ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 502–510
doi:10.1002/ejhf.3147

REVIEW ARTICLE

Neuromodulation interventions in the management of heart failure

Amr Abdin[1]*, Lucas Lauder[1], Marat Fudim[2,3], William T. Abraham[4], Stefan D. Anker[5], Michael Böhm[1], and Felix Mahfoud[1]

[1]Internal Medicine Clinic III, Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Homburg, Germany; [2]Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; [3]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [4]Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; and [5]Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany

Received 30 August 2023; revised 30 December 2023; accepted 2 January 2024; online publish-ahead-of-print 21 January 2024

Despite remarkable improvements in the management of heart failure (HF), HF remains one of the most rapidly growing cardiovascular condition resulting in a substantial burden on healthcare systems worldwide. In clinical practice, however, a relevant proportion of patients are treated with suboptimal combinations and doses lower than those recommended in the current guidelines. Against this background, it remains important to identify new targets and investigate additional therapeutic options to alleviate symptoms and potentially improve prognosis in HF. Therefore, non-pharmacological interventions targeting autonomic imbalance in HF have been evaluated. This paper aims to review the physiology, available clinical data, and potential therapeutic role of device-based neuromodulation in HF.

Keywords Heart failure • Neuromodulation • Devices

Introduction

Despite remarkable improvements in the management of heart failure (HF), HF remains one of the most rapidly growing cardiovascular (CV) conditions resulting in a substantial burden on healthcare systems worldwide.[1,2] In addition, HF is associated with high mortality, which is 6–7% per year in patients with stable HF and approximately 25% per year in patients with acute HF.[2] Guideline-directed medical therapy (GDMT) remains the cornerstone to improve outcomes in patients with HF and reduced ejection fraction (HFrEF).[3] In clinical practice, however, a relevant proportion of patients are treated with suboptimal combinations and doses lower than those recommended in the current guidelines, which is often due to concerns about adverse effects, fear of intolerability, and non-adherence to medication.[4–6] In HF with preserved ejection fraction (HFpEF), treatment options are limited and the management ranges from treatment of comorbidities to pharmacological therapy with sodium–glucose cotransporter 2 inhibitors (SGLT2i).[5,6] Against this background, it remains important to identify new targets and investigate additional therapeutic options to alleviate symptoms and potentially improve prognosis in HF.

In HF, neuroendocrine pathways are activated and become maladaptive over time.[7,8] Among these, excessive activation of the sympathetic nervous system and the renin–angiotensin–aldosterone (RAAS) system, are leading to sodium and water retention, vasoconstriction, myocardial inflammation, as well as interstitial and myocyte remodelling.[7,8] Volume overload with resultant congestion increases myocardial wall stress, resulting in direct damage to cardiomyocytes but also involves neurohormonal activation, causing extracellular matrix accumulation, and myocyte apoptosis and necrosis.[9] Currently, beta-blockers and RAAS inhibitors are the only available pharmacological HF therapies that target this pathway either at the receptor level or at closely linked signalling pathways.[3] Therefore, non-pharmacological interventions targeting the autonomic imbalance in HF have been investigated and act at the level of receptors such as beta-blockers and may potentially reduce heart rate or target-associated signalling pathways by altering RAAS levels.[10,11] This paper aims to review the physiology, available clinical data, and potential therapeutic role of device-based neuromodulation in HF (*Figures 1* and *2*).

*Corresponding author. Internal Medicine Clinic III, Cardiology, Angiology and Intensive Care Medicine, Saarland University Hospital, Kirrberger Street 100, 66421 Homburg, Germany. Tel: +49 6841 1615029, Fax: +49 6841 1615032, Email: amr.abdin@uks.eu

