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STATE-OF-THE-ART REVIEW

Refractory Angina

From Pathophysiology to New Therapeutic Nonpharmacological Technologies

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CME/MOC/ECME Objectives for This Article: Upon completion, the reader should be able to: 1) discuss the definition and the changing epidemiology of refractory angina; 2) discuss the complex model of heart-brain interactions underlying angina physiopathology; 3) recognize the rationale and compare the current clinical evidence of nonpharmacological treatment technologies for refractory angina; and 4) discuss with the refractory angina patient regarding the available therapeutic options with the aim to pursue an individualized therapeutic strategy.

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ABSTRACT

Despite optimal combination of guideline-directed anti-ischemic therapies and myocardial revascularization, a substantial proportion of patients with stable coronary artery disease continues to experience disabling symptoms and is often referred as "no-option." The appraisal of the pathways linking ischemia to symptom perception indicates a complex model of heart-brain interactions in the generation of the subjective anginal experience and inspired novel approaches that may be clinically effective in alleviating the angina burden of this population. Conversely, the prevailing ischemia-centered view of angina, with the focus on traditional myocardial revascularization as the sole option to address ischemia on top of medical therapy, hinders the experimental characterization and broad-scale clinical implementation of strongly needed therapeutic options. The interventionist, often the first physician to establish the diagnosis of refractory angina pectoris (RAP) following coronary angiography, should be aware of the numerous emerging technologies with the potential to improve quality of life in the growing population of RAP patients. This review describes the current landscape and the future perspectives on nonpharmacological treatment technologies for patients with RAP, with a view on the underlying physiopathological rationale and current clinical evidence. (J Am Coll Cardiol Intv 2020;13:1–19)

The ultimate goal of medicine is to improve patients' quantity and quality of life. In the field of coronary artery disease (CAD), cardiovascular mortality has steadily decreased as an effect of continuous advances in disease-modifying treatments (1,2). The same benefit does not necessarily apply to symptoms and quality of life, for which therapeutic approaches have remained mostly unchanged over the last 2 decades. Specifically, the mainstay of anginal pain treatment is still based on nitrates, beta-blockers, calcium antagonists (with the sole recent addition of ranolazine and ivabradine), and coronary revascularization. These treatments match myocardial O_2 supply and demand through variable mechanisms: coronary flow reserve increase, heart rate reduction, myocardial inotropy modulation, and improvements in cellular metabolism (3). Despite optimal combination of such therapeutics, a substantial proportion of stable CAD patients continues to experience disabling angina with resultant impairment in quality of life constituting the refractory angina pectoris (RAP) population.

Knowledge of the mechanisms leading to myocardial ischemia and of the pathways linking ischemia to the subjective experience of angina indicates a complex model that considers the heart-brain axis as a whole. From "heart to brain," a multitude of therapeutic targets encompassing myocyte metabolism, coronary microcirculation, nociception and neuromodulatory pathways may be effectively addressed by emerging treatment options. Of note, disruption of these mechanisms may be of particular relevance in RAP, as it may account for suboptimal response to traditional anti-ischemic drugs in this population. In spite of new emerging treatment techniques, the large placebo effect highlighted in previous blinded studies in the field of RAP is an important concern in the cardiology community, hampering experimental characterization and broad-scale clinical implementation of such novel therapeutic options (4,5). The frequent scotomization of RAP by interventionists, often labeling nonrevascularizable patients as "no option" patients or overlooking patients with symptoms despite complete revascularization or nonobstructive disease adds up to this issue (6).

The aim of this review is to describe the current landscape and the future perspectives of nonpharmacological treatment technologies for patients with RAP, with a view on the underlying physiopathological rationale. New pharmacological options, equally important in this setting, have been exhaustively described (7) and will not be addressed in this dissertation.

HIGHLIGHTS

- Refractory angina may be prevalent in 5% to 10% of stable coronary artery disease patients.
- Many emerging therapeutics may be suitable and efficacious to improve quality of life in refractory angina.
- Standardized sham-controlled trials' design will be key to these treatments' wide implementation.

EPIDEMIOLOGY OF REFRACTORY ANGINA

RAP is defined as "a chronic condition caused by clinically established reversible myocardial ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty, or coronary artery bypass grafting" (8,9). This general definition includes heterogeneous phenotypes of patients not amenable to revascularization, encompassing those with unsuitable coronary anatomy (diffuse disease, thread-like coronary arteries, lack of graft conduits for CABG), risk-benefit profile opposing the procedure (advanced age, comorbidities, high-risk procedure), and coronary disorders other than obstructive CAD causing angina (6).

Sixteen years ago, a statement was made of "an urgent need to clarify the epidemiology of this condition" by a dedicated Study Group of the European Society of Cardiology; however, figures on RAP epidemiology remain limited and outdated. Main reports addressing this subject are presented in **Table 1** with an emphasis on the related limits in RAP definition. Overall, RAP prevalence is estimated to be 5% to 10% in stable CAD patients, possibly accounting for 50,000 to 100,000 new cases/year in the United States and 30,000 to 50,000 new cases/year in Europe (7). Because of the aging population with more prevalent CAD and of the widespread access to coronary revascularization (driven by technical progresses and safety improvement in interventional procedures), the epidemiology of this condition may be rapidly changing. Further, many series either excluded patients with nonobstructive CAD or did not report on microvascular dysfunction in patients with obstructive CAD as a possible con-cause of RAP. This condition is likely much more common than previously thought (10,11) and in light of infrequent assessment of microcirculatory physiology in clinical practice, many patients deemed to have noncardiac pain may in fact be experiencing microvascular angina (12).

Although epidemiologic data is limited and possibly unreliable, more robust evidence on the prognosis of RAP patients indicates outcomes comparable to the general stable CAD population. The modest mortality of 3.9% at 1 year and the high survival rate at long-term follow-up (77.6% of patients alive at 9 years) reported in a large prospective cohort of RAP patients (13) highlight the unmet clinical need of symptoms control in a population with long life expectancy and poor health status.

ANGINA PATHOPHYSIOLOGY: THE CONUNDRUM OF ISCHEMIA-ANGINA RELATIONSHIP

An ischemia-centered paradigm of angina currently prevails, according to which an oxygen supply-demand imbalance, generally due to a critical coronary stenosis, leads to tissue level activation of nociceptive fibers, conveying the signal to the central nervous system in which cardiac pain perception is elaborated (14). Today, this simplistic mechanistic view is being challenged by clinical and experimental evidence revealing an extremely complex picture of angina physiology. Indeed, the relation between ischemia and anginal symptoms encompasses a wide spectrum of manifestations ranging from ischemic episodes in the absence of symptoms (silent ischemia) (15) to the presence of angina-like symptoms in patients without evidence of ischemia (the "sensitive heart") (16). This observation establishes ischemia as a neither sufficient nor necessary condition to elicit the subjective experience of angina, thus calling for a complex interplay of factors linking the anatomical substratum to the perception of cardiac pain. Speculatively, the interaction of dysfunctional coronary macro- and microcirculation with the myocyte metabolic status may account, at a given O_2 supply level, for different microenvironmental milieux of algogenic stimuli variably modulating nociceptive pathways activation. The plethora of clinical manifestations, beyond anginal pain, that can be subjectively experienced by a patient during an ischemic episode further stress the variability in the triggers, elaboration, and final perception of afferent signals from the heart. Clinical experience of strong symptomatic improvement with placebo treatment in RAP is the most supportive evidence of these concepts. Comprehension of the complex interactions among angina determinants (**Figure 1**) is key to understanding the therapeutic technologies under current investigation in the RAP field.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CCS = Canadian Cardiovascular Society

CS = coronary sinus

EECP = enhanced external counterpulsation

ESMR = extracorporeal shockwave myocardial revascularization

RAP = refractory angina pectoris

SCS = spinal cord stimulation

SENS = subcutaneous electrical nerve stimulation

TENS = transcutaneous electrical nerve stimulation

TMLR = transmyocardial laser revascularization

VEGF = vascular endothelial growth factor

TABLE 1 Incidence of Refractory Angina

Study (Enrollment Period)	Population	Angina Status	Nonrevascularization Rate	Reason for Nonrevascularization	OMT
Swedish Registry (1994–1995) N = 827	SIHD considered for revascularization	Present	9.6%	NA	NA
Cleveland Clinic (1998) N = 500	SHID (confirmed/suspected)	Present	11.8%	CTO 64.4% Poor target 74.5% Degenerated SVG 23.7% No conduit 5.0% Comorbidities 3.3%	<50%
European Heart Survey (2001–2002) N = 4,409	SIHD/NSTE-ACS	Present	7%	Technically unfeasible 68% Comorbidities 10% High procedural risk 22%	NA
Minneapolis (2005) N = 493	Any-reason coronary angiography (only 11% with SIHD indication)	Unspecified	16%	CTO 69.7% Diffuse disease 45.5% Collateral dependent 42.2% Restenoses 6.1% Poor targets 3.0% Comorbidities 12.1%	NA
Euro Heart Survey (2001–2002) N = 4,409	SIHD	61% (n = 2,319)	15.2% of patients with angina (n = 415)	Multivessel disease, CTO, lower ejection fractions significantly more common in nonrevascularized patients vs. revascularized patients	Beta-blocker 73% Calcium-channel blocker 32%
Duke University (1997–2010) N = 77,257	Any-reason coronary angiography	Present	2.47%	NA	NA

The table outlines the limits in our understanding of refractory angina epidemiology. Figures on the incidence of refractory angina are drawn from outdated reports, which may no longer reflect the current epidemiology of this condition. No data on coronary vasomotor and microvascular dysfunction as possible causes of refractory angina are reported.

