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INVITED SPOTLIGHT REVIEW

Neuroscientific therapies for atrial fibrillation

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Abstract

The cardiac autonomic nervous system (ANS) plays an integral role in normal cardiac physiology as well as in disease states that cause cardiac arrhythmias. The cardiac ANS, comprised of a complex neural hierarchy in a nested series of interacting feedback loops, regulates atrial electrophysiology and is itself susceptible to remodelling by atrial rhythm. In light of the challenges of treating atrial fibrillation (AF) with conventional pharmacologic and myoablative techniques, increasingly interest has begun to focus on targeting the cardiac neuraxis for AF. Strong evidence from animal models and clinical patients demonstrates that parasympathetic and sympathetic activity within this neuraxis may trigger AF, and the ANS may either induce atrial remodelling or undergo remodelling itself to serve as a substrate for AF. Multiple nexus points within the cardiac neuraxis are therapeutic targets, and neuroablative and neuromodulatory therapies for AF include ganglionated plexus ablation, epicardial botulinum toxin injection, vagal nerve (tragus) stimulation, renal denervation, stellate ganglion block/resection, baroreceptor activation therapy, and spinal cord stimulation. Pre-clinical and clinical studies on these modalities have had promising results and are reviewed here.

Keywords Atrial fibrillation • Autonomic nervous system • Neurocardiology • Neuromodulation • Vagus nerve

This article is part of the Spotlight Issue on Atrial Fibrillation.

1. Introduction

The cardiac autonomic nervous system (ANS) is integral to normal cardiac physiology to maintain electrical activity and mechanical contraction, and its dysfunction is involved in the pathogenesis of cardiovascular diseases including arrhythmias, such as atrial fibrillation (AF).[1] Given the variable success of pharmacologic and catheter-based treatments for AF and the supporting evidence of the role of the cardiac ANS in AF,[2–4] attention has turned to interventions, both neuroablative and neuromodulatory, targeting the ANS. These therapeutic strategies include ganglionated plexus (GP) ablation, epicardial botulinum toxin injection, vagal nerve (tragus) stimulation, renal denervation, stellate ganglion block, baroreceptor activation therapy, and spinal cord stimulation. Although some of these modalities have been assessed in heart failure and have had mixed results, several are at various stages of development and translation to the clinical setting for AF. In this review, we explore the supporting evidence for the cardiac ANS in AF and autonomic interventions that have been evaluated for AF.

2. Cardiac neuroanatomy—defining targets for neuromodulation

The cardiac ANS has been studied across mammals and appears quite conserved in humans.[5] The cardiac neural hierarchy is composed of the central nervous system (brainstem and spinal cord); extrinsic intrathoracic ganglia (e.g. stellate ganglia); and the intrinsic cardiac nervous system (ICNS) (*Figure 1*).[5] Beat-to-beat information is sensed by cardiac afferents expressing chemo- and mechanoreceptors and transduced to different levels of the cardiac ANS via the vagal nerve to the nodose ganglia and sympathetic fibres to the dorsal root ganglia. These afferent signals are processed across different levels within the neuraxis in a series of interacting feedback loops to modulate efferent outflow in the form of parasympathetic output via the vagus nerve and sympathetic output via the intrathoracic extracardiac ganglia. To maintain volume homeostasis, cardiopulmonary receptors in the atria, ventricles, and pulmonary vessels provide inputs to modulate sympathovagal balance. Systemic

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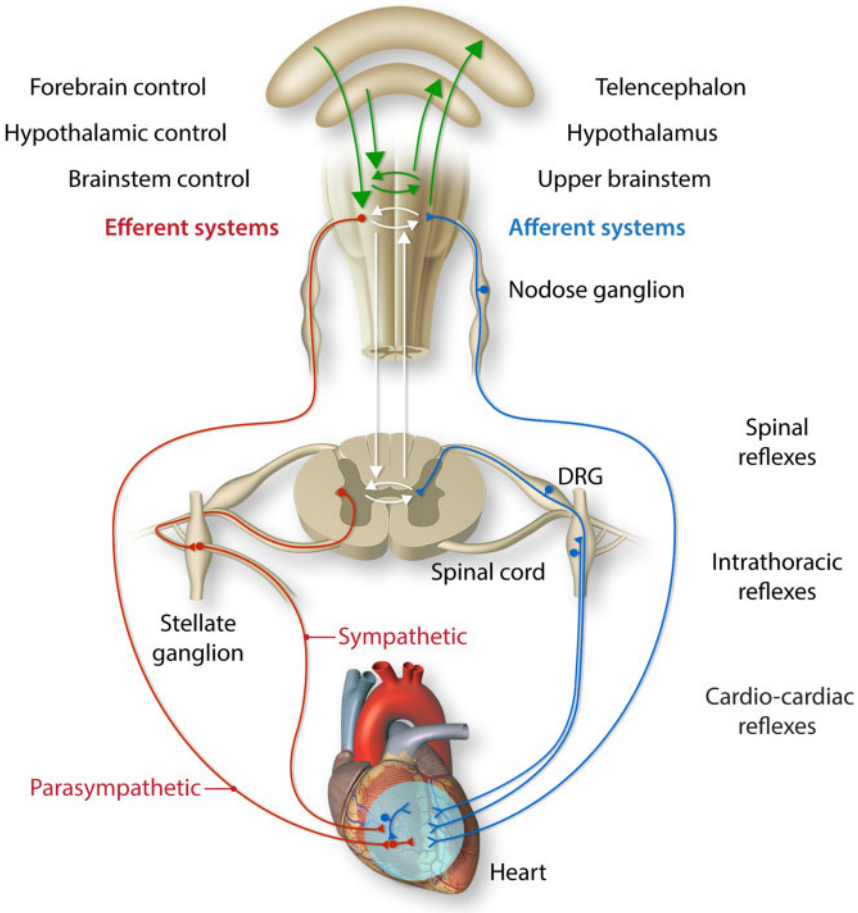

Figure 1 Cardiac ANS. The cardiac ANS is composed of afferent and efferent (sympathetic and parasympathetic) components that interact at multiple levels within the hierarchy that spans the heart, intrathoracic extracardiac ganglia, and central nervous system (brain and spinal cord). DRG indicates dorsal root ganglion. Adapted from Shivkumar *et al.*, 2016.

blood pressure is sensed by baroreceptors in the carotid arteries and large vessels, and activation of the baroreceptor reflex triggers changes to sympathovagal balance of the heart and vasculature. Oxygen sensing via chemoreceptors in the circulation (carotid body and aortic arch) additionally mediates autonomic circuitry controlling heart rate.

