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The Role of Coronary Sinus Reducer Devices in Patients with Refractory Angina

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Take Home Messages

- In the UK, angina affects 3-4% of the adult population with 20,000 new cases each year. Refractory angina leads to significant disability, limited quality of life, multiple medications, and frequent hospital admissions
- The Coronary Sinus Reducer device is implanted percutaneously into the coronary sinus and creates a controlled narrowing of the lumen which leads to an increase in pressure in the coronary sinus and hence improves perfusion to ischaemic territories of the myocardium
- This device is a potentially safe, efficient and cost-effective solution for patients with refractory angina when standard of care treatment with anti-angina medication and revascularisation fails.

Introduction

Ischaemic heart disease is a leading cause of death worldwide and stable angina is the commonest symptomatic manifestation affecting 112 million people (1, 2). In the UK, angina affects 3-4% of the adult population with 20,000 new cases each year (3). The majority of these patients improve symptomatically with interventions such as percutaneous coronary intervention (PCI) or coronary artery by-pass graft surgery (CABG) (4,32). However, there is a group of patients with refractory angina who are increasingly challenging to manage in clinical practice (4).

Refractory Angina

Refractory angina is a chronic condition (>3 months) characterised by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease, which cannot be controlled by a combination of medical therapy, PCI or CABG (4). European Society of Cardiology (ESC) estimates that 10% of all angina patients have refractory angina (12). A focused analysis of the SYNTAX trial reported a prevalence of recurrent angina of 28.5% at 1 year and 25.9% at 5 years after PCI (13). Refractory angina leads to significant disability, limited quality of life, multiple medications, and frequent hospital admissions (4,11). The costs of treating these patients in the UK exceeds £40,000 per patient over a 5-year period (including up to 10 hospital days per patient per year) and growing in incidence (14).

Refractory angina in the absence of obstructive coronary artery disease also exists and includes coronary microvascular angina (11). Microvascular angina is a disease of the coronary circulation which is invisible to the eye on a coronary angiogram or other imaging techniques (6,7). This is under-diagnosed and under-managed. Beyond standard anti-anginal therapy to symptomatically treat microvascular angina, there is currently no effective treatment to reverse the condition. In addition, microvascular disease appears to be a marker of higher risk patients with a more aggressive disease (8). Unfortunately, the majority of these patients continue to have refractory angina (5).

A potential treatment is the coronary sinus reducer (CSR) device.

Coronary Sinus Reducer Device

The Coronary Sinus Reducer (CSR) device is an hourglass shaped metal mesh which is implanted percutaneously into the coronary sinus. This creates a controlled narrowing of the lumen which leads to an increase in pressure in the coronary sinus and hence improves perfusion to ischaemic territories of the myocardium (16).

Randomized controlled trials and observational studies (Table 1) have shown that the CSR device is safe and effective in reducing symptoms and improving quality of life in patients with obstructive coronary artery disease and refractory angina.

Parikh et al. in 2018 followed up the patients from the first in human trial in 2007 at 12 years. They evaluated the location, patency, dislocation of the CSR device using a CT coronary angiogram and noted that all devices were positioned properly in the proximal segment of the

coronary sinus with no migration, occlusion or thrombosis. Furthermore, it confirmed sustained improvement in Angina class over the 12-year period. (17).

UK data by Ali et al. in 2018 showed that the CSR implantation in 18 patients is safe and associated with significant improvements in angina symptoms and quality of life (23).

In 2018, Bazoukis et al. carried out a systematic review to evaluate the efficacy of the coronary sinus reducer device in patients with refractory angina. This looked at 196 patients and showed that the device was effective in 78.5% of patients. The Implantation failed in 2% of patients and 2.5% had a complication during the 30-day follow-up (18).

Furthermore, clinical trials have looked at the safety and efficacy of the coronary reducer device in patients with non-obstructive coronary artery disease and refractory angina. In 2017, Giannini et al. published their work showing that the coronary sinus reducer was safe and effective in the management of patients with refractory angina in spite of complete epicardial revascularisation (24).

