

Novel Nonpharmacologic Therapies for Patients With Refractory Angina Pectoris

A review of available treatment options.

BY FRANCESCO GALLO, MD; FRANCESCO PONTICELLI, MD; ANTONIO COLOMBO, MD; AND FRANCESCO GIANNINI, MD

In the era of next-generation medical therapies and advanced coronary revascularization, an increasing proportion of the population survives acute cardiovascular events and eventually develops chronic coronary syndromes (CCSs).¹ Given this longer life expectancy, patients can live with coronary artery disease (CAD) for many years, which exposes them to continued disease progression, further acute events, and, ultimately, multiple revascularization procedures.

A significant and growing proportion of this population eventually develops an advanced stage of CAD with symptoms of angina that are unresponsive to optimized pharmacologic therapy and further coronary revascularization. Because refractory angina pectoris (RAP) has similar long-term survival to asymptomatic stable CAD,² it represents a major physical limitation that can profoundly impact the quality of life (QOL) of affected patients.

Such patients are not eligible for further coronary revascularization and are known to respond poorly to available anti-ischemic and antianginal medical therapies.^{3,4} Alternative treatment routes have been extensively investigated, but only a few have proved to be effective in randomized clinical trials, and even fewer are currently recommended by the 2019 European Society of Cardiology (ESC) guidelines for CCSs. This article describes the major nonpharmacologic strategies that should be considered when treating patients with RAP. Table 1 illustrates the level of evidence (when available) for each treatment strategy.

CORONARY SINUS REDUCER

In the early 1950s, Claude S. Beck demonstrated that surgical narrowing of the coronary sinus in patients with ischemic heart disease was associated with significant

TABLE 1. LEVEL OF EVIDENCE FOR TREATMENT STRATEGIES

Treatment Strategy	2019 ESC Guidelines		2014 ACC Guidelines	
	Class	LoE	Class	LoE
Coronary sinus reducer	IIb	B	–	–
Enhanced external counterpulsation	IIb	B	IIb	B
Extracorporeal shockwave myocardial revascularization therapy	–	–	–	–
Spinal cord stimulation	IIb	B	IIb	C
Transcutaneous electrical nerve stimulation	–	–	–	–
Subcutaneous electrical nerve stimulation	–	–	–	–
Stem cell therapy	–	–	–	–
Transmyocardial revascularization	III	A	IIb	B

Abbreviations: ACC, American College of Cardiology; ESC, European Society of Cardiology; LoE, level of evidence.

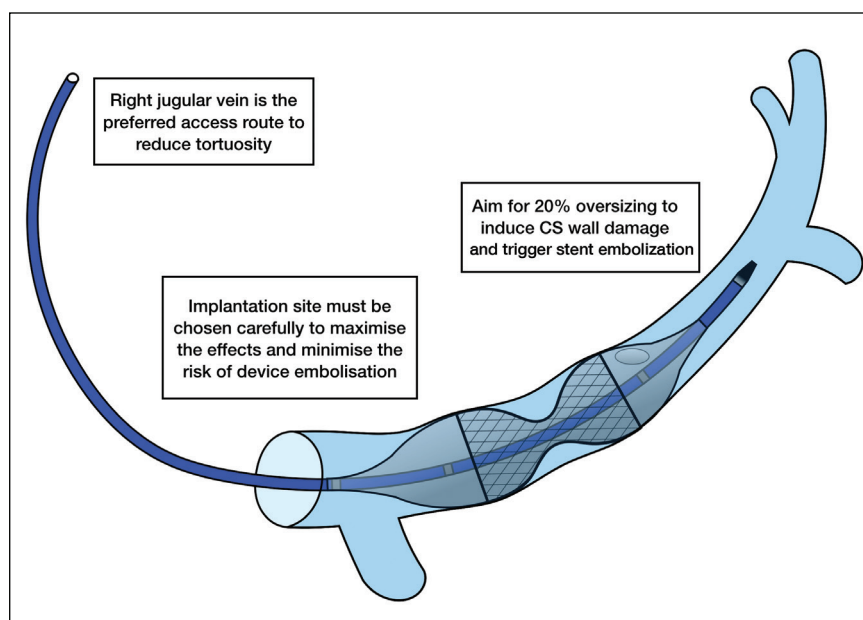


Figure 1. Coronary sinus reducer. The right jugular vein is the preferred access route due to reduced tortuosity, facilitating optimal coronary sinus cannulation. Careful angiographic evaluation is recommended to identify the ideal implantation site. Proximal implantation potentially includes more myocardial tissue but at the expense of a more significant risk of device embolization. During scaffold delivery, approximately 20% oversizing (compared to the nominal vessel diameter) is warranted to trigger vessel repair and promote device endothelialization. CS, coronary sinus.

