientInnen gefährdet

The patient groups in focus of this assessment are refractory AP patients who were, for the most part, heavily pre-treated to begin (no information of previous antianginal medication intake in [12-14]) with and so they are susceptible to be harmed by SADEs and ADEs related to CSRS. Furthermore, as the mean age varied between 65 to 71.4 years, the elderly population is to be considered a patient group likely to be harmed through the use of CSRS.

C0007 – Are CSRS and comparator(s) associated with user-dependent harms?

keine Evidenz

No evidence was found to answer this research questions.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of CSRS and the comparator?

RCTs, prospektive Registerdaten und daraus gewonnene Langzeitdaten benötigt

Larger RCTs and prospective registry data are needed to monitor the use of CSRS and thus provide longer-term follow-up data.

7 Quality of evidence

RoB mittels Cochrane Collaborations Tool und IHE-Checklist bewertet

The risk of bias (RoB) for individual studies was assessed with the Cochrane Collaboration's tool for randomised trials [35] as well as with the Institute of Health Economics (IHE) checklist for single-arm studies [36]. Both assessments are presented in Table A-5 and Table A-6 in the Appendix.

RCT: niedriges RoB, Beobachtungsstudien: RoB niedrig bis moderat

The RCT [9] was rated with a low RoB and the RoB for the observational studies ranged from low [10, 11, 13, 14] to moderate [12, 15]. None of the case series stated the source of financial support, there was assumed selective outcome reporting of ADEs in [12, 13], and it was unclear if two studies were conducted prospectively [12, 15].

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [22] for each endpoint individually. Each study was rated by two independent researchers (MS, ER). All disagreements were resolved through discussion. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [22].

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 below and in the evidence profile in Appendix Table A-5.

Gesamtstärke der Evidenz für Wirksamkeit und Sicherheit von CSRS: moderat

Overall the strength of evidence for the effectiveness and safety of CSRS is moderate. For the comparison of CSRS with best practice comparators, no evidence is available.

Table 7-1: Summary of findings table of CSRS

Outcome	Anticipated absolute effects (95% CI)		№ of analysed pts (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham	Risk with CSRS			
Efficacy					
CCS angina score improvement of at least 2 classes at 6 mos, n of pts	150 per 1000	350 per 1000	104 (1)	⊕⊕⊕◯ MODERATE [a]	Statistically significant (P=0.02)
SAQ QoL score improvement, n of points	The improvement in the number of SAQ QoL points was 10 in favor of IG (IG vs. CG: 17.6 vs. 7.6).		104 (1)	⊕⊕⊕◯ MODERATE [a]	Statistically significant (P=0.048)
Total exercise duration improvement, n of seconds	The difference in the total exercise duration was 55 seconds in favor of IG (IG vs. CG: 59 vs. 4).		104 (1)	⊕⊕⊕◯ MODERATE [a]	Statistically not significant (P=0.07)
Safety					
SADEs, 6 mos follow-up	212 per 1000 (based on 52 pts)	132 per 1000 (based on 348 pts)	400 (6)	⊕⊕⊕◯ MODERATE [b, c]	-

Abbreviations: ***CCS*** *– Canadian Cardiovascular Society,* ***CG*** *– control group,* ***CI*** *–confidence interval,* ***IG*** *– intervention group,* ***mos*** *– months,* ***n*** *– number,* ***QoL*** *– quality of life,* ***SADE*** *– serious adverse device effect,* ***SAQ*** *– Seattle Angina Questionnaire*

Explanations:

[a] *Optimal information size is not met and the sample size is small,*

[b] *Source of financial support is unclear,*

[c] *One case series study unclear if retrospective.*

GRADE Working Group grades of evidence:

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*

Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different*

Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect*

Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect*

8 Discussion

To our knowledge, this is the first systematic review on the CSRS therapy for refractory AP patients that is based on prospective evidence only. The only other systematic review found was published in 2018 and included both prospective as well as retrospective evidence [37]. It concludes that CSRS is a promising treatment option for patients with refractory AP, however, that larger RCTs with long-term follow-up are needed to elucidate its role [37]. We included one RCT for the analysis of clinical effectiveness with 104 patients, of which 52 received the CSRS therapy [9]. Furthermore, we included additional six prospective observational studies complementing the analysis of safety with 296 patients [10-15]. Together with 104 RCT patients, the safety analysis included the total of 400 patients.