The MACCUS trial showed that inflation of the coronary sinus balloon caused a significant increase in coronary sinus pressure which in turn led to a decrease in microvascular resistances in patients with microvascular angina. Therefore, highlighting the mechanism of the CSR device (29).

Table 1: Clinical trials assessing the safety and efficacy of the coronary sinus reducer device in obstructive coronary artery disease and refractory angina

Trial	Cohort	Participants	Treatment	Primary Outcome	Follow Up	Results
Banai et al. 2007 (FIH) (19)	CAD - not amenable to PCI/CABG or high risk Severe angina - CCS Class II to IV Reversible ischaemia	15	CSR device	Absence of major adverse cardiac events	6 months	No adverse events. Angina score improved. Myocardial ischaemia reduced.
COSIRA (Verheye et al. 2015) (20)	CAD - not candidates for PCI/CABG Angina - CCS Class III or IV Reversible ischaemia	104	CSR device vs Sham	Improvement of Angina symptoms	6 months	Improvement of angina (p=0.02) and quality of life (p=0.03)
Giannini et al. 2016 (21)	CAD - not suitable for PCI/CABG Angina - CCS Class II and higher	104	CSR device vs Sham	Improvement of Angina symptoms	6 months	Improvement of angina (p=0.001) and quality of life (p=0.048)

Parikh et al. 2018 (17)	CAD Angina - CCS Class	7	CTCA	Evaluate location, patency and dislocation of CSR device	12 years	All positioned properly, no migration, occlusion or thrombosis
Konigstein et al. 2018 (22)	CAD - not suitable for PCI/CABG Refractory angina - CCS Class	48	CSR device	Improvement of angina symptoms	6 months	Angina reduced ($p<0.001$), mean exercise increased ($p<0.025$), No adverse effects
Ali et al. 2018 (23)	CAD - not amenable to PCI/CABG Refractory angina - CCS scores	18	CSR device	Improvement of angina symptoms and quality of life	21 months	Angina reduced ($p<0.01$) and quality of life improved ($p<0.01$), No adverse events

CCS - Canadian Cardiovascular Society

Clinical Guidance

The CSR device is part of both the European Society of Cardiology (ESC) and the National Institute for Health and Excellence (NICE) guidance for management of refractory angina.

Table 2: Current clinical guidance on the use of the Coronary Sinus Reducer Device in patients with Angina

GUIDANCE	**Coronary Sinus Reducer Device**
European Society of Cardiology (ESC) (4)	The coronary sinus reducer device represents an alternative option in patients with refractory angina, which is resistant after having exhausted all options for medical therapy and mechanical revascularisation (IIb)

National Institute for Health and Care Excellence (NICE) (24)	The coronary sinus narrowing device implantation is indicated for angina when other treatment options (medical or surgical) have failed or are not possible (refractory angina). The aim is to reduce symptoms and to improve quality of life.
American College of Cardiology/American Heart Association (ACC/AHA) (30)	No specific recommendations of the coronary sinus reducer device

Cost-Effectiveness

Gallone et al. in 2020 evaluated the potential cost-effectiveness of the CSR device and its impact on the healthcare resource use. Data was collected from 215 refractory angina patients undergoing implantation of the device in Belgium, Netherlands and Italy. This resulted in a significant reduction in angina driven hospitalisations, outpatient visits, coronary angiograms and PCI per patient per year. This translated to significantly reduced healthcare costs per patient-year. In Belgian, this reduced from 6255 euros to 1467, in Netherlands from 3888 euros to 946 and in Italy from 7159 euros to 1403. The CSR device was associated with higher quality-adjusted life years compared to standard of care (0.665 vs 0.580, $p<0.001$) (31).

Limitations

The efficacy of the CSR device is limited in certain patient groups. For instance, in patients with a mean right atrium pressure of >15mmHg, as it results in an inadequate pressure gradient across the device (36,37).