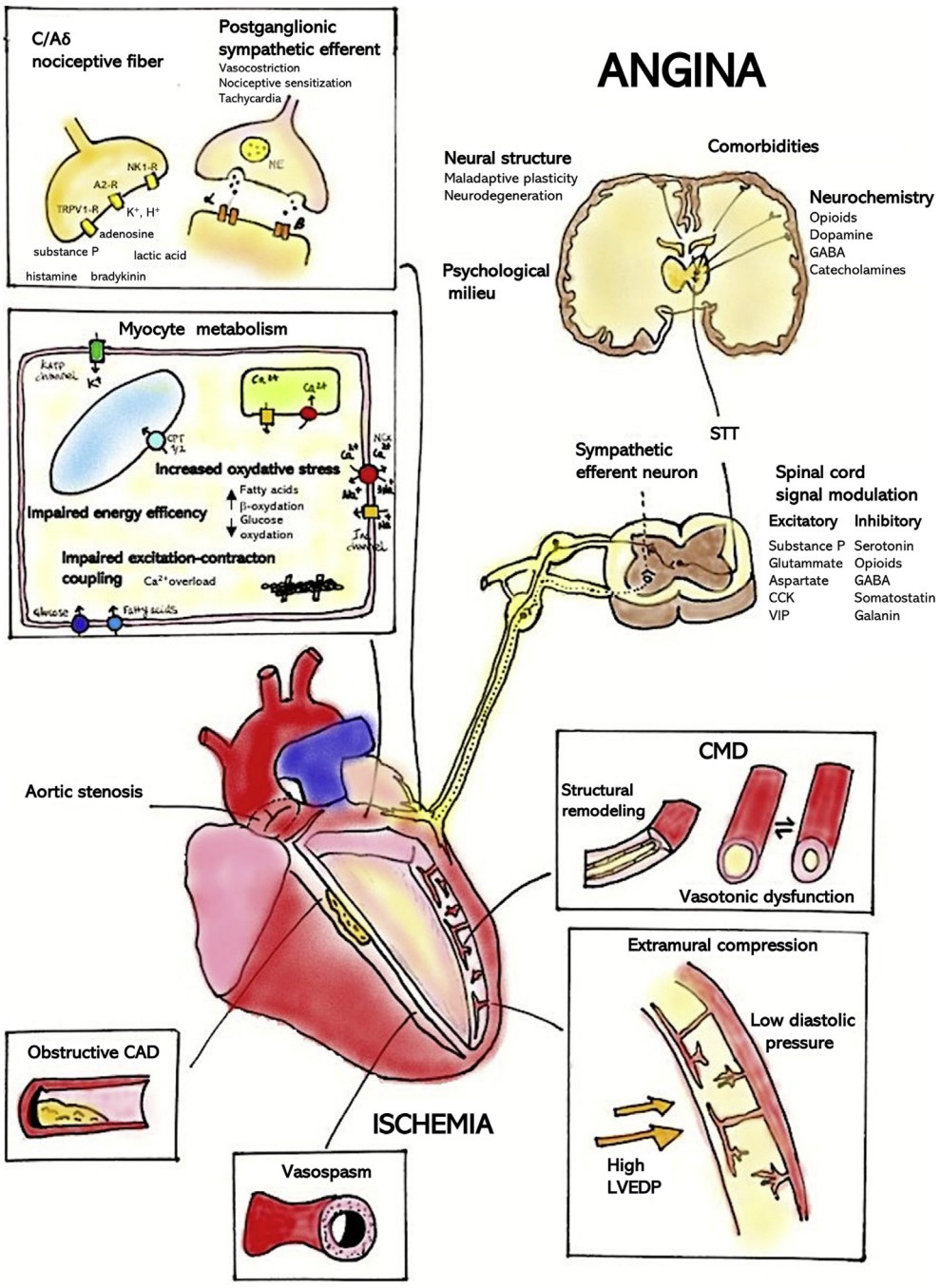
CTO = chronic total occlusion; NA = not available; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OMT = optimal medical therapy; SIHD = stable ischemic heart disease; SVG = saphenous vein graft.

MYOCARDIAL ISCHEMIA: THE TIP OF THE ICEBERG AND BELOW. Myocardial demand ischemia has been traditionally attributed to obstructive epicardial CAD, blunting vessel capacity to overcome increased flow demand (17). However, 90% of the pressure drop along the healthy coronary circulation occurs between the pre-arterioles and the coronary sinus (CS). Thus, maximal blood flow reaching a given myocardial territory (at a given driving blood pressure) is the result, beyond epicardial CAD anatomical and functional status, of intraventricular, intramyocardial, and right atrial pressures during the cardiac cycle, and by the anatomical and functional integrity of the coronary microvasculature (12,18). Following percutaneous coronary intervention and despite adequate anti-ischemic therapy, 20% to 30% of patients continue to experience angina (19-21). There is growing evidence that coronary microvascular dysfunction is highly prevalent in both patients with suspected CAD without (50% to 60%) and with (39%) obstructive disease (10,11,22). Coronary vasomotor disorders (of both epicardial and microvascular vessels) occur in up to 37% of angina patients without obstructive CAD (23).

Moreover, hypoperfusion as a surrogate of ischemia may be oversimplistic, as impaired myocardial blood flow is not necessarily commensurate with myocardial hypoxia (24,25). Specifically, the ischemic threshold may be increased by metabolic adaptative responses to avert ischemia in the face of hypoperfusion (26) or may be lowered by compromised adaptability of the myocyte metabolic demand, which may result from impaired flexibility in switching toward metabolic substrates with higher energetic efficiency (generated adenosine triphosphate-to-consumed oxygen ratio: higher for glucose oxidation than for beta-oxidation of fatty acids) (27).

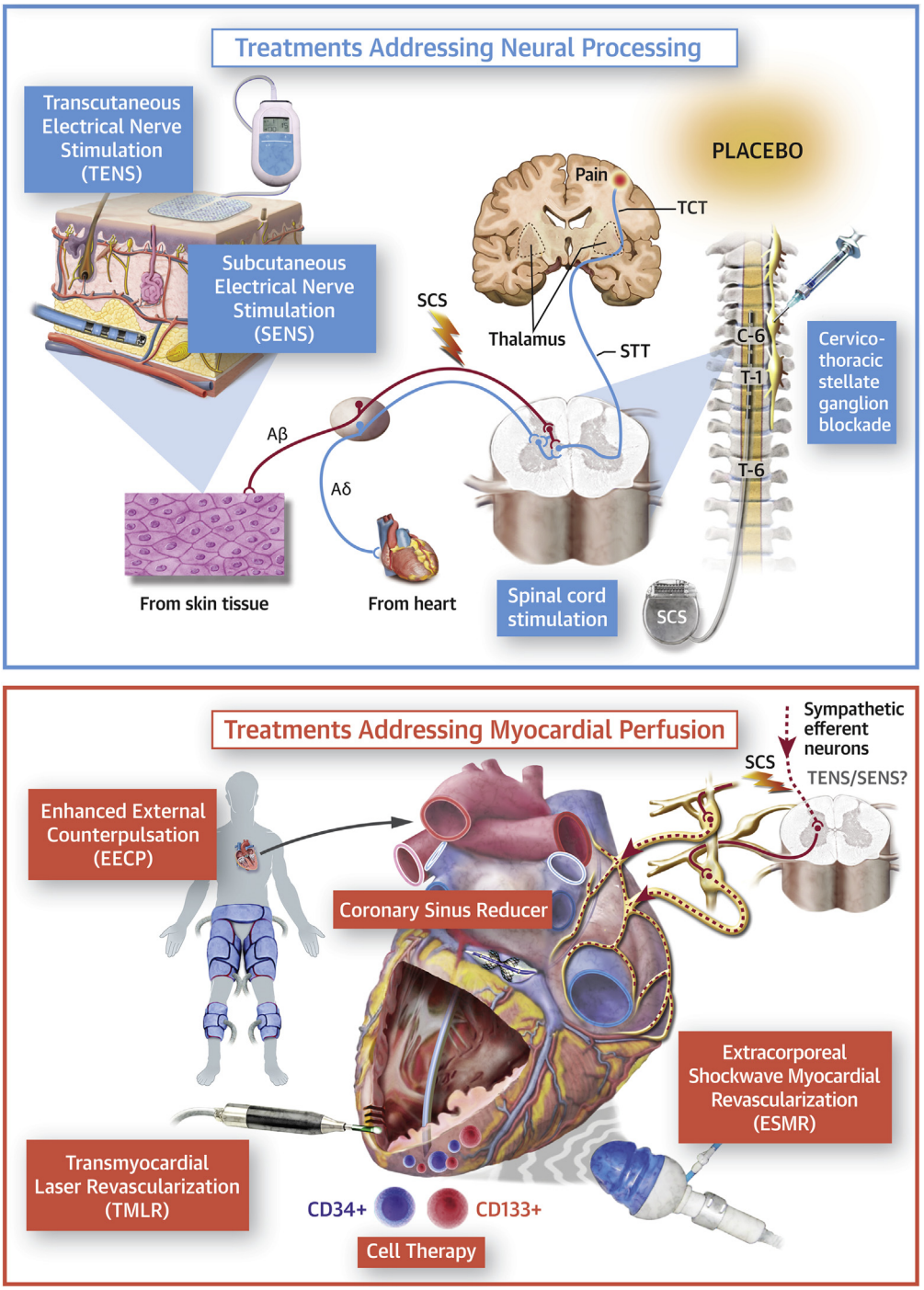
CARDIAC NOCICEPTION: WHERE THE HEART AND THE BRAIN FIRST MEET. Nociception occurs at the free ends of mixed myelinated (Adelta) and unmyelinated (C) fibers running as bundles among myocytic septa, progressively forming the cardiac visceral afferent sensory nerves, organized in the sympathetic and vagal systems (28,29). Following ischemia, a number of substances including adenosine, bradykinin, histamine, potassium, prostaglandins, and substance P are released, which trigger action potentials of chemosensitive fibers implied in nociceptive transmission (28,30). Although still incompletely characterized, algogenesis transduction may be mainly dependent on transient receptor potential vanilloid-1 receptor channel complexes expressed in the plasma membrane of chemosensitive fibers, which are activated by most of the above noxious stimuli (31). Importantly, the molecular inflammatory