erste Übersichtsarbeit basierend auf prospektiver Evidenz

Analyse der Wirksamkeit: 104 PatientInnen inkludiert (52 mit CSRS), Sicherheitsanalyse: 400 PatientInnen inkludiert

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 [9]:

- CCS angina score improvement of at least two classes at six months follow-up (35% of IG as opposed to 15% of CG (p=0.02)),
- CCS angina score improvement by one class (71% of IG and 42% of CG (p=0.003)),
- Overall mean reduction of CCS class (1.1 classes in IG and 0.5 classes in CG (p=0.001)), and
- SAQ QoL score improvement in IG by 17.6 points and in CG by 7.6 points (p=0.048).

statistisch signifikante Ergebnisse

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) [9].

Outcomes ohne statistische Signifikanz

Concerning safety, the sham-controlled trial data indicate that there were less SADEs in the IG (19%) than in CG (46%) [9]. SADEs reported in observation studies remain to be a point of concern as they range from none [10, 13] to 30% [11]. The most frequently reported SADEs were death and stable angina. In the RCT, the only case of death occurred in CG [9]. 8% of observational studies patient died, while 5% of deaths were explicitly claimed not to be related to CSRS [11, 12, 14, 15].

The same concern over underreporting of complications pertains also to ADEs. While there were 64% patients in IG and 69% in CG that experienced ADEs, in observational evidence, ADEs ranged from none [10] to 45% [15].

Bedenken über zu geringe Angaben von ADEs

Internal validity

Concerning clinical effectiveness (RCT [9]), the RoB was rated to be low and concerning safety, the RoB was rated to range from low [10, 11, 13, 14] to moderate [12, 15]. The main reasons for increased risk was assumed selective outcome reporting [12, 13] and the lack of clarity whether two studies were conducted prospectively [12, 15]. As assessed by GRADE, the overall strength of evidence for effectiveness and safety was moderate.

GRADE: Gesamtstärke der Evidenz moderat

Clinical effectiveness

bei der Interpretation der klinischen Wirksamkeit sollte berücksichtigt werden, dass ...

When interpreting the findings on clinical effectiveness, the issues with mechanism of action, placebo effect, sample size, randomization procedure, inconsistency between outcomes, and inappropriate inclusion criteria should be taken into account.

1. der Wirkmechanismus von CSRS ungeklärt ist ...

First, the mechanism of action of CSRS is unclear. Even though CSRS is hypothesized to alleviate symptoms by improving perfusion in ischemic myocardial territories, no study has evaluated its effect upon myocardial perfusion with no clear demonstration of its mechanism of action [18]. A potential issue is that the claimed beneficial hemodynamic changes are at odds with one of the principles of use of intermittent and pressure-controlled increase in coronary sinus pressure – a release of obstruction [38] and the resulting rapid reduction of coronary sinus pressure after the prolonged phase of plateau may induce a sort of aspirating effect on fluids and toxic metabolites accumulated in the ischemic segment [39]. In addition, it is known that CS flow at rest and hyperemic states are in agreement with myocardial blood flow values and reduced coronary flow reserve measured at CS level may be associated with adverse outcome [40].

... unklar ist warum 15-30 % der PatientInnen nicht auf die Behandlung ansprechen ...

Concerning mechanism of action, it is also unclear why there remains to be a 15-30% rate of non-responders [41]. One line of interpretation suggests that individual anatomic variants of the cardiac venous system may lead to insufficient pressure gradient generation across the device [41]. Another line of interpretation assumes that the lack of endothelialization may be the cause – meaning that in some patients, the device's surface does not get to be completely covered by endothelium (the vein's inner lining) – and hence the pressure gradient is not created [42].

2. die CSRS-Implantation zu einem Placebo-Effekt in dieser speziellen Patientengruppe führen könnte ...