Moreover, patients with ischaemia in the right coronary artery (RCA) may not benefit from the CSR device. The venous drainage of the RCA drains into the ostium of the coronary sinus (CS) via the middle cardiac vein, whereas the CSR device is more distal in the CS and therefore not effective (36,37). This may be overcome by implanting a CSR device in the middle cardiac vein (38).

In addition, patients eligible for cardiac resynchronisation therapy (CRT) may not be candidates for a CSR device. However, Grebmer et al. presented a case series illustrating that a left ventricle

(LV) lead can pass through the CSR device, thus showing this is feasible but with a greater risk of complications (35).

In the future, further trials are warranted to evaluate the efficacy and safety of CSR devices in various positions in the coronary venous system. Furthermore, potentially designing the CSR device to accommodate an LV lead would be beneficial for patients with CRT devices.

Finally, other treatment options are highlighted in Table 3 for the non-responder patients to the CSR device.

Table 3: Other Treatment Options for Refractory Angina			
Treatment	**Mechanism**	**Trials**	**Current Society Guidance**
Enhanced External Counterpulsation (EECP) (34,41)	Inflating blood pressure cuffs on both legs during early diastole leading to retrograde aortic blood flow in late diastole and improving coronary perfusion	Arora et al (1999) - MUST-EECP trial - 139 patients - reduces angina, extends time to exercise induced ischaemia, well tolerated	Level of Evidence IIb
External Shockwave Myocardial Revascularisation (ESMR) (34)	Targeted shockwaves to improve myocardial perfusion	Small trials (<50 patients) showing symptom improvement	No recommendation
Psycotherapy (33,39)	Cognitive behavioural therapy programme	Peysh et al (2016) - 33 patients - improves quality of life and mood Tinson et al (2016) - 148 patients - significant improvements in angina	No recommendation
Spinal Cord Stimulation (34,40)	Inhibiting pain fibre signals via epidural leads	Imran et al (2016) - Meta-analysis - 518 patients from 14 studies - longer exercise duration and lower angina frequency	Level of Evidence IIb

Conclusions

In conclusion, refractory angina results in disability, limited quality of life, multiple medications, frequent hospital admissions and ongoing rising costs to the NHS. The CSR device is a potential safe, efficient and cost-effective solution for patients with refractory angina when standard of care treatment with anti-angina medication and revascularisation fails.

Disclosures

None

References

(1)Spoletini I, Ferrari R, Rosano GMC. Living with stable angina. Journal of Cardiovascular Medicine [Internet]. 2020 May 1;21(5):377–82. Available from: https://journals.lww.com/jcardiovascularmedicine/Fulltext/2020/05000/Living_with_stable_angina__patients__pathway_and.5.aspx

(2) Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus [Internet]. 2020 Jul 23;12(7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7384703/

(3) Ford TJ, Berry C. Angina: contemporary diagnosis and management. Heart. 2020 Feb 12;106(5):387–98.

(4) ESC guidelines on chronic coronary syndromes (previously titled Stable coronary artery disease) [Internet]. [cited 2023 Aug 29]. Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

(5) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. The Lancet. 2015 Jun;385(9985):2383–91.

(6) Berry C, Duncker DJ. Coronary microvascular disease: the next frontier for Cardiovascular Research. Cardiovascular Research. 2020 Mar 1;116(4):737–40.

(7)Chang X, Lochner A, Wang H-H, Wang S, Zhu H, Ren J, et al. Coronary microvascular injury in myocardial infarction: perception and knowledge for mitochondrial quality control. Theranostics. 2021;11(14):6766–85.

(8) Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal [Internet]. 2019 Aug 31;41(3). Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehz425/5556137

(9) Antonio Lanza G, Vita AD, Kaski J-C. "Primary" Microvascular Angina: Clinical Characteristics, Pathogenesis and Management. Interventional Cardiology Review. 2018;13(3):108.