FIGURE 1 **The Heart-Brain Axis Model of Angina Physiopathology and Related Therapeutic Targets**



Clinical and experimental evidence reveals an extremely complex picture of angina physiopathology, calling for an interplay of factors linking the anatomical substratum to the perception of cardiac pain. Technological advances in coronary physiology assessment shed new light on the multifaceted, often coexisting, mechanisms underlying impaired myocardial perfusion. When impaired perfusion does not match myocyte metabolic demand, myocardial ischemia ensues. Despite less clearly characterized, the peculiar myocyte metabolic profile may be critical for hypoperfusion to translate into overt ischemia. Ischemia leads to increased production of algogenic molecules, which stimulate the chemosensitive nerve endings of nociceptive fibers (Aδ and C). Intrinsic neuromodulation at tissue, spinal cord, and brain levels are key factors contributing to the subjective experience of angina. A multitude of therapeutic targets encompassing myocyte metabolism, coronary microcirculation, nociception, and neuromodulatory pathways may be effectively addressed by emerging treatment options. CAD = coronary artery disease; CCK = cholecystokinin; CMD = coronary microvascular dysfunction; GABA = gamma-aminobutyric acid; LVEDP = left ventricular end diastolic pressure; STT = spinothalamic tract.

CENTRAL ILLUSTRATION **New Therapeutic Nonpharmacological Technologies in Refractory Angina**



Gallone, G. et al. J Am Coll Cardiol Intv. 2020;13(1):1–19.

Several nonpharmacological treatments addressing angina beyond percutaneous coronary intervention have been developed, targeting heterogeneous and complex pathophysiological targets of the heart-brain pathway underlying angina. Many of these therapeutics may be suitable, feasible, and clinically efficacious. The interventionist, often the first physician to establish the refractory angina diagnosis following coronary angiography, should thus avoid the disqualifying "no-option" designation. More importantly, he should be aware of the numerous emerging options for this group of patients, which should be tailored based on the patient's subjective symptom burden and preferences, underlying physiopathology, and local expertise. STT = spinothalamic tract; TCT = thalamocortical tract.

milieu including prostaglandins, leukotrienes, and substance P may sensitize chemosensitive receptors modifying the threshold for ischemic stimuli to be translated into pain signals (30,32).

PERIPHERAL AND CENTRAL NEUROMODULATORY PATHWAYS: FROM PHYSIOLOGY TO PERCEPTION. The elicited painful stimuli travel through sympathetic (passing by the dorsal root ganglion) or vagal afferents (passing by the nucleus of tractus solitarius) to reach the posterior thalamus (33). Cardiac nociceptive transmission may be controlled at the spinal cord level, where a complex signaling of neuropeptides modulate afferent pain signals among neural and non-neural cells (the "gating") (28).

Positron emission tomography studies have shown that from the posterior thalamus several cortical structures are activated and that this is required for anginal pain perception (34). Consistently, patients with silent myocardial ischemia have blunted activatory patterns, with gating of afferent pain messages possibly occurring at the thalamic level (35). Furthermore, patients with microvascular angina exhibit enhanced activation of cortical areas with respect to patients with angina and obstructive CAD, suggesting that central abnormalities may be concausal with ischemia to the generation of cardiac pain in this population (16,36,37). In general, the activatory status of different brain areas at a given moment may contribute to the range of the ischemia-angina association going from silent ischemia to severe cardiac pain despite little or no peripheral stimulus (33). A body of knowledge demonstrating the impact of depression, anxiety, anticipation, belief, empathy, and attention on pain perception consistently supports this concept (7).

Of note, the autonomic outputs triggered by pain, inducing tachycardia, hypertension, and coronary vasoconstriction may themselves cause ischemia, which may thus be consequential, beyond causal, to angina.

The physiological bases of angina described previously have led to the development of several therapeutics (**Central Illustration**), which are moving into the clinical arena to improve symptoms and quality of life beyond traditional anti-ischemic treatments.

Of note, optimized efficacy of these treatments for any individual patient is likely bound to a tailored diagnostic approach aiming at establishing the specific pathways involved in one's angina pathophysiology. To this aim, a broad range of functional noninvasive and invasive tests are emerging together with specific diagnostic algorithms (23,38), whose use still needs extensive validation and is currently mostly limited to tertiary centers.

NOVEL THERAPEUTIC TECHNOLOGIES IN REFRACTORY ANGINA

TREATMENTS ADDRESSING MYOCARDIAL PERFUSION. Several treatments addressing myocardial perfusion beyond percutaneous coronary intervention, surgical revascularization, or traditional anti-ischemic drugs have been developed (**Table 2**).

Viral transfer-based angiogenesis. The use of biological agents to stimulate myocardial angiogenesis has been the subject of intense research over the last years. Intracoronary or intramyocardial delivery of angiogenetic factors led to the development and trial of genetically modified plasmid or viral vectors. Trialed angiogenetic factors chiefly included vascular endothelial growth factor (VEGF) and fibroblast growth factor.

Pioneering experience with mini-thoracotomy based injection of naked plasmid DNA encoding VEGF-A (phVEGF165) in ischemic myocardium showed promising results (39) and prompted investigation of VEGF-A administration approaches that either were less invasive (with percutaneous NOGA Myostar catheter [Biosense Webster, Diamond Bar, California] mapping guided intramyocardial injections) (40) or had higher gene transfer efficiency (i.e., with adenoviral vectors) (41,42). Placebo-controlled trials resulted in controversial clinical- and ischemia-related outcomes (40–42), stimulating research toward proangiogenic molecules with better pharmacologic profiles. Specifically, VEGF-D$^{\Delta N \Delta C}$, a newly identified member of the VEGF family stimulating both angiogenesis and lymphangiogenesis, displaying better signaling kinetics and diffusibility, and having-unlike VEGF-A-no proinflammatory and proarrhythmogenic properties, demonstrated a safe and feasible clinical profile (43). In the early phase placebo-controlled randomized KAT301 (Kuopio Angiogenesis Trial 301) trial, 30 RA patients were randomized to NOGA mapping-guided AdVEGF-D$^{\Delta N \Delta C}$ or placebo intramyocardial injections. At dynamic radiowater positron emission tomography analysis, 3- and 12-month follow-up myocardial perfusion reserve was significantly improved over placebo, with more pronounced benefits in patients with high Lipoprotein(a) serum levels, hinting at a potential response marker. Consistently, Canadian Cardiovascular Society (CCS) class and quality of life significantly improved in the AdVEGF-D$^{\Delta N \Delta C}$ group (43).