improvement in symptoms and reduced 5-year mortality.⁵ The Neovasc Reducer (Neovasc Inc.) represents the percutaneous evolution of the Beck technique: a balloon-expandable, stainless-steel, hourglass-shaped stent designed to create a focal narrowing of the coronary sinus and generate a backward pressure gradient along the coronary venous system (Figure 1). The Reducer device is implanted percutaneously, typically via the right jugular vein, into the coronary sinus.⁶ The hourglass shape and oversized peripheral domes promote endothelial injury and trigger stent endothelialization. This process increases transscaffold venous pressure, promoting capillary recruitment and blood redistribution through myocardial layers. Ultimately, this process reestablishes normal endocardial/epicardial blood flow ratios.⁷

After promising results of the first-in-human study,⁸ the

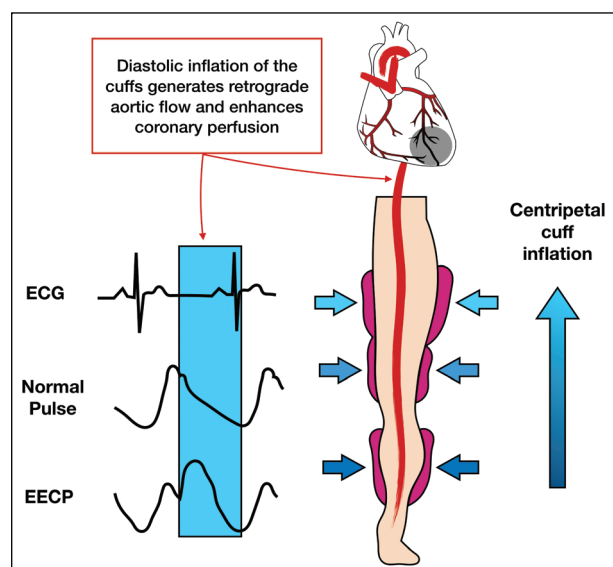


Figure 2. For EECP, pressure cuffs are applied on the arms, thighs, and calves, and inflation is electrocardiographic gated to ensure diastolic inflation and systolic deflation. Cuffs are synchronized to exert a centripetal pushing force. ECG, electrocardiogram.

randomized, double-blind, sham-controlled COSIRA trial demonstrated significant improvements in anginal symptoms after Reducer implantation in patients with obstructive CAD and reversible myocardial ischemia.⁹ Subsequent real-world prospective registries confirmed the findings of the COSIRA trial, reporting symptomatic improvement in > 70% of patients, coupled with a significant increase in 6-minute walk distance after a median follow-up of 12 months.^{10,11} Moreover, among 15 patients who also underwent cardiac MRI at baseline and at 4-month follow-up, Reducer implantation was also associated with a significant increase of the myocardial perfusion reserve index, a semiquantitative method used to quantify ischemic burden.¹² These results support the safety and efficacy of Reducer implantation, which should be considered for patients with RAP, according to 2019 ESC guidelines on CCs.¹

ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) (Vasomedical, Inc.) consists of three pairs of pneumatic cuffs that are placed around the calves, thighs, and arms to generate a centripetal pressure wave by inflating and

deflating synchronously with diastole and systole, respectively (Figure 2).^{13,14} These cyclic compressions noninvasively imitate the rationale of intra-aortic balloon pumps and may eventually enhance coronary flow and stimulate angiogenesis while reducing left ventricular afterload and cardiac work overall.¹⁵ The standard protocol involves 35 1-hour sessions distributed 5 days/week for a total of 7 weeks. Three prospective international registries¹⁶⁻¹⁸ and one substudy of a randomized controlled trial¹⁹ examining EECP documented a significant increase in time to exercise-induced ST-segment depression and a significant decrease in the frequency of anginal episodes in the RAP population. Furthermore, a systematic review and meta-analysis by Qin et al showed that EECP therapy significantly increases myocardial perfusion in patients with CAD.²⁰ Guidelines from American (2014) and European (2019) associations recommend EECP as a therapeutic alternative for patients with invalidating RAP,^{1,21} although its adoption in everyday practice is limited by the impractical nature of the treatment protocols.