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, 18]. Moreover, large placebo effect may not result in a persistent long-term benefit [18], which is also underscored by the short term follow-up (up to six months) of all the prospective studies published on CSRS (except for [11]).

3. die Fallzahl für endgültige Schlussfolgerungen zu klein ist ...

Third, the clinical benefit of CSRS may be overstated because the sample size is too small to reject a true null hypothesis and thus to allow for any definitive conclusions [19].

4. Bedenken hinsichtlich des Randomisierungsprozesses bestehen ...

Fourth, concerns about the randomization process (of the only RCT [9]) were highlighted for instance with the use of intravenous heparin that was used only in patients assigned to the treatment group and hence, post-procedural laboratory testing might have unveiled the study assignment of the patients [19].

5. es Inkonsistenzen zwischen objektiveren Parametern und CCS/SAQ QoL Scores gibt und ...

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) [9].

6. die Definition der refraktären AP und die Einschlusskriterien aller prospektiven Studien ...

And last, there is a major disagreement between the definition of refractory AP and the inclusion criteria in all prospective CSRS studies concerning the duration of symptoms and the use of antianginal medication. According to ESC, refractory AP refers to long-lasting symptoms (for ≥3 months), which cannot be controlled by escalating medical therapy with the use of second- and third-line pharmacological agents, CABG, or PCI [2]. None of the studies

in the analysis includes patients with such long-lasting symptoms and with regards to previous pharmacological therapy, three studies did not report on it [12-14], in two it ranged from 1-5 courses of pharmacological treatment [10, 11], in one it ranged from 1.34-3.3 [15], and in the RCT, 25% of patients had 0-1 course of medications and 31% had ≥3 courses [9].

... (bzgl. Dauer der Symptomatik und antianginöser Medikation) nicht übereinstimmen

Safety

Concerning the interpretation of safety findings, issues surrounding potential SADEs, obstruction of future therapy, and underreporting of complications related to DAPT should be taken into account.

Hinsichtlich der Interpretation der Sicherheitsdaten sollte berücksichtigt werden dass ...

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. The considerations include the close proximity of the circumflex coronary artery, which, if accidentally damaged, provokes an acute MI, and the presence of a thebesian valve or a valve of Vieussens in up to 85% of patients that could hamper device implantation [21]. Furthermore, the SADEs of CSRS migration presents a potential issue as cases of CSRS migration into right atrium have been reported [20].

... anatomische Variabilität die Implantation unmöglich machen bzw. zu Komplikationen beim Eingriff führen kann ...

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) [19].

... durch die Position des CSRS im CS zukünftige Eingriffe verhindert werden könnten ...

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 [9, 15] and none of the studies reported on bleeding events associated with DAPT.

... mögliche (zusätzliche) Komplikationen durch die empfohlene DAPT berücksichtigt werden müssen

External validity

In terms of external validity, the data is not considered generalizable to refractory AP patient from other contexts. Even though the studies were conducted in contexts are similar to the Austrian one (Germany, India, Italy, Israel, Belgium, Canada, Denmark, the Netherland, Sweden, and the UK), the fact that the CSRS patient population does not include only refractory AP patients undermines the generalizability of the results. 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.

Daten nicht generalisierbar, da nicht nur PatientInnen mit refraktärer AP inkludiert

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.

überzogene Schlussfolgerungen zu Wirksamkeit und Sicherheit

Furthermore, discussions surrounding the use of CSRS in other target populations are present in the literature. In particular, the patients with other chronic cardiac conditions characterized by angina and subendocardial ischaemia (such as microvascular angina, diastolic dysfunction, hypertrophic cardiomyopathy, chronic total occlusion, and severe diffuse coronary artery disease [5]) are suggested to be potential candidates for CSRS [4].

mögliche Anwendung auch bei anderen chronischen Herzerkrankungen

Limitations of evidence

umfangreiche RCTs mit längerem Follow-up sind erforderlich

The evidence base found was only partly relevant in answering the research question as the evidence base does not exclusively include refractory AP patients. Also, the only RCT identified was relevant for excluding placebo effects, but even this result is partially undermined by large placebo effect associated with novel therapies in this specific patient population [2]. Larger RCTs with longer follow-up are required to define the role of each treatment modality for specific subgroups, to decrease non-responder rates, and ascertain benefit beyond potential placebo effects [2].