Following early experience with the fibroblast growth factor transfection in the AGENT (Angiogenic GENe Therapy) and AGENT-2 studies (44,45) involving intracoronary Ad5FGF-4 (serotype 5 adenovirus with the FGF-4 gene) administration in RAP patients,

TABLE 2 General Characteristics of Nonpharmacological Treatments in Refractory Angina

Proposed Antianginal Pathophysiological Target	Proposed Mechanism of Action	Treatment Description	Side Effects/ Complications	Placebo-Controlled Evidence	ACC/AHA and ESC Recommendations
Viral transfer-based angiogenesis					
Neovascularization	Angiogenesis stimulation, with reduced apoptosis and fibrosis, and recruitment of resident and circulating stem cells	Intracoronary or intramyocardial delivery of angiogenetic factors through genetically modified plasmid or viral vectors	Transient minor febrile reactions Access site bleeding and pericardial effusion	Controversial	NA (currently only for research purposes)
CD34+/CD133+ cell therapy					
Neovascularization Endothelial protection Cardioprotection	Blood flow recovery and increased capillary density through differentiation in endothelial cells, recruited at sites of active neovascularization Paracrine effects through proangiogenic factors stimulation, with reduced apoptosis and fibrosis and recruitment of resident and circulating stem cells	Mobilization of autologous bone marrow with granulocyte colony stimulating factor and apheresis or direct bone marrow puncture to collect mobilized mononuclear cells and intramyocardial/ intracoronary injection	Catheter-induced ventricular tachycardia during mapping Post-procedural myocardial infarction during cell mobilization and collection Access site bleeding	Positive	NA (currently only for research purposes)
Coronary sinus reducer					
Coronary flow redistribution Neoangiogenesis	Coronary sinus narrowing by Reducer stent with resulting increase of backward pressure in the venules, capillaries and pre-arterioles promoting blood redistribution from less ischemic to more ischemic myocardial territories	Percutaneous Reducer scaffold implantation in the coronary sinus through right internal jugular access	Device migration Coronary sinus perforation Access site bleeding	Positive	NA (CE mark in Europe)
Enhanced external counterpulsation					
Improved coronary diastolic perfusion Reduced afterload Coronary flow redistribution Neoangiogenesis Endothelial protection	Diastolic retrograde blood flow resulting in flow-mediated vasodilation and increased shear-stress triggering release of pro-angiogenic factors Systolic unloading	Sequential distal to proximal compression of calves, thighs and buttocks at around 300 mm Hg in early diastole, followed by deflation just before the systole, by 3 pairs of pneumatic cuffs (usually 1-h sessions, 5 days/week for 7 weeks)	Mild equipment-related side effects including paresthesia, skin abrasion or ecchymosis, bruises, leg or waist pain	Controversial	ACC/AHA: IIB/B ESC: IIA/B
Extracorporeal shockwave myocardial revascularization					
Neoangiogenesis Improved coronary perfusion	Shockwaves mechanotransduction triggering activation of multiple angiogenic and endothelium-protective pathways resulting in vasodilation and neo-capillarization	Low-energy shockwaves to the ischemic myocardium, delivered using a generator system accompanied by a cardiac ultrasound imaging system to target the myocardial ischemic area of interest. (usually 9 sessions of 1,000 shocks each)	No side effects	Controversial	NA (ESC guidelines stating that more data are needed before establishing a potential recommendation)
Transmyocardial laser revascularization					
Direct left ventricle coronary perfusion Angiogenesis Sympathetic myocardial denervation	Laser-created intramyocardial transmural channels Injury-induced stimulation of angiogenic pathways Injury-induced myocardial denervation	Surgical (epicardial) or percutaneous (endocardial) laser ablation to create transmural 1 mm channels in the ischemic myocardium	Postprocedural myocardial infarction, heart failure, cardiac tamponade, death	Negative	ACC/AHA: IIb/B ESC: III/A

Continued on the next page

showing trends toward reduction in inducible myocardial ischemia, 2 phase 2b/3 trials were conducted. Both studies were interrupted due to lack of efficacy at interim analyses. However, pooling of the 2 trials revealed a significant sex-specific improvement in total exercise treadmill test time, time to 1-mm ST-segment depression, time to angina, and CCS class in women (46). In conclusion, small-sized studies hint at a potential benefit of gene transfer-based therapeutic angiogenesis, but, to date, larger-scale clinical trials held negative or inconsistent results, although with no prohibitive feasibility or safety concerns.

Clinical trials are planned or ongoing (AdVEGF-All6A+: NCT01757223; Ad5FGF-4: NCT01550614, [ASPIRE study] and NCT00438867 [AWARE study]) and may help to draw definite conclusions on this therapy.

TABLE 2 Continued

Proposed Antianginal Pathophysiological Target	Proposed Mechanism of Action	Treatment Description	Side Effects/ Complications	Placebo-Controlled Evidence	ACC/AHA and ESC Recommendations
Transcutaneous electrical nerve stimulation					
Pain signal neuromodulation Reduced afterload	Stimulation of large-diameter afferent fibers (Abeta) resulting in inhibition of small diameter fibers in the substantia gelatinosa of the spinal cord (segmental pathway) and activation of periaqueductal grey in the midbrain and rostral ventromedial medulla with descending inhibition (extrasegmental pathway) Systemic vasodilatation though efferent sympathetic activity reduction	Application of low-intensity electrical currents by means of chest electrodes	No side effects	NA	ACC/AHA: NA ESC: IIb/C
Spinal cord stimulation					
Pain signal neuromodulation Reducer O_2 demand Improved coronary perfusion	Inhibition of intrinsic cardiac neurons through stimulation of γ-aminobutyric acid release Efferent sympathetic activity reduction with reduced heart rate and systemic blood pressure, and local improvement of endothelium-mediated vasomotor function	Low-intensity electrical stimulation by electrode leads inserted in the epidural space (C5-T2), connected to a pulse generator, implanted subcutaneously below the left costal arch (usual regimen: three 1-h stimulations/day plus on-demand stimulation during angina attacks)	Hardware-related (lead migration, device failure, lead fracture) and biological complications (infection and pain over the implant site, dural puncture headache, dural infection, and neurological damage)	Positive	ACC/AHA: IIb/B ESC: IIb/B
Subcutaneous electrical nerve stimulation					
Pain signal neuromodulation	Modulation of large-fibers (Abeta) subcutaneous nerve endings in the area where angina is perceived	Low-intensity electrical stimulation by peripheral subcutaneous electrodes implanted in the parasternal area stimulating nerve endings. The electrode is tunneled to a pulse generator generally implanted in the upper abdomen.	No significant side effects/ complications reported in the single existing small pilot study	NA	NA
Sympathectomy					
Improved coronary perfusion Pain signal neuromodulation	Inhibition of the efferent sympathetic synapse in the cervicothoracic (stellate) ganglion with resulting vasotonic, myoelectrical, and myocontractile modulation through cardiopulmonary nerves Modulation of pain signal through feedback loops of afferent fibers at the cervicothoracic level	Stellate ganglion pharmacological blockade: injection of a local anesthetic solution close to the ganglion (C6) Surgical sympathectomy: permanent denervation through an endoscopic thoracic or a video-assisted external approaches Radiofrequency-sympathectomy: percutaneous approach	Vasovagal reactions (hypotensive response) and anesthetic vascular injection Frozen shoulder Access site bleeding Surgical complications	Negative	NA

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; NA = not available.

Cell-based angiogenesis. The controversial efficacy of protein growth factor and gene therapy approaches, lead to test cell-based angiogenetic strategies. Autologous CD34+ bone marrow-derived endothelial progenitor cells demonstrated the highest in vivo angiogenetic properties. Circulating levels of CD34+ cells are inversely associated with the severity of CAD, physical function, adverse clinical outcomes following myocardial infarction, and overall survival (47-49). Consistently, CD34+ administration in preclinical models is associated with improved myocardial performance, fibrosis reduction and enhanced angiogenesis (50).

In vivo, CD34+ cell treatment is achieved through mobilization of bone marrow with granulocyte colony-stimulating factor, apheresis, and intramyocardial injection. Electromechanical NOGA mapping is used to identify ischemic regions of myocardium, which are then injected transendocardially. More recently, intracoronary transfusion of CD34+ cells have been described.

The phase I (51) and II (52) ACT-34 (Injection of Autologous CD34-Positive Cells for Neovascularization and Symptom Relief in Patients With Myocardial Ischemia) trials randomizing 24 and 167 CAD patients with RAP to receive intramyocardial

TABLE 3 Placebo-Controlled Evidence Base for Nonpharmacological Treatments in Refractory Angina