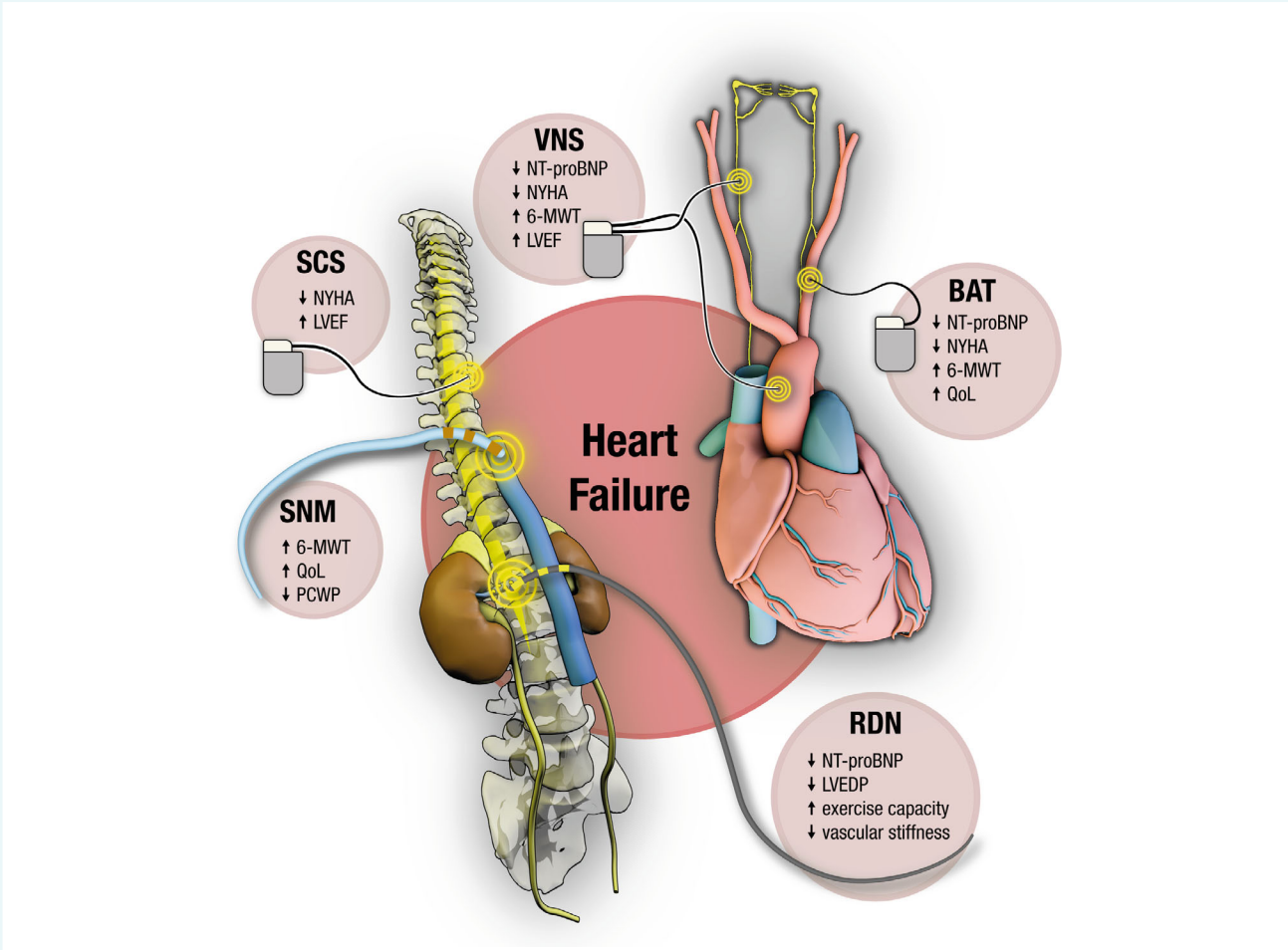

Figure 1 The potential clinical benefits of device-based neuromodulation in heart failure according to the available evidence. 6-MWT, 6-min walk test; BAT, baroreflex activation therapy; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; RDN, renal denervation; SCS, spinal cord stimulation; VNS, vagus nerve stimulation; QoL, quality of life; SNM, splanchnic nerve modulation.

Renal denervation

Renal denervation (RDN) has proven its safety and efficacy and emerged as an adjunct device-based therapy in uncontrolled hypertension.[12–14] RDN modulates the renal sensory afferent and sympathetic efferent nerve fibre activity, resulting in a reduction in plasma renin activity and aldosterone concentrations, and lowering of central sympathetic activity.[15,16] This makes RDN a potential treatment option for some sympathetically mediated CV diseases such as hypertension and possibly HF.

Renal denervation in heart failure with reduced ejection fraction

A decrease in renal sympathetic activity could increase renal function and restore renal blood flow by decreasing renin release, sodium, and water retention.[17,18] This might be coupled with attenuation of RAAS activation as a key beneficial effect of RDN in HF. Preclinical data showed that the modulation of renal sympathetic nerve activity by RDN can decrease neprilysin activity, leading to increased levels of cardioprotective natriuretic peptide.[17,18] This may reduce end-systolic volume and restore left ventricular (LV) function.[18] In hypertensive patients, RDN was associated with reduced plasma renin activity and aldosterone levels when compared with sham controls, both representing key targets in the management of HF patients.[16]

The Renal Artery Denervation in Chronic Heart Failure (REACH)-Pilot study was the first-in-human study investigating the utility of RDN in HF.[19] This uncontrolled study included only seven patients with a mean LV ejection fraction (LVEF) of 43%. RDN was associated with improvements in both symptoms and exercise capacity measured by a 6-min walk distance at 6 months post-RDN with no adverse events. This study was followed by the Symplicity-HF (RDN in patients with chronic HF and impaired renal function) study,[20] in which 39 patients with symptomatic

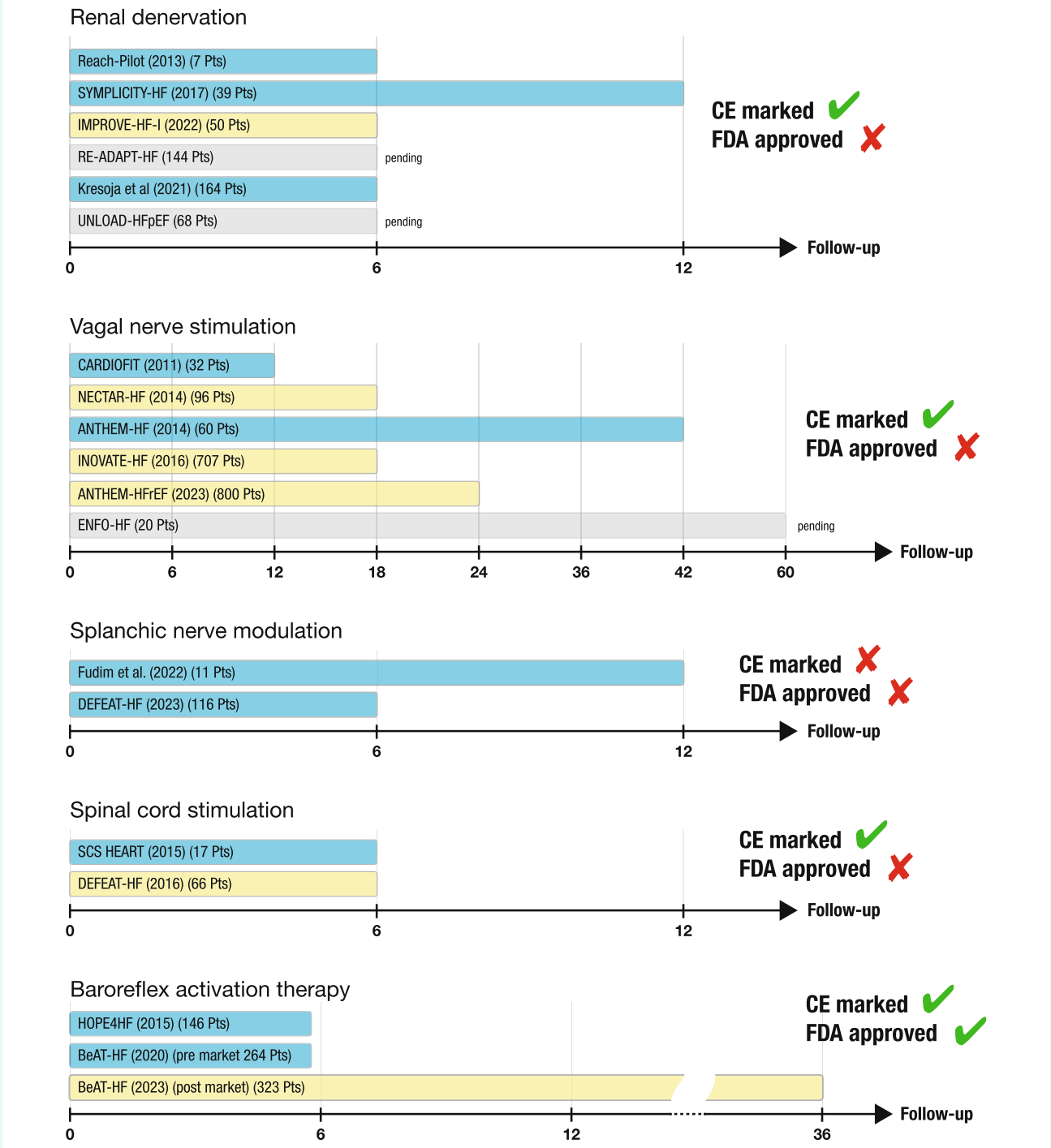

Figure 2 Device-based neuromodulation trials in heart failure and the period of follow-up of these studies. Also, this figure depicts which trial did (in purple) or did not (in yellow) meet its primary endpoint. FDA, Food and Drug Administration.

