NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of coronary sinus narrowing device implantation for refractory angina

Angina is chest pain caused by reduced blood flow to the heart muscle. It is refractory when it cannot be controlled using medication, by inserting a small wire-mesh device (stent) to unblock or widen an artery that supplies the heart or with conventional open-heart surgery. In this procedure, a device is inserted through a vein in the neck. It is guided into the vessel (the coronary sinus) that drains blood from the heart muscle into 1 of the right heart chambers and expanded using a balloon. The device narrows the coronary sinus, which is thought to improve the flow of oxygenated blood throughout the heart muscle. The aim is to reduce chest pain and improve quality of life.

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Abbreviations

Word or phrase	Abbreviation
Canadian Cardiovascular Society	CCS
Coronary total occlusion	CTO
Interquartile range	IQR
Randomised controlled trial	RCT
Seattle Angina Questionnaire	SAQ

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2021 and updated in September 2021.

Procedure name

- Coronary sinus narrowing device implantation for refractory angina

Professional societies

- British Cardiovascular Society
- British Cardiovascular Intervention Society
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

Angina is pain or constricting discomfort that typically occurs in the front of the chest (but may radiate to the neck, shoulders, jaw or arms). It is brought on by physical exertion or emotional stress. Some people can have atypical symptoms, such as gastrointestinal discomfort, breathlessness or nausea. Angina is the main symptom of myocardial ischaemia. It is usually caused by atherosclerotic obstructive coronary artery disease restricting blood flow and therefore oxygen delivery to the heart muscle. Being diagnosed with angina can have a significant effect on a person's quality of life, restricting daily work and leisure activities. NICE's guideline on stable angina describes recommendations on managing stable angina. Options include lifestyle advice, drug treatment and revascularisation using percutaneous or surgical techniques.

For people with refractory angina, these treatments do not control symptoms or are not clinically suitable. Coronary sinus narrowing device implantation is indicated for angina when other treatment options (medical or surgical) have failed or are not possible. The aim is to reduce symptoms and to improve quality of life.

What the procedure involves

The coronary sinus is a large venous structure formed by the merging of veins that drain blood away from the myocardium. It receives most of the cardiac venous blood, which then flows into the right atrium (along with deoxygenated blood from the superior and inferior venae cavae).

This procedure uses a percutaneously inserted balloon-expandable device to narrow the coronary sinus. In current practice, an hourglass-shaped device made of stainless steel mesh is used. The device is put into the main vessel of the coronary sinus by a catheter in the right side of the heart, typically through the right or left jugular vein. To define and measure the most suitable position for the device injected contrast is used to visualise the anatomy of the coronary sinus. A guiding catheter is then used to advance the device to the implantation site. The device is mounted on a balloon, which is inflated to expand it. Once the device is correctly placed, the balloon is deflated and the catheter pulled back. Imaging is used to confirm that there is 'hour-glass' device expansion in the coronary sinus.

Over time, endothelialisation occurs which creates a functional stenosis. This leads to an increase in postcapillary venous pressure and redistribution of blood from the less ischaemic epicardium to the more ischaemic endocardium.

Outcome measures

CCS angina grading scale

The CCS angina grading scale is used for classification of angina severity, as follows:

- Class 1 – angina only during strenuous or prolonged physical activity
- Class 2 – slight limitation, with angina only during vigorous physical activity
- Class 3 – symptoms with everyday living activities (moderate limitation)
- Class 4 – inability to perform any activity without angina or angina at rest (severe limitation)

SAQ

The SAQ is a 19-item questionnaire that measures 5 domains of health status related to coronary artery disease: angina stability, angina frequency, physical limitation, treatment satisfaction and quality of life. Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status.

Efficacy summary

Technical success

In an RCT of 104 patients who had either a coronary sinus narrowing device implanted or a sham procedure, technical success was 96% (50/52) with the narrowing device. Implantation failed in 2 patients because of a venous valve in the coronary sinus that could not be crossed with the device (Verheye 2015).

In a case series of 187 patients, technical success with coronary sinus narrowing device implantation was 98% (183/187). Implantation was not possible in 2 patients because of unfavourable anatomy of the coronary sinus or a venous anomaly, and the device failed in the other 2 patients (1 coronary sinus dissection and 1 device embolisation; D'Amico 2021).

In 3 case series of 141, 132 and 215 patients, technical success was 99% (139/141 and 131/132) and 98% (211/215). In all 7 unsuccessful procedures, implantation was not possible because of unfavourable anatomy of the coronary sinus (Giannini 2018; Silvis 2020; Gallone 2019).

In a case series of 658 patients, procedural success was 97% (641/653). Of the 22 unsuccessful procedures, 20 were abandoned either for anatomical

unsuitability or for complications (5 of these 20 were reattempted with a successful outcome) and 2 procedures failed (Ponticelli 2021).

CCS angina class improvement

In the RCT of 104 patients, 35% (18/52) of patients in the coronary sinus narrowing device group and 15% (8/52) of patients in the sham-control group had an improvement of at least 2 CCS angina classes at 6-month follow up (p=0.02). Improvement of at least 1 CCS angina class was reported in 71% (37/52) and 42% (22/52) of patients respectively (p=0.003). The mean CCS class reduced from 3.2 at baseline to 2.1 in the coronary sinus narrowing device group and from 3.1 to 2.6 in the control group (p=0.001; Verheye 2015).

In the case series of 187 patients, CCS angina class improved by at least 1 class in 83% (135/163) of patients and by at least 2 classes in 49% (80/163) of patients at follow up (median 18 months). The mean CCS class improved from 3.2 at baseline to 1.8 at follow up (p<0.001; D'Amico 2021).

In the case series of 141 patients, CCS angina class improved by at least 1 class in 81% (113/139) of patients, 2 classes in 45% (63/139) and 3 classes in 14% (20/139) of patients at follow up (median 14 months). The mean CCS class improved from 3.05 at baseline to 1.63 at follow up (p<0.001; Giannini 2018). In a case series of 99 patients from the same study, the mean CCS class was 3.1 at baseline and 1.71 at median follow up of 3.4 years (Konigstein 2021).

In a case series of 50 patients, the CCS angina score improved by at least 1 class in 76% (34/45) of patients and at least 2 classes in 36% (16/45) of patients at 2-year follow up. The mean CCS class improved from 3.00 at baseline to 1.74 at 2-year follow up (p<0.001; Ponticelli 2019).

In the case series of 132 patients, the CCS angina score improved by at least 1 class in 68% of patients and at least 2 classes in 34% of patients at 6-month follow up. The mean CCS class improved from 3.17 at baseline to 2.12 at follow up (p<0.001; Silvis 2020).

In a case series of 205 patients, 73% (144/194) had an improvement in CCS class at 6-month follow up. The proportion was 66% (65/98) for patients without a chronic CTO compared with 81% (79/96) for patients with a chronic CTO (p=0.03; Zivelonghi 2020).

In the case series of 658 patients, 40% (238/599) of patients had an improvement of at least 2 CCS angina classes with a median follow up of 502 days. Improvement of at least 1 CCS angina class was reported in 76% (455/599) of patients. The median CCS class improved from 3 at baseline to 2 at follow up (p<0.001). At baseline, 89% (588/658) of patients had CCS angina

class 3 or above compared with 25% (148/599) at the last follow up (p<0.001) (Ponticelli 2021).

Health status and quality of life (SAQ scores)

In the RCT of 104 patients, the SAQ score for quality of life improved by 17.6 points in the coronary sinus narrowing device group compared with 7.6 points in the sham-control group at 6-month follow up (p=0.03). There were no statistically significant differences between the groups with respect to improvement in the domains of angina stability (18.1 compared with 8.3 points, p=0.16) or angina frequency (15.3 compared with 11 points, p=0.4; Verheye 2015).

In the 3 case series of 187, 141 and 215 patients, there were statistically significant improvements (p<0.001) in all domains of the SAQ at follow up (D'Amico 2021; Giannini 2018; Gallone 2019). In the case series of 187 patients with a median follow up of 18 months, the physical limitation score improved from 43.8 to 63.9, angina stability from 40.2 to 61.7, angina frequency from 45.6 to 71.1, treatment satisfaction from 46.9 to 74.7 and quality of life from 32.4 to 63.2 (D'Amico 2021). In the case series of 141 patients with a median follow up of 14 months, the physical limitation score improved from 43.9 to 62.2, angina stability from 36.9 to 66.6, angina frequency from 45.6 to 66.7, treatment satisfaction from 51.9 to 68.4 and quality of life from 26.6 to 52.2 (Giannini 2018). In the case series of 141 patients with a median follow up of 14 months, the median physical limitation score improved from 47 to 57, angina stability from 40 to 60, angina frequency from 50 to 61, treatment satisfaction from 48 to 80 and quality of life from 29 to 62 (Gallone 2019).

In the case series of 50 patients, at 2-year follow up, the physical limitation score improved from 47.9 to 67.1 (p<0.001), the angina stability score from 39.8 to 45.2 (p=0.08), the angina frequency score from 44.4 to 69.0 (p<0.001), the treatment satisfaction score from 37.9 to 74.0 (p<0.001) and the quality-of-life score from 25.7 to 58.8 (p<0.001; Ponticelli 2019).

Exercise duration

In the RCT of 104 patients, the mean total exercise duration improved by 60 seconds (13% improvement) in the coronary sinus narrowing device group and 4 seconds (1% improvement) in the sham-control group (p=0.07; Verheye 2015).

In the case series of 141 patients, total exercise duration increased from 375 seconds to 388 seconds (p=0.561). The 6-minute walk test distance improved from 307.5 m to 386.9 m (p<0.001). The frequency of limiting angina at peak stress reduced from 62% (32/51) to 36% (18/51) of patients (p=0.002), with a median follow up of 14 months (Giannini 2018).

Anti-angina medication

In the case series of 187 and 141 patients, the mean number of anti-angina drugs prescribed reduced from 2.8 to 2.0 ($p<0.001$; D'Amico 2021) and from 2.4 to 2.2 ($p=0.003$; Giannini 2018).

In the case series of 50 patients, there was no statistically significant difference in the number of anti-angina drugs prescribed at 2-year follow up compared with baseline and 1-year follow up (Ponticelli 2019).

Other events at follow up

In the case series of 187 patients, mortality during follow up (median 18 months) was 8% (14/177); 7 deaths were cardiovascular and 7 were non-cardiovascular. Myocardial infarction was reported in 8% (14/177) of patients. Of the 177 patients who were followed up, 17% (30/177) had a new coronary angiography and 13% (23/177) had new revascularisation (21 for coronary artery disease progression and 2 for more aggressive treatment of previously failed procedures; D'Amico 2021).