At the level of the heart, the ICNS consists of GPs embedded in epicardial fat pads and in cardiac muscle, primarily at the posterior aspect of the atria (*Figure 2*).[6,7] Within these GPs are autonomic ganglia that contain afferent, efferent (parasympathetic and sympathetic, as well as peptidergic, neurons), and interconnecting, local circuit neurons. While the local circuit neurons compose the majority of intrinsic cardiac neurons, a significant proportion are post-ganglionic parasympathetic neurons.[8] The GPs serve as integration centers for afferent information of sensed stimuli and efferent outflow to regulate cardiac electrical and contractile function and vasomotor tone via cardio-cardiac reflexes. They are mainly found circumferentially around the pulmonary veins (PVs) as they enter the posterior left atrium. The five major GPs are variably named in the literature and include the right atrial GP (RAGP), inferior vena cava-inferior atrium GP (IVC-IAGP), left inferior GP, left superior GP, and ligament of Marshall tract. PV isolation (PVI) may inadvertently cause damage to some of these GPs, particularly the left superior GP, left inferior GP, RAGP, and Marshall tract GP, that harbour neuronal cell bodies and/or their axons[9] resulting in changes to cardiac autonomic control.[10–12] Several studies have demonstrated an acute increase in average heart rate following PVI to suggest partial vagal denervation that generally persists at up to 1-year follow-up and is associated with decreased risk of AF recurrence.[11,13–23] PVI-induced release of S100B from ablation may also modulate cardiac ganglia and result in reduction of AF recurrence.[24] The functional effects of GPs based on anatomic distribution has been evaluated in patients, and the GPs may be subdivided into two groups: those that cause atrioventricular (AV) dissociation and those that cause atrial ectopy.[25–27] Identification of these functional types and enrichment of ectopy-triggering GPs at the left atrial roof and around PVs further supports the notion that the benefits of PVI may be due to non-specific and unintentional destruction of GPs.

3. The role of cardiac ANS in AF

While the aetiology of AF, the most common clinical arrhythmia, is often considered multifactorial, aberrations in autonomic tone based on heart rate variability analysis have been implicated in paroxysmal and post-operative AF (POAF).[28–30] Coumel described a case series in which autonomic tone was correlated with AF.[31] The Euro Heart Survey found that

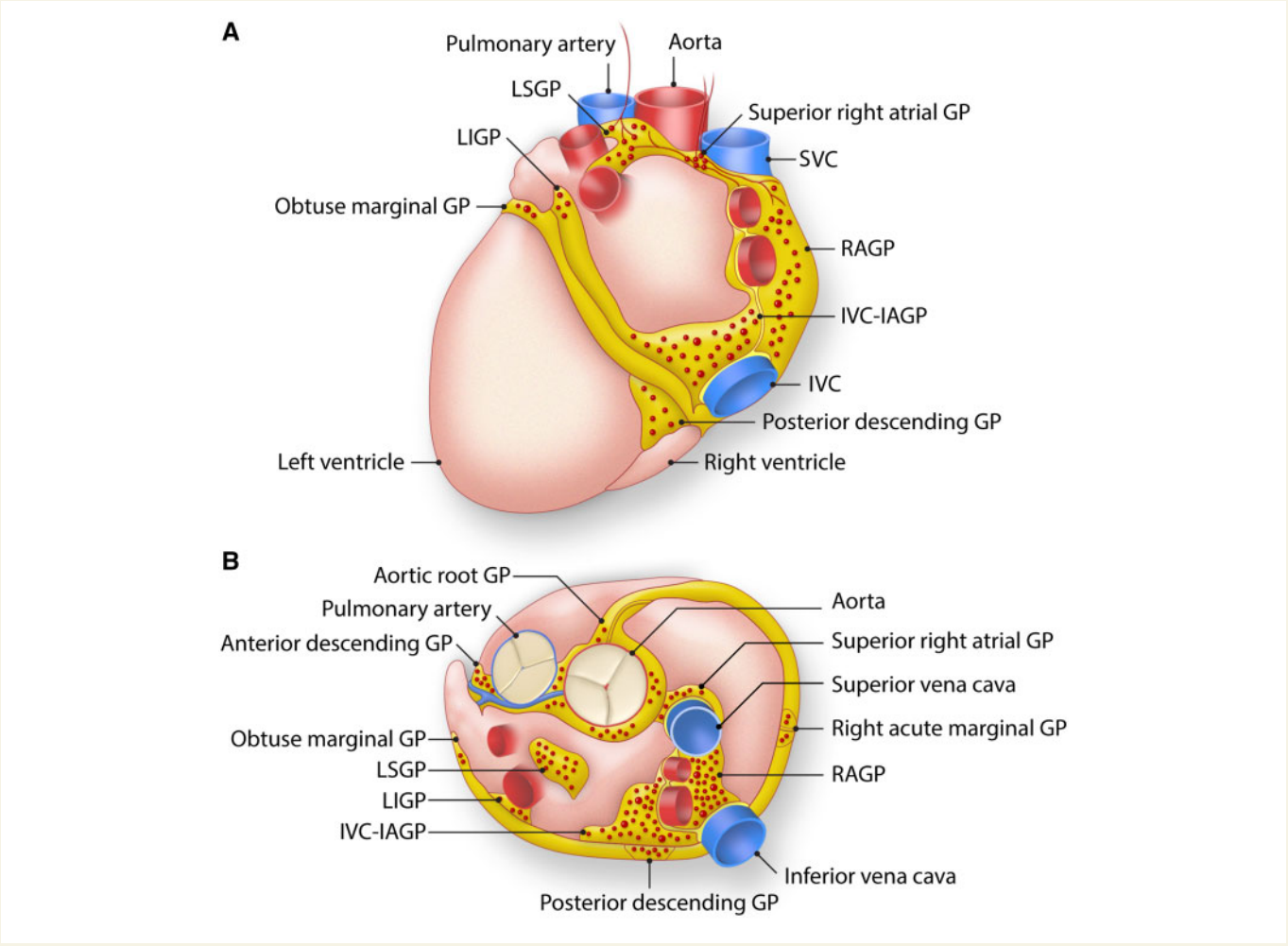

Figure 2 ICNS. The ICNS is composed of ganglionated plexi that cluster at the hilum of the heart, close to where the PVs enter the left atrium. Anatomy of the ganglionated plexuses (GPs) that comprise the intrinsic cardiac nervous system. These GPs are typically found on the posterior (A) and superior (B) epicardial surfaces of the heart. IVC indicates inferior vena cava; IVC-IAGP, inferior vena cava-inferior atrial ganglionated plexus; LIGP, left inferior ganglionated plexus; LSGP, left superior ganglionated plexus; RAGP, right atrial ganglionated plexus; SVC, superior vena cava. Adapted from Rajendran *et al.*, 2017.