HFrEF underwent RDN. At 12 months of follow-up, there were significant reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels but no improvements in LVEF or 6-min walk distance. Recently, RDN was evaluated in 50 patients with symptomatic HF with LVEF ≤35%.[21] In this study, patients were randomized to either RDN and optimal GDMT or GDMT alone. After 6 months, no significant change in cardiac sympathetic nerve activity measured by iodine-123-meta-iodobenzylguanidine was found (*Table 1*). The latter study, however, used a bipolar radio-frequency device (Vessix RDN System), which failed to prove its efficacy in patients with hypertension[22] and thus challenges the interpretation of these results.

Table 1 Baseline characteristics of the included studies

	Study design	Age (years)	No. patients	FU (months)	Intervention	Device or catheter used	LVEF	Primary endpoint	Secondary endpoints
Renal denervation									
REACH-Pilot, 2013[19]	Prospective, single-arm	59 ± 7	7	6	RDN	Symplicity Ardian/Medtronic	43 ± 15%	Safety	6MWT, NYHA class
Symplicity-HF, 2017[20]	Prospective, single-arm	65 ± 11	39	12	RDN	Symplicity Flex, Medtronic	28 ± 9%	Safety	6MWT, NT-proBNP, change in LVEF
IMPROVE-HF-I, 2022[21]	RCT	60 ± 9	50	6	RDN vs. GDMT	Vessix System, Boston Scientific	33 ± 8%	Cardiac sympathetic nerve activity (^{123}I-MIBG)	CV death, HFH, AKI
Kresoja *et al.*, 2021[25]	Retrospective	66 ± 5	164	6	RDN in HFpEF vs. RDN in no HF	Symplicity Flex + Spyral, Medtronic and Paradise, ReCor Medical	60 ± 6%	NT-proBNP and symptoms	Stroke volume index, vascular and LV stiffness
Vagal nerve stimulation									
CardioFit, 2011[34]	Prospective, single-arm	56 ± 11	32	12	cVNS	CardioFit, BioControl Medical	23 ± 8%	Safety	NYHA class, 6MWT
NECTAR-HF, 2017[35]	RCT	59.8 ± 12.2	91	18	2:1 fashion to active or inactive cVNS	Precision, Boston Scientific	33.2 ± 4	LVEDV	NYHA class, QoL, NT-proBNP
ANTHEM-HF, 2020[36]	Prospective	51.5 ± 12.2	60	6	cVNS	Cyberonic IPG: Model 103	32.4 ± 7	LVESV, LVESD, LVEF	NYHA class, 6MWT, NT-proBNP, QoL
INOVATE-HF, 2016[37]	RCT	61.7 ± 10.5	707	16	3:2 to cVNS vs. GDMT	Cardiofit, BioControl Medical	23.9 ± 6	All-cause mortality or HFH	NYHA class, 6MWT, NT-proBNP, QoL
ANTHEM-HFrEF, 2019[38]	RCT	NA	500	12	cVNS vs. GDMT	VITARIA System, LivaNova	33.2 ± 7	CV death or HFH	NYHA class, 6MWT, NT-proBNP, QoL
Spinal cord stimulation									
SCS HEART, 2015[49]	Prospective, single-arm	62.9 ± 10	17	6	SCS	Eon Mini, St Jude	24.9 ± 6	Safety	NYHA class, NT-proBNP, QoL
DEFEAT-HF, 2016[50]	RCT	61 ± 10	81	6	3:2 to SCS vs. GDMT	Prime Neurostimulat, Medtronic (Model 37 702)	27 ± 6	LVESVi	
Baroreflex activation therapy									
HOPE4HF, 2015[56]	RCT	65 ± 11	146	6	BAT vs. GDMT	Barostim Neo System, CVRx	25 ± 7	QoL, 6MWT, NT-proBNP	
BeAT-HF (pre-market), 2020[57]	RCT	62 ± 11	408	6	BAT vs. GDMT	Barostim Neo System, CVRx	27 ± 7	QoL, 6MWT, NT-proBNP	
BeAT-HF (post-market), 2023[58]	RCT	NA	323	43	BAT vs. GDMT	Barostim Neo System, CVRx	27 ± 7	CV death and HF morbidity	
Splanchnic nerve modulation									
Fudim *et al.*, 2022[64]	Prospective, single-arm	70 ± 8	11	12	SNM	Axon Ablation System	57 ± 6	QoL, 6MWT	
REBALANCE-HF 2023 (unpublished data)	RCT, sham-controlled	NA	116	6	SNM vs. Sham procedure	Satera™ Ablation System	≥50%	Safety, PCWP change	QoL, NT-proBNP, 6MWT

6MWT, 6-min walk test; AKI, acute kidney injury; BAT, baroreflex activation therapy; CV, cardiovascular; cVNS, cervical vagus nerve stimulation; FU, follow-up; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; NA, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; QoL, quality of life; RCT, randomized controlled trial; RDN, renal denervation; SCS, spinal cord stimulation; SNM, splanchnic nerve modulation.

There is a sound pathophysiological basis for RDN in patients with HF but robust evidence in support of the hypothesis is lacking. The Prospective, Multicenter, Randomized, Blinded, Sham-controlled, Feasibility Study of Renal Denervation in Patients With Chronic Heart Failure (RE-ADAPT-HF, NCT04947670) trial is currently recruiting up to 144 symptomatic HF patients with an LVEF <45% despite GDMT to undergo ultrasound RDN or sham procedure. The primary outcome is the change in 6-min walk distance at 6-month follow-up between groups. This study will provide important insight into the potential role of RDN in HF with (mildly) reduced LVEF.