In the case series of 141 patients, mortality during follow up (median 14 months) was 10% (14/139); 4 deaths were cardiovascular (2 fatal myocardial infarctions, 1 advanced heart failure and 1 refractory angina leading to anorexia and decubitus). Hospitalisations for recurrent angina during 12-month follow up were reported in 17% (23/139) of patients. Coronary angiography was reported in 19% (26/139) of patients and revascularisation procedures for new coronary lesions were reported in 11% (15/139) of patients (Giannini 2018). In the case series of 99 patients from the same study with longer follow up, mortality was 15% (15/99), 9.0% (9/99) of patients had a myocardial infarction and 3.0% (3/99) had a stroke. Angiography was reported in 31% (31/99) of patients and percutaneous coronary intervention in 21% (21/99) and 28% (28/99) of patients had a hospitalisation related to angina (Konigstein 2021).

In the case series of 50 patients, mortality during the 2-year follow up was 10% (5/50); 2 deaths were in the first 12 months after the procedure and the remaining 3 were after the first year. Clinically driven coronary angiography was reported in 31% (13/42) of patients and 21% (9/42) had a percutaneous coronary intervention (Ponticelli 2019).

In the case series of 215 patients, there were 15 (7%) non-fatal myocardial infarctions during follow up (median 15 months) and 21 (10%) deaths, 10 of which were cardiovascular (Gallone 2019).

In the case series of 658 patients, mortality during follow up was 10% (65/625) and the cardiovascular mortality was 29.1 per 1,000 patient-years. Major adverse

cardiovascular events were reported in 15% (91/625) of patients (Ponticelli 2021).

Safety summary

General

At least 1 adverse event was reported in 64% (32/50) of patients who had a coronary sinus narrowing device implanted and 69% (37/54) of patients who had a sham procedure (p=0.68) in the RCT of 104 patients. The number of serious adverse events was 10 and 24 respectively (Verheye 2015).

Myocardial infarction

Periprocedural myocardial infarction was reported in 1 patient who had a coronary sinus narrowing device implanted in the RCT of 104 patients; 3 patients in the sham-control group had myocardial infarctions within 6 months of the procedure (Verheye 2015).

Device embolisation, migration or dislocation

Device embolisation was reported in 1 patient in the case series of 187 patients (D'Amico 2021) and in 1.5% (2/132) of patients in the case series of 132 patients (Silvis 2020).

Device embolisation was reported in 1% (2/205) of patients in the case series of 205 patients; in both patients, the device was successfully retrieved, and the procedure was completed with a second device implantation (Zivelonghi 2020).

Device dislocation was reported in 2% (4/187) of patients in the case series of 187 patients. In 2 patients the narrowing device was snared and retrieved through a femoral access and a second device was successfully implanted. In the other 2 patients the dislocated device was implanted proximally, and a second device was successfully implanted more distally without complication (D'Amico 2021).

Device migration was reported in 1 patient in the case series of 141 patients. This was treated by successful snaring the narrowing device and implanting another device at a more distal location (Giannini 2018).

Device dislocation before it reached the target area was reported in 2% (3/132) of patients in the case series of 132 patients; all were subsequently successfully placed (Silvis 2020).

Device migration was reported in 1 patient in the case series of 215 patients; this was treated by successful snaring and there were no adverse clinical events (Gallone 2019).

Device embolisation was reported in 2% (15/658) of patients in the case series of 658 patients. In 14 of the 15 patients, the scaffold was successfully retrieved. In 1 patient, an embolisation into the pulmonary artery was left in place. Device dislodgment from the delivery catheter was reported in 0.6% (4/658) of patients. In 3 of these, it was possible to either reposition the device and proceed with implantation, or to recapture and remove it from a peripheral vein (Ponticelli 2021).

Coronary sinus dissection or perforation

Coronary sinus dissection was reported in 1 patient and coronary sinus perforation was reported in 1% (2/187) of patients in the case series of 187 patients. Of the 2 perforations, 1 was in the right ventricle and treated by prolonged balloon inflation, and the other was self-limiting in the pericardial space, resulting in a mild pericardial effusion that did not need treating (D'Amico 2021).

Wire perforation was reported in 1 patient in the case series of 132 patients (Silvis 2020).

Coronary sinus perforation was reported in 0.5% (3/658) of patients and coronary sinus dissection was reported in 1% (9/658) of patients in the case series of 658 patients. All had conservative management (Ponticelli 2021).

Other

Access site complications were reported in 2% (2/132) of patients in the case series of 132 patients (Silvis 2020).

Periprocedural rapid atrial fibrillation that spontaneously converted to sinus rhythm, dislocation of a pacemaker right atrial lead and bleeding at the access puncture site 10 days after implantation were reported in 1 patient each in the case series of 141 patients (Giannini 2018).

Intra- or periprocedural stroke was reported in 1 patient in the case series of 658 patients. Neck haematoma was reported in 1.5% (10/658) of patients in the same study. All had conservative management (Ponticelli 2021).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and

about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts described the following anecdotal adverse event: occasional pain may be experienced by instrumenting coronary sinus but is very unusual. They considered that the following was a theoretical adverse event: complete coronary sinus occlusion or coronary sinus thrombosis in the longer term.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to coronary sinus narrowing device implantation for refractory angina. The following databases were searched, covering the period from their start to 30 June 2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identifying relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with refractory angina.
Intervention/test	Coronary sinus narrowing device implantation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1 RCT (Verheye 2015) and 8 case series, 1 of which is reported in 2 publications (D'Amico 2021; Giannini 2018; Ponticelli 2019; Silvis 2020; Zivelonghi 2020; Gallone 2019; Konigstein 2021; Ponticelli 2021; Verheye 2020). The reported total number of patients having treatment with coronary sinus narrowing device implantation in these studies was about 1,850, but the actual number of patients is likely to be lower because there appears to be considerable overlap between the studies.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on coronary sinus narrowing device implantation for refractory angina

Study 1 Verheye S (2015)

Study details

Study type	RCT (COSIRA)
Country	Belgium, Canada, UK, Sweden, the Netherlands, Denmark, US, Israel
Recruitment period	2010 to 2013
Study population and number	n=104 (52 coronary sinus narrowing device, 52 sham control) Patients with refractory angina
Age and sex	Mean age 67.8±9.4 years (range: 35 to 87); 81% male
Patient selection criteria	Inclusion criteria: over 18 years old with CCS class 3 to 4 angina, despite medical therapy (beta-blockers, calcium-channel blockers, nicorandil, ivabradine or short- and long-acting nitrates used at maximally tolerable doses) for at least 30 days before screening. All patients had to have evidence of reversible myocardial ischaemia and a left ventricular ejection fraction of greater than 25%. Only patients for whom coronary revascularisation was deemed unsuitable were eligible to participate. Exclusion criteria: recent revascularisation procedure (within 6 months), recent acute coronary syndrome (within 3 months), or permanent pacemaker or defibrillator leads in the right heart.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada) Dual antiplatelet therapy was given for at least 1 week before the procedure and for 6 months after the procedure in both groups. Those randomised to the Reducer had intravenous heparin at the time of implantation. Patients were offered either headsets playing music or conscious sedation to mask the conversation in the room about the randomisation and the procedure. The implanting physicians were instructed to behave similarly during both Reducer and sham implantations, including spending a comparable amount of procedure time in the 2 groups. A diagnostic catheter was introduced into the right atrium. Right atrial pressure was measured and recorded. The catheter was then introduced into the coronary sinus and an angiogram was done. Implantation site was determined according to the vessel diameter and to avoid side branch bifurcation. Patients assigned to the sham-control group had no additional invasive manipulation. In patients assigned to the treatment group, a guiding catheter was introduced into the coronary sinus and a Reducer was implanted at the desired site. Postimplantation angiography was done to ensure appropriate implantation.
Follow up	6 months
Conflict of interest/source of funding	The trial was sponsored by Neovasc.

Analysis

Follow-up issues: There were no losses to follow up.

Study design issues: Randomised, double-blind, sham-controlled, multicentre clinical trial. Patients were randomised in a 1:1 ratio using a computer-generated random allocation sequence to implantation of a Reducer (treatment group) or sham procedure (control group). Treatment assignments were concealed in numbered sealed envelopes. All patients remained blinded throughout the 6-month study period. The investigator responsible for assessing the angina class at follow up, all core laboratories, the biostatisticians doing the analysis and the members of the clinical events committee were also blinded to treatment assignment. The prespecified primary end point was the proportion of patients with an improvement of 2 or more CCS classes from baseline to 6 months after the procedure. A sample size of 124 patients was calculated to give 80% power to test the 2-sided hypothesis at a Type I error level of 0.05 that 40% of participants assigned to the Reducer group would improve by 2 or more CCS angina classes compared to 15% of participants assigned to the sham-control group. A dropout rate of 10% was assumed. Enrolment took longer than expected and the dropout rate was better than expected so enrolment was stopped after 104 patients had been randomised.

Secondary end points included the proportion of patients with an improvement of 1 or more CCS classes from baseline to 6 months and exercise tolerance assessed on a symptom-limited stress test. All efficacy outcomes were analysed on an intention-to-treat basis. The study was underpowered to detect differences in the prespecified secondary outcomes.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 study groups. Of the 104 patients, 92% had hypercholesterolaemia, 44% had diabetes mellitus, 80% had hypertension and 56% were current or previous smokers. 55% of patients had a previous myocardial infarction, 77% had previous coronary artery bypass grafting and 73% had previous percutaneous coronary intervention.

Key efficacy findings

Number of patients analysed: 104 (52 coronary sinus narrowing device, 52 sham control)

Technical success=96% (50/52)

Implantation failed in 2 patients because of a venous valve in the coronary sinus that could not be crossed with the device.

Improvement of at least 2 CCS angina classes at 6-month follow up

- Coronary sinus narrowing device=34.6% (18/52)
- Sham control=15.3% (8/52), p=0.02

Improvement of at least 1 CCS angina class at 6-month follow up

- Coronary sinus narrowing device=71.1% (37/52)
- Sham control=42.3% (22/52), p=0.003

Mean CCS class was reduced from 3.2±0.4 at baseline to 2.1±1.0 at 6-month follow up in the coronary sinus narrowing device implantation group compared to 3.1±0.3 to 2.6±0.9 in the control group, p=0.001.