EXTRACORPOREAL SHOCKWAVE MYOCARDIAL REVASCULARIZATION THERAPY

Extracorporeal shockwave myocardial revascularization (ESMR) therapy is a noninvasive treatment based on the principle of transmission of acoustic energy through a liquid medium. When applied to the myocardium, a review by Ruiz-Garcia and Lerman showed that ESMR has been shown to improve myocardial perfusion and reduce ischemic symptoms.²² Shockwaves are delivered via a proprietary applicator through the anatomic acoustic window and are electrocardiographically gated to avert the induction of malignant ventricular arrhythmias. A single ESMR session typically consists of 1,000 shocks delivered in a sequence of 100 shocks per 10 thoracic areas. ESMR mainly induces vasodilatation and neovascularization.²³ Although there are no reported side effects of ESMR, the quality of each acoustic window represents a major limitation, preventing proper targeting of the various ischemic areas. Although a meta-analysis of 39 studies reported significant improvement in angina class, QOL, and exercise capacity,²⁴

the real effects of this therapy and its clinical applications need better characterization with adequately powered, well-structured, placebo-controlled trials.

NEUROMODULATORY THERAPIES

Neuromodulation uses chemical, mechanical, or electrical stimuli to interfere with the transmission of pain signals and reduce sympathetic afference responsible for vasoconstriction.^{2,25}

Spinal Cord Stimulation

Spinal cord stimulation (SCS) consists of a subcutaneous generator connected to multipolar leads that are implanted under local anesthesia and fluoroscopic guidance up to the C5-T2 spinal cord segments (Figure 3). The therapy is self-administered on presentation of angina. A typical therapeutic regimen of SCS is three baseline stimulations per day, plus a strong self-administered stimulation during angina attacks.³ The pivotal mechanism involves inducing the release of γ -aminobutyric acid (GABA) to antagonize the transmission of nociceptive signals through the descending inhibitory pathways.²⁶ Reported complication rates with SCS vary between 30% and 40% and are most frequently lead migration, device failure, lead fractures, and skin infections and pain over the implant site. Meningeal (dural) infections and neurologic damage are less frequent but potentially

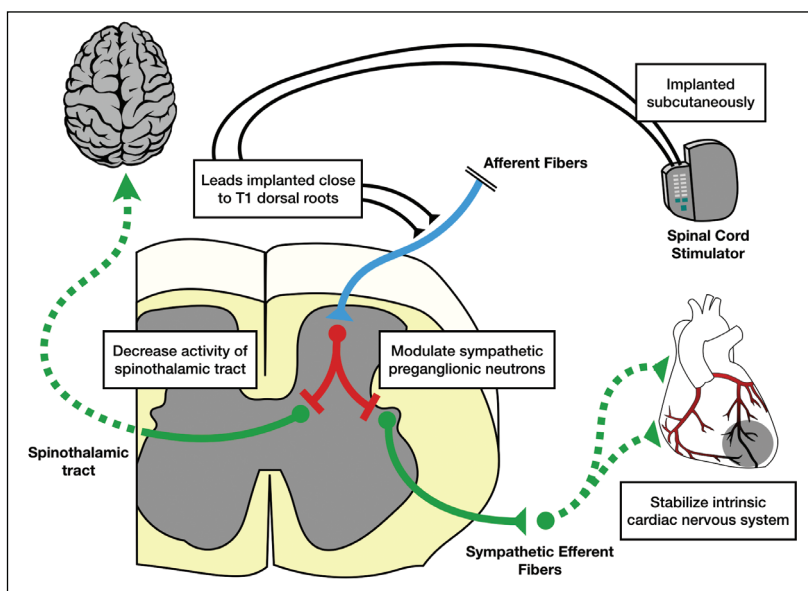


Figure 3. In SCS, a subcutaneous generator is connected to multipolar leads, which are implanted up to the C5-T2 spinal cord segments. On activation, the leads stimulate inhibitory interneurons, in turn inducing the release of GABA and antagonizing the transmission of nociceptive signals.