(10) Brown JC, Gerhardt TE, Kwon E. Risk Factors For Coronary Artery Disease [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554410/

(11) Davies A, Fox K, Galassi AR, Banai S, Ylä-Herttuala S, Lüscher TF. Management of refractory angina: An update [Internet]. Oxford University Press; 2020 [cited 2024 Feb 24]. Available from: https://academic.oup.com/eurheartj/article/42/3/269/6046144

(12) Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina. Eur Heart J 2002; 23: 355 – 370.

(13) Abdallah MS, Wang K, Magnuson EA, et al. Quality of life after surgery or DES in patients with 3-vessel or left main disease. J Am Coll Cardiol 2017;69:2039–50.

(14) Fox K, Garcia MAA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: full text: The Task Force on the management of stable angina pectoris of the European Society of Cardiology. Eur Heart J 2006;27(11): 1341 -81; doi:10.1093/eurheartj/ehl002

(15) Neovasc Reducer Business case document

(16) Wang JJ, O'Brien AB, Shrive NG, et al. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol 2003; 284:H1358-H1368.

(17) Parikh P, Bhatt P, Shah D, Thakar P, Naik A, Baxi H, et al. First-in-Human Use of Coronary Sinus Reducer in Patients With Refractory Angina. Journal of the American College of Cardiology. 2018 Dec;72(24):3227–8.

(18) Bazoukis G, Brilakis ES, Tse G, Letsas KP, Panagiotis Kitsoulis, Liu T, et al. The efficacy of coronary sinus reducer in patients with refractory angina-A systematic review of the literature. Journal of Interventional Cardiology. 2018 Sep 7;31(6):775–9.

(19) Banai S, Ben Muvhar S, Parikh KH, Medina A, Sievert H, Seth A, et al. Coronary Sinus Reducer Stent for the Treatment of Chronic Refractory Angina Pectoris. Journal of the American College of Cardiology. 2007 May;49(17):1783–9.

(20) Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, et al. Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina. New England Journal of Medicine. 2015 Feb 5;372(6):519–27.

(21) Giannini F, Aurelio A, Chieffo A. Impianto del dispositivo Reducer in seno coronarico: un nuovo trattamento per l'angina refrattaria. Giornale Italiano di Cardiologia [Internet]. 2016 Oct 1 [cited 2023 Aug 29];17(10):3–9. Available from: https://www.giornaledicardiologia.it/archivio/2372/articoli/25470/

(22) Konigstein M, Bazan S, Revivo M, Banai S. Coronary Sinus Reducer implantation improves symptoms, ischaemia and physical capacity in patients with refractory angina unsuitable for myocardial revascularisation: a single-centre experience. EuroIntervention. 2018 Jul;14(4):e452–8.

(23) The coronary sinus reducerTM system for the treatment of patients with refractory angina: A single centre UK experience [Internet]. [cited 2024 Feb 23]. Available from: https://www.henrypublishinggroups.com/the-coronary-sinus-reducer-system-for-the-treatment-of-patients-with-refractory-angina-a-single-centre-uk-experience/

(24) Giannini F, Baldetti L, Ielasi A, Ruparelia N, Ponticelli F, Latib A, et al. First Experience With the Coronary Sinus Reducer System for the Management of Refractory Angina in Patients Without Obstructive Coronary Artery Disease. JACC: Cardiovascular Interventions. 2017 Sep;10(18):1901–3.

(25) The condition, current treatments and procedure | Coronary sinus narrowing device implantation for refractory angina | Guidance | NICE [Internet]. www.nice.org.uk. Available from: https://www.nice.org.uk/guidance/ipg712/chapter/2-The-condition-current-treatments-and-procedure

(26) Neovasc Reducer Business Case

(27) Yu W, Maru F, Edner M, et al. Spinal cord stimulation for refractory angina pectoris: a retrospective analysis of efficacy and cost-benefit. Coron Artery Dis 2004; 15(1): 31 – 7.