Improvement in quality of life – change in points on the SAQ

- Coronary sinus narrowing device=17.6
- Sham control=7.6, p=0.03

There were no statistically significant differences between the groups with respect to improvement in angina stability (18.1 compared with 8.3 points, respectively; p=0.16) or angina frequency (15.3 compared with 11 points, respectively; p=0.4)

Improvement in mean total exercise duration at 6-month follow up

- Coronary sinus narrowing device=60 seconds (13% improvement)
- Sham control=4 seconds (1% improvement), p=0.07

Key safety findings

Proportion of patients with at least 1 adverse event

- Coronary sinus narrowing device=64.0% (32/50)
- Sham control=68.5% (37/54), p=0.68

Number of serious adverse events

- Coronary sinus narrowing device=10
- Sham control=24

Myocardial infarction

- Coronary sinus narrowing device, n=1 (periprocedural)
- Sham control, n=3

Deaths

- Coronary sinus narrowing device, n=0
- Sham control, n=1 (multi-organ failure at day 118)

CT angiography at 6 months showed no evidence of device migration or occlusion in any of the patients (n=36).

Study 2 D'Amico G (2021)

Study details

Study type	Case series
Country	Italy (16 centres)
Recruitment period	2015 to 2019
Study population and number	n=187 Patients with refractory angina pectoris
Age and sex	Mean 70 years; 83% (155/187) male
Patient selection criteria	Inclusion criteria: patients with chronic disabling angina pectoris (CCS classes 2 to 4) refractory to maximum tolerated medical therapy and considered not amenable for percutaneous or surgical revascularisation procedures by the local heart team. Exclusion criteria: Patients were excluded when (1) ischaemia was related mainly to the right coronary artery, (2) pacemaker lead was present in the coronary sinus, (3) index event was an acute coronary syndrome (<3 months), (4) a recent coronary revascularisation was done <6 months, and (5) right atrial pressure was higher than 15 mm Hg.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada) Right internal jugular vein was the preferred access (97%). Dual antiplatelet therapy was recommended for 6 months after the procedure. Centres were proctored for the first 2 cases.
Follow up	Median clinical follow up 18.4 months
Conflict of interest/source of funding	Two authors declared speaker honoraria for GADA. One is a consultant for Neovasc. The authors declared that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Analysis

Follow-up issues: Follow up was done either by telephone or by office clinical visit at different time points. Six (3.2%) patients were lost to follow up. Of the 163 patients who survived and were not lost to follow up, 105 (64.4%) were followed up for more than 1 year.

Study design issues: Multicentre, single-arm registry. The efficacy end point was assessed as change in angina severity from baseline to the last available follow up, using the CCS classification of angina and the SAQ scores, and as change in number or dose of antianginal drug therapy. Technical success was defined as the successful delivery and deployment of the narrowing device to the intended site and procedural success was defined as technical success plus the absence of acute need for intervention to address any adverse device-related event before hospital discharge. The safety end point was the rate of any adverse device- or procedure-related event that occurred periprocedurally or before hospital discharge.

Study population issues: Of 183 (98%) patients previously revascularised, 134 (72%) patients had a coronary artery bypass grafting and 158 (85%) had previous percutaneous coronary intervention. The mean number of anti-ischaemic drugs prescribed at baseline was 2.8. Of the 187 patients, 88% had arterial hypertension, 48%

had diabetes mellitus, 93% had dyslipidaemia, 43% had a family history of coronary artery disease, 55% were current or previous smokers, 16% had atrial fibrillation, 7% had a permanent pacemaker, 65% had a previous myocardial infarction, 4% had a previous stroke and 31% had peripheral vascular disease.

Key efficacy findings

Number of patients analysed: 187

Technical success=98% (183/187)

Device implantation was not possible in 2 patients because of unfavourable anatomy of the coronary sinus or venous anomaly. There were 2 device failures caused by proximal non-flow-limiting coronary sinus dissection (treated conservatively) and a device embolisation.

CCS angina class

- Improvement of at least 1 CCS angina class at follow up = 82.8% (135/163) (excluding 14 patients who died)
- Improvement of at least 2 CCS angina classes at follow up = 49.1% (80/163) (excluding 14 patients who died)
- Mean CCS class improved statistically significantly from 3.2±0.5 at baseline to 1.8±0.9 at follow up ($p<0.001$).

Quality of life (SAQ scores)

- Physical limitation score improved from 43.8±16.8 at baseline to 63.9±17.2 points ($p<0.001$).
- Angina stability score improved from 40.2±13.4 at baseline to 61.7±22.1 points ($p<0.001$).
- Angina frequency score improved from 45.6±18 at baseline to 71.1±18.2 points ($p<0.001$).
- Treatment satisfaction score improved from 46.9±20.8 to 74.7±15.4 ($p<0.001$).
- Quality-of-life score improved from 32.4±14.3 to 63.2±18.7 ($p<0.001$).

Use of anti-angina drugs

The mean number of anti-angina drugs prescribed reduced from 2.77±1.04 to 2.00±1.2 ($p<0.001$).

Events at follow up (n=177)

- Death=7.9% (14/177); 7 were cardiovascular and 7 were non-cardiovascular
- Myocardial infarction=7.9% (14/177)
- New coronary angiography=16.9% (30/177)
- New revascularisation=12.9% (23/177)

- Coronary artery disease progression, n=21
- More aggressive treatment of previously failed procedures, n=2

Key safety findings

Periprocedural complications=4.3% (8/187)

- Device embolisation=0.5% (1/187).
- Device dislocation=2.1% (4/187); In 2 patients the device was snared and retrieved through a femoral access and a second device was successfully implanted. In the other 2 patients the dislocated device was implanted proximally, and a second device was successfully implanted more distally without complication.
- Coronary sinus dissection=0.5% (1/187).
- Coronary sinus perforation=1.1% (2/187); 1 was in the right ventricle and treated by prolonged balloon inflation, and the other was self-limiting in the pericardial space, resulting in a mild pericardial effusion that did not need treating.

There were no vascular complications, cardiac tamponade, periprocedural myocardial infarctions or periprocedural deaths.

Study 3 Giannini F (2018)

Study details

Study type	Case series (registry data); REDUCE study
Country	Italy, Israel, Belgium
Recruitment period	2010 to 2017
Study population and number	n=141 Patients with obstructive coronary artery disease and chronic disabling angina pectoris
Age and sex	Mean 69.4 years; 52% (74/141) male
Patient selection criteria	Inclusion criteria: patients with obstructive coronary artery disease and chronic disabling angina pectoris (CCS classes 2 to 4) despite maximally tolerated medical therapy, who were considered not amenable for further percutaneous or surgical revascularisation procedures by the local heart team. Objective demonstration of ischaemia with either treadmill or pharmacologic stress test, myocardial stress scintigraphy, stress echocardiography or myocardial magnetic resonance was mandatory. Specific contraindications to implantation were: ischaemia related exclusively to the right coronary artery, the presence of a pacemaker lead in the coronary sinus, recent acute coronary syndrome (within 3 months), recent coronary revascularisation (within 6 months) or a mean right atrial pressure higher than 15 mmHg.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	Median 14 months (range 6 to 70 months)
Conflict of interest/source of funding	One author is Medical Director of Neovasc Inc. Two authors are consultants for Neovasc Inc.

Analysis

Follow-up issues: A minimum of 6-month follow up was available for all patients. Follow up was done either by telephone or a face-to-face clinic visit and was conducted at variable times depending on the centres' practice, and patients' clinical status.

Study design issues: Prospective, single-arm multicentre registry data from 3 high volume centres. The primary efficacy endpoint was the change in angina severity at follow up, compared with baseline as assessed by CCS class status and SAQ scores. The primary safety endpoint was successful device delivery and deployment in the intended site and the absence of any adverse or serious adverse device-related events before hospital discharge and during the follow-up period.

Study population issues: Of the 141 patients, 76% had a history of coronary artery bypass grafting surgery, 82% had previous percutaneous coronary intervention and 63% had both, 54% of patients had a history of previous myocardial infarction and 32% had chronic kidney disease. At baseline, 84% of patients had arterial hypertension, 45% had diabetes mellitus, 32% had dyslipidaemia and 37% were current or previous smokers.

Key efficacy findings

Number of patients analysed: 141

Procedural success=98.6% (139/141)

Implantation failed in 2 patients because of unfavourable anatomy of the coronary sinus.

CCS angina class

- Improvement of at least 1 CCS angina class at follow up = 81% (113/139)
- Improvement of at least 2 CCS angina classes at follow up = 45% (63/139)
- Improvement of at least 3 CCS angina classes at follow up = 14% (20/139)
- Mean CCS class improved statistically significantly from 3.05±0.53 at baseline to 1.63±0.98 at follow up ($p<0.001$).

Quality of life (SAQ scores), n=83

- Physical limitation score improved from 43.9±17.6 at baseline to 62.2±20.7 points ($p<0.001$).
- Angina stability score improved from 36.9±20.4 at baseline to 66.6±27.0 points ($p<0.001$).
- Angina frequency score improved from 45.6±22.1 at baseline to 66.7±20.8 points ($p<0.001$).
- Treatment satisfaction score improved from 51.9±22.0 to 68.4±17.6 ($p<0.001$).
- Quality-of-life score improved from 26.6±16.5 to 52.2±19.9 ($p<0.001$).

Use of anti-angina drugs

The mean number of anti-angina drugs prescribed reduced from 2.37±0.97 to 2.17±0.95 ($p=0.003$)

Exercise treadmill stress test, n=51

- Total exercise duration changed from 375±169 seconds to 388±224 seconds ($p=0.561$)
- Frequency of limiting angina at peak stress reduced from 62% (32/51) to 36% (18/51) of patients ($p=0.002$)
- Six-minute walk test distance improved from 307.5±129.0 metres to 386.9±99.9 metres ($p<0.001$)

Events at follow up

- Death=10% (14/139); 4 were cardiovascular: 2 fatal myocardial infarctions, 1 advanced heart failure and 1 refractory angina leading to anorexia and decubitus
- Hospitalisations for recurrent angina during 12-month follow up: 17% (23/139)
- At least 1 invasive coronary angiogram during 12-month follow up: 19% (26/139)
- Coronary revascularisation procedure for de novo coronary lesion: 11% (15/139)

Key safety findings

Periprocedural events and early outcomes

- Device migration=0.7% (1/139); treated by successful snaring and implantation of another device at a more distal location
- Periprocedural rapid atrial fibrillation=0.7% (1/139); spontaneously converted to sinus rhythm
- Dislocation of pacemaker right atrial lead, implanted less than 3 months earlier, during procedure=0.7% (1/139)
- Bleeding at access puncture site 10 days after implant=0.7% (1/139); the patient was taking oral anticoagulants bridging with low molecular weight heparin

Study 4 Ponticelli F (2019)

Study details

Study type	Case series
Country	Italy
Recruitment period	2015 to 2016
Study population and number	n=50 Patients with angina refractory to medical therapy and not amenable to further revascularisation
Age and sex	Mean 61 years; 78% male
Patient selection criteria	Inclusion criteria: 1) refractory angina of at least CCS class 2, despite optimal or maximally tolerated medical antianginal therapy; 2) objective evidence of inducible myocardial ischaemia in the left coronary artery distribution territory (as determined by myocardial perfusion imaging, dobutamine stress echocardiography, or stress perfusion cardiac magnetic resonance imaging); and 3) coronary artery disease not amenable to percutaneous coronary intervention or coronary artery bypass grafting because of unsuitable coronary anatomy, diffuse disease, or absence of satisfactory distal graft anastomosis sites, following evaluation by the heart team. Exclusion criteria: ischaemia related exclusively to the right coronary artery, the presence of a foreign body (such as a pacemaker lead) in the coronary sinus, recent acute coronary syndrome (within 3 months), recent coronary revascularisation (within 6 months), or a mean right atrial pressure higher than 15 mmHg.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	2 years
Conflict of interest/source of funding	One author is a consultant for Neovasc Inc. All other authors report no relationships that could be construed as a conflict of interest.