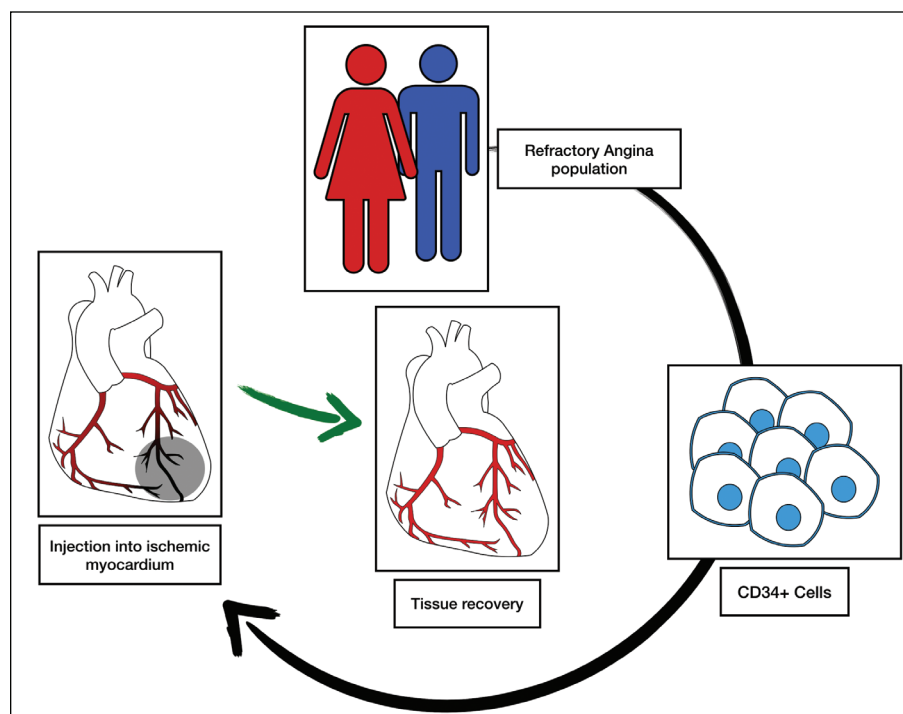


Figure 4. CD34+ stem cells have the highest angiogenetic properties in vivo. Two clinical trials and a recent meta-analysis demonstrated durable improvements in exercise capacity, angina frequency, and reduced 2-year all-cause mortality compared with placebo.

serious.²⁷ The ESBY trial randomized 104 high-risk patients to undergo either cardiac surgery or SCS and revealed comparable symptom relief but lower overall mortality and cerebrovascular morbidity in the SCS group.²⁸ A recent meta-analysis of 12 studies, including 476 patients with RAP, showed that SCS is associated with prolonged exercise tolerance, lower angina frequency, and lower nitrate consumption as compared with medical therapy alone.²⁹ According to American and European guidelines, SCS may be considered to improve symptoms and QOL in patients with invalidating angina refractory to optimal medical therapy and revascularization strategies (class IIb).^{1,21}

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is less invasive than SCS. Low-intensity electrical currents generated by electrodes and applied externally to the chest may reduce the activity of the central nociceptive cells via the descending inhibitory pathways.²⁵ Major side effects are skin irritation, paresthesia, and potential interactions with pacemakers/defibrillators.³⁰ Some studies demonstrated increased work capacity, reduced frequency of anginal attacks, and decreased consumption of short-acting nitrates

after TENS treatment.³⁰⁻³² Despite its apparent efficacy, TENS is often used as bridge to SCS or subcutaneous electrical nerve stimulation (SENS).

Subcutaneous Electrical Nerve Stimulation

There is very limited available literature on the feasibility, safety, and efficacy of this recent approach to neurostimulation for the treatment of RAP.^{33,34} In a pilot study, SENS demonstrated safety and feasibility, showing clinically relevant improvements in exercise tolerance and QOL. The number of angina attacks decreased by approximately 82%, and sublingual nitrate usage decreased by 90%, while no major adverse event was observed.³⁵

In SENS, peripheral multipolar electrodes (usually 4–8) are implanted subcutaneously in the parasternal area (where patients typically perceive angina), bypassing spinal cord and peripheral nerves. Subcutaneous lead implantation is less invasive and carries a lower risk of serious complications compared with epidural lead implantation. Subcutaneous access could also be safer in patients taking dual antiplatelet or anticoagulation therapies.³⁶ Larger-scale randomized trials are needed to elucidate the potential applications of this therapeutic approach.