Renal denervation in heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction frequently associates with CV and non-CV comorbidities such as hypertension, which is one of the most prevalent conditions in HFpEF.[23] The central pathophysiology in HFpEF is ventricular hypertrophy and fibrosis, which causes relaxation deficits, stiffness, and finally diastolic dysfunction.[24] An increased peripheral vascular and aortic stiffness[24] elevates ventricular afterload, ventricular end-diastolic pressure, and finally pulmonary capillary wedge pressure (PCWP).[25] High sympathetic activity is involved in structural and dynamic changes contributing to vascular and aortic remodelling.[25,26] Early data have shown that RDN could also improve arterial stiffness and central haemodynamics.[27]

A post-hoc analysis investigated the haemodynamic and physiological changes in patients undergoing radiofrequency or ultrasound-based RDN for hypertension with and without HFpEF.[25] Patients underwent detailed CV phenotyping with echocardiography and magnetic resonance imaging at baseline and follow-up, which allowed an examination of specific myocardial/vascular parameters through 6 months after RDN. Following RDN, systolic and diastolic LV stiffness and stroke volume index were partly normalized.[25,26] This study provided supportive evidence that RDN could be a potential therapeutic option for patients with hypertension and HFpEF.

The single-centre, randomized, double-blind, sham-controlled Renal Denervation to Treat Heart Failure with Preserved Ejection Fraction (UNLOAD-HFpEF, NCT05030987) study currently investigates the role of RDN in HFpEF. Symptomatic HFpEF patients with hypertension and elevated cardiac filling pressures (LV end-diastolic pressure ≥ 16 mmHg and PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise) will be randomized to receive either ultrasound RDN or a sham procedure. The primary outcome is PCWP at 20 W workload at 6 months between groups.

Based on the sound physiological concept and available data, RDN may represent a potentially valuable therapy for HFpEF patients, particularly in the presence of hypertension. However, further randomized studies are needed – and in part ongoing – to provide solid evidence for the use of RDN in these patients.

Vagal nerve stimulation

Cervical vagal nerve stimulation

Autonomic imbalance with increased sympathetic activation and reduced parasympathetic tone, represented by reduced carotid baroreceptor reflex sensitivity and abnormal heart rate variability, has been demonstrated to be a maladaptive response in HF.[28,29] This imbalance contributes to the progression of HF and associates with poor outcomes.[28–30] Increasing parasympathetic tone by cervical vagus nerve stimulation (cVNS) showed a beneficial effect on cardiac function and improved long-term survival in rats with HF.[31] This and other preclinical studies[32] opened the door to study the effect of cVNS in patients with HF.

The first human experience of cVNS was obtained in eight patients with advanced HF using the CardioFit device (BioControl Medical) implanted to stimulate the cervical vagus nerve approximately 3 cm below the bifurcation of the carotid artery. This device delivered low-current electrical pulses to stimulate the vagus nerve. After 6 months, cVNS improved New York Heart Association (NYHA) class and 6-min walk distance and reduced LV end-systolic volume.[33] This study was extended by a phase II study, the European multicentre CardioFit study, which included 32 patients with symptomatic HF (NYHA class II–IV) and LVEF ≤35%. After 12 months, cVNS was safe, well tolerated, and improved 6-min walk distance (mean difference 60 m, $p < 0.001$) and LV function (mean difference +6.4%, $p < 0.001$).[34] However, the multicentre, sham-controlled Neural Cardiac Therapy for Heart Failure (NECTAR-HF) study failed to show an improvement in the efficacy endpoints with cVNS at 18 months of follow-up. This study randomized 96 patients (NYHA classes II and III, LVEF ≤35%) in a 2:1 fashion to active or inactive cVNS (Precision, Boston Scientific) for 6 months, thereafter cVNS was activated in all patients. The primary safety endpoint was 18-month all-cause mortality, which was not different between the groups (12.6% vs. 3.2%, $p = 0.17$).[35]

Recently, two other randomized trials were performed to assess the utility of cVNS in HF. The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study evaluated the efficacy and safety of cVNS (Cyberonic IPG: Model 103) in 60 symptomatic HFrEF patients.[36] At 42-month follow-up, cVNS was associated with beneficial effects on LVEF (+4.5%, $p < 0.001$) and 6-min walking distance (+56 m, $p < 0.001$) without safety concerns.

The Increase of Vagal Tone in Heart Failure (INOVATE-HF) trial, which was the largest randomized trial on cVNS in HF, assessed the safety and efficacy among 707 HFrEF patients. Patients were randomized 3:2 to cVNS (CardioFit, BioControl Medical) plus GDMT or GDMT alone. The trial failed to meet its primary efficacy endpoint of mortality or HF hospitalization, which was not significantly different between groups after a mean follow-up of 16 months (30.3% vs. 25.8%, $p = 0.37$)[37] (*Table 1*).

The ANTHEM-HFrEF study, originally planned for up to 800 participants randomized to cVNS plus GDMT or GDMT alone, uses a novel design with an adaptive sample size and assesses the impact on morbidity and symptoms and functional status.[38] This study was early terminated and following the second interim analysis, which was conducted after enrolling 500 patients, the

Company is stopping enrolment, beginning the process to close the clinical study and winding down the HF programme. Further evaluation of the study data has not revealed a sufficiently strong positive impact on functional or mortality endpoints, and it is unlikely that the study would demonstrate such an impact. While it appears that there may be benefit for some patients, the magnitude of the expected benefit is insufficient to continue the study. It is important to note that the decision to stop enrolling was not associated with any safety concerns.

In summary, and based on the available evidence, the long-term effects of cVS on HF outcomes remain uncertain.

Aortic vagal nerve stimulation

Ventricular–arterial coupling (which characterizes the interaction between the contractile function of the myocardium and the arterial circulatory load) and aortic compliance are controlled by aortic endothelial cells and neural parasympathetic transmission, which are involved in the maintenance of autonomic balance.[39,40] In addition, the vagal aortic afferent nerves, located in the upper part of the thoracic aorta, mediate parasympathetic neuronal transmission to the brain.[39–41] Device-based aortic stimulation targets these vagal afferents (mechanoreceptors) in the descending aorta to modulate parasympathetic tone via chronic stimulation. The Endovascular NeuromoDulation Treatment for Heart Failure Patients (ENDO-HF, NCT02633644) feasibility study evaluates the safety and feasibility of the Harmony aortic stimulation system in the treatment of up to 20 patients with HF over 5 years of follow-up. This self-expandable stent is implanted in the descending aorta after verification of response to stimulation with an acute decrease in heart rate. Long-term stimulation aims at decreasing sympathetic tone and increasing parasympathetic tone, resulting in lowering of heart rate and LV afterload.[41] However, according to the United States Clinical Trials Registry, the ENDO-HF trial has been terminated.[42]