Analysis

Follow-up issues: Data for the efficacy endpoint was available for 93% (42/45) of living patients, while 3 were unreachable by means of telephone calls or emails and were considered lost to follow up. Of the original 50 patients, 5 died (1 ischaemic stroke, 1 urological malignancy, 1 out-of-hospital cardiac arrest, 1 pulmonary malignancy and 1 nosocomial infection during a hospitalisation for heart failure).

Study design issues: Prospective, single-centre, observational study. The clinical efficacy endpoints included CCS angina class and SAQ score at 2-year follow up. New York Heart Association score and antianginal therapy at follow up were also evaluated. Device safety was defined as absence of device-related events during follow up. Information on death, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, cardiac tamponade, life-threatening arrhythmias and respiratory failure needing invasive ventilation were also recorded.

Study population issues: At baseline, 85% of patients had 3-vessel disease.

Key efficacy findings

Number of patients analysed: 42 for efficacy

CCS angina class

- CCS score improved ≥1 class in 34 patients (75.6%), and ≥2 classes in 16 patients (35.6%).
- Mean CCS class improved statistically significantly from 3.00±0.51 at baseline to 1.74±0.86 at 2-year follow up (p<0.001).

New York Heart Association class

- The New York Heart Association class improved from 1.67±0.72 at baseline to 1.2±0.65 at 1-year follow up (p<0.001).
- The improvement was lost at 2-year follow up (1.68±0.73 compared with 1.67±0.72 at baseline, p=1).

Quality of life (SAQ scores) at 2-year follow up

- Physical limitation score improved from 47.85±14.72 at baseline to 67.10±13.79 points (p<0.001).
- Angina stability score improved from 39.76±11.98 at baseline to 45.24±14.01 points (p=0.08).
- Angina frequency score improved from 44.43±19.2 at baseline to 69.02±15.07 points (p<0.001).
- Treatment satisfaction score improved from 37.89±14.74 to 74.02±8.43 (p<0.001).
- Quality-of-life score improved from 25.67±12.35 to 58.76±18.08 (p<0.001).

Use of anti-angina drugs

The number of anti-angina drugs prescribed was not statistically significantly different when compared to baseline or 1-year follow up (median number of drugs at 2 years: 3 [IQR: 2 to 4] compared with baseline: 3 [IQR: 2 to 4], p= 0.101; 1 year: 3 [IQR: 2 to 3.25], p=0.484).

Events during follow up

- Death=10% (5/50); 2 were in the first 12 months (1 ischaemic stroke and 1 urological malignancy) and the remaining 3 were after the first year (1 out-of-hospital cardiac arrest, 1 pulmonary malignancy and 1 nosocomial infection during a hospitalisation for heart failure).
- Clinically driven coronary angiography=31% (13/42).
- Percutaneous coronary intervention=21% (9/42) (10 procedures: 3 for myocardial infarctions, 7 for progression of coronary artery disease).

Key safety findings

There were no device-related complications.

Study 5 Silvis M (2020)

Study details

Study type	Case series
Country	The Netherlands (2 sites)
Recruitment period	2014 to 2020
Study population and number	n=132 Patients with refractory angina
Age and sex	Mean 66 years; 76% (100/132) male
Patient selection criteria	Inclusion criteria: symptomatic angina despite; (1) maximum tolerated pharmacological therapy, (2) no revascularisation options with percutaneous coronary intervention or coronary artery bypass grafting and (3) proven stress-induced myocardial ischaemia by non-invasive stress tests. Exclusion criteria included: successful revascularisation in the last 30 days, or previous cardiac resynchronisation therapy device with a left ventricular lead.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada) After successful implantation and closure of the access site, patients were discharged from hospital on the same day. Clopidogrel, in addition to aspirin or anticoagulation, was prescribed for 3 months. After 3 months, the pre-implant anticoagulation regimen was continued.
Follow up	6 months
Conflict of interest/source of funding	The research received no grant from any funding agency in the public, commercial or not-for-profit sectors. One author is a proctor for Neovasc and another is a consultant for DEKRA.

Analysis

Follow-up issues: Follow-up details were available for 96% (127/132) of patients.

Study design issues: Retrospective, multicentre case series. The primary endpoint of the study was CCS class improvement between baseline and 6-month follow up, assessed by the treating cardiologist. A responder was defined as a patient with at least 1 CCS class improvement.

Study population issues: At baseline, most patients had a history of coronary revascularisation (83% previous percutaneous coronary intervention and 77% coronary artery bypass graft). Of the 132 patients, 44% had diabetes mellitus, 57% had hypercholesterolaemia, 73% had hypertension, 16% were current smokers and 63% had a previous myocardial infarction. 84% of patients used 2 or more antianginal drugs and 44% used 3 or more.

Key efficacy findings

Number of patients analysed: 132

Procedural success=99% (131/132)

IP overview: Coronary sinus narrowing device implantation for refractory angina

The device could not be placed in 1 patient because the coronary sinus was too small.

CCS angina class

- Mean CCS score improved from 3.17±0.61 at baseline to 2.12±1.07 at 6-month follow up (p<0.001)
- 67.5% of all patients improved at least 1 CCS class
- 34.1% of patients improved 2 or more CCS classes and 7.1% improved 3 or more

Distribution of CCS class at baseline and 6-month follow up

CCS class	Baseline (n=132)	6-month follow up (n=127)
0	0%	5.5%
1	0.8%	23.6%
2	9.2%	36.2%
3	62.3%	22.8%
4	27.7%	11.8%

Hospitalisation for anginal complaints and visits to emergency department

- Hospitalisations reduced from 34.4% at baseline to 11.7% (p<0.001)
- Visits to the emergency department reduced from 28% to 15.8% (p=0.009)

Revascularisation

- 2 patients had coronary revascularisation within 6 months after implantation

There were no differences in blood pressure and heart rate during the 6 months before and after the procedure.

Key safety findings

Complications=4.5% (6/132) of patients

- Access site complication, n=2
- Device embolisation, n=2
- Device dislocation before it reached target area, n=3 (all were subsequently successfully placed)

- Wire perforation, n=1
- Intraprocedural death, n=0
- Procedural tamponade, n=0

Multiple complications occurred in 1 patient (access site complication, wire perforation and dislocation of the device), but they were all solved, and the device was successfully placed.

Study 6 Zivelonghi C (2020)

Study details

Study type	Case series
Country	The Netherlands, Belgium and Italy
Recruitment period	2014 to 2018
Study population and number	n=205 (103 with a chronic CTO lesion at coronary angiogram) Patients with refractory angina
Age and sex	Mean 68.3 years; 74% (155/205) male
Patient selection criteria	Inclusion criteria: age over 18 years, coronary artery disease with chronic refractory angina, CCS grade 2 to 4 despite maximally tolerated antianginal medical therapy. In addition, all patients had evidence of reversible myocardial ischaemia at non-invasive stress tests (including cardiac stress magnetic resonance imaging, cardiac scintigraphy or stress echocardiography), left ventricular ejection fraction of more than 25%, and no option or extremely high-risk for revascularisation. Medical therapy included beta-blockers, calcium-channel blockers, short-acting or long-acting nitrates, ranolazine and ivabradine, used at maximum tolerated doses.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	6 months for primary outcome (mean follow up 570 days)
Conflict of interest/source of funding	One of the authors is Medical Director of Neovasc Inc. and 2 authors are consultants for Neovasc Inc. The authors declared that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Analysis

Follow-up issues: Clinical follow up in outpatient clinic was available for 194 (94.6%) patients.

Study design issues: Patients were divided in 2 groups according to the presence or absence of a CTO at baseline coronary angiogram. CTO was defined as a total occlusion in any major epicardial coronary vessel or relevant side branches (reference vessel diameter ≥2.5mm), with thrombolysis in myocardial infarction 0 in the distal segment and at least 3 months old (according to clinical information or previous coronary angiograms). In patients with history of coronary artery bypass graft, a CTO was considered when located in a major epicardial branch without a patent graft leading to the distal vessel. All angiograms were reviewed by an expert cardiologist independent from the procedures, to define the presence of CTO. The primary endpoint was the improvement in CCS class at 6-month follow up.

Study population issues: Baseline characteristics were similar in patients with or without CTO, apart from the proportion of men (82% compared with 67%, p=0.01) and the proportion of patients with previous coronary bypass graft (86% compared with 63%, p<0.01). Of the 205 patients, 79% had hypertension, 82% had dyslipidaemia, 35% smoked, 43% had diabetes mellitus, 58% had previous myocardial infarction and 79% had previous percutaneous coronary intervention. Baseline CCS class was 3±0.5 in the CTO group and 3.1±0.6 in the non-CTO group (p=0.45).

Key efficacy findings

Number of patients analysed: 205

Successful implantation=100% (205/205)

Clinical outcomes at 6-month follow up

Variable	Total population (n=194)	Patients with CTO (n=96)	Patients without CTO (n=98)	p
CCS class				0.10
0	14 (7%)	9 (9%)	5 (5%)	
1	67 (34%)	38 (40%)	29 (30%)	
2	66 (34%)	32 (33%)	34 (35%)	
3	30 (15%)	13 (13%)	17 (17%)	
4	17 (9%)	4 (4%)	13 (13%)	
Mean CCS class ± standard deviation	1.8±1.1	1.6±0.9	2±1.1	<0.01
Change in CCS class				0.02
+1 (worsening)	4 (2%)	1 (1%)	3 (3%)	
0 (No change)	46 (24%)	16 (17%)	30 (31%)	
-1 (improvement)	65 (33%)	31 (32%)	34 (35%)	
-2 (improvement)	58 (30%)	38 (40%)	20 (20%)	
-3 (improvement)	21 (11%)	10 (10%)	11 (11%)	
Mean change in CCS class ± standard deviation	1.2±1	1.4±0.9	1±1	0.01
Patients with improvement	144 (73%)	79 (81%)	65 (66%)	0.03
Need for revascularisation at follow up	30 (15%)	13 (13%)	17 (17%)	0.44
Percutaneous coronary intervention of CTO at follow up	3 (1%)	3 (3%)	-	
Cardiovascular death	7 (3%)	3 (3%)	4 (4%)	0.72

Key safety findings

There were 2 device embolisations, both in the group of patients without CTO. The device was successfully retrieved and the procedure was completed with a second device implantation.