Socio-economic and ethical considerations, conclusion

wenn die Wirksamkeit von CSRS weiterhin bestätigt werden kann, wären die Prinzipien der Fürsorge und Autonomie der PatientInnen gesichert

When considering socio-economic and ethical aspects of this new intervention CSRS, the effects have to be reflected over against the principles of beneficence, non-maleficence, autonomy, distribute justice, and uncertainty. On the one hand, CSRS is claimed to reduce the pharmacological and other healthcare spending [17]. In patients with refractory AP, CSRS device decreased healthcare resource use and related costs in a limited 1-year timeframe according to a range of cost-effectiveness thresholds [17]. Also, CSRS targets a patient population where no established interventions [2] are in use and so, if further proven to be effective, fulfilling this "gap" secures the principles of medical beneficence and patient's autonomy.

umfangreichere RCTs nötig, um das Prinzip der Schadensvermeidung zu wahren

Ergebnisse der ISCHEMIA-Studie könnten potenziell die Leitlinie für die Behandlung der refraktären AP maßgeblich verändern

On the other hand, however, the lack of clarity behind the mechanism of action and the lack of longer-term data cast doubts over the positive safety profile of CSRS [18]. This is further coupled by the concerns of further SADEs highlighted above that can, for instance, preclude the use of CRT for future heart failure patients [19]. Hence, as outlined above, to prevent breaching the principle of non-maleficence, larger controlled trials are needed. Currently, there is no ongoing (larger) RCT that would allow for making any definitive conclusions. The only currently recruiting RCT includes 40 patients and measures the impact of CSRS on exertional capacity measured by maximal oxygen consumption (VO2) during cardio-pulmonary exercise testing and is to be completed by the end of 2021 (NCT04121845). However, there is an ongoing ISCHEMIA trial (NCT01471522) that aims to determine the best management strategy for higher-risk patients with stable ischemic heart disease that has the potential to change the guideline for refractory AP patients considerably.

unklar, ob CSRS wirksamer und gleich sicher ist verglichen mit Scheinprozedur

laut ESC Leitlinie 2019 kann CSRS für die Behandlung refraktärer AP in Betracht gezogen werden

To conclude, it is unclear whether CSRS has the potential to improve CCS angina score and QoL (as measured by SAQ) without bringing about more SADEs than the sham intervention (based on moderate quality of evidence). The reasons are inappropriate inclusion criteria in the studies, incomplete blinding in the RCT, inconsistent results, and incomplete safety data with regards to DAPT. The potential to fulfill the therapeutic gap (and thus improve patients' autonomy) 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. Moreover, the potential cost-effectiveness of CSRS needs to be contrasted with the inflated placebo effect in this specific (relatively small) target population. Against the backdrop of this complex picture of CSRS, however, it needs to be noted that according to the ESC 2019 guideline, CSRS received the recommendation 2b – meaning that the usefulness of CSRS is less well established by evidence/opinion, but that it may be considered for use in clinical practice.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: 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:

Even though the current evidence indicates 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, the lacking internal validity of the studies undermines the partially positive results. For the establishment in clinical practice, larger RCTs that can potentially influence the effect estimate are needed.

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

The re-evaluation is recommended in 2022 when results from ISCHEMIA trial (NCT01471522) might be published because those may change the effect estimate considerably.