Spinal cord stimulation

Spinal cord stimulation (SCS) is performed by placing electrodes in the upper thoracic segments of the spinal cord.[43] SCS reduces cardiac sympathetic nerve activity by attenuating the signalling through the spinal cord and the dorsal root ganglia and the preganglionic sympathetic efferents.[44,45] The sympatholytic effects of SCS have shown to reverse remodelling and exhibit antiarrhythmic effects in animal models with HF.[46–48]

Two randomized clinical trials evaluated the safety and efficacy of this therapy in HF.[49,50] The Spinal Cord Stimulation for Heart Failure (SCS HEART) study enrolled 17 patients with symptomatic HF with an LVEF of 20–35% and implanted cardioverter-defibrillator.[49] Dual thoracic SCS leads were used at the T1–T3 level, and the device was programmed to provide SCS during 24 h per day. At 6 months, SCS improved symptoms (NYHA class −1, $p = 0.002$) and LVEF (+5%, $p < 0.001$). However, the Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF) study failed to document significant changes in clinical outcomes in patients with HF who received SCS.[50] In this prospective, randomized study, 66 patients with symptomatic HF with LVEF ≤35% were randomized to SCS (stimulation at the T2–T4 level for 12 h per day) versus stimulation off. The primary endpoint was the reduction in LV end-systolic volume index at 6 months (*Table 1*). One may speculate that the discordant results of these two studies are related to differences in both electrode positioning and duration of stimulation. Larger, randomized trials are necessary to evaluate the optimal location, rate, and intensity of SCS and its potential impact on clinical outcomes in HF patients.

Baroreflex activation therapy

Baroreflex activation therapy (BAT) was initially developed and clinically used in resistant hypertension.[51] It acts by applying electrical impulses and stimulating baroreceptors in the carotid sinus region. This stimulation of afferent nerves through the dorsal medulla may cause sympathetic attenuation and increased vagal tone, leading to decreases in blood pressure and heart rate.[52,53] In HF, the excessive sympathetic tone and chronic autonomic imbalance causes impaired baroreceptor sensitivity and abnormal inhibitory function.[10,53]

The first-in-human proof-of-concept study of chronic BAT in HFrEF included 11 patients with advanced HF (NYHA class III) on GDMT.[53] All patients underwent unilateral BAT and showed improvement in HF symptoms, 6-min walk distance, and LVEF at 6 months.[54] These findings persisted through 2 years of follow-up.[55] Following this study, the randomized controlled trial HOPE4HF was conducted and enrolled 146 symptomatic HFrEF patients, who were randomized to receive GDMT alone or GDMT plus BAT. At 6 months, there was a significant improvement in NYHA functional class, quality of life (QoL), and 6-min walk distance.[56]

The larger Baroreflex Activation Therapy for Heart Failure (BeAT-HF) study included 408 symptomatic HF patients with LVEF ≤35% on GDMT who were ineligible for cardiac resynchronization therapy (CRT).[57] Patients were randomized 1:1 to receive either GDMT alone or GDMT plus unilateral BAT. This pivotal trial utilized an adaptive design and divided into two phases, i.e. the pre-market ($n = 264$) and post-market phase. After 6 months of follow-up, BAT was safe and significantly improved QoL (mean difference in Minnesota Living with Heart Failure Questionnaire −14, $p < 0.001$), 6-min walk distance (+60 m, $p < 0.001$), and NT-proBNP reduction (−25%, $p = 0.004$).[57]

The post-market phase of the BeAT-HF study evaluated the potential of this therapy to reduce mortality and hospitalizations in HFrEF patients.[57,58] The patients were randomized into two groups, treatment with BAT plus GDMT versus GDMT alone. The trial included 323 HFrEF patients with a median follow-up of 3.7 years. According to a preliminary results report, the study did not meet its primary endpoint demonstrating a neutral effect on CV death and HF hospitalizations. It did, however, demonstrate the long-term durability in symptomatic improvement (QoL, 6-min walking distance, and NYHA class) and confirmed the safety of this approach to neuromodulation in HFrEF patients[58] (*Table 1*).

Recently, a meta-analysis of patient-level randomized controlled trials evaluating BAT in 554 patients with HFrEF receiving GDMT

confirmed that BAT may improve exercise capacity, NYHA functional class, and QoL.[59] BAT demonstrated a statistically significant improvement in 6-min walking distance, QoL and NYHA class in all patients irrespective of gender, age, presence or absence of CRT or the presence or absence of atrial fibrillation. NT-proBNP levels appeared to improve in all patients, but only achieved statistical significance in the cohorts that excluded patients with NT-proBNP values >1600 pg/ml. Consequently, BAT with the Barostim Neo System was approved by the Food and Drug Administration (FDA) in 2019 for the use in HFrEF with NYHA class II or III, an NT-proBNP of <1600 pg/ml or ineligibility for CRT.[11]

The MobiusHD System (Vascular Dynamics) is an endovascular, device-based baroreceptor enhancement system that works by inducing passive activation of the baroreceptors through changes in the geometric shape of the carotid body thereby increasing carotid artery wall stretch while maintaining pulsatility.[60,61] This change in signalling causes a negative feedback response, resulting in decreased sympathetic activity and increased parasympathetic activity. The device has initially been investigated in a first-in-human trial in patients with resistant hypertension.[61] Data on its performance in patients with HF are scarse.[60] The Effect of the MobiusHD in Patients With Heart Failure (HF-FIM, NCT04590001) study is an ongoing, open-label, single-arm study with the primary objective of evaluating the safety and effectiveness of the MobiusHD system in HFrEF patients.

The recent European Society of Cardiology guidelines for the management of HF, in light of the lack of hard outcome data, deemed the available evidence for improvements in exercise capacity and QoL insufficient to support specific guideline recommendations for BAT therapy in HFrEF.[3] BAT could represent an adjunctive device-based approach for HFrEF in case all guideline-recommended HF therapies have been implemented and patients remain symptomatic. However, until further evidence on the safety and efficacy of BAT in HF patients becomes available, careful patient selection for BAT is recommended.