of 1517 patients with paroxysmal AF, 33% had autonomic triggers.[32] Sympathetic and parasympathetic coactivation through the cold face test unmasked altered sinus nodal control and, in some patients, induced atrial ectopy.[12] Vagally mediated AF is more common in men compared to women (30–50-year-old age group compared to older age groups), and typically occurs in the absence of structural heart disease. Paroxysms of AF occur predominantly at night, post-prandially and during relaxation, especially following physical or emotional stress. In contrast, adrenergically induced AF is most recognized in rarer endocrinopathies, such as hyperthyroidism and pheochromocytoma. More often, the role of the sympathetic nervous system is implied by clinical history, such as episodes of AF occurring during times of stress or intensive exercise. While identifying the autonomic triggers of AF has the potential for tailored treatment and lifestyle modification, limited evidence exists for this approach.[33] Previous versions of the European Society of Cardiology Guidelines on management of AF recommend disopyramide for vagal AF and β blockers, sotalol and dronedarone for adrenergically mediated AF, but only the recommendation for disopyramide (Class IIb, Level of evidence B) remains in the most recent guidelines.[34,35] The AHA/ACC Guidelines on the management of AF do not recommend specific anti-arrhythmic therapies based on autonomic triggers.[36] Furthermore, catheter ablation targeting GPs mediating a vagal reflex only successfully mitigated AF in 2 of 7 patients in one series.[37] This highlights that while the contributions of the parasympathetic and sympathetic limbs of the cardiac ANS are generally somewhat oversimplified as opposing forces, they interact in a complex and dynamic manner across multiple levels of the cardiac neuraxis in AF.[38,39] To clarify the rationale for current clinical studies on autonomic modulation in AF, we first review the pre-clinical models and human data that have provided supporting evidence for these lines of investigation (*Figure 3*).

3.1 Neural control of the atria and its role in electrical remodelling

The ANS is involved in the electrical remodelling that is characteristic of the initiation and maintenance of AF, as suggested following electrical or pharmacological stimulation of the cardiac ANS in pre-clinical models. In animal models, parasympathetic stimulation increases susceptibility to AF. Vagal nerve stimulation (VNS) in canines, at levels that cause significant bradycardia, increases the likelihood that a premature stimulus will initiate AF as well as the duration of AF episodes.[4] Pharmacologic stimulation via injection of cholinergic agents into epicardial fat pads in a canine