Study/Meta-Analysis	Population	Study Design and FU	Primary Outcome	Secondary Outcome
Gene transfer therapy				
Patient-level data pooled from the AGENT-3 and AGENT-4 trials	CCS II-IV RAP with not indicated/technically unfeasible revascularization T = 355 P = 177	Two RCT comparing intracoronary Ad5FGF-4 (higher and lower dose) injections with intracoronary P injections FU: 2, 4, 8, and 12 weeks and 6, 12, 18, and 24 months	Change from baseline in total ETT time at 12 weeks 12-week: not significantly different from P. Women subgroup: +60 ± 99 s (lower dose) and +69 ± 83 s (higher dose); p < 0.05* 6 months: not significantly different from P	Time to 1-mm ST-segment depression, change in CCS class 12 weeks: not significantly different from P in time to 1-mm ST-segment depression 12 weeks and 6 months: improvement in CCS class in higher-dose group; p < 0.05*
KAT301 trial	Severe RAP with no revascularization options T = 24 P = 6	RCT comparing electromechanically guided intramyocardial AdVEGF-$D^{\Delta N \Delta C}$ injection with intramyocardial P injection FU: 3 and 12 months	Safety and feasibility 12 months: no differences in procedure-related adverse events or in MACE	MPR (PET), CCS class, QoL measures (15 days) 12 months MPR: increase from 1.00 ± 0.36 to 1.44 ± 0.48; p = 0.009* 12 months CCS class: decrease from 2.83 ± 0.38 to 2.11 ± 0.47; p = 0.001* 3 months 15D: increase from 0.787 ± 0.108 to 0.803 ± 0.101 (not clinically meaningful)
Euroinject One trial	CCS III–IV RAP with documented CAD, inducible ischemia at SPECT and no revascularization options T = 72 N = 67	RCT comparing electro-mechanically guided VEGF-A_{165} plasmid injection with intramyocardial P plasmid injection FU: 3 months	Change in myocardial perfusion defects at stress and rest (SPECT) 3-month SPECT: stress perfusion defects did not differ significantly between the groups (38 ± 3% vs. 44 ± 2%; p = 0.18)	CCS class variation, NOGA mapping 3-month CCS: increased significantly in both groups without intergroup difference (2.3 ± 0.2 and 1.9 ± 0.1) 3-month NOGA mapping: improvement in local linear shortening in VEGF-A_{165} group (12.6 ± 0.9 vs. 9.9 ± 0.9%; p = 0.04)*
CD34+/CD133+ cell therapy				
Patient-level data pooled from the Phase I, phase II ACT-34, ACT-34 extension, and phase III RENEW trials	CCS III-IV RAP and inducible ischemia on stress testing T = 187 P = 89	Three RCT comparing intramyocardial auto-CD34+ cells with intramyocardial P injections FU: 3, 6, 12, and 24 months	Difference in change of total exercise time 3 months: +46.6 s; 95% CI: 13.0 to 80.3 s; p = 0.007* 6 months: +49.5 s; 95% CI: 9.3 to 89.7 s; p = 0.016* 12 months: +44.7 s; 95% CI: -2.7 to 92.1 s; p = 0.065	Difference in change of angina frequency 3 months: 0.78; 95% CI: 0.63 to 0.98; p = 0.032* 6 months: 0.66; 95% CI: 0.48 to 0.91; p = 0.012* 12 months: 0.58; 95% CI: 0.38 to 0.88; p = 0.011* 2-years mortality: 2.5% vs. 12.1%: p = 0.0025*
REGENT-VSEL trial	CCS II-IV RAP and ≥1 myocardial segment with inducible ischemia by SPECT T = 16 P = 15	RCT comparing electro-mechanically guided trans-endocardial auto-CD133+ stem cells injection with transendocardial P injection FU: 1,4, 6, and 12 months	Extent of inducible ischemia by 4-month SPECT SDS: 2.60 ± 2.6 vs. 3.63 ± 3.6; p = 0.52 Total perfusion deficit: 3.60 ± 3.69 vs. 5.01 ± 4.3; p = 0.32 Change of SDS: -1.38 ± 5.2 vs. -0.73 ± 1.9; p = 0.65 Change of total perfusion deficit: -1.33 ± 3.3 vs. -2.19 ± 6.6; p = 0.65	ESV change: -4.3 ± 11.3 mm vs. 7.4 ± 11.8 mm; p = 0.02 EDV change: -9.1 ± 14.9 mm vs. 7.4 ± 15.8 mm; p = 0.02 Patients with ≥1 CCS class improvement 1 month: 41.7% vs. 58.3%; p = 0.68 4 months: 50% vs. 33.3%; p = 0.63 6 months: 70% vs. 50.0%; p = 0.42 12 months: 55.6% vs. 81.8%; p = 0.33
Coronary sinus reducer				
COSIRA trial	CCS III-IV RAP and inducible ischemia T = 52 P = 52	RCT comparing implantation of the coronary sinus Reducer with a sham-procedure FU: 6 months	Patients with ≥2 CCS classes improvement at 6 months: 35% vs. 15%; p = 0.02*	SAQ domains change at 6 months -QoL: +17.6 points vs. +7.6 points; p = 0.03* -Angina stability: +18.1 points vs. +8.3 points; p = 0.16 -Angina frequency: +15.3 points vs. +11.0 points; p = 0.44 Total exercise time change +59 s (13%) vs. +4 s (1%); p = 0.07
Enhanced external counterpulsation				
MUST-EECP trial	CCS I-III chronic angina with documented CAD and inducible ischemia at ETT T = 72 N = 67	RCT comparing 35 h of active counterpulsation or inactive counterpulsation (P) over a 4- to 7-week period FU: within 1 week of treatment termination	Change in total exercise time +42.6 ± 11 s vs. +26.6 ± 12 s; p = 0.3 Change in time to 1-mm ST-segment depression +37.6 ± 11 s vs. +24.6 ± 12 s; p = 0.01*	Patients with ≥50% improvement in angina frequency: 45% vs. 32%; p < 0.05* Change in NTG usage: -0.32 ± 0.12 vs. -0.10 ± 0.12; p = 0.1

Continued on the next page

TABLE 3 Continued

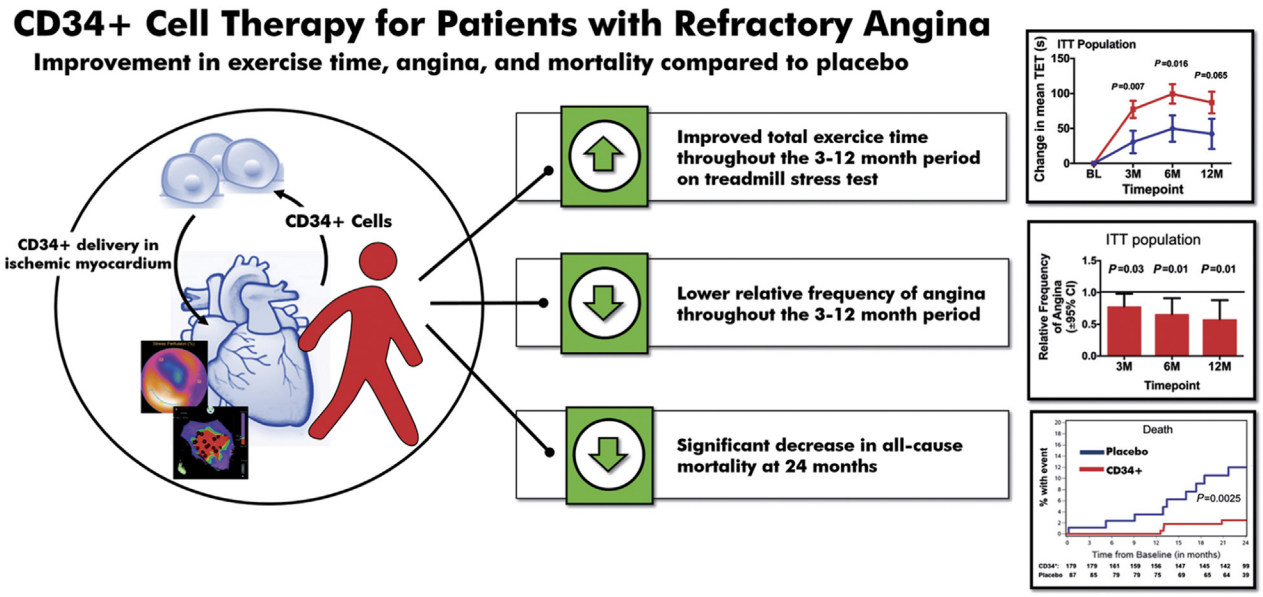
Study/Meta-Analysis	Population	Study Design and FU	Primary Outcome	Secondary Outcome
Extracorporeal shockwave myocardial revascularization				
Schmid et al. (85)	Chronic RAP and inducible ischemia by SPECT T = 11 P = 10	RCT comparing 3 months of cardiac shock waves therapy with acoustic simulation without energy application (P) FU: 3 months	Change in the ischemic threshold: 19.4% (p = 0.036 vs. baseline) vs. 8.4% (p = 0.141 vs. baseline)†	Changes in SF-36: 3 of 8 domains improved (p < 0.05) vs. 0 of 8 domains improved†
Transmyocardial laser revascularization‡				
DIRECT trial	CCS III–IV RAP and inducible ischemia by SPECT T (high-dose) = 98 T (low-dose) = 98 P = 102	RCT comparing low-dose or high-dose myocardial laser channels with a sham procedure FU: 6 and 12 months	Change in total exercise time 28.0 s (high-dose) vs. 33.2 s (low-dose) vs. 28.0 s (P); p = 0.94	Patients with ≥2 CCS classes improvement at 6 months: 41% (high dose) vs. 48% (low dose) vs. 41% (P); p = NS
Transcutaneous electrical nerve stimulation				
–	–	–	–	–
Spinal cord stimulation				
Eddicks et al. (100)	Chronic RAP and inducible ischemia with SCS implant received between 3 and 6 months before enrolment and evidence of clinical response T/P = 12 pts undergoing 4 consecutive phases (3 T, 1 P)	RCT comparing 4 consecutive treatment arms, each for 4 weeks, with various stimulation timing and output parameters, with phase 4 using SCS at 0.1-V output (P) FU: at the end of each 4-week period	Walking distance at 6MWT at the end of each period 394 m vs. 403 m vs. 381 m vs. 337 m (P); p for each group vs. P <0.05*	CCS class at the end of each period 1.6 vs. 1.5 vs. 2.1 vs. 3.1 (P); p for each group vs. P <0.05* Nitrate usage during each period 1.0 (IQR: 0–21) vs. 2.0 (IQR: 0–32) vs. 5.0 (IQR: 0–27 vs) 9.0 (IQR: 2–31); p for each group vs. P <0.05* VAS at the end of each period 56.3 ± 20.4 vs. 57.5 ± 19.6 vs. 53.8 ± 21.4 vs. 45.9 ± 21.7; p for each group vs. P <0.05*
Subcutaneous electrical nerve stimulation				
–	–	–	–	–
Sympathectomy‡				
Denby et al. (106)	RAP patients scheduled for stellate ganglion blockade T = 29 P = 22	RCT comparing temporary sympathectomy at the site of the left stellate ganglion by injection of bupivacaine with saline injection (P) FU: 1 week	Difference in change of angina frequency between the 7-day periods before and after injection: -31% vs. -31%; p = NS	No significant changes in autonomic activity by heart rate variability on the day of injection

Heterogeneous placebo-controlled level of evidence is available for nonpharmacological treatments in refractory angina: for some treatments, the explored endpoints display encouraging and consistent results; for some others, lack of methodological rigor or small sample size preclude confident efficacy evaluations; and for some others, no current placebo-controlled evidence is available. Primary and secondary outcome comparisons refer to T vs. P values. Unless otherwise specified, delta values refer to follow-up minus baseline values. *Significant. †No T vs. P statistical comparison performed. ‡No placebo-controlled trials are available for surgical TMLR and surgical or percutaneous radiofrequency sympathectomy.