Splanchnic nerve modulation

The visceral abdominal organs contain a large venous system, i.e. the splanchnic venous compartment, which accounts for about 30% of the total blood volume and is heavily innervated by sympathetic nerves.[62] Stimulation of the splanchnic vein leads to vasoconstriction and can mobilize up to 25% of the total blood volume from the splanchnic blood pool into the central venous system, thereby rapidly increasing cardiac preload and cardiac index.[62,63]

This first-in-human study of splanchnic nerve modulation included 11 patients with HFpEF and showed both the safety of the procedure over 12 months of follow-up and sustained improvement in NT-proBNP, health status and 6-min walk distance compared to this time window.[64] The REBALANCE-HF trial randomized 116 patients with HFpEF to greater right splanchnic nerve ablation with the Satera™ Ablation System or a sham procedure (Fudim M., unpublished data presented at the Heart Failure Society of America 2023 Annual Scientific Meeting). Patients in the ablation group demonstrated a 13-point improvement of the Kansas City Cardiomyopathy Questionnaire overall summary score ($p = 0.02$), a 36 m improvement of the 6-min walk test ($p = 0.08$), and a 39% relative improvement of NT-proBNP ($p = 0.10$). Furthermore, ablation resulted in a PCWP reduction of −4.5 mmHg at 1 month, compared to a maximum PCWP of −1.6 mmHg with sham treatment ($p = 0.10$).

These favourable outcomes in HFpEF patients are promising but the results need to be confirmed by larger, powered trials to assess the safety and efficacy of splanchnic nerve modulation in HF mangament.

Conclusion and future direction

Despite the significant improvements in HF therapies, there remains an unmet need for additional therapeutic strategies beyond drug therapy to further improve symptoms and prognosis in both HFrEF and HFpEF. Because the autonomic nervous system plays a crucial role in the pathophysiology of HF, therapeutic interventions that reverse autonomic imbalance are potentially promising and currently under investigation. However, robust data demonstrating the efficacy and safety of these devices in HF are currently lacking and larger studies are needed to finally evaluate their potential role in the armamentarium of HF therapies. Therefore, it is still a challenge to identify the ideal patient group for interventions with neuromodulation devices. The first important step remains the initiation and optimization of treatment with the available prognosis-improving drug classes (GDMT) and, potentially, the implementation of evidence-based device therapies such as CRT, when indicated. When HF patients remain symptomatic despite optimally recommended guideline HF therapies, patient phenotyping using clinical, haemodynamic and structural approaches is required to determine which device may be utilized to exert additional effects, such as BAT, which is currently the only FDA-approved and CE-marked device. Another crucial element of this approach is its intensity, which is associated with the quantity and frequency of stimulation administered during therapeutic procedures. The idea of treatment intensity within neuromodulation emphasizes the significance of customizing therapeutic approaches based on individual patient characteristics, optimizing settings for sustained efficacy, and continually advancing our understanding of how to modulate neural circuits effectively.

More robust clinical evidence is needed for other therapies and ongoing studies will hopefully provide more insights into the potential benefits of such therapies in HF patients.

Acknowledgements

We are grateful to Armin Schweitzer for his technical and artwork help.

Conflict of interest: A.A. reports speaker's honoraria from Boston Scientific and Bayer. L.L. received speaker honoraria from ReCor Medical and Medtronic. M.F. is supported by the American Heart Association (20IPA35310955). W.T.A. reports personal fees from Abbott, consulting fees from Boehringer Ingelheim, Impulse Dynamics, and Respicardia; has received salary support from V-Wave Medical; and has received research

support from the NHLBI, all for studies performed within the heart failure arena. S.D.A. reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious, and V-Wave. Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents. M.B. reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier, and Vifor; is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939). F.M. is supported by Deutsche Gesellschaft für Kardiologie (DGK), Deutsche Forschungsgemeinschaft (SFB TRR219, Project-ID 322900939), and Deutsche Herzstiftung; has received scientific support from Ablative Solutions, Medtronic and ReCor Medical and speaker honoraria/consulting fees from Ablative Solutions, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Inari, Medtronic, Merck, ReCor Medical, Servier, and Terumo. Open Access funding enabled and organized by Projekt DEAL.