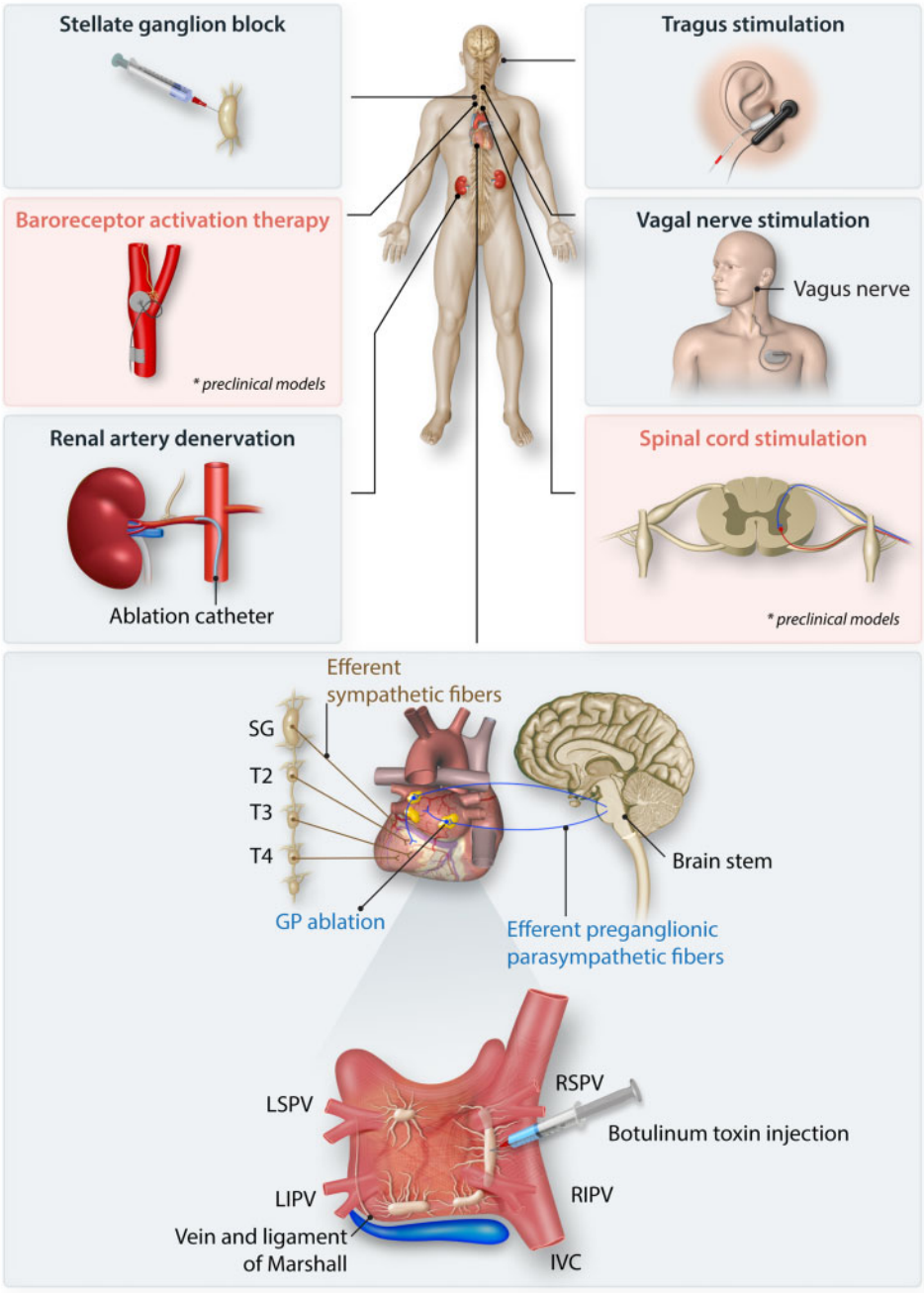

Figure 3 Neuroscientific interventions for AF. Multiple approaches to neuroscientific therapies for AF have been developed at multiple levels of the cardiac neuraxis and include ganglionated plexus (GP) ablation; botulinum toxin injection in the GPs; vagal nerve and tragus stimulation; renal artery denervation; stellate ganglionic blockade; spinal cord stimulation; and baroreceptor activation therapy. Baroreceptor activation therapy and spinal cord stimulation have only been evaluated in preclinical models. IVC indicates inferior vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein. Adapted from Zhu *et al.*, 2019.

model causes heart rate slowing, spontaneous premature depolarization, and AF.[40,41] Furthermore, in canine, application of atropine mitigated the pro-fibrillatory effect of high frequency stimulation (HFS), implicating the parasympathetic nervous system as predominating autonomic influences on AF. Acetylcholine administration and VNS have been shown to shorten the atrial effective refractory period (AERP) and action potential duration (APD) while increasing AERP dispersion, providing a substrate for AF.[42,43] Of note, while moderate-high levels of VNS promote AF,[44] low-level VNS (LLVNS) through stimulation of vagal preganglionics in the vicinity of the superior vena cava could mitigate the effects on atrial electrical (AERP dispersion and AF inducibility) and autonomic (RAGP) remodelling.[45] An important and attractive property for autonomic modulation for arrhythmia is that short-duration interventions have long-lasting effects, a corollary to long-term potentiation/depression in cellular neurophysiology. Specifically, in a canine study of neurally induced AF, short 3 min bursts of pre-emptive VNS prior to mediastinal

nerve stimulation reduced AF inducibility, and its effects persisted for an average of 26 min indicating memory.[46]

The sympathetic nervous system also plays a role in AF. Predominantly adrenergic nerves that course through the ligament of Marshall contribute to atrial tachycardia and AF in canine and human AF and heterogeneous atrial sympathetic denervation in a canine model was demonstrated to sustain AF.[47–50] In contrast, an autopsy study of 39 human subjects suggested a higher density of adrenergic fibres in the atria of humans with history of persistent AF.[51] Functionally, sympathetic stimulation in canines decreases AERP and the re-entrant wavelength.[42] However, in normal hearts, VNS is more effective in promoting AF, attributed to a more pronounced effect on AERP heterogeneity.[52–54] Relative contributions of neural inputs may depend on remodelling of the cardiac substrate. For example, a Cardiac Arrhythmias and Risk Stratification after Myocardial Infarction substudy of patients post-myocardial infarction demonstrated changes in heart rate variability, a measure of autonomic tone, were associated with increased risk of new-onset AF.[55] In a myocardial infarction heart failure model in rats, AF was more easily induced by sympathetic stimulation than VNS.[56]

At the level of the heart, the ICNS is another important integrative neural network relevant to cardiac autonomic control and AF pathophysiology. In large animal models, HFS during the atrial refractory period activates cardiac ganglia and/or nerves and induces atrial ectopy and fibrillation.[57] In further evaluation of the role of the ICNS in acute atrial electrical remodelling, Lu *et al.*[58] demonstrated that rapid atrial pacing following GP ablation prolonged AERP and AF was less inducible, as compared to a control group that did not undergo GP ablation. Pharmacologic stimulation of dendrites and cell bodies of intrinsic cardiac neurons within GPs using nicotine demonstrated spatially divergent changes in atrial repolarization.[59] Recordings in conscious dogs identified a rise in intrinsic cardiac neural activity prior to episodes of atrial tachyarrhythmia.[60] The contribution of the ICNS was further demonstrated with autonomic blockade using atropine and propranolol suggesting that disruption of the ICNS reduces triggered activity and limits AERP dispersion as a substrate for AF.[57]

With the identification of PV triggers of AF, it was determined that the parasympathetic and sympathetic nervous system influence the electrophysiological properties of PV muscle.[57,61] For example, HFS in the PVs shortened AERPs in the PV muscle sleeves, but not the left atrial appendage. *In vitro* experiments further demonstrated that autonomic nerve stimulation of both sympathetic and parasympathetic components decreases PV sleeve APD and initiated rapid firing from early afterdepolarizations.[62] In a canine model of focal AF mimicking the clinical arrhythmia, atropine abolished AF in response to HFS. In humans, autonomic modulation via phenylephrine injection has been shown to suppress PV triggers of AF.[63] In addition to PV triggers, atrial appendage aetiologies of AF have been modulated by autonomic influences. In a canine model, acetylcholine applied to the right atrial appendage was shown to induce AF.[41] In short, pre-clinical models of AF indicate that autonomic modulation of APD, atrial refractoriness, and conduction velocity provide the triggers and substrate for AF. Notably, electrical remodelling and autonomic remodelling form a vicious cycle, one perpetuating the other to maintain AF.[64]

3.2 Electrically induced autonomic remodelling

While the ANS has downstream effects on cardiac electrophysiology, cardiac electrical activity can also induce changes in the cardiac ANS. Rapid atrial pacing has been shown to heterogeneously increase sympathetic innervation in the atria in rabbit and canine models.[65–67] In addition to increases in sympathetic innervation, a heterogeneous increase in parasympathetic innervation was noted throughout the left atrium following right atrial pacing in a canine model.[68] At the molecular level, atrial tachycardia reduces protein expression of muscarinic receptors and their downstream potassium currents in canine atrial tissue.[69] As well as causing AERP dispersion and AF, 6 h of rapid atrial pacing in canine increased activity in the adjacent RAGP. Therefore, changes in atrial electrophysiology may induce remodelling of the cardiac ANS.