LATEST THERAPEUTIC OPTIONS

CD34+ Stem Cells

Autologous CD34+ bone marrow-derived endothelial progenitor cells have the highest angiogenetic properties in vivo (Figure 4). They are inversely associated with CAD severity, physical function, and hard clinical outcomes after myocardial infarction.³⁷ The use of CD34+ cells in RAP was evaluated in two clinical trials,^{38,39} demonstrating persistent improvement of angina. A recent meta-analysis including 304 patients demonstrated durable improvement in exercise capacity, lower angina frequency throughout a 3- to 12-month period, and reduced 2-year all-cause mortality as compared with placebo.⁴⁰

CD133+ Stem Cells

The application of bone marrow–derived CD133+ cell therapy has also been assessed in a trial enrolling 10 RAP patients with ischemic cardiomyopathy. CD133+ therapy resulted in improvement in anginal symptoms together with increased myocardial perfusion and function on single-photon emission CT assessment.⁴¹ However, despite these promising findings, cell therapy for RAP currently remains limited to research studies.

CONCLUSION

RAP represents a challenging clinical scenario for both patient and physician. In the last few years, novel therapies have progressively changed the natural history of the disease. Among these options, coronary sinus reducer implantation appears to have the most rigorously trialed and relevant impact of reducing angina symptoms and increasing QOL. ■