6MWT = 6-min walking test; ACT-34 = Injection of Autologous CD34-Positive Cells for Neovascularization and Symptom Relief in Patients With Myocardial Ischemia; AGENT = Angiogenic GENe Therapy; CAD = coronary artery disease; CCS = Canadian cardiovascular society; COSIRA = Coronary Sinus Reducer for Treatment of Refractory Angina; DIRECT = A Blinded, Randomized, Placebo-Controlled Trial of Percutaneous Laser Myocardial Revascularization to Improve Angina Symptoms in Patients With Severe Coronary Disease; EDV = end-diastolic volume; ESV = end-systolic volume; ETT = exercise treadmill test; FU = follow-up; KAT301 = Kuopio Angiogenesis Trial 301; MACE = major adverse cardiovascular events; MPR = myocardial perfusion reserve; MUST-EECP = Multicenter study of enhanced external counterpulsation; P = placebo; PCI = percutaneous coronary intervention; PET = positron emission tomography; QoL = quality of life; RAP = refractory angina pectoris; RCT = randomized controlled trial; REGENT-VSEL = A Randomized, Prospective, Double-blind Study to Evaluate Intracardiac Injections of Bone Marrow, Autologous CD133+Cells in Patients With Resistant Angina and no Effective Revascularization Option; RENEW = Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina; SAQ = Seattle Angina Questionnaire; SCS = spinal cord stimulation; SDS = summed difference score; SF-36 = 36-Item Short Form Survey; SPECT = single-photon emission computed tomography; T = treatment; TMLR = transmyocardial laser revascularization; VAS = visual analog scale; VEGF = vascular endothelial growth factor; WMSI = wall motion score index.

auto-CD34+ or placebo injections provided evidence for feasibility, safety, bioactivity, and clinical improvements. At 2 years, CD34+ treatment was associated with persistent improvement of angina and a trend for mortality reduction (53). The early termination for financial reasons of the following double-blind phase III RENEW (Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina) trial resulted in strong underpower to test the primary endpoint of 12-month total exercise time, which was not met (54). A recent meta-analysis including the previously described 3 randomized trials (304 patients in total) demonstrated durable improvement in treadmill exercise capacity, lower angina frequency throughout a 3- to 12-month period and, intriguingly, reduced 2-year all-cause mortality with auto-CD34+ cells treatment as compared with placebo (55) (**Table 3, Figure 2**). Similar quality outcomes were observed in a double-blinded phase 1 clinical trial testing auto-CD34+ cell therapy by intracoronary transfusion in 38 patients with left

FIGURE 2 CD34+ Cell Therapy



Quality of life and prognostic outcomes in the patient-level meta-analysis of the 3 placebo-controlled trial of CD34+ cell therapy for patients with refractory angina pectoris (55). Reprinted with permission from the European Society of Cardiology. CI = confidence interval; ITT= intention to treat.

ventricular dysfunction and unrevascularizable CAD (56), with an associated increase in left ventricular ejection fraction and evidence of neovascularization, persisting at 5-year follow-up (57).

The application of bone marrow-derived CD133+ cell therapy in the RAP setting has also been assessed, with 2 randomized trials supporting safety and feasibility (58,59).The recent ischemic refractory cardiomyopathy trial (RECARDIO [Endocavitary Injection of Bone Marrow Derived CD133+ Cells in Ischemic Refractory Cardiomyopathy]), testing bone marrow-derived CD133+ cell therapy in 10 RAP patients with ischemic cardiomyopathy, showed significant improvement in angina symptoms in parallel with increased myocardial perfusion and function at single-photon emission computed tomography assessment, providing the bases for further clinical studies (60).

Of note, the observed improvement in myocardial function in this trial suggests a role for therapeutic angiogenesis in the management of ischemic cardiomyopathy with reduced ejection fraction, regardless of angina status.

Despite these promising findings, cell therapy for RAP remains currently limited to research studies. The U.S. Food and Drug Administration recently granted the Regenerative Medicine Advanced Therapy Designation to CD34+ cell therapy for refractory angina, boding well for clinical implementation of this technology in a near future.

CS reducer. Increase of CS backward pressure to improve redistribution of myocardial blood flow into ischemic myocardial territories (61) for the treatment of chronic angina was first conceived by Beck et al. (62). These pioneering works provided the rationale for the development of a percutaneous approach, the CS Reducer device (Neovasc Inc., Richmond B.C., Canada).

The Neovasc Reducer (Neovasc Inc., Richmond, Canada) is a percutaneous balloon-expandable, stainless steel, hourglass-shaped stent designed to create a focal narrowing of the CS and a consequent increase in the coronary venous pressure. The Reducer System, designed to fit the range of anatomies encountered in most patients, comprises the Reducer scaffold premounted on a customized hourglass-shaped balloon catheter. When inflated, the expanded balloon gives the metal mesh its final configuration (63,64) (**Figure 3**).

In patients with advanced CAD, the normal sympathetically mediated constriction of subepicardial vessels favoring blood flow toward the subendocardial layers during exercise, is dysfunctional (65). Moreover, subsequent elevated left ventricular end-diastolic pressures compress subendocardial small vessels, further worsening ischemia (66). The chronic elevation of venous pressure following Reducer

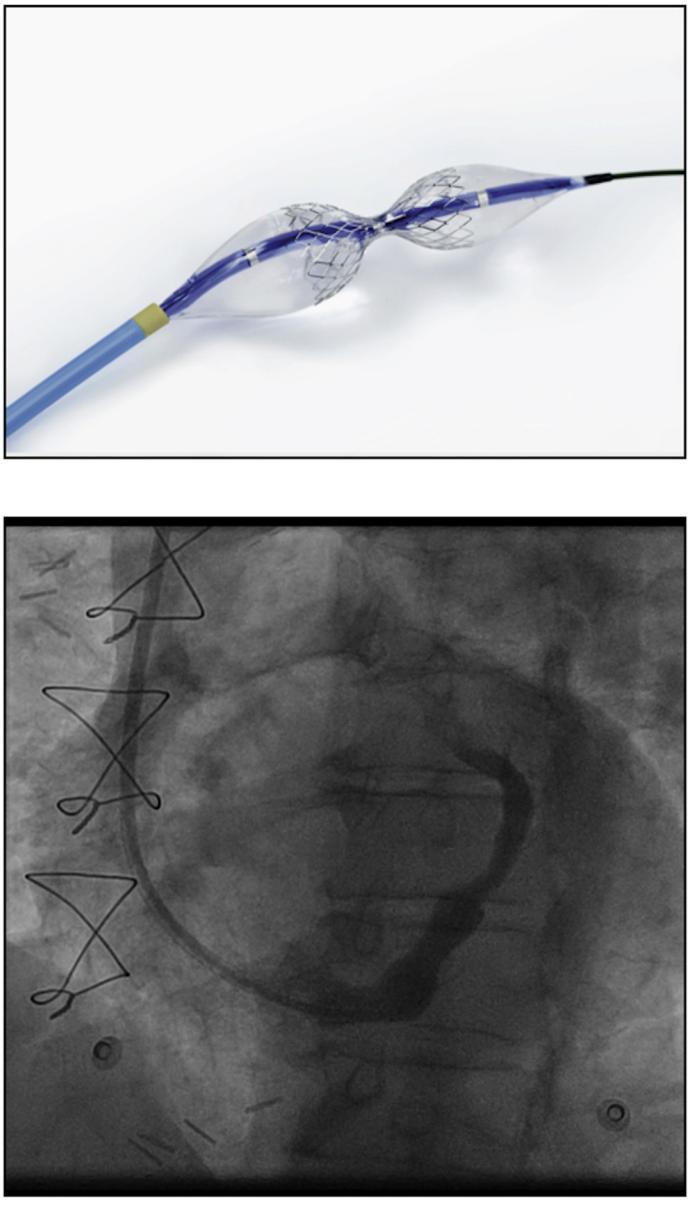
implantation should increase the backward pressure in the venules and capillaries, promoting blood redistribution and re-establishing the normal endocardial/epicardial blood flow ratio (63).