4. Key concepts of cardiac neuromodulation

Three main concepts in neuromodulation for cardiac disease bear specific mention (*Figure 1*).[70] First, neural control of cardiac function integrates multi-level reflexes across the neuraxis. Centrally, neural networks involve the spinal cord, brainstem and higher, cortical centres including the insular cortex.[71] Preganglionic neurons housed in the brainstem (parasympathetic) and intermediolateral cell column (sympathetic) mediate outflow that is modulated by local circuits in the brainstem and higher, cortical centres. Peripherally, neural networks involved in cardiac control involve intrinsic cardiac and extracardiac intrathoracic ganglia to coordinate reflex control of the heart.[72] Cardiac sensory afferents transduce information to intrathoracic ganglia and to the CNS via sensory ganglia (dorsal root, nodose, and petrosal). The central and peripheral processing of this information results in an integrated autonomic response to precisely control cardiac function. Second, the interdependent cardiac electrical and autonomic remodelling induced by cardiac pathology facilitates progression of cardiac disease in a vicious cycle. Heightened sympathoexcitation further contributes to progression of disease as evidenced by increased risk of sudden cardiac death following infarction or reduced freedom from AF recurrence in severely hypertensive patients undergoing PVI for AF.[73,74] This autonomic remodelling is a result of neural plasticity, in the form of changes in strength of interconnections, loss of neuronal subpopulations, and memory.[75] Finally, neuromodulatory interventions act on axons of passage, neurons, and neural networks to impact the heart, and the effects are a product of stimulation parameters, nexus point within the neuraxis, and cardioneural pathologic substrate involved.[76] Furthermore, because of autonomic remodelling and the interdependence of central and peripheral networks and remodelling, interventions may result in shifts to a new operating point in the cardiac ANS. Given the heterogeneity in aetiologies underlying AF, such as increased vagal or sympathetic tone or left atrial hypertension (systemic hypertension and heart failure), patient selection should also be factored in when considering an autonomic intervention. As a result, 'one-size-fits-all' approach is unlikely to be successful in neuromodulatory therapy and a therapy may require titration and further adjustments in time, even within a given patient.

5. Neuroscientific interventions for AF

5.1 GP ablation

Following the discovery that GP stimulation result in triggered activity in PVs and fractionated action potentials thought to maintain AF, targeted

ablation of atrial GPs has been pursued.[41,77–80] The GPs may be localized during an electrophysiology study via endocardial HFS and subsequently targeted for ablation.[78,79] HFS is performed by delivering 20–50 Hz stimulation with a pulse width of 10 m at 5–24 V to elicit a vagal response, defined as induction of AV block (>2 s) and hypotension or >50% R–R interval prolongation during AF.[78] During catheter ablation and/or HFS, the presence of fractionated atrial electrograms in conjunction with a vagal response indicates the location of GPs and parasympathetic innervation.[78,80] If HFS does not elicit a response or the patient is unable to tolerate (conscious patients may not withstand >15 V stimulation), an anatomic approach may be used.[81] Once localized, the GPs may be ablated using radiofrequency energy with the endpoint of abolition of a vagal response upon repeat HFS.[77] Because of the interconnectedness of the GPs and the predominant influence of the IVC-IAGP over the AV node, it may be best to ablate the IVC-IAGP last. This is to preserve a measurable outcome of vagal response to HFS until the final GP (IVC-IAGP) is ablated. One recommended order is: Marshall tract GP, left superior GP, RAGP, left inferior GP, and, finally, the IVC-IAGP. Wide area circumferential ablation of PVs, and isolation of the left atrial posterior wall or other substrate, may inadvertently ablate GPs; autonomic responses are sometimes observed even when GPs are not specifically targeted.

How GP ablation may be incorporated into the AF therapeutic approach has been studied in several clinical studies. Patients undergoing PVI that lose the expected vagal response to HFS of GPs have a reduced rate of AF recurrence.[82] Initial investigations of GP ablation were performed without PVI and had variable success with freedom from AF recurrence ranging from 26% to 77% in the first year.[25,37,79,81,83,84] Our understanding of the localization of GPs in human hearts is mainly based on autopsy studies[6,7,51,85] and, when compared against a functional (HFS) approach, anatomic-guided ablation had superior outcomes.[79,84,86] Advances in nuclear cardiology allow *in vivo* imaging of smaller structures, such as the GPs with improved spatial resolution.[87] A pilot study of SPECT/CT imaging using radionuclide ^{123}I-metaiodobenzylguanindine showed that the technique may be used to identify sympathetic innervation based on correlation with response to HFS.[88] In prospective studies comparing GP ablation alone directly against PVI, anatomic-guided GP ablation was shown to have significantly reduced freedom from AF recurrence 26–34% compared to 63–66% in PVI groups at up to 3-year follow-up.[81,89] Adjunctive anatomic-guided GP ablation with PVI has shown improved outcomes with success rates up to 80%.[90,91] A randomized controlled trial evaluating PVI alone against combination GP ablation and PVI demonstrated improved freedom from AF recurrence in the combination group at 1-year follow-up (85.3% vs. 60.6%, log-rank P=0.19).[90] This was further supported by another randomized controlled trial in which freedom from arrhythmia recurrence was 48% in the GP ablation alone, 56% in the PVI alone group and 74% PVI with GP ablation group at 2-year follow-up (log-rank P=0.004).[91] It should be noted that the typical AF ablation procedure, which includes PVI, interrupts the axons of at least three major GP (Marshall tract GP, left superior GP, and RAGP), which may contribute to the success of the procedure.[64]

For those undergoing surgical AF ablation, the epicardial fat pads containing GPs may be directly visualized and HFS applied to localize GPs for ablation.[92–94] The addition of GP ablation to the Cox maze procedure yielded significantly improved success rates over the first year postoperatively in single-centre studies.[95,96] Furthermore, a minimally invasive approach to perform thoracoscopic GP ablation as an adjunct to surgical PVI was developed.[97–100] While early studies appeared promising, the randomized controlled trial of 240 patients with paroxysmal or persistent AF in the AF Ablation and Autonomic Modulation via Thoracoscopic Surgery (AFACT) study showed no reduction in AF recurrence at 2-year follow-up and was associated with significant adverse events of major bleeding, sinus node dysfunction, and need for pacemaker implantation.[101,102] It should be noted, however, that a significant proportion of patients had persistent AF (59%) with enlarged LA (68%, mean 42.2±5.6 mm). The mixed results of GP ablation may be due, in part, to the variability in how studies are conducted with respect to patient selection and AF burden. Several ongoing clinical trials are further evaluating the role of GP ablation in AF (*Table 1*).