Study 7 Gallone G (2019)

Study details

Study type	Case series
Country	Belgium, Italy, the Netherlands (8 centres)
Recruitment period	2010 to 2017
Study population and number	n=215 Patients with refractory angina
Age and sex	median 68 years; 56% (121/215) males
Patient selection criteria	Patients with severe refractory angina (CCS classes 2 to 4 despite maximally tolerated medical therapy and considered not amenable for further percutaneous or surgical revascularisation procedures). Pre-implant objective demonstration of myocardial ischaemia with either treadmill or pharmacologic stress test, myocardial stress scintigraphy, stress echocardiography, or myocardial magnetic resonance was mandatory. Specific contraindications for implantation (as defined by the manufacturer) were: recent acute coronary syndrome (within 3 months), recent coronary revascularisation (within 6 months), or a mean right atrial pressure higher than 15mmHg.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	median 15 months (range 8 to 23 months)
Conflict of interest/source of funding	3 authors are consultants for Neovasc Inc. All other authors declared no conflict of interest.

Analysis

Follow-up issues: Baseline and follow up information about CCS angina class was available for all patients.

Study design issues: Retrospective, multicentre observational study. The main aim of the study was to assess cost-effectiveness which is not within the remit of this overview. However, the study also reported some clinical outcomes that have been summarised below.

Study population issues: Of all patients, 70% had history of coronary artery bypass grafting and 81% of percutaneous coronary intervention. There was a high prevalence of 3-vessel coronary artery disease (68%). All patients had disabling angina symptoms, with 11% of patients in CCS Class 2, 67% in CCS Class 3, and 21% in CCS Class 4. 53% of patients were taking at least 3 anti-ischaemic medications.

Key efficacy findings

Number of patients analysed: 215

Procedural success=98.1% (211/215) of patients

The device could not be implanted in 4 patients because of unfavourable anatomy (device migration happened in 1 of these patients, treated by successful snaring and no adverse clinical events).

CCS angina class (n=211)

- CCS class improved from 3 (IQR 3 to 3) at baseline to 2 (IQR range 1 to 2) at follow up (p<0.001).

SAQ scores (n=117; median follow up from baseline=13 months; IQR 8 to 18); median (IQR)

- Physical limitation score improved from 47 (35 to 55) to 57 (47 to 52), p<0.001.
- Angina stability score improved from 40 (25 to 43) to 60 (40 to 80), p<0.001.
- Angina frequency score improved from 50 (40 to 63) to 61 (50 to 83), p<0.001.
- Treatment satisfaction score improved from 48 (34 to 73) to 80 (70 to 82), p<0.001.
- Quality-of-life score improved from 29 (17 to 40) to 62 (47 to 75), p<0.001.

Anti-angina medication

- The median number of anti-angina medications prescribed per patient reduced from 3 (IQR 2 to 3) to 2 (IQR 2 to 3), p<0.001.

Events during follow up

- There were 15 (7.1%) non-fatal myocardial infarctions and 21 (9.9%) deaths, 10 (4.7%) of which were of cardiovascular origin (3 fatal myocardial infarction, 1 arrhythmic, 6 endstage heart failure).

Key safety findings

- Device migration, n=1 (described in efficacy section above)

There were no other intraprocedural or follow-up adverse events associated with coronary sinus narrowing device implantation.

Study 8 Konigstein M (2021)

Study details

Study type	Case series (registry data) – longer term follow up of REDUCE study
Country	Italy, Israel, Belgium
Recruitment period	2010 to 2017
Study population and number	n=99 Patients with obstructive coronary artery disease and chronic angina pectoris and at least 2 years of follow up after coronary sinus narrowing device implantation
Age and sex	Mean 69.8 years; male 77% (76/99)
Patient selection criteria	All patients had obstructive coronary artery disease and chronic angina pectoris (CCS classes 2 to 4) despite maximally tolerated medical therapy, and further percutaneous or surgical revascularisation were considered to be unsuitable. Pre-implant objective demonstration of ischaemia with either treadmill or pharmacologic stress test, myocardial stress scintigraphy, stress echocardiography or myocardial magnetic resonance was mandatory.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	Mean 3.9 years (median 3.4 years)
Conflict of interest/source of funding	Two authors serve as proctors for Neovasc Inc. and 1 author is the Medical Director of Neovasc Inc. All other authors have no conflicts of interest.

Analysis

Follow-up issues: Of the 197 patients who were in the original study, 45 patients were excluded because they had the procedure less than 2 years before the study, 16 patients did not survive to 2 years and 33 patients were lost to clinical long term (more than 2 years) follow up.

Study design issues: Prospective, single-arm multicentre registry data from 3 high volume centres. Long-term data was collected from medical documents, and by personal interviews. Periprocedural data, data about adverse events, and current evaluation of angina severity (CCS class) were collected. Mortality data was extracted from national health registries. Because the study population included only patients who survived and completed at least 2 years of follow up, the authors did another analysis of mortality rate that also included patients who were enrolled in the clinical study but did not reach 2 years of follow up.

Study population issues: The study population was characterised by a high prevalence of cardiovascular risk factors and previous percutaneous coronary intervention and coronary artery bypass grafting in 83% and 79% of patients, respectively.

Key efficacy findings

Number of patients analysed: 99

Distribution of CCS class at baseline and during follow up

CCS class	Baseline	1 year	2 years	Last follow up (median 3.4 years)
Mean	3.1	1.66*	1.72	1.71
Class 1	0%	49.5%	44.7%	49.5%
Class 2	9.1%	32.6%	36.8%	31.6%
Class 3	72.7%	15.8%	18.4%	16.8%
Class 4	18.2%	2.1%	0%	2.1%
Class 3 or 4	90.9%	17.9%*	18.4%	18.9%

* $p<0.001$ compared with baseline

Events at follow up

- Mortality=15.1% (15/99); when patients with less than 2 years of follow up were included, mortality was 15.7% (31/197) with a mean time to death of 3.2 ± 2.3 years.
- Myocardial infarction=9.0% (9/99)
- Stroke=3.0% (3/99)
- Angiography=31.3% (31/99)
- Percutaneous coronary intervention=21.2% (21/99)
- Hospitalisation related to angina=28.2% (28/99)

Key safety findings

Procedural complications

- Device migration, n=1

Study 9 Ponticelli F (2021)

Study details

Study type	Case series (registry data - RESOURCE)
Country	Europe, UK and Israel (20 centres)
Recruitment period	2010 to 2020
Study population and number	n=658 Patients with chronic refractory angina
Age and sex	Mean 68.7 years; 78% male
Patient selection criteria	Patients with chronic angina pectoris (CCS classes 2 to 4) refractory to guideline directed optimal medical therapy, objective evidence of myocardial ischaemia in the left coronary artery territory, and no further coronary revascularisation option according to the heart team were deemed eligible. Specific contraindications included recent acute coronary syndrome (within 3 months), recent coronary revascularisation (within 6 months) or a mean right atrial pressure higher than 15 mmHg.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow up	Median 502 days (IQR 225 to 1091).
Conflict of interest/source of funding	One author is medical director of Neovasc Inc. and 3 authors are consultants for Neovasc Inc. All other authors have no potential conflict of interest to disclose.

Analysis

Follow-up issues: Clinical follow up was available for 95% (625/658) of patients, and 91% (599/658) had a follow up CCS class evaluation.

Study design issues: The Reducer Efficacy and Safety from an internatiOnal mUlticenteR Clinical rEgistry (RESOURCE) is a retrospective, single arm, “real world” registry that includes all consecutive patients with refractory angina who were eligible for coronary sinus narrowing device implantation and who had at least 1 attempt of coronary sinus narrowing device implantation across 20 high volume centres in Europe, UK and Israel. The primary and secondary efficacy endpoints were defined as the percentage of patients with at least a 2 CCS class reduction or 1 CCS class reduction respectively, in their anginal symptoms at last available follow up. Patients who had no reduction of CCS angina class at follow up were defined as “non-responders”. Patients in whom the procedure failed or follow up was not available were excluded from the efficacy analysis. Procedural success was defined as successful implantation of the coronary sinus narrowing device at the intended location without loss of neck narrowing.

Study population issues: Mean body mass index at baseline was 28.6 kg/m^2, 47% of patients had diabetes mellitus (type 1 or type 2), and 31% had chronic kidney disease. With regard to their cardiovascular history, 60% had a previous acute myocardial infarction, 70% had had coronary artery bypass grafting, 81% had had percutaneous coronary revascularisation and 94% had had either coronary artery bypass grafting or percutaneous coronary revascularisation.

Key efficacy findings

Number of patients analysed: 658

Procedural success=96.7% (641/663) of attempted procedures

20 procedures (3.0%) were abandoned either for anatomical unsuitability (16/20) or for complications (4/20). 5 of the 20 procedures were reattempted with a successful outcome.

2 (0.3%) procedures failed: 1 device was partially dislodged from the delivery balloon, which eventually needed dilation to anchor to the coronary sinus walls with loss of neck narrowing, and 1 device embolisation into the pulmonary artery, which was left in-situ and did not result in any further complications.

CCS angina class

- Improvement of at least 2 CCS angina classes at follow up = 39.7% (238/599)
- Improvement of at least 1 CCS angina class at follow up = 76.0% (455/599)
- Median CCS class improved statistically significantly from 3 (IQR 3 to 3) at baseline to 2 (IQR 1 to 2) at follow up ($p<0.001$).
- Of the 144 patients who had no reduction in CCS class, 133 had no change and 11 reported the worsening of 1 CCS angina class.
- At baseline, 89.4% (588/658) of patients had CCS angina class 3 or above compared with 24.7% (148/599) at the last follow up ($p<0.001$).