In 2007, the first-in-man study of CS Reducer implantation in 15 patients with RAP reported no periprocedural and 11 months major adverse cardiac events. The average CCS class was reduced at 1-year follow-up (67), with sustained effect at 3 years. Importantly, device patency was documented at 12 years in 10 patients with available follow-up (68). In the double-blind placebo-controlled COSIRA (Coronary Sinus Reducer for Treatment of Refractory Angina) trial (69) randomizing 104 RAP patients in a 1:1 ratio to CS Reducer implantation or a sham procedure, device implantation was associated with improved symptoms and quality of life (**Table 3**). Real-world data across several centers recently confirmed the safety and the efficacy of the procedure, with success rate exceeding 98%, no severe periprocedural complications, and a consistent 70% to 85% rate of symptomatic responders at 1- and 2-year follow-up (70–73), further providing insights on potential cost-effectiveness (74). Beyond symptomatic efficacy, objective evidence of inducible ischemia reduction by dobutamine stress echocardiography and treadmill exercise test were recently reported (63) as well as functional status benefits at the cardiopulmonary exercise test (75). Notably, initial studies with stress cardiac magnetic resonance following Reducer implantation demonstrating myocardial perfusion improvement accompanied by improved left ventricular function suggest this may be a pivotal effect underlying anginal symptoms reduction (76–80). Last, insights on Reducer impact on myocardial perfusion and symptoms in patients with refractory microvascular angina suggest high clinical efficacy in this population (currently lacking established non-pharmacological therapeutic options) (72).

Enhanced external counterpulsation. Enhanced external counterpulsation (EECP) is a noninvasive device aiming to induce arterial diastolic retrograde blood flow to improve coronary perfusion. It is composed of 3 pairs of pneumatic cuffs compressing the calves, thighs and buttocks intermittently inflating at around 300 mm Hg in a distal-to-proximal sequence during early diastole, and subsequently deflating just before the systole with an electrocardiogram guide. The standard treatment protocol involves 1-h sessions, 5 days/week for 7 weeks.

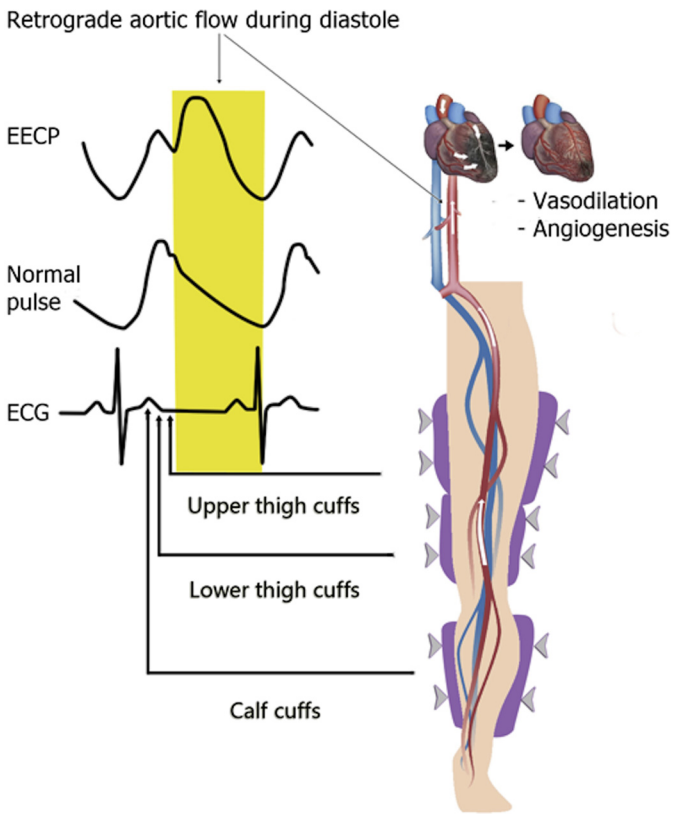
The improved coronary diastolic perfusion results in flow-mediated vasodilation, which may further enhance capillary blood flow redistribution and angiogenesis. After EECP therapy, increased coronary shear stress triggers release of angiogenic factors and increases circulating CD34+ stem cells. The rapid presystolic decompression of the cuffs generates systolic left ventricular unloading, increasing cardiac output and possibly resulting in a superimposed peripheral training effect (80) (**Figure 4**).

FIGURE 3 **CS Reducer Device**



The Reducer (Neovasc Inc., Richmond, Canada) is a stainless-steel balloon expandable laser cut mesh designed to create a focal narrowing in the lumen of the coronary sinus (CS) and generate a pressure gradient. The resulting increase in backward pressure is hypothesized to force redistribution from well perfused segments to ischemic ones, thus alleviating the symptoms of angina **(top)**. Final angiography of the CS in the left anterior oblique 30° projection demonstrating the characteristic central narrowing **(bottom)**.

FIGURE 4 Schematic Presentation of the EECP Device and Putative Mechanisms of Action



Enhanced external counterpulsation (EECP) produces a diastolic retrograde aortic flow that enhances coronary artery mean and peak diastolic pressure. Retrograde flow further improves myocardial perfusion through flow-mediated coronary vasodilation and shear-stress triggered angiogenesis. Reprinted with permission from Qin et al. (82).
ECG = electrocardiography.

EECP is well tolerated, with side effects usually being mild and equipment related (paresthesia, skin abrasion or ecchymosis, bruises, leg or waist pain).

The double-blinded MUST-EECP (Multicenter study of enhanced external counterpulsation) randomized trial compared active counterpulsation with EECP (300-mm Hg inflation pressure) versus placebo (inactive EECP counterpulsation at 75 mm Hg inflation pressure) in patients with angina pectoris and documented coronary ischemia (81). EECP reduced angina and extended time to exercise-induced ischemia over placebo (**Table 3**). Further trials confirmed this positive findings and a recent meta-analysis showed EECP therapy to significantly increase myocardial perfusion in CAD patients (82). Despite consistent body of evidence and guidelines recommendations (**Table 2**) (9,83), EECP is not widely adopted because of the lack of specialized centers and to the time-consuming regimen.

Extracorporeal shockwave myocardial revascularization. Extracorporeal shockwave myocardial revascularization (ESMR) is a treatment designed to improve myocardial perfusion by applying acoustic energy (shockwaves). Low-energy shockwaves may increase blood flow in treated tissues because of local vasodilation and neocapillarization through the interplay of multiple angiogenic pathways triggered by shockwave mechanotransduction (84).

ESMR therapy is delivered using a generator accompanied by a cardiac ultrasound system to target the myocardial ischemic area of interest. Electrocardiogram synchronization averts impulse delivery during myocardial repolarization, which could trigger arrhythmias. A single ESMR session typically consists of 1,000 shocks, delivered in a sequence of 100 shocks per area. The patient usually undergoes 9 treatment sessions. There are no side effects and the relative contraindications include bad acoustic window and left ventricular thrombus.

Reduction in hospitalizations and improvement in symptoms, quality of life, cardiac function, and ischemic thresholds have been reported with ESMR therapy administration in both double-blind, small, placebo-controlled trials and real-world experiences (84-87) (**Table 3**). Although a meta-analysis of 39 studies reported encouraging results (88), the beneficial effects of this therapy and its clinical application needs better characterization in adequately powered well-conducted placebo-controlled trials.

Transmyocardial laser revascularization. Transmyocardial laser revascularization (TMLR) uses laser ablation to create transmural channels in the ischemic regions of myocardium to restore myocardial perfusion. TMLR can be performed either surgically or percutaneously TMLR. In the TMLR surgical procedure, a laser is placed on the epicardial surface via thoracotomy, vaporizing ventricular muscle and creating 20 to 40 transmural 1-mm channels from the epicardium to the endocardium. Several clinical open-label trials of surgical TMLR in patients with RAP reported significant symptomatic improvement. These benefits were not consistent across all trials with a notable average perioperative mortality of 3% to 5%. The evaluation of surgical TMLR by The National Institute for Health and Care Excellence included 10 trials accounting for 1,359 patients randomized to surgical TMLR versus medical therapy (7 trials) or CABG (2 trials, CABG performed in both trial arms): treadmill exercise time at 5-month follow-up and CCS angina class at 6- and 12-month follow-up were improved with TMLR. No significant objective improvement of myocardial perfusion could be documented. In the 7 trials comparing

TMLR with medical therapy, this came at a cost of greater post-operative mortality (odds ratio: 2.85; 95% confidence interval: 1.08 to 7.69), higher 12-month myocardial infarction rate (6% vs. 2%), and increased risk of post-operative heart failure (34% vs. 0%) and of thromboembolic events (10% vs. 3%) (89).

A minimally invasive percutaneous approach using a holmium: YAG laser was also developed. The results of the only double-blinded study of percutaneous TMLR available, the DIRECT (A Blinded, Randomized, Placebo-Controlled Trial of Percutaneous Laser Myocardial Revascularization to Improve Angina Symptoms in Patients With Severe Coronary Disease) trial, reported no benefit for percutaneous TMLR over a sham procedure, rather showing potential harm with this treatment (90) (**Table 3**).