The need for pacemaker implantation in the AFACT study highlights the need for improved understanding cardiac morphological and functional neuroanatomy. The difficulty in localizing GPs, such as in instances in which HFS does not elicit a vagal response; incomplete endocardial approaches restricted to a unilateral atrium; or epicardial vs. endocardial targeting of epicardial fat pads in which neurons span the thickness may explain variable success of the technique and limit generalizability of findings. As ablating GPs may prove beneficial for atrial electrophysiology and AF, off-target effects on the SA and AV nodes and ventricles must be considered. For instance, the RAGP controls the sinoatrial node, and ablation of this GP may explain the increased sinus node dysfunction and need for pacemaker implantation in the GP ablation group.[103] Moreover, in a canine study on GP ablation in myocardial infarction, GP ablation increased the risk of ventricular arrhythmias.[104] Another study in dogs showed that ablation of another GP located between the superior vena cava and aorta (aorta-SVC GP) shortened AERP and increased AF/atrial tachycardia burden.[105] Disruption of cardiac cholinergic neurons in the murine heart was also shown to shorten ventricular refractoriness and increase the risk of ventricular arrhythmia, raising the possibility that bystander autonomic denervation during PVI for human AF may explain the increased premature ventricular contraction burden often noted post-procedure.[106] Interestingly, similar to PVI alone, adjunctive surgical GP ablation performed as part of the AFACT study was associated with an initial increase in mean heart rates at 6- and 9-month follow-up, but this effect dissipated by 12 and 24 months.[101,102] A recent study of endocardial GP ablation for paroxysmal AF similarly did not show significant differences in mean heart rate between the GP ablation and control groups at 3, 6, 9, and 12-month follow-up, suggesting that GP ablation does not provide improved rate control in AF.[107] Cases have also been reported of coronary vasospasm following GP ablation that precipitate life-threatening ventricular arrhythmias.[108] Lastly, the permanence of GP ablation is as yet unclear, as reinnervation has been suggested following GP ablation in a canine model.[109]

5.2 Epicardial botulinum toxin injection

As opposed to the destructive approach of GP ablation, neuromodulatory approaches seek to harness neural control of myocardial tissue. Botulinum toxin is a neurotoxin that has been shown to reduce vagal-induced AERP shortening in animal models and prevent autonomic remodelling.[110–112] The transient nature of the toxin is attractive as a therapeutic for the short-term increased risk of POAF following cardiac surgery. Thus far, botulinum toxin injection has been evaluated in two small clinical trials. In one study, 60 patients with paroxysmal AF undergoing coronary artery bypass graft surgery received either botulinum toxin or placebo injection in four major atrial GPs (RAGP, IVCI-IAGP, left superior GP, and left inferior GP). The results demonstrated reduced incidence of POAF in the month and up to 3 years following surgery.[113–115] In a second study, 130 patients undergoing CABG or valve surgery

Table 1 Ongoing clinical trials evaluating autonomic therapies for AF

Intervention	Target	Trial design	Disease	*n*	ClinicalTrials.gov identifier	Description
GP ablation	GPs	RCT	AF	60	NCT03535818	Adjunctive Ganglionated Plexus Ablation in Redo-PVI (ADD-GP); testing efficacy of GP ablation in patients with paroxysmal or persistent AF undergoing redo PVI for recurrent paroxysms of arrhythmia
GP ablation	GPs	RCT	POAF	62	NCT02035163	AF Prevention in Post-Coronary Artery Bypass Graft Surgery with Cryoablation for Ganglionic Plexi; evaluating cryoablation of GPs during cardiac surgery to prevent POAF
GP ablation	GPs	RCT	AF	180	NCT02487654	Ectopy-Triggering GP Ablation to Prevent AF (GANGLIA-AF); evaluating GP ablation alone vs. PVI alone
GP ablation	GPs	Single-arm feasibility	AF	16	NCT04642976	Prospective Evaluation of CT-Guided Ablation of Cardiac GPs; evaluating feasibility and efficacy of CT-guided GP localization to guide AF ablation
Botulinum toxin	GPs	RCT	POAF	330	NCT03779841	Botulinum Toxin Type A (AGN-151607) for the Prevention of POAF in Patients Undergoing Open-chest Cardiac Surgery (NOVA); evaluating epicardial fat pad injection of botulinum toxin A to prevent post-operative AF
Botulinum toxin	GPs	RCT	POAF	220	NCT04075981	Prevention AF by BOTulinum Toxin Injections (BOTAF) ; evaluating botulinum toxin injection into epicardial fat pads during cardiac surgery to reduce POAF
LLVNS	Tragus	RCT	POAF	266	NCT04514757	Transcutaneous (Tragus) Vagal Nerve Stimulation for POAF (tVNS_POAF); evaluating low-level tragus stimulation for POAF
LLVNS	Tragus	RCT	POAF	80	NCT03392649	Tragus Stimulation to Prevent AF After Cardiac Surgery (TraP-AF); evaluating low-level tragus vagal nerve stimulation for POAF
LLVNS	Tragus	RCT	HRV, MAST	90	NCT04682704	The Effect of Different Low-Level Tragus Stimulation Parameters On Autonomic Nervous System Function (LLT-SPANS); evaluating different stimulation parameters on the autonomic nervous system
RDN	Renal nerves	RCT	AF	40	NCT03246568	Renal Nerve Denervation After Pulmonary Vein Isolation for Persistent AF; evaluating the effect of RDN in addition to PVI for persistent AF
RDN	Renal nerves	RCT	AF	130	NCT04182620	Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy During AF Ablation (ULTRA-HFIB); evaluating RDN as adjunctive treatment for patients undergoing PVI for AF
RDN	Renal nerves	RCT	AF	100	NCT01686542	CPVI Plus Renal Sympathetic Modification Versus CPVI Alone for AF Ablation; evaluating RDN as adjunctive treatment for patients undergoing PVI for AF
RDN	Renal nerves	RCT	AF	138	NCT02115100	Treatment of AF in Patients by PVI in Combination With Renal Denervation or PVI Only (ASAF); evaluating RDN as adjunctive treatment for patients undergoing PVI for AF and resistant hypertension