Events at follow up

- Mortality=10.4% (65/625); of these, 35 deaths were either cardiovascular or undetermined (5.6%), which is equivalent to a cardiovascular mortality rate of 29.1 per 1000 patient-years. The 35 deaths classified as cardiovascular or undetermined consisted of endstage heart failure (n=8), out-of-hospital cardiac arrest (no additional information available, n=6), acute myocardial infarction (n=4), and undetermined cause (n=17).
- Major adverse cardiovascular event=14.6% (91/625); the individual components were all-cause mortality (n=54), acute coronary syndromes (n=31) and stroke (n=6)

Survival rate (Kaplan-Meier analysis)

- 1 year=96%
- 3 years=86.3%
- 5 years=76.6%

Key safety findings

Periprocedural adverse events=5.7% (38/663) of attempted procedures, n=42

- Intra- or periprocedural stroke, n=1; the patient had fully recovered at the time of last out-patient visit (10 months after procedure), presenting with no residual symptoms.
- Coronary sinus perforation, n=3 (all had conservative management)
- Coronary sinus dissection, n=9 (all had conservative management)
- Device embolisation, n=15 (in all but 1 of these, the scaffold was successfully retrieved, after snaring, via introducer sheaths inserted from the femoral or jugular veins without further complications. The 1 exception was an embolisation into the pulmonary artery, which was left in place).
- Device dislodgment from delivery catheter, n=4 (in 3 of the 4 procedures, it was possible to either reposition the device and proceed with implantation, or to recapture and remove it from a peripheral vein.
- Neck haematoma, n=10 (all had conservative management)

All procedural complications were managed without the need for bailout surgery.

5.6% (37/658) of patients had a permanent pacemaker lead in the right ventricle and 2 patients (0.3%) in the coronary sinus. The presence of pacemaker leads did not affect the rates of procedural success (p=0.52), procedural complications (p=0.12), or access site complications (p=0.47).

Study 10 Verheye S (2020)

Study details

Study type	2-arm case series (REDUCER-I)
Country	Europe (20 centres)
Recruitment period	2016 to 2020
Study population and number	n=228 (180 in arm 1, 48 in arm 2) Patients with refractory angina
Age and sex	Mean 68.3 years; 81% male
Patient selection criteria	Patients with chronic angina, CCS class 2 to 4 with no or limited revascularisation option were eligible for the procedure. In arm 1, patients with objective evidence of myocardial ischaemia at baseline were prospectively enrolled. In arm 2, patients who had previously had treatment with the Reducer during the COSIRA study or under CE Mark were invited to participate.
Technique	Device: coronary sinus Reducer device (Neovasc Inc., Canada)
Follow-up	Median follow up time for arm 1 was 666 days (range 0 to 1,386)
Conflict of interest/source of funding	The REDUCER-I study was funded by Neovasc Inc. 3 authors serve as proctors for Neovasc Inc. and 1 author is the Medical Director of Neovasc Inc. All other authors have no conflicts of interest.

Analysis

Follow-up issues: In arm 1, patients were followed at 30 days, 6- and 12-months, and annually through 5 years after treatment. In arm 2, data previously collected in the COSIRA study (baseline, procedure, 30 days and 6 months) was included, as well as prospective data collected annually through 5 years after treatment. Overall, 158 patients had reached the 1-year and 111 the 2-year follow-up visit.

Study design issues: Multicentre, international, non-randomised, open label, 2-arm observational study. The primary efficacy endpoint was the proportion of patients who had improvement in their angina symptoms defined as a reduction in CCS grade at 6 months as compared to baseline. The main safety endpoints were the rate of device or procedure-related periprocedural serious adverse events and major adverse cardiac events (a composite of cardiac death, major stroke, and myocardial infarction) within 30 days. EQ-5D-5L and the visual analogue scale (EQ-VAS) were only collected from patients in arm 1. Severity levels for each dimension were dichotomised as having no problems (“No problems”) or slight to extreme problems (“Problems”).

Study population issues: The study population was characterised by high rates of cardiovascular risk factors and coexisting comorbidities.

Key efficacy findings

Number of patients analysed: 228

Procedural success=99% (226/228)

In 1 patient, there was a guiding catheter-induced coronary sinus dissection with no clinical sequelae and in the other patient, the coronary sinus ostium could not be found.

In 3 other patients the first implantation attempt failed either because of coronary sinus dissection without clinical sequelae (n=1), or technical difficulty to engage the guiding catheter into the coronary sinus (n=2). However, in all 3 patients a successful implantation was accomplished in a second attempt.

CCS angina class

- Improvement of at least 1 CCS angina class at 1 year = 74%
- Improvement of at least 1 CCS angina class at 2 years = 82%
- Improvement of at least 2 CCS angina classes at 2 years = 31%
- Proportion of patients with no improvement in CCS angina class at 1 year = 24%
- Proportion of patients with no improvement in CCS angina class at 2 years = 17%
- 2 patients reported a worsening of CCS angina class at 1 year.
- Mean CCS class improved from 2.8 at baseline to 1.8 at 6 months, 1.7 at 1 year, and 1.8 at 2 years for the whole cohort. In arm 1, it improved from 2.7 at baseline to 1.8 at 6 months, 1.8 at 1 year and 1.8 at 2 years ($p<0.0001$, for all).
- At baseline, 70% of patients had severe disabling angina (CCS class 3 to 4). This reduced to 15% of patients at 1 and 2 years after treatment.

Anti-anginal medication

- There was no change in the use of antianginal medications over time (3.1 at baseline and 3.0 at 1 and 2 years respectively, $p>0.1$ for both)

Six-minute walk test and exercise duration

- For the whole cohort, the 6-minute walk test improved from 327.5 m at baseline to 378.5 m and 364.3 m at 6- and 12-month follow up, respectively $p<0.0001$ for 6-month and 0.0004 for 12- month).
- Exercise duration increased from 359.9 seconds at baseline to 383.1 seconds at 6-month and to 409.4 at 12-month follow up, $p=0.025$ and $p=0.0011$ respectively.

SAQ, EQ-5D-5L Score

- The percentage of patients who reported having problems in mobility and usual activities decreased at 6- and 12-month follow up, as well as the percentage of patients reporting anxiety and pain.

- EQVAS improved from 57.5 at baseline to 67.7 at 6-month and to 67.5 at 12-month follow up, p<0.0001 for both.
- There was an improvement in all 5 domains of the SAQ at 6- and 12-month follow up (p<0.0001 for all). Improvement in 4 of 5 domains was sustained at 24 months.

Number of documented Emergency Department visits because of angina (n=113, all arm 1)

- In the year before the procedure, 41.6% (47/113) of patients had at least 1 emergency department visit with a total of 78 visits (mean 0.69 visits per patient, range 0 to 5 visits).
- After the procedure, 13.3% (15/113) of patients had at least 1 emergency department visits with a total of 22 visits (mean 0.19, range 0 to 4 visits; p<0.0001).

Events at follow up

- Mortality=5.7% (13/228)
- Cardiovascular death=2.6% (6/228)
- Myocardial infarction=7.0% (16/228)

Key safety findings

Periprocedural adverse events

- There was 1 periprocedural myocardial infarction within 3 weeks of the procedure, adjudicated as unknown if device- or procedure-related.

Validity and generalisability of the studies

- There is likely to be some patient overlap between the studies. Several studies report data from the same centres and it is unclear how much overlap there is.
- There is data from Europe (including the UK), North America and Asia.
- The inclusion criteria and definition of refractory angina varied between studies.
- There is a randomised, double-blind sham-controlled clinical trial with short term follow up of 6 months (Verheye 2015). Although patients were blinded to their treatment allocation, only patients who had the coronary sinus narrowing device implanted were given intravenous heparin at the time of the procedure.
- The longest mean follow up period is 3.9 years, which was reported in a case series of 99 patients (Konigstein 2021).
- There is potentially a large placebo effect associated with this procedure.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Interventional procedures

- Percutaneous laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 302 (2009). Available from http://www.nice.org.uk/guidance/IPG302
- Transmyocardial laser revascularisation for refractory angina pectoris. NICE interventional procedures guidance 301 (2009). Available from http://www.nice.org.uk/guidance/IPG301

Technology appraisals

IP overview: Coronary sinus narrowing device implantation for refractory angina

- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal 73 (2003; last updated 2011). Available from http://www.nice.org.uk/guidance/TA73

NICE guidelines

- Acute coronary syndromes. NICE guideline 185 (2020). Available from http://www.nice.org.uk/guidance/NG185
- Stable angina: management. NICE clinical guideline 126 (2011; last updated 2016). Available from http://www.nice.org.uk/guidance/CG126

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Professional expert questionnaires for coronary sinus narrowing device implantation for refractory angina were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- Use of the Neovasc Coronary Sinus Reducer System for the Treatment of Refractory Angina Pectoris in Patients With Angina Class 3-4 Who Are Not Candidates for Revascularization (NCT01566175); Israel; single group; n=100; completion date December 2031.

- CoROnary SinuS Reducer implantatiOn for ischemiA reDuction (CrossRoad) (NCT04121845); Slovenia; RCT; n=40; completion date June 2022.

- REDUCER-I: An Observational Study of the Neovasc Reducer™ System (NCT02710435); Belgium, Germany, Italy, Netherlands, Switzerland, UK; observational; n=400; completion date December 2027.

- Coronary Sinus Reducer Objective Impact on Symptoms, MRI Ischaemia and Microvascular Resistance (NCT04892537); UK; RCT; n=40; completion date January 2024.