On these bases, surgical TMLR and percutaneous TMLR are not recommended in Europe (Class III recommendation) while a Class IIb, Level of Evidence: B recommendation is still made in the last 2012 American College of Cardiology/American Heart Association guidelines for stable CAD (91).

TREATMENTS ADDRESSING NEURAL PROCESSING. Electric neuromodulation was initially founded on the pain "gate control" theory proposed by Melzack and Wall (92) in 1965 claiming that stimulation of somatosensorial myelinated thick A-fibers could modulate pain signals, carried by unmyelinated slow-conducting C-fibers, via interneurons in the spinal cord. The concept was later extended to sympathetic modulation beyond afferent pain signals suppression, with the potential of exerting anti-ischemic effects through suppression of sympathetic maladaptive compensatory mechanisms (93). These effects were clearly demonstrated by Braunwald et al. (93) in 1967, through stimulation of the stellate ganglion by means of a modified cardiac pacemaker.

Neuromodulation consists of using chemical, mechanical, or electrical stimuli to interfere with transmission of a pain signal anywhere along its pathway from periphery to the brain (**Table 2**).

Transcutaneous electrical nerve stimulation. Transcutaneous electrical nerve stimulation (TENS) exploits low-intensity electrical currents, applied by means of chest electrodes, to stimulate large-diameter afferent fibers. This may result in afferent pain signal suppression, translating in pain quality modulation with patients referring replacement of pain with a vibrating sensation.

Electrical neurostimulation might reduce afterload by systemic vasodilatation possibly though efferent sympathetic activity reduction, resulting in increased tolerance to pacing, improved lactate metabolism and less pronounced stress ST-segment depression (94), although these hemodynamic effects have not been consistently described (95).

Improved exercise capacity, reduced incidence of angina, and decreased nitrates usage with TENS were initially reported (96). Overall evidence is sparse and lacks the methodological rigor needed to make a confident efficacy assessment.

TENS for RAP is rarely a definitive therapy, in many cases preceding spinal cord stimulation (SCS) or subcutaneous electrical nerve stimulation (SENS). In this regard, TENS can be helpful to assess patient responsiveness to neuromodulation before considering a more-definitive option such as SCS.

Spinal cord stimulation. SCS device comprises multipolar electrode leads, extension wires, and an impulse generator. The electrode leads are inserted, under local anesthesia, through the epidural space at the level of T6 to T8 and are then advanced under fluoroscopic guidance up to the C5-T2 segments, where the myocardial afferent sympathetic fibers synapse with second-order sensory neurons in the dorsal horns. The final location is then adjusted to where stimulation evokes paresthesia in the area of perceived anginal pain. Last, electrodes are connected to the pulse generator, which is usually implanted subcutaneously below the left costal arch. The therapy is self-administered, a typical therapeutic regimen consisting of three 1-h low-amplitude stimulations per day plus on demand stimulation during angina attacks (7). SCS implantation is not a risk-free procedure, with reported incidence of post-implant complications of around 30% to 40%. Adverse events may be hardware-related (lead migration, device failure, lead fracture) or biological (infection and pain over the implant site, dural puncture headache, dural infection, and neurological injury). Moreover, discontinuation of antithrombotic therapy is required during implantation, which may pose specific concerns in the CAD population. Careful balancing of the risk-benefit trade-off should be thus established when considering SCS implantation.

The impact on angina reduction with SCS may be related to the inhibition of intrinsic cardiac neurons during myocardial ischemia, via descending inhibitory pathways. Intriguingly, SCS may correct abnormal sympathetic activation (97) possibly translating into improved myocardial perfusion through several mechanisms. In in 18 RAP patients undergoing ^{15}O-water positron emission tomography before and after 3 weeks treatment, SCS was associated with improved myocardial perfusion reserve, increased adenosine-induced myocardial blood flow in the ischemic regions and cold-pressure test-induced

global myocardial blood flow, indicating that SCS may improve endothelium-mediated vasomotor function and alleviate myocardial perfusion abnormalities (98).

Outcome studies on SCS are mainly limited to small, open-label studies. The largest trial (ESBY [Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris] trial) available involved 104 patients randomly assigned to either CABG surgery or SCS (99). Both groups presented symptom relief after treatment, with lower symptomatic and functional benefit in the SCS group, counterbalanced by lower mortality and cerebrovascular morbidity.

Effective patient blinding in placebo-controlled trials remains challenging due to the retrosternal prickling sensation during SCS active treatment. The first placebo-controlled trial of SCS enrolled 12 RAP patients already treated with SCS, who were subsequently randomized into 4 consecutive treatment phases of different SCS duration and intensity, the latter providing a low output with no physiological effects and serving as placebo. The 3 phases of active treatment were associated with improved functional status and symptoms as compared with the low-output phase (100) (**Table 3**). A recent meta-analysis of 14 studies including 518 patients with RAP showed SCS to be associated with longer exercise duration, lower angina frequency and nitrate consumption (101).

Importantly, SCS may be effective also in patients with microvascular angina, where it was associated with improved symptoms and ischemia parameters during stress electrocardiography and echocardiography (102). This is consistent with the neuromodulatory nature of SCS, which may prevent pain signals transmission regardless of the underlying mechanism of ischemia.

Subcutaneous electrical nerve stimulation. SENS is commonly used in noncardiac chronic pain disorders. Its application for RAP is recent, with limited clinical data.

SENS consists in peripheral subcutaneous multipolar electrodes implanted in the parasternal area where patients typically feel angina, stimulating subcutaneous nerve terminations. The electrode is tunneled to a pulse generator generally implanted in the upper abdomen. The use of the subcutaneous route over the anterior chest wall is technically easier and quicker, and may avoid most of the SCS implantation drawbacks, with no need for antithrombotic withdrawal during the procedure.

In the pilot study of 7 patients undergoing SENS implantation, the procedure had 100% feasibility. All patients presented improvement in exercise capacity and quality of life and no major periprocedural adverse events were observed (103).

Sympathectomy. Left stellate ganglion blockade has been long used as an effective treatment for angina in the past. The introduction of revascularization techniques likely contributed to the subsequent relative abandonment of this approach. In recent times, renewed interest ensued from the recognition of left stellate ganglion blockade as an effective target to blunt arrhythmic storms (104).

Sympathetic efferent preganglionic neurons synapse with postganglionic cardiac fibers in the cervicothoracic (stellate) ganglion. Postganglionic neurons project axons via multiple cardiopulmonary nerves to the atrial and ventricular myocardium, where vasotonic, myoelectrical, and myocontractile sympathetic modulation is exerted. The feedback loops at the cervicothoracic level may further interacts in pain responses elaboration. These mechanisms furnish the bases for a direct anti-ischemic action (105), beyond the pain-modulator role of sympathectomy in RAP. Of note, these effects may best suit coronary vasomotion disorders.

Several pharmacological and surgical techniques have been developed to achieve sympathetic blockade in RAP.

Left stellate ganglion blockade is performed with an injection of a local anesthetic solution close to the medial aspect of the ganglion, usually at the level of the C6 vertebra. It may offer temporary (1 to 4 weeks) but effective relief from angina and is commonly adopted in many RAP centers across the United Kingdom (106).

The single existing left stellate ganglion blockade double-blind placebo-controlled trial found no differences between the active (bupivacaine injection) and placebo (saline injection) groups in frequency and intensity of angina episodes (106) (**Table 3**). Despite small sample size and usage of very subjective outcome parameters, this study raises doubts on the impact of left stellate ganglion blockade in RAP, which deserves further investigation.

Surgical sympathectomy, achievable through minimally invasive procedures results in permanent denervation, thus potentially accounting for more effective inhibition. These procedures, tested in small observational studies, have shown to relieve vasospastic angina refractory to pharmacotherapy (107) and advanced obstructive CAD-related RAP (108). Similarly, a radiofrequency-based percutaneous sympathectomy procedure has shown favorable outcomes (109).

Substantial lack of sympathectomy trials in the RAP populations hampers wide adoption of this approach, despite a founded physiopathological rationale.

CONCLUSIONS

Patients with RAP are often addressed as "no-option." The focus on new targets involved in angina physiopathology is demonstrating how, instead, many therapeutics may be suitable, clinically feasible, and efficacious to alleviate the angina burden in this population. Better understanding of RAP natural history, characterization of the individual physiopathological substratum underlying angina, the classification of these patients in relevant clinical categories (6), and the establishment of standardized protocols to improve study design quality in RAP (with a focus on proper sham-controlled trials' design) will be key to the development of a solid body of evidence, allowing safety and efficacy comparisons, tailored medicine, and economic evaluations as it currently is for CAD prognostic treatments.

The "no-option" definition carries a significant burden on the patient's disease perception and on the care-provider attitude toward pursuing new treatment strategies. The interventionist, often the first physician to establish RAP diagnosis following coronary angiography, should avoid such disqualifying designation. More importantly, he should be aware of the numerous emerging pharmacological and non-pharmacological options for this group of patients. The awareness and the embracement of this new paradigm is the basis to improve quality of life in this growing suffering population.

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