Continued

Table 1 *Continued*

Intervention	Target	Trial design	Disease	*n*	ClinicalTrials.gov identifier	Description
RDN	Renal nerves	RCT	AF	50	NCT01635998	Adjunctive Renal Denervation in the Treatment of AF (H-FIB); evaluating adjunctive RDN in patients with hypertension undergoing PVI for AF
RDN	Renal nerves	RCT	AF	100	NCT01990911	Renal Sympathetic Denervation Prevents AF in Patients With Hypertensive Heart Disease: a Pilot Study (RDPAF); evaluating whether RDN in patients with hypertensive heart disease reduces new-onset AF
RDN	Renal nerves	RCT	AF	61	NCT01907828	A feasibility study to evaluating the Effect of Concomitant Renal Denervation and Cardiac Ablation on AF Recurrence (RDN+AF); evaluating adjunctive RDN in patients with paroxysmal or persistent AF and uncontrolled hypertension.

AF indicates atrial fibrillation; CPVI, circumferential pulmonary vein isolation; GP, ganglionated plexus; LLVNS, low-level vagal nerve stimulation; POAF, post-operative atrial fibrillation; RCT, randomized controlled trial; PVI, pulmonary vein isolation; RDN, renal denervation.

were randomized to botulinum toxin injection in the four epicardial fat pads as well as the aorta-SVC fat pad.[116] In contrast, this study demonstrated no reduction in POAF, although POAF episodes were shorter with botulinum toxin injections. Ongoing clinical trials are further evaluating the efficacy of botulinum toxin injections for POAF post-cardiac surgery (*Table 1*). Lastly, a recently published randomized, sham-controlled trial of 200 patients demonstrated that injection of $CaCl_2$ into the four major atrial GPs reduces risk of POAF by 63%.[117] As opposed to the purported transient effects of botulinum toxin, the $CaCl_2$ is thought to cause intracellular calcium overload to induce neurotoxicity. This neurotoxicity increase AERP and limiting sympathetic effects to reduce AF vulnerability in the post-operative period.[118,119]

5.3 Low-level vagal nerve (tragus) stimulation

Although initially developed for treatment in epilepsy and refractory depression, VNS devices have been used in cardiac disease, namely heart failure.[120–122] VNS is thought to increase parasympathetic tone and tamp down adrenergic outflow to the heart by way of reflex pathways. Benefits of VNS are also thought to include limiting cardiomyocyte apoptosis and remodelling as well as inflammation.[123–126] VNS reduces inflammatory cytokine release via the 'cholinergic anti-inflammatory pathway' to mitigate myocardial injury.[127] Activation of parasympathetic efferent neurons induces release of acetylcholine at the heart, which binds nicotinic acetylcholine receptors on tissue macrophages to inhibit the release of pro-inflammatory cytokines, such as tumour necrosis factor-alpha, C-reactive protein, and interleukin-6.[64,128] In a rat model of ischaemia-induced arrhythmias, VNS was also shown to reduce connexin 43 loss to promote electrical stability.[129]

Stimulation parameters are critical in determining the effects of VNS on end-organ function, a concept previously described as the neural fulcrum.[76] In the case of arrhythmia, while VNS induces shortening and dispersion of AERP to promote AF, LLVNS, at currents significantly below threshold for bradycardia, has been shown to be anti-arrhythmic. LLVNS damages the stellate ganglia; increases IVC-IAGP and RAGP neural activity; reduces AF inducibility; and ventricular rate in dogs with pacing-induced persistent AF.[45,130–132] In a randomized sham-controlled trial, Stavrakis *et al.*[128] demonstrated in 54 patients undergoing cardiac surgery that temporary LLVNS of preganglionic vagal nerve fibres at the lateral aspect of the superior vena cava in the post-operative period suppresses POAF.

Transcutaneous stimulation of the auricular branch of the VNS is an emerging non-invasive approach to VNS that acts via afferent neurotransmission to elicit changes in neural activity in the brainstem and reduces sympathetic activity and centrally mediated parasympathetic outflow.[133–135] Yu *et al.*[136] showed that low-level tragus stimulation (LLTS) increases neural activity in the RAGP and decreased risk of AF in dogs. In a pilot study of 40 patients with paroxysmal AF randomized to LLTS at 50% threshold for sinus rate slowing vs. sham stimulation, LLTS reduced pacing-induced AF duration and increased AERP.[64] More recently, in the Transcutaneous Electrical Vagus Nerve Stimulation to Suppress AF study, 53 patients with paroxysmal AF were randomized to LLTS or sham in the ambulatory setting for 1 h daily for 6 months.[137] LLTS was shown to reduce AF burden by 85% compared to control. As opposed to cervical VNS, tragus stimulation preferentially engages afferent vagal fibres and decreases central sympathetic outflow.[138,139] Furthermore, this approach obviates the potential for incidental concomitant stimulation of sympathetic fibres of the cervical vagus.[140] This is a promising, non-invasive approach to autonomic modulation that is currently being evaluated in several randomized controlled trials (*Table 1*).

5.4 Stellate ganglion block

The stellate ganglion may be targeted via a percutaneous approach to inhibit cardioneural signalling. Recordings of left stellate ganglion and vagal nerve activity demonstrated sympathovagal imbalance associated with tachybrady syndrome in dogs with pacing-induced heart failure, and cryoablation of the lower half of the stellate and T2-4 thoracic ganglia abolished atrial tachycardia episodes.[141,142] In humans, a pilot study of 36 patients undergoing PVI demonstrated that unilateral (either left or right) stellate ganglion block prolongs atrial ERP and decreased AF inducibility

and duration.[143] Another pilot study of 25 patients undergoing CABG and/or aortic valve surgery showed efficacy of left-sided stellate ganglion block.[144] As opposed to temporary blockade, cardiac sympathetic denervation via a stellate ganglionectomy has been shown to impact atrial rhythm.[145] However, at this time, there are currently no ongoing clinical trials evaluating stellate ganglionic blockade further.