(28) Murray S, Carson KGS, Ewings PD, et al. Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart 1999; 82: 89 – 92.

(29) Ullrich H, Hammer P, Olschewski M, Münzel T, Escaned J, Gori T. Coronary Venous Pressure and Microvascular Hemodynamics in Patients With Microvascular Angina: A Randomized Clinical Trial. JAMA Cardiology [Internet]. 2023 Aug 23 [cited 2023 Aug 30]; Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2808768

(30) Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology [Internet]. 2023 Aug 29 [cited 2023 Aug 23];82(9):833–955. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0735109723052816?via%3Dihub

(31) Gallone G, Armeni P, Verheye S, Agostoni P, Timmers L, Campo G, et al. Cost-effectiveness of the coronary sinus Reducer and its impact on the healthcare burden of refractory angina patients. European Heart Journal Quality of Care & Clinical Outcomes [Internet]. 2020 Jan 1 [cited 2023 Aug 30];6(1):32–40. Available from: https://pubmed.ncbi.nlm.nih.gov/31124556/

(32) Rajkumar C, Foley M, Fiyyaz Ahmed-Jushuf, Nowbar AN, Simader F, Davies JR, et al. A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina. The New England Journal of Medicine. 2023 Nov 11

(33) Patel PA. The short- and long-term impact of psychotherapy in patients with chronic, refractory angina [Internet]. 2016 [cited 2024 Feb 22]. Available from: https://bjcardio.co.uk/2016/06/the-short-and-long-term-impact-of-psychotherapy-in-patients-with-chronic-refractory-angina/

(34) Davies A, Fox K, Galassi AR, Banai S, Ylä-Herttuala S, Lüscher TF. Management of refractory angina: An update [Internet]. Oxford University Press; 2020 [cited 2024 Feb 22]. Available from: https://academic.oup.com/eurheartj/article/42/3/269/6046144

(35) Grebmer C, Bossard M, Attinger-Toller A, Kobza R, Hilfiker G, Berte B, et al. Cardiac resynchronisation therapy in patients with a coronary sinus reducer: A case series. European Heart Journal - Case Reports [Internet]. 2023 Sep 1 [cited 2024 Feb 24];7(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10516338/

(36) Zivelonghi C, Verheye S. The Coronary Sinus Reducer – Clinical Evidence and New Perspectives On An Emerging Tool in the Treatment of Refractory Angina. Heart International. 2020;14(1):29

(37) Konigstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. European Heart Journal. 2017 Aug 31;39(11):925–33

(38) Gorla R, et al. Unusual Implantation of a Coronary Sinus Reducer in the Middle Cardiac Vein [Internet]. 2018 [cited 2024 Feb 24]. Available from: https://www.hmpgloballearningnetwork.com/site/jic/articles/unusual-implantation-coronary-sinus-reducer-middle-cardiac-vein

(39) Tinson D. Clinical and psychological outcomes of an angina management programme [Internet]. 2016 [cited 2024 Feb 24]. Available from: https://bjcardio.co.uk/2016/06/clinical-and-psychological-outcomes-of-an-angina-management-programme/

(40) Imran TF;Malapero R;Qavi AH;Hasan Z;de la Torre B;Patel YR;Yong RJ;Djousse L;Gaziano JM;Gerhard-Herman MD; Efficacy of spinal cord stimulation as an adjunct therapy for chronic refractory angina pectoris [Internet]. U.S. National Library of Medicine; [cited 2024 Feb 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/27836302/

(41) Arora RR;Chou TM;Jain D;Fleishman B;Crawford L;McKiernan T;Nesto RW; The Multicenter Study of Enhanced External Counterpulsation (must-EECP): Effect of EECP on exercise-induced myocardial ischemia and anginal episodes

[Internet]. U.S. National Library of Medicine; [cited 2024 Feb 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/10362181/