Re-Evaluierung für 2022 empfohlen

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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. [9] (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. [9] (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)
Epigastric pain, n (%)	0 (0) vs. 1 (2)
Atypical chest pain, n (%)	1 (2) vs. 6 (12)

[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. [9] (2015)
Acute coronary syndrome, n (%)	0 (0) vs. 2 (4)
Arrhythmia, n (%)	0 (0) vs. 1 (2)
Multi-system failure/death, n (%)	0 (0) vs. 1 (2)
Pulmonary edema, n (%)	0 (0) vs. 1 (2)
COPD, n (%)	1 (2) vs. 1 (2)
Cough, n (%)	0 (0) vs. 1 (2)
Decompensated heart failure, n (%)	1 (2) vs. 0 (0)
Gastrointestinal bleeding, n (%)	1 (2) vs. 0 (0)
Injury, n (%)	1 (2) vs. 0 (0)
Bleeding events associated with dual antiplatelet therapy	NA
ADEs (at least 1 AE in n of pts (%))	32[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)

Author, year	Banai et al. [13] (2007)	Giannini and Baldetti et al. [15] (2018)	Königstein et al. [12] (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. [13] (2007)	Giannini and Baldetti et al. [15] (2018)	Königstein et al. [12] (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. [13] (2007)	Giannini and Baldetti et al. [15] (2018)	Königstein et al. [12] (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]
Crohn's disease flare, n (%)	NA	NA	NA

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. [13] (2007)	Giannini and Baldetti et al. [15] (2018)	Königstein et al. [12] (2014)
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-2: CSRS: Results from observational studies (part 2)

Author, year	Königstein et al. [14] (2018)	Ponticelli et al. [11] (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 [43].

Author, year	Königstein et al. [14] (2018)	Ponticelli et al. [11] (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
Loss to follow-up, n (%)	3[36]	8[37]	0

[29] All baseline criteria reported from the 12 mos publication from Giannini 2018 [43].

[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.

[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.

Author, year	Königstein et al. [14] (2018)	Ponticelli et al. [11] (2019)	Tzanis et al. [10] (2019)
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
Stable angina, n (%)	2 (4)	NA	NA
Crohn's disease flare, n (%)	NA	NA	NA
Unstable angina, n (%)	1 (2)	NA	NA

[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. [14] (2018)	Ponticelli et al. [11] (2019)	Tzanis et al. [10] (2019)
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.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. No cases of disagreement occurred. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [44] and in the Guidelines of EUnetHTA [45].

Table A-3: Risk of bias – study level (RCTs), see [2]

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, [9]	Yes	Yes	Yes	No	No	Yes	Low

Table A-4: Risk of bias – study level (case series), see [4]

Study reference/ID	Banai et al., 2007, [13]	Giannini & Baldetti et al., 2018, [15]	Konigstein et al., 2014, [12]	Konigstein et al., 2018, [14]	Ponticelli et al., 2019, [11]	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[45]	Unclear[46]	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[47]	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[48]
Intervention and co-intervention						
8. Was the intervention clearly described?	Yes	Partial[49]	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes

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

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

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

[48] Insufficient baseline information provided.

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

Study reference/ID	Banai et al., 2007, [13]	Giannini & Baldetti et al., 2018, [15]	Konigstein et al., 2014, [12]	Konigstein et al., 2018, [14]	Ponticelli et al., 2019, [11]	Tzanis et al., 2019, [10]
Outcome measure						
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial[50]	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No[51]	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[52]
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[53]	Yes	Partial[53]	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	No[54]	Yes	No[54]	No[54]	No[54]
Competing interest and source of support						
20. Were both competing interest and source of support for the study reported?	Partial[55]	Partial[55]	Partial[55]	Partial[55]	Partial[55]	Partial[55]
Overall Risk of bias	Low	Moderate	Moderate	Low	Low	Low

[50] Only efficacy measure was clearly established.

[51] 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.

[52] 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.