5.5 Renal denervation

Renal nerves are composed of afferent nerves that transduce mechanosensitive and chemosensitive stimuli centrally and efferent nerves. Renal denervation was initially studied for refractory hypertension and is performed by placing an ablation catheter just proximal to the origin of the second-order renal artery branch and ablating 4–6 regions in a spiral fashion along the length of each of the two arteries.[146] Catheter ablation is performed by applying radiofrequency energy of 8–12 W based on anatomy or by HFS eliciting a hypertensive response, defined as 15 mmHg increase in blood pressure. The randomized controlled Symplicity HTN trials have had mixed results stemming from inadequate technique for assessing successful ablation of renal nerves.[147,148] In instances in which HFS does elicit a hypertensive response, abolition of this response serves as a readily identifiable endpoint. However, in the anatomic-guided approach, there is no clear intraprocedural measure of success. Endovascular ultrasound renal denervation has emerged as an alternative technology in which short bursts of sonication are delivered in the main branches of the renal arteries in a longitudinal manner. A porcine model demonstrated that the catheter, supported centrally in the vessel lumen by a water-filled cooling balloon, allows for circumferential ablation at depths of 1–6 mm while preserving the arterial wall.[149,150] The randomized sham-controlled trial RADIANCE-HTN SOLO trial showed that this approach of thermal ablation was effective in reducing blood pressure at 2-month follow-up.[151]

Studies of renal denervation in AF have thus far been encouraging. Renal denervation in conjunction with PVI has been used in AF and improved outcomes, as 61–69% of patients with AF undergoing renal denervation with PVI were free from AF recurrence at 12-month follow-up compared to 29–36% of patients undergoing PVI alone.[152,153] A pooled analysis of five randomized controlled trials identified a more pronounced benefit in patients with a combination of AF and hypertension undergoing renal denervation and PVI, of whom 61.9% were AF-free at 12 months compared to 37.3% in the PVI only group (OR = 0.40, 95% CI 0.20–0.78).[154] Patients with AF and moderate hypertension did not have significantly improved outcomes with combination renal denervation and PVI therapy compared to PVI alone (65% vs. 52%, P=0.19). Patients with paroxysmal AF and chronic kidney disease undergoing PVI alone had increased incidence of AF recurrence at 22-month follow-up compared to those patients undergoing both renal denervation PVI with HR of 1.86 (95% CI 1.14–3.03).[155] A pilot study of 20 patients with 1-year follow-up demonstrated that renal denervation decreased AF burden from a median (IQR) of 1.39 (0–11) to 0.67 (0–31.6) min/day and improved quality of life.[156] Ablating renal nerves may reduce systemic and cardiac catecholamine levels and reduce atrial fibrosis through attenuation of the renin–angiotensin–aldosterone system. Beneficial effects on atrial electrophysiological properties have been measured including increases in global conduction velocity and reduction in complex fractionated activity.[157] In addition to electrical remodelling, renal denervation impacts structural remodelling, as it has been shown to reduce atrial nerve sprouting and AF in goats and reduces atrial fibrosis and the number and duration of AF episodes in a pacing-induced AF model in dogs.[158–161] Conversely, renal nerve stimulation has been shown to be proarrhythmic by inducing AERP shortening, increasing AERP dispersion and AF inducibility.[162] In the largest randomized controlled trial to date, the Effect of Renal Denervation and Catheter Ablation vs. Catheter Ablation Alone on AF Recurrence study randomized 302 patients with uncontrolled hypertension and paroxysmal AF to PVI alone or PVI plus renal denervation. At 12 months, 72.1% of patients who underwent adjunctive renal denervation had freedom from recurrence of AF and atrial flutter or tachycardia compared to 56.5% in the PVI alone group (P=0.006).[163] Many clinical trials are evaluating adjunctive renal denervation to PVI (*Table 1*).

5.6 Pre-clinical studies of spinal cord stimulation

In a canine model of AF, spinal cord stimulation prolonged the AERP and reduces AF burden and inducibility.[164] These effects are thought to be mediated through reduced activity in the ICNS.[165] Autonomic remodelling of the RAGP and left stellate ganglion induced by rapid atrial pacing-induced AF was shown to be mitigated by spinal cord stimulation in a canine model.[166] The invasive nature of this approach likely limits its translational potential to human patients.

5.7 Pre-clinical studies of baroreceptor stimulation

Baroreceptor activation therapy has been studied in cardiovascular diseases, such as hypertension and heart failure.[122] In pigs, stimulation of carotid baroreceptors at levels typically used for hypertension increased vagal tone resulting in shortening of AERP and increased AF inducibility.[167] Conversely, lowering the stimulation level below the threshold to lower blood pressure reduced RAGP neural activity, increased AERP, and, hence, reduced AF inducibility in a canine model.[168] As such, similar to LLVNS, low-level baroreceptor activation therapy exerts anti-arrhythmic effects. However, as with spinal cord stimulation, the invasiveness of this approach limits its applicability in clinical AF.

6. Conclusions

Interest in intervention of the cardiac neuraxis for cardiac arrhythmias has increased in recent years. Indeed, cardiac sympathetic denervation is now accepted as guideline-based treatment for inherited arrhythmia syndromes of long QT and catecholaminergic polymorphic VT and acquired refractory ventricular arrhythmias.[169] For the treatment of AF, neuroscientific interventions have spanned from destructive to modulatory and additional understanding of cardiac neuroanatomy and potential off-target effects will help tailor therapies. In addition, as a patient's sympathovagal balance may be dynamic during the natural history of disease progression, neuromodulatory (akin to pharmacologic) therapy may need to be titrated. Although data are mixed for GP ablations and botulinum toxin injection, randomized controlled studies have been encouraging for therapies, such as LLTS and renal denervation but additional studies with larger sample sizes are necessary.

Conflict of interest: University of California, Los Angeles has patents developed by J.L.A. and K.S. relating to cardiac neural diagnostics and therapeutics. J.L.A. and K.S. are co-founders of NeuCures, Inc. E.B. has served as a consultant for Biosense Webster. P.H., S.S., C.M., and J.D.T. have no disclosures to declare.

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