References

1. McClellan M, Brown N, Califf RM, Warner JJ. Call to action: Urgent challenges in cardiovascular disease: A presidential advisory from the American Heart Association. *Circulation* 2019;**139**:e44–e54. https://doi.org/10.1161/CIR.0000000000000652
2. Metra M, Teerlink J. Heart failure. *Lancet* 2017;**390**:1981–1995. https://doi.org/10.1016/S0140-6736(17)31071-1
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
4. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, *et al.* Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;**73**:2365–2383. https://doi.org/10.1016/j.jacc.2019.02.015
5. Abdin A, Bauersachs J, Soltani S, Eden M, Frey N, Böhm M. A practical approach to the guideline-directed pharmacological treatment of heart failure with reduced ejection fraction. *ESC Heart Fail.* 2023;**10**:24–31. https://doi.org/10.1002/ehf2.14197
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;**44**:3627–3639. https://doi.org/10.1093/eurheartj/ehad195
7. Kemp CD, Conte JV. The pathophysiology of heart failure. *Cardiovasc Pathol* 2012;**21**:365–371. https://doi.org/10.1016/j.carpath.2011.11.007
8. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol* 2016;**13**:28–35. https://doi.org/10.1038/nrcardio.2015.134
9. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, *et al.* Acute heart failure. *Nat Rev Dis Primers* 2020;**5**:16. https://doi.org/10.1038/s41572-020-0151-7
10. Sobowale CO, Hori Y, Ajijola OA. Neuromodulation therapy in heart failure: Combined use of drugs and devices. *J Innov Card Rhythm Manag* 2020;**11**:4151–4159. https://doi.org/10.19102/icrm.2020.110705
11. Duncker D, Bauersachs J. Current and future use of neuromodulation in heart failure. *Eur Heart J Suppl* 2022;**24**:E28–E34. https://doi.org/10.1093/eurheartjsupp/suac031
12. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, *et al.* 2023 ESH guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens* 2023;**41**:1874–2071. https://doi.org/10.1097/HJH.0000000000003480
13. Barbato E, Azizi M, Schmieder RE, Lauder L, Böhm M, Brouwers S, *et al.* Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2023;**44**:1313–1330. https://doi.org/10.1093/eurheartj/ehad054
14. Lauder L, Azizi M, Kirtane AJ, Böhm M, Mahfoud F. Device-based therapies for arterial hypertension. *Nat Rev Cardiol* 2020;**17**:614–628. https://doi.org/10.1038/s41569-020-0364-1
15. Mahfoud F, Mancia G, Schmieder RE, Ruilope L, Narkiewicz K, Schlaich M, *et al.* Cardiovascular risk reduction after renal denervation according to time in therapeutic systolic blood pressure range. *J Am Coll Cardiol* 2022;**80**:1871–1880. https://doi.org/10.1016/j.jacc.2022.08.802
16. Mahfoud F, Townsend RR, Kandzari DE, Kario K, Schmieder RE, Tsioufis K, *et al.* Changes in plasma renin activity after renal artery sympathetic denervation. *J Am Coll Cardiol* 2021;**77**:2909–2919. https://doi.org/10.1016/j.jacc.2021.04.044
17. Böhm M, Ewen S, Wolf M. Renal denervation halts left ventricular remodeling and dysfunction in heart failure: New shores ahead. *J Am Coll Cardiol* 2018;**72**:2622–2624. https://doi.org/10.1016/j.jacc.2018.09.027
18. Sharp TE 3rd, Polhemus DJ, Li Z, Spaletra P, Jenkins JS, Reilly JP, *et al.* Renal denervation prevents heart failure progression via inhibition of the renin-angiotensin system. *J Am Coll Cardiol* 2018;**72**:2609–2621. https://doi.org/10.1016/j.jacc.2018.08.2186
19. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, *et al.* First-in-man safety evaluation of renal denervation for chronic systolic heart failure: Primary outcome from REACH-Pilot study. *Int J Cardiol* 2013;**162**:189–192. https://doi.org/10.1016/j.ijcard.2012.09.019
20. Hopper I, Gronda E, Hoppe UC, Rundqvist B, Marwick TH, Shetty S, *et al.* Sympathetic response and outcomes following renal denervation in patients with chronic heart failure: 12-month outcomes from the Symplicity HF feasibility study. *J Card Fail* 2017;**23**:702–707. https://doi.org/10.1016/j.cardfail.2017.06.004
21. Feyz L, Nannan Panday R, Henneman M, Verzijlbergen F, Constantinescu AA, van Dalen BM, *et al.* Endovascular renal sympathetic denervation to improve heart failure with reduced ejection fraction: The IMPROVE-HF-I study. *Neth Heart J* 2022;**30**:149–159. https://doi.org/10.1007/s12471-021-01633-z
22. Weber MA, Kirtane AJ, Weir MR, Radhakrishnan J, Das T, Berk M, *et al.* The REDUCE HTN: REINFORCE: Randomized, sham-controlled trial of bipolar radiofrequency renal denervation for the treatment of hypertension. *JACC Cardiovasc Interv* 2020;**13**:461–470. https://doi.org/10.1016/j.jcin.2019.10.061
23. Hage C, Löfgren L, Michopoulos F, Nilsson R, Davidsson P, Kumar C, *et al.* Metabolomic profile in HFpEF vs HFrEF patients. *J Card Fail* 2020;**26**:1050–1059. https://doi.org/10.1016/j.cardfail.2020.07.010
24. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, *et al.* Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2017;**70**:136–148. https://doi.org/10.1016/j.jacc.2017.05.029
25. Kresoja KP, Rommel KP, Fengler K, von Roeder M, Besler C, Lücke C, *et al.* Renal sympathetic denervation in patients with heart failure with preserved ejection fraction. *Circ Heart Fail* 2021;**14**:e007421. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007421
26. Fudim M, Sobotka PA, Piccini JP, Patel MR. Renal denervation for patients with heart failure: Making a full circle. *Circ Heart Fail* 2021;**14**:e008301. https://doi.org/10.1161/CIRCHEARTFAILURE.121.008301
27. Brandt MC, Reda S, Mahfoud F, Lenski M, Böhm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Am Coll Cardiol* 2012;**60**:1956–1965. https://doi.org/10.1016/j.jacc.2012.08.959
28. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol* 2009;**54**:1747–1762. https://doi.org/10.1016/j.jacc.2009.05.01
29. Dusi V, De Ferrari GM. Vagal stimulation in heart failure. *Herz* 2021;**46**:541–554. https://doi.org/10.1007/s00059-021-05076-5
30. Nijenhuis VJ, Sanchis L, van der Heyden JAS, Klein P, Rensing BJWM, Latib A, *et al.* The last frontier: Transcatheter devices for percutaneous or minimally invasive treatment of chronic heart failure. *Neth Heart J.* 2017;**25**:536–544. https://doi.org/10.1007/s12471-017-1018
31. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation* 2004;**109**:120–124. https://doi.org/10.1161/01.CIR.0000105721.71640.DA
32. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, Van Wagoner DR, *et al.* Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail* 2009;**2**:692–699. https://doi.org/10.1161/CIRCHEARTFAILURE.109.873968
33. Schwartz PJ, De Ferrari GM, Sanzo A, Landolina M, Rordorf R, Raineri C, *et al.* Long term vagal stimulation in patients with advanced heart failure: First