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

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

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

Table A-5: Evidence profile: efficacy and safety of CSRS in patients with angina pectoris

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)	
CCS angina score improvement of at least 2 classes at 6 mos follow-up, %											
1	Randomised trial	Not serious	Not serious	Not serious	Serious[a)]	-	52	52	-	20% more in IG than CG pts	⊕⊕⊕◯ moderate
SAQ QoL score improvement at 6 mos follow-up, n of points											
1	Randomised trial	Not serious	Not serious	Not serious	Serious [a)]	-	52	52	-	10 points more in IG than CG pts	⊕⊕⊕◯ moderate
Total exercise duration improvement at 6 most follow-up, n of seconds											
1	Randomised trial	Not serious	Not serious	Not serious	Serious [a)]	-	52	52	-	55 sec more in IG than CG pts	⊕⊕⊕◯ moderate
SADEs at 6 mos follow-up, n of events											
6	Randomised trial and case series	Serious [b), c)]	Not serious	Not serious	Not serious	-	348	52	-	8% fewer in IG than CG	⊕⊕⊕◯ moderate

Abbreviations: ***CCS*** *– Canadian Cardiovascular Society,* ***CG*** *– control group,* ***CI*** *–confidence interval,* ***CSRS*** *– coronary sinus reducing stent,* ***IG*** *– intervention group,* ***mos*** *– months,* ***n*** *– number,* ***QoL*** *– quality of life,* ***SADE*** *– serious adverse device effect,* ***SAQ*** *– Seattle Angina Questionnaire*

Comments:

[a] *Optimal information size is not met and the sample size is small,*

[b] *Source of financial support is unclear,*

[c] *One case series study unclear if retrospective.*

GRADE Working Group grades of evidence:

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect*

Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different*

Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect*

Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect*

Applicability table

Table A-6: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population enrolled in the studies does not fully reflect the target population of the intervetion in that a substantial proportion of patients included in the studies did not meet the definition of refractory AP. Furthermore, the selection of patients in the studies included was highly specific and hence, it remains a quesiton to what extent will the real world use of the device mirror such patient population. While the inclusion criteria were, in general, homogenous, the exclusion criteria varied with respect to previous CABG/PCI, decompensated heart failure, the presence of life threatening arrhythmias, severe valvular heart disease, tricuspid valve replacement, and the presence of a pacemaker lead.
Intervention	CSRS is a CS reducing device/stent made of stainless steel that is implanted in the CS and pre-mounted on a customized hourglass shaped balloon catheter. The catheter is inserted into its place via the jugular vein under local anaesthesia. The only available device is Neovasc Reducer™-System produced by Neovasc Inc., British Columbia, Canada.
Comparators	The CSRS aims to fulfill a therapeutic gap and so no established intervention is currently in place. The only other intervention with a controlled evidence base is external counterpulsation.
Outcomes	For clinical effectiveness, the list of crucial outcomes considered included: CCS angina score, SAQ for QoL, SAQ for treatment satisfaction, and SADEs. Furhter outcomes considered were exercise tolerance as assessed with the use of a symptom-limited stress test (ST-segment depression during exercise), modified wall motion index, antianginal medications intake, and ADEs.
Setting	All of the studies included were either single-centre or multi-centre studies, with clinical centres based in Europe and Asia. The studies were specifically conducted in Germany, India, Italy, Israel, Belgium, Canada, Denmark, the Netherland, Sweden, and the UK, and these contexts are considered similar to the Austrian one.

List of ongoing randomised controlled trials

Table A-7: List of ongoing RCTs of CSRS

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT01566175	100	CSRS	NA	Decrease of two or more CCS Angina Score grades from baseline to six-months	31.12.2028	Tel-Aviv Sourasky Medical Center| Neovasc Inc.
NCT04121845	40	CSRS	RCT	Impact of CSRS on exertional capacity measured by maximal oxygen consumption (VO2) during cardio-pulmonary exercise testing	31.12.2021	University Medical Centre Ljubljana
NCT02710435	400	CSRS	NA	Reduction in CCS Angina Score grades from baseline to six-months Rate of occurrence of device and/or procedure related peri-procedural SADEs 30 days post implant Occurrence of major cardiac AEs 30 days post implant	Dec 2022	Neovasc Inc.
NCT01471522	5179	Routine invasive strategy with cardiac catheterization followed by revascularization plus optimal medical therapy.	Optimal medical therapy with cardiac catheterization and revascularization reserved for patients with acute coronary syndrome, ischemic heart failure, resuscitated cardiac arrest or refractory symptoms.	Composite of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure	30.06.2019	NYU Langone Health