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407-477.
2. Henry TD, Satran D, Hodges JS, et al. Long-term survival in patients with refractory angina. *Eur Heart J*. 2013;34:2683-2688.
3. Henry TD, Satran D, Jolicœur EM. Treatment of refractory angina in patients not suitable for revascularization. *Nat Rev Cardiol*. 2014;11:78-95.
4. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina: report from the ESC Joint Study Group on the treatment of refractory angina. *Eur Heart J*. 2002;23:355-370.
5. Sandler G, Slesser BV, Lawson CW. The Beck operation in the treatment of angina pectoris. *Thorax*. 1967;22:34-37.
6. Giannini F, Aurelio A, Jabbour RJ, et al. The coronary sinus reducer: clinical evidence and technical aspects. *Expert Rev Cardiovasc Ther*. 2017;15:47-58.
7. Königstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. *Eur Heart J*. 2018;39:925-933.
8. Banai S, Ben Muvhar S, Parikh KH, et al. Coronary sinus reducer stent for the treatment of chronic refractory angina pectoris: a prospective, open-label, multicenter, safety feasibility first-in-man study. *J Am Coll Cardiol*. 2007;49:1783-1789.
9. Verheyde S, Jolicœur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. *N Engl J Med*. 2015;372:519-527.
10. Abawi M, Nijhoff F, Stella PR, et al. Safety and efficacy of a device to narrow the coronary sinus for the treatment of refractory angina: a single-centre real-world experience. *Neth Heart J*. 2016;24:544-551.
11. Giannini F, Baldetti L, Ponticelli F, et al. Coronary sinus reducer implantation for the treatment of chronic refractory angina: a single-centre experience. *JACC Cardiovasc Interv*. 2018;11:784-792.
12. Giannini F, Palmisano A, Baldetti L, et al. Patterns of regional myocardial perfusion following coronary sinus reducer implantation. *Circ Cardiovasc Imaging*. 2019;12:e009148.
13. Raza A, Steinberg K, Tartaglia J, et al. Enhanced external counterpulsation therapy: past, present, and future. *Cardiol Rev*. 2017;25:59-67.
14. Sharma U, Ramsey HK, Tak T. The role of enhanced external counterpulsation therapy in clinical practice. *Clin Med Res*. 2013;11:226-232.
15. Yang DY, Wu GF. Vasculoprotective properties of enhanced external counterpulsation for coronary artery disease: beyond the hemodynamics. *Int J Cardiol*. 2013;166:38-43.
16. Urano H, Ikeda H, Ueno T, et al. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. *J Am Coll Cardiol*. 2001;37:93-99.
17. Soran O, Kennard ED, Kfoury AG, et al. Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the International EECP Patient Registry). *Am J Cardiol*. 2006;97:17-20.
18. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study. *Clin Cardiol*. 2000;23:254-258.
19. Arora RR, Chou TM, Jain D, et al. Effects of enhanced external counterpulsation on health-related quality of life continue 12 months after treatment: a substudy of the multicenter study of enhanced external counterpulsation. *J Investig Med*. 2002;50:25-32.
20. Qin X, Deng Y, Wu D, et al. Does enhanced external counterpulsation (EECP) significantly affect myocardial perfusion?: a systematic review & meta-analysis. *PLoS One*. 2016;11:e0151822.
21. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64:1929-1949.
22. Ruiz-García J, Lerman A. Cardiac shock-wave therapy in the treatment of refractory angina pectoris. *Interv Cardiol*. 2011;3:191-201.
23. Maisonneuve E, Prado C, White PC, Compton RG. Surface acoustic cavitation understood via nanosecond electrochemistry. Part III: shear stress in ultrasonic cleaning. *Ultrason Sonochem*. 2002;9:297-303.
24. Burneikaite G, Shkolnik E, Celutkienė J, et al. Cardiac shock-wave therapy in the treatment of coronary artery disease: systematic review and meta-analysis. *Cardiovasc Ultrasound*. 2017;15:11.
25. Dobias M, Michalek P, Neuzil P, et al. Interventional treatment of pain in refractory angina. A review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158:518-527.
26. Prager JP. What does the mechanism of spinal cord stimulation tell us about complex regional pain syndrome? *Pain Med*. 2010;11:1278-1283.
27. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. *Pain Med*. 2016;17:325-336.
28. Mannheimer C, Eliasson T, Augustinsson LE, et al. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. *Circulation*. 1998;97:1157-1163.
29. Pan X, Bao H, Si Y, et al. Spinal cord stimulation for refractory angina pectoris: a systematic review and meta-analysis. *Clin J Pain*. 2017;33:543-551.
30. Mannheimer C, Carlsson C, Emanuelsson H, et al. The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. *Circulation*. 1985;71:308-316.
31. Jessurun GA, Tio RA, De Jongste MJ, et al. Coronary blood flow dynamics during transcutaneous electrical nerve stimulation for stable angina pectoris associated with severe narrowing of one major coronary artery. *Am J Cardiol*. 1998;82:921-926.
32. Börjesson M, Eriksson P, Dellborg M, et al. Transcutaneous electrical nerve stimulation in unstable angina pectoris. *Coron Artery Dis*. 1997;8:543-550.
33. Buiten MS, De Jongste MJ, et al. Subcutaneous electrical nerve stimulation: a feasible and new method for the treatment of patients with refractory angina. *Neuromodulation*. 2011;14:258-265.
34. Goroszeniuk T, Kothari S. Targeted external area stimulation: 240. *Reg Anesth Pain Med*. 2004;29:98.
35. Goroszeniuk T, Kothari S, Hamann W. Subcutaneous neuromodulating implant targeted at the site of pain. *Reg Anesth Pain Med*. 2006;31:168-171.
36. Goroszeniuk T, Pang D, Al-Kaisy A, Sanderson K. Subcutaneous target stimulation-peripheral subcutaneous field stimulation in the treatment of refractory angina: preliminary case reports. *Pain Pract*. 2012;12:71-79.
37. Patel RS, Li Q, Ghasemzadeh N, et al. Circulating CD34+ progenitor cells and risk of mortality in a population with coronary artery disease. *Circ Res*. 2015;116:289-297.
38. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. 2011;109:428-436.
39. Henry TD, Schaer GL, Traverse JH, et al. Autologous CD34+ cell therapy for refractory angina: 2-year outcomes from the ACT34-CMI study. *Cell Transplant*. 2016;25:1701-1711.
40. Henry TD, Losordo DW, Traverse JH, et al. Autologous CD34+ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials. *Eur Heart J*. 2018;39:2208-2216.
41. Bassetti B, Carubicchio C, Catto V, et al. Linking cell function with perfusion: insights from the transcatheter delivery of bone marrow-derived CD133+ cells in ischemic refractory cardiomyopathy trial (RECARDIO). *Stem Cell Res Ther*. 2018;9:235.

Francesco Gallo, MD

Interventional Cardiology Unit
Maria Cecilia Hospital, GVM Care & Research
Cotignola, Italy
Disclosures: None.

Francesco Ponticelli, MD

Interventional Cardiology Unit
Maria Cecilia Hospital, GVM Care & Research
Cotignola, Italy
Disclosures: None.

Antonio Colombo, MD

Interventional Cardiology Unit
Maria Cecilia Hospital, GVM Care & Research
Cotignola, Italy
Interventional Cardiology Unit
Emo GVM Centro Cuore Columbus
Milan, Italy
Disclosures: None.

Francesco Giannini, MD

Interventional Cardiology Unit
Maria Cecilia Hospital, GVM Care & Research
Cotignola, Italy
giannini_fra@yahoo.it
Disclosures: Consultant to Neovasc Inc.