experience in man. *Eur J Heart Fail* 2008;**10**:884–891. https://doi.org/10.1016/j.ejheart.2008.07.016
34. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M; CardioFit Multicenter Trial Investigators. Chronic vagus nerve stimulation: A new and promising therapeutic approach for chronic heart failure. *Eur Heart J* 2011;**32**:847–855. https://doi.org/10.1093/eurheartj/ehq391
35. De Ferrari GM, Stolen C, Tuinenburg AE, Wright DJ, Brugada J, Butter C, *et al.* Long-term vagal stimulation for heart failure: Eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. *Int J Cardiol* 2017;**244**:229–234. https://doi.org/10.1016/j.ijcard.2017.06.036
36. Sharma K, Premchand RK, Mittal S, Monteiro R, Libbus I, DiCarlo LA, *et al.* Long-term follow-up of patients with heart failure and reduced ejection fraction receiving autonomic regulation therapy in the ANTHEM-HF pilot study. *Int J Cardiol* 2020;**323**:175–178. https://doi.org/10.1016/j.ijcard.2020.09.072
37. Gold MR, Veldhuisen DJV, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, *et al.* Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF trial. *J Am Coll Cardiol* 2016;**68**:149–158. https://doi.org/10.1016/j.jacc.2016.03.525
38. Konstam MA, Udelson JE, Butler J, Klein HU, Parker JD, Teerlink JR, *et al.*; ANTHEM-HFrEF Investigators and Coordinators. Impact of autonomic regulation therapy in patients with heart failure: ANTHEM-HFrEF pivotal study design. *Circ Heart Fail* 2019;**12**:e005879. https://doi.org/10.1161/CIRCHEARTFAILURE.119.005879
39. Li L, Huang C, Ai J, Yan B, Gu H, Ma Z, *et al.* Structural re-modeling of vagal afferent innervation of aortic arch and nucleus ambiguous (NA) projections to cardiac ganglia in a transgenic mouse model of type 1 diabetes (OVE26). *J Comp Neurol* 2010;**518**:2771–2793. https://doi.org/10.1002/cne.22363
40. Min S, Chang RB, Prescott SL, Beeler B, Joshi NR, Strochlic DE, *et al.* Arterial baroreceptors sense blood pressure through decorated aortic claws. *Cell Rep* 2019;**29**:2192–2201.e3. https://doi.org/10.1016/j.celrep.2019.10.040
41. Paolisso P, Dagan A, Gallinoro E, De Colle C, Bertolone DT, Moya A, *et al.* Aortic thoracic neuromodulation in heart failure with preserved ejection fraction. *ESC Heart Fail* 2023;**10**:699–704. https://doi.org/10.1002/ehf2.14136
42. ClinicalTrials.gov. Endovascular NeuromoDulation Treatment fOr Heart Failure Patients (ENDO-HF). Identifier number NCT02633644. https://ichgcp.net/clinical-trials-registry/NCT02633644. Accessed 10 January 2024.
43. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science* 1967;**155**:108–109. https://doi.org/10.1126/science.155.3758.108
44. Ardell JL. Heart failure: Mechanisms of spinal cord neuromodulation for heart disease. *Nat Rev Cardiol* 2016;**13**:127–128. https://doi.org/10.1038/nrcardio.2016.8
45. Dusi V, Angelini F, Zile MR, De Ferrari GM. Neuromodulation devices for heart failure. *Eur Heart J Suppl* 2022;**24**:E12–E27. https://doi.org/10.1093/eurheartjsupp/suac036
46. Wang S, Zhou X, Huang B, Wang Z, Liao K, Saren G, *et al.* Spinal cord stimulation protects against ventricular arrhythmias by suppressing left stellate ganglion neural activity in an acute myocardial infarction canine model. *Heart Rhythm* 2015;**12**:1628–1635. https://doi.org/10.1016/j.hrthm.2015.03.023
47. Liu Y, Yue WS, Liao SY, Zhang Y, Au KW, Shuto C, *et al.* Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *J Cardiovasc Electrophysiol* 2012;**23**:534–540. https://doi.org/10.1111/j.1540-8167.2011.02230.x
48. Lopshire JC, Zhou X, Dusa C, Ueyama T, Rosenberger J, Courtney N, *et al.* Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. *Circulation* 2009;**120**:286–294. https://doi.org/10.1161/CIRCULATIONAHA.108.812412
49. Tse HF, Turner S, Sanders P, Okuyama Y, Fujii K, Cheung CW, *et al.* Thoracic Spinal Cord Stimulation for Heart Failure as a Restorative Treatment (SCS HEART study): First-in-man experience. *Heart Rhythm* 2015;**12**:588–595. https://doi.org/10.1016/j.hrthm.2014.12.014
50. Zipes DP, Neuzil P, Theres H, Caraway D, Mann DL, Mannheimer C, *et al.*; DEFEAT-HF Trial Investigators. Determining the feasibility of spinal cord neuromodulation for the treatment of chronic systolic heart failure: The DEFEAT-HF study. *JACC Heart Fail* 2016;**4**:129–136. https://doi.org/10.1016/j.jchf.2015.10.006
51. Wallbach M, Böhning E, Lehnig LY, Schroer C, Müller GA, Wachter R, *et al.* Safety profile of baroreflex activation therapy (NEO) in patients with resistant hypertension. *J Hypertens* 2018;**36**:1762–1769. https://doi.org/10.1097/HJH.0000000000001753
52. Schwartz PJ, La Rovere MT, De Ferrari GM, Mann DL. Autonomic modulation for the management of patients with chronic heart failure. *Circ Heart Fail* 2015;**8**:619–628. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001964
53. Chatterjee NA, Singh JP. Novel interventional therapies to modulate the autonomic tone in heart failure. *JACC Heart Fail.* 2015;**3**:786–802. https://doi.org/10.1016/j.jchf.2015.05.008
54. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, *et al.* Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: A proof-of-concept study. *Eur J Heart Fail* 2014;**16**:977–983. https://doi.org/10.1002/ejhf.138
55. Gronda E, Seravalle G, Trevano FQ, Costantino G, Casini A, Alsheraei A, *et al.* Long-term chronic baroreflex activation. *J Hypertens* 2015;**33**:1704–1708. https://doi.org/10.1097/HJH.0000000000000603
56. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, *et al.* Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015;**3**:487–496. https://doi.org/10.1016/j.jchf.2015.02.006
57. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, *et al.* Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:1–13. https://doi.org/10.1016/j.jacc.2020.05.015
58. CVRx reports preliminary results of the BeAT-HF post-market randomized clinical trial. 21 February 2023. https://ir.cvrx.com/news-releases/news-release-details/cvrx-reports-preliminary-results-beat-hf-post-market-randomized. Accessed 10 January 2024
59. Coats AS, Abraham W, Zile M, Lindenfeld J, Weaver F, Fudim M, *et al.* Baroreflex activation therapy with the Barostim™ device in patients with heart failure with reduced ejection fraction: A patient level meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2022;**24**:1665–1673. https://doi.org/10.1002/ejhf.2573
60. Salah HM, Fudim M, Burkhoff D. Device interventions for heart failure. *JACC Heart Fail* 2023;**11**:1039–1054. https://doi.org/10.1016/j.jchf.2023.07.002
61. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, *et al.*; CALM-FIM_EUR Investigators. Endovascular baroreflex amplification for resistant hypertension: A safety and proof-of principle clinical study. *Lancet* 2017;**390**:2655–2661. https://doi.org/10.1016/S0140-6736(17)32337-1
62. Fudim M, Sobotka PA, Dunlap ME. Extracardiac abnormalities of preload reserve. *Circ Heart Fail* 2021;**14**:e007308. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007308
63. Fudim M, Boortz-Marx RL, Ganesh A, DeVore AD, Patel CB, Rogers JG, *et al.* Splanchnic nerve block for chronic heart failure. *JACC Heart Fail* 2020;**8**:742–752. https://doi.org/10.1016/j.jchf.2020.04.010
64. Fudim M, Zirakashvili T, Shaburishvili N, Shaishmelashvili G, Sievert H, Sievert K, *et al.* Transvenous right greater splanchnic nerve ablation in heart failure and preserved ejection fraction: First-in-human study. *JACC Heart Fail* 2022;**10**:744–752. https://doi.org/10.1016/j.jchf.2022.05.009