Abbreviations: ***AE*** *– adverse event,* ***CSRS*** *– coronary sinus reducing stent,* ***CCS*** *– Canadian Cardiovascular Society,* ***NA*** *– not available,* ***SADE*** *– serious adverse device effect*

Literature search strategies

Search strategy for Cochrane

Search Name: Coronary Sinus Reducer	
Search Date: 13/12/2018	
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 (Word variations have been searched)
#21	sTNS (Word variations have been searched)
#22	t-SNS (Word variations have been searched)
#23	tSNS (Word variations have been searched)
#24	Cefaly (Word variations have been searched)
#25	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#3 and #25
#27	supraorbital transcutaneous near (nerve stimul* or neurostimul* or neuro-stimul*):ti,ab,kw (Word variations have been searched)
#28	#26 or #27
Total: 42 Hits	

Search strategy for CDR

Search Name: Coronary Sinus Reducer	
Search Date: 13/12/2020	
ID	Search
#1	(coronary sinus NEAR (reduc* OR narrow*))
#2	(reducer*)
#3	#1 OR #2
Total:1 Hits	

Search strategy for Medline

Search Name: Coronary Sinus Reducer		
Search Date: 10/12/2020		
ID	Search	Results
#1	exp Coronary Artery Disease/	74,267
#2	Corona* Arter*.mp.	274,243
#3	CAD.ti,ab.	44,794
#4	1 or 2 or 3	290,046
#5	exp Angina Pectoris/	45,232
#6	Angina*.mp.	75,238
#7	angor pectoris.mp.	58
#8	stenocardia*.mp.	958
#9	5 or 6 or 7 or 8	75,401
#10	4 or 9	336,256
#11	exp Coronary Sinus/	1,925
#12	Sinus.mp.	146,716
#13	11 or 12	146,716
#14	10 and 13	8,102
#15	(corona* sinus adj5 (reduc* or narrow*)).mp.	241
#16	reducer*.mp.	2,480
#17	neovasc.mp.	16
#18	15 or 16 or 17	2,646
#19	14 and 18	166
#20	remove duplicates from 19	125
Total: 125 hits		

Search strategy for Embase

Search Name: Coronary Sinus Reducer	
Search Date: 13/12/2020	
ID	Search
#1	'coronary artery disease'/exp
#2	'corona* arter*':ti,ab,de,kw
#3	cad:ti,ab
#4	#1 OR #2 OR #3
#5	angina pectoris'/exp
#6	angina*:ti,ab,de,kw
#7	'angor pectoris':ti,ab,de,kw
#8	stenocardia*:ti,ab,de,kw
#9	'steno cardia*':ti,ab,de,kw
#10	#5 OR #6 OR #7 OR #8 OR #9
#11	#4 OR #10
#12	'coronary sinus'/exp
#13	sinus:ti,ab,de,kw
#14	#12 OR #13
#15	#11 AND #14

#16	'coronary sinus reducer'/exp
#17	corona*:ti,ab,de,kw AND ((sinus NEAR/4 (reduc* OR narrow*)):ti,ab,de,kw)
#18	reducer*:ti,ab,de,kw,dn
#19	neovasc*:df
#20	#16 OR #17 OR #18 OR #19
#21	#15 AND #20
Total: 305 hits	

Search strategies for clinical trial databases

ClinicalTrials.gov (Expert Search Mode) 29-30.01.2020

AREA[ConditionSearch] (Coronary Artery Disease OR CAD OR Angina Pectoris OR Stenocardia) AND AREA[InterventionSearch] ((Coronary Sinus OR Sinus) AND (reducer OR reduce OR reducing OR reduction OR narrowing OR narrow OR neovasc))

5 Studies identified

WHO ICTRP (Basic Search Mode) 29-30.01.2020

coronary sinus AND (reducer OR neovasc)

9 (5 further) studies identified

EU Clinical Trials [EudraCT] (Basic Search Mode) 29-30.01.2020

"coronary sinus" AND (reducer OR reduce OR reducing OR reduction OR narrowing OR narrow OR neovasc)

3 further studies identified

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Health Technology Assessment