References

1. Verheye S, Jolicoeur EM, Behan MW et al. (2015) Efficacy of a device to narrow the coronary sinus in refractory angina. The New England Journal of Medicine 372: 519–27
2. D'Amico G, Giannini F, Massussi M et al. (2021) Usefulness of coronary sinus Reducer implantation for the treatment of chronic refractory angina pectoris. American Journal of Cardiology 139:22–7
3. Giannini F, Baldetti L, Konigstein M et al. (2018) Safety and efficacy of the reducer: A multi-center clinical registry - REDUCE study. International Journal of Cardiology 269: 40–4
4. Ponticelli F, Tzanis G, Gallone G et al. (2019) Safety and efficacy of Coronary Sinus Reducer implantation at 2-year follow-up. International Journal of Cardiology 292: 87–90
5. Silvis MJM, Dekker M, Zivelonghi C et al. (2020) The Coronary Sinus Reducer; 5-year Dutch experience. Netherlands Heart Journal https://doi.org/10.1007/s12471-020-01525-8
6. Zivelonghi C, Verheye S, Timmers L et al. (2020) Efficacy of Coronary Sinus Reducer in patients with non-revascularized chronic total occlusions. The American Journal of Cardiology 126: 1–7
7. Gallone G, Armeni P, Verheye S et al. (2020) Cost-effectiveness of the coronary sinus Reducer and its impact on the healthcare burden of refractory angina patients. European Heart Journal - Quality of Care and Clinical Outcomes 6: 32–40
8. Konigstein M, Merdler I, Revivo M et al. (2021) Long-term outcomes of patients undergoing coronary sinus reducer implantation - A multicenter study. Clinical Cardiology 44: 424–8
9. Ponticelli F, Khokhar AA, Colombo A et al. (2021) Safety and efficacy of coronary sinus narrowing in chronic refractory angina: Insights from the RESOURCE study. International Journal of Cardiology 337: 29–37
10. Verheye S, Agostoni P, Giannini F et al. (2020) Coronary sinus narrowing for the treatment of refractory angina A multi-center prospective open-label clinical study (The REDUCER-I study). EuroIntervention doi: 10.4244/EIJ-D-20-00873

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/06/2021	Issue 6 of 12, June 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/06/2021	Issue 6 of 12, June 2021
International HTA database (INAHTA)	30/06/2021	
MEDLINE (Ovid)	30/06/2021	1946 to June 29, 2021
MEDLINE In-Process (Ovid)	30/06/2021	1946 to June 29, 2021
MEDLINE Epubs ahead of print (Ovid)	30/06/2021	June 29, 2021
EMBASE (Ovid)	30/06/2021	1974 to 2021 July 01

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Number	Search term
1	exp Angina Pectoris/
2	(angina* or angor*).tw.
3	((myocardial adj4 preinfarction) or stenocardia*).tw.
4	((syndrome adj1 x) or (syndrome adj1 xs) or CSX).tw.
5	((chest or cardiac or precordial) adj4 (pain* or pressure* or discomfort)).tw.
6	or/1-5
7	Coronary Artery Disease/
8	exp Coronary Stenosis/
9	Coronary Circulation/
10	Ventricular Function, Left/
11	(coronary adj4 arter* adj4 (disease* or insufficien*)).tw.
12	CAD.tw.
13	(coronary adj4 (vessel* or lumen* or arter*) adj4 (narrow* or constrict* or stenos* or restenos*)).tw.
14	or/7-13
15	Myocardial Ischemia/
16	((Ischemi* or ischaemi*) adj4 (heart or myocardial or cardiac)).tw.
17	exp Atherosclerosis/
18	(atherosclero* or arteriosclero* or atherogenes* or ASHD).tw.
19	(arter* adj4 (plaque* or atheroma*)).tw.
20	((Decrease* or insufficien* or reduce* or block* or interrupt*) adj4 blood* adj4 (heart or cardi*)).tw.
21	or/15-20
22	6 or 14 or 21
23	Coronary Sinus/
24	Blood Vessel Prosthesis/
25	Stents/
26	Angioplasty, Balloon, Coronary/
27	Catheterization, Central Venous/

28	Cardiac catheterization/
29	Cardiac Catheters/
30	or/24-29
31	23 and 30
32	("CS reduc*" or "CS narrow*").tw.
33	(coronary adj4 sinus* adj4 (reduc* or narrow* or implant* or device* or stent* or prosthe* or balloon* or catheter*)).tw.
34	or/31-33
35	22 and 34
36	Neovasc.tw.
37	35 or 36
38	animals/ not humans/
39	37 not 38

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Abawi M, Nijhoff F, Stella, PR et al. (2016) Safety and efficacy of a device to narrow the coronary sinus for the treatment of refractory angina: A single-centre real-world experience. Netherlands Heart Journal 24: 544–51	Case series n=23 follow up: median 9 months	The safety endpoint was met in all patients. The efficacy (any reduction in CCS class and revascularisation-free survival) was reached in 17 patients (74%): 8 patients (35%) improved by 1 CCS class, 7 (30%) by 2 CCS classes and 2 (9%) by 3 CCS classes.	Studies with more patients or longer follow up are included.
Baldetti L, Colombo A, Banai S et al. (2018) Coronary sinus Reducer non-responders: insights and perspectives. EuroIntervention 13: 1667–69	Case reports n=2	In most patients, most of the left coronary artery venous return is drained by the coronary sinus. Patients with developed accessory venous drainage systems will show low differential pressures due to preserved alternative coronary venous outflow. In these patients, coronary sinus narrowing device implantation results in an insufficient pressure gradient across the coronary sinus and the anti-ischaemic effects and benefits might be minimal.	The paper uses the example of 2 patients to highlight a method of selecting patients who might benefit most from the procedure.
Banai S, Ben MS, Parikh KH et al. (2007) Coronary sinus reducer stent for	Case series n=15	No procedure-related adverse events occurred during the periprocedural	Studies with more patients or longer

the treatment of chronic refractory angina pectoris: a prospective, open-label, multicenter, safety feasibility first-in-man study. Journal of the American College of Cardiology 49: 1783–9	follow up: 6 months	and the follow-up periods. Angina score improved in 12 of 14 patients. Average CCS score was 3.07 at baseline and 1.64 at follow up (n=14, p<0.0001). Stress-induced ST-segment depression was reduced in 6 of 9 patients and was eliminated in 2 of these 6 (p=0.047). The extent and severity of myocardial ischaemia by dobutamine echocardiography and by thallium single-photon emission computed tomography was reduced (p=0.004 [n=13] and p=0.042 [n= 0], respectively.	follow up are included.
Bazoukis G, Brilakis ES Tse G et al. (2018) The efficacy of coronary sinus reducer in patients with refractory angina-A systematic review of the literature. Journal of Interventional Cardiology 31: 775–79	Systematic review n=196 (6 studies)	The coronary sinus reducer is a promising treatment option for patients with refractory angina who are not candidates for revascularisation. However, larger randomised control trials with long-term follow up are needed to elucidate its role.	No meta-analysis. All included studies are in the overview.
Benedetto D, Abawi M, Stella PR et al. (2016) Percutaneous device to narrow the coronary sinus: shifting paradigm in the treatment of refractory angina? A review of the literature. Frontiers in cardiovascular medicine 3: 42	review	Among the choices for alternative options to offer to patients with refractory angina, the coronary sinus Reducer should be considered, because it is a secure device and apparently effective in reducing anginal symptoms and in improving the quality of life in this category of patients. Future studies are needed to investigate and confirm the mechanism of action	All relevant cited studies are in the overview.

		with more accurate imaging techniques such as single-photon emission computerised tomography or functional MRI.	
Biscaglia S, Tebaldi M, Mele D et al. (2019) Angina and left ventricular dysfunction: Can we 'reduce' it? European Heart Journal, Supplement 21: c28-c31	Case report n=1 follow up: 2 months	A combination of percutaneous and pharmacological strategies were used to reduce the angina burden in a patient with multiple comorbidities and left ventricular dysfunction.	Case report.
Bunc M, Sustersic M, Langel C et al. (2020) Coronary sinus reducer transfemoral extraction after intraprocedural device migration: A case report. Clinical Case Reports	Case report n=1	The coronary sinus Reducer migration during implantation procedure is a rare complication with no standard bailout strategy. This case report describes successful transfemoral extraction of the reducer.	Case report of device migration, which is already described in the overview.
Cheng K, de Silva R (2020) Implantation of a coronary sinus reducer to treat refractory angina in a 38-year-old with an anomalous left coronary artery and no revascularisation options. Cardiology 145: 126–29	Case report n=1	A 38-year-old female with anomalous left coronary artery from the pulmonary artery presented with refractory angina (CCS class 4). She had 2 previous internal mammary artery grafts to the left anterior descending artery that failed. With no percutaneous revascularisation options, she had coronary sinus Reducer implantation, which improved her symptoms (CCS 0), quality of life, and corresponded to an improvement in ischaemia on myocardial perfusion scanning.	Case report.
Ciardetti M, Coceani M, Pastormerlo LE et al. (2020) Let's go fishing: snaring a Reducer coronary sinus stent in the right atrium. Journal	Case report n=1	The first described case of percutaneous Reducer stent retrieval. After the first stent was removed, a second stent was implanted in a more distal	Case report.

of Cardiovascular Medicine 21: 73-74		position in the coronary sinus and with a higher inflation pressure.	
Cortese B, di Palma G, Latini R (2018) Coronary sinus perforation during reducer implantation. Catheterization and Cardiovascular Interventions 91: 1291–93	Case report n=1	The first case of coronary sinus perforation after a sinus Reducer implantation. The patient remained haemodynamically stable during the procedure and the complication was managed with a semicompliant balloon inflation, to seal the perforation.	Case report of coronary sinus perforation, which is already described in the overview.
ElMallah W (2016) Coronary sinus stent: could it help in refractory chronic stable angina?. Current Cardiology Reports 18: 35	review	Continued use is supported by: 1) the encouraging outcomes in all reported clinical evidence, 2) the safety profile of the device, 3) the lack of any alternative to improve the quality of life in refractory angina patients, and 4) the ease of implantation of coronary sinus stents. Patient selection needs to be refined and long-term follow up is needed. It is imperative to recognise that these are not an alternative for maximal medical treatment, lifestyle modification or revascularisation procedure. The selection process for these patients should be rigorous and may need a multidisciplinary approach.	All relevant cited studies are in the overview.
Gallone G, Beneduce A, Tzanis G et al. (2021) Coronary sinus size and ischemia improvement after reducer implantation; "one size to fit them all?"	Case series n=15 follow up: 4 months	Greater benefits, in terms of ischaemia improvement, after coronary sinus Reducer implantation were seen in patients with smaller coronary sinus sizes,	Small case series.

Catheterization and Cardiovascular Interventions		suggesting a potential mechanism underlying the observed rates of reducer non-responsiveness.	
Gallone G, Baldetti L, Palmisano A et al. (2019) Coronary Sinus Reducer implantation to reduce the ischemic burden in refractory angina. JACC. Cardiovascular interventions 12: e11-e13	Case report n=1 follow up: 4 months	At follow up, the patient was asymptomatic for angina and reported improved quality of life (SAQ mean domain score improved from 45 to 73 points).	Case report.
Gallone G, Palmisano A, Baldetti L et al. (2020) Improved myocardial function with coronary sinus reducer in a patient with refractory angina and heart failure with reduced ejection fraction. The Canadian Journal of Cardiology 36: 589e1-589e4	Case report n=1 follow up: 4 months	At follow up, the patient was asymptomatic for angina, in New York Heart Association class I. In this case, improvement in myocardial perfusion after coronary sinus Reducer implantation translated into a clinically significant improvement in resting left ventricular ejection fraction.	Case report.
Giannini F, Baldetti L, Ponticelli F et al. (2018) Coronary Sinus Reducer implantation for the treatment of chronic refractory angina: a single-center experience. JACC. Cardiovascular interventions 11: 784–92	Case series n=50 follow up: 12 months	In this real-world, single-centre experience, implantation of the coronary sinus Reducer appeared safe and was associated with reduction in anginal symptoms and improvement in quality of life in patients with refractory angina who were not candidates for further revascularisation.	Patients from the same centre are included in another study (Giannini 2018a).
Giannini F, Aurelio A, Jabbour RJ et al. (2017) The coronary sinus reducer: clinical evidence and technical aspects. Expert Review of Cardiovascular Therapy 15: 47–58	Review	Larger randomised trials with longer follow up are needed to confirm the efficacy of coronary sinus Reducer implantation and to evaluate whether it objectively improves myocardial perfusion. Moreover, further studies are needed to understand	All relevant cited studies are in the overview.

		why approximately 20 to 30% of patients are non-responders.	
Grandjean T, Haefliger D, Arroyo D et al. (2018) Coronary sinus reduction for the treatment of refractory angina. Kardiovaskulare Medizin 21: 170–3	Case report n=1	A 67-year-old man with chronic refractory angina was effectively treated with a coronary sinus Reducer.	Case report.
Jolicoeur EM, Verheye S, Henry TD et al. (2020) A novel method to interpret early phase trials shows how the narrowing of the coronary sinus concordantly improves symptoms, functional status and quality of life in refractory angina. Heart (British Cardiac Society)	Post-hoc analysis of RCT n=104	The Reducer concordantly improved symptoms, functionality and quality of life compared with a sham intervention in patients with angina unsuitable for coronary revascularisation.	Post-hoc analysis of RCT, which is included.
Kahr PC, Giannopoulos AA, Buechel RR et al. (2018) Coronary sinus reducer device for patients with refractory angina. Kardiovaskulare Medizin 21: 105–10	Case report n=1	Case report of 70-year-old man. At 8 weeks the patient had reduced symptoms and was able to climb 3 floors without angina or dyspnoea (CCS I, NYHA I).	Case report.
Konigstein M, Bazan S, Revivo M et al. (2018) Coronary Sinus Reducer implantation improves symptoms, ischaemia and physical capacity in patients with refractory angina unsuitable for myocardial revascularisation: a single-centre experience. EuroIntervention 14: e452-e458	Case series n=48 follow up: median 12.5 months	No periprocedural or long-term adverse events were recorded. CCS class diminished from a mean of 3.4±0.5 at baseline to 2.0±1 ($p<0.001$), and all domains of the SAQ improved statistically significantly following Reducer implantation. Mean exercise duration increased from 03:43±01:30 to 04:36±02:18 min:sec ($p=0.025$) and 6MWT distance increased from 299.9±97.9 m to 352.9±75.3 m ($p=0.002$). Ejection fraction (EF%) at	A larger study that included patients from the same centre who were had treatment during the same period is included.

		stress increased from 51.0±10 to 56.5±10 (p=0.004), and wall motion score index improved from 1.58±0.4 to 1.37±0.3 (p=0.004).	
Konigstein M, Giannini F, Banai S (2018) The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. European Heart Journal 39: 925–33	Review	Accumulating evidence supports the clinical benefit of the Reducer in alleviating symptoms of angina in 70% to 80% of patients with obstructive coronary artery disease who are not candidates for revascularisation. Appropriate patient selection and referral to specialised centres are important to maximise efficacy of this treatment and improve success rates. While the Reducer's clinical efficacy on reducing angina burden is apparent, studies using objective methods of assessment of myocardial ischaemia in larger cohorts are needed because of the large placebo effect reported related to novel therapies in this specific patient population.	No meta-analysis and more recent studies are included.
Konigstein M, Meyten N, Verheye S et al. (2014) Transcatheter treatment for refractory angina with the Coronary Sinus Reducer. EuroIntervention 9: 1158–64	Case series n=23 follow up: 6 months	Coronary sinus Reducer implantation was safe and resulted in significant improvement of angina class.	Studies with more patients or longer follow up are included.
Madeira S, Brizido C, Raposo L et al. (2021) non-pharmacological treatment of refractory angina: The coronary	review	The primary focus of this review is the coronary sinus Reducer, supporting evidence for which,	Review

sinus reducer, the new kid on the block. Revista Portuguesa de Cardiologia 40: 371–82		although scarce, is promising about safety and efficacy in improving anginal symptoms and quality of life.	
Medranda GA, Waksman R, Torguson R (2021) Overview of the virtual 2020 FDA's circulatory system devices advisory panel on Neovasc reducer system. Catheterization and Cardiovascular Interventions DOI: 10.1002/ccd.29730	FDA advisory panel discussion	The panel voted 14–4 to affirm that the Neovasc device is safe. However, by a 17–1 vote, the panel said it was not effective, and the group voted 13–3, with 2 abstentions, to say that the device's benefits do not outweigh the risks.	Details of the deliberation and discussion among the FDA circulatory panel members on the Reducer's safety and effectiveness.
Montone RA, Russo M, Giannini F et al. (2018) The coronary sinus Reducer device for refractory chronic angina: rationale, clinical evidence and future perspectives. Expert review of medical devices 15: 611–13	Review	In patients with chronic angina, refractory to medical therapies, coronary sinus Reducer is effective in about 70 to 80% of patients in reducing symptoms of angina, myocardial ischaemia and improving quality of life and it is candidate to become the standard of care for these patients. Further studies are needed to identify the target population that can get benefit.	All relevant cited studies are in the overview.
Palmisano A, Giannini F, Rancoita P et al. (2020) Feature tracking and mapping analysis of myocardial response to improved perfusion reserve in patients with refractory angina treated by coronary sinus Reducer implantation: a CMR study. International Journal of Cardiovascular Imaging	Case series n=28	Coronary sinus Reducer improves myocardial longitudinal and circumferential strain, without microstructural remodelling and no impact on diastolic proprieties.	Small case series, focusing on the possible impact r on myocardial systolic-diastolic deformation and microstructural remodelling.
Stanak M, Rothschedl E, Szymanski P (2020)	Systematic review	Even though the current evidence indicates that the	No meta-analysis; all 7

Coronary sinus reducing stent for the treatment of refractory angina pectoris: A health technology assessment. Medical Devices: Evidence and Research 13: 259–76	n=348 (plus 52 controls); 7 studies	assessed technology is potentially more effective than sham intervention for refractory angina pectoris patients, the lack of internal validity of the studies undermines the partially positive results.	studies are included in the overview.
Szekely Y, Topilsky Y, Bazan S et al. (2019) The impact of coronary sinus narrowing on diastolic function in patients with refractory angina. International Journal of Cardiology 291: 8–12	Case series n=24 follow up: 6 months	Coronary sinus narrowing in patients with myocardial ischaemia and refractory angina does not adversely affect diastolic function and may improve it.	Studies with more patients or longer follow up are included.
Tzanis G, Palmisano A, Gallone G et al. (2020) The impact of the coronary sinus reducer upon left ventricular function in patients with refractory angina pectoris. Catheterization and Cardiovascular Interventions 95: 1104–8	Case series n=19 follow up: 4 months	Coronary sinus Reducer improved angina symptoms and improved left ventricular function. The improvement was pronounced in the subgroup of patients with reduced ejection fraction. Myocardial perfusion improvement could represent the underlying mechanism for the observed benefits.	Studies with more patients or longer follow up are included.
Tzanis G, Durante A, Mitomo S et al. (2019) Percutaneous management of periprocedural coronary sinus Reducer migration. Catheterization and Cardiovascular Interventions 93: e235–7	Case report n=1	The paper describes a case of successful, percutaneous, management of device migration into the right atrium.	Case report of complication already described.
Vescovo GM, Zivelonghi C, Bellamoli M et al. (2021) Coronary Sinus Reducer for the treatment of chronic refractory angina: will this challenge the treatment of coronary chronic total occlusions? Current Cardiology Reports 23: 31	Review	A recently published study suggests a clear value of this device in patients with chronic total occlusions. This is likely to be related to the presence of a well-developed collateral circulation. A careful evaluation of risks and benefits of both	Review

		myocardial revascularisation and coronary sinus Reducer implantation should be done in all the cases in order to better define the optimal strategy for the patient.	
Wilgenhof A, Zivelonghi C, Verheye S et al. (2020) Coronary sinus anatomical features: Description and procedural implications during coronary sinus Reducer implantation. Catheterization and Cardiovascular Interventions	Case series n=47	This study is the first systematic evaluation of coronary sinus anatomy and its procedural implications. A favourable C-shape anatomy was identified, which allows for a more straightforward implantation. Operators should be aware of the different implications of coronary sinus anatomy, their influence on guiding catheter stability and overall procedure complexity.	Studies with more patients or longer follow up are included.
Wojciech Z, Kuliczkowski W, Reczuch K (2021) Coronary sinus reducer implantation in patients with refractory angina: first experience in Poland. Kardiologia polska 79: 471–2	Case reports n=2 follow up: 3 months	Both patients reported improvement in physical activity and reduction of symptoms (CCS class I). These observations were confirmed by an increase in the SAQ results (from 51 to 88 points and from 58 to 78 points).	2 case reports
Zivelonghi C, Verheye S (2020) The coronary sinus reducer - clinical evidence and new perspectives on an emerging tool in the treatment of refractory angina. Heart International 14: 29–33	Review	Refractory angina has a relevant impact on the quality of life of affected patients and is associated with significant healthcare costs. From this perspective, the growing and consistent evidence supporting the benefits of the coronary sinus Reducer in this population suggests that this device significantly relieves angina symptoms, may significantly reduce	Review

		myocardial ischaemia, and has an excellent safety profile. It is for these reasons that the coronary sinus Reducer should be considered in this setting, after accurate patient selection according to the appropriate indications.	
Zivelonghi C, Konigstein M, Azzano A et al. (2020) Coronary sinus Reducer implantation results in improved oxygen kinetics at cardiopulmonary exercise test in patients with refractory angina. EuroIntervention	Case series n=37 follow up: 6 months	In patients with obstructive coronary artery disease suffering from refractory angina, the implantation of coronary sinus Reducer was associated with objective improvement in exercise capacity and oxygen kinetics at cardiopulmonary exercise testing, suggesting a possible reduction of myocardial ischaemia.	Studies with more patients or longer follow up are included.
Zivelonghi C, Vermeersch G, Verheye S et al. (2019) Incomplete coronary sinus reducer endothelialization as potential mechanism of clinical failure. Catheterization and Cardiovascular 94: 120–2	Case series n=5 follow up: 6 months	In 5 patients who were classified as 'non-responders' a flow of contrast was appreciable through the device struts or behind its structure in the narrow part of the device 6 months after implantation, suggesting that the device's surface was not completely covered by endothelium.	Small case series, focusing on potential mechanism of failure.