ORIGINAL RESEARCH ARTICLE

Comparison of symptomatic and functional responses to vagus nerve stimulation in ANTHEM-HF, INOVATE-HF, and NECTAR-HF

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Abstract

Aims   Clinical studies of vagal nerve stimulation (VNS) for heart failure with reduced ejection fraction have had mixed results to date. We sought to compare VNS delivery and associated changes in symptoms and function in autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure (ANTHEM-HF), increase of vagal tone in heart failure (INOVATE-HF), and neural cardiac therapy for heart failure (NECTAR-HF) for hypothesis generation.

Methods and results   Descriptive statistics were used to analyse data from the public domain for differences in proportions using Pearson's chi-square test, differences in mean values using Student's unpaired *t*-test, and differences in changes of mean values using two-sample *t*-tests.

Guideline-directed medical therapy recommendations were similar across studies. Fewer patients were in New York Heart Association 3, and baseline heart rate (HR) was higher in ANTHEM-HF. In INOVATE-HF, VNS was aimed at peripheral neural targets, using closed-loop delivery that required synchronization of VNS to R-wave sensing by an intracardiac lead. Pulse frequency was low (1–2 Hz) because of a timing schedule allowing ≤3 pulses of VNS following at most 25% of detected R waves. NECTAR-HF and ANTHEM-HF used open-loop VNS delivery (i.e. independent of any external signal) aimed at both central and peripheral targets. In NECTAR-HF, VNS delivery at 20 Hz caused off-target effects that limited VNS up-titration in a majority of patients. In ANTHEM-HF, VNS delivery at 10 Hz allowed up-titration until changes in HR dynamics were confirmed. Six months after VNS titration, significant improvements in both HR and HR variability occurred only in ANTHEM-HF. When ANTHEM-HF and NECTAR-HF were compared, greater improvements from baseline were observed in ANTHEM-HF in standard deviation in normal-to-normal R-R intervals (94 ± 26 to 111 ± 50 vs. 146 ± 48 to 130 ± 52 ms; $P < 0.001$), left ventricular ejection fraction (32 ± 7 to 37 ± 0.4 vs. 31 ± 6 to 33 ± 6; $P < 0.05$), and Minnesota Living with Heart Failure mean score (40 ± 14 to 21 ± 10 vs. 44 ± 22 to 36 ± 21; $P < 0.002$). When compared with INOVATE-HF, greater improvement in 6-min walk distance was observed in ANTHEM-HF (287 ± 66 to 346 ± 78 vs. 304 ± 111 to 334 ± 111 m; $P < 0.04$).

Conclusions   In this post-hoc analysis, differences in patient demographics were seen and may have caused the differential responses in symptoms and function observed in association with VNS. Major differences in technology platforms, neural targets, VNS delivery, and HR and HR variability responses could have also potentially played a very important role. Further study is underway in a randomized controlled trial with these considerations in mind.

Keywords   Autonomic regulation therapy; Guideline-directed medical therapy; Heart failure; Vagus nerve stimulation

Introduction

Vagus nerve stimulation (VNS) is approved for the management of drug-refractory epilepsy[1,2] and is currently in development to deliver autonomic regulation therapy (ART) for patients with chronic heart failure and reduced ejection fraction (HFrEF).[3]

Cardiac function and homeostasis comprises processes within the central nervous system as well as local circuit neurons for networked control within the peripheral nervous system. Network interactions occur within the local circuit neural populations. These integrate activities, within and between peripheral ganglia and the central nervous system, for reflex control of the heart (*Figure 1*).

VNS is delivered utilizing a system that includes an implantable pulse generator and an electrical lead that requires no intraoperative mapping for placement around the cervical vagus nerve (CVN).[4–6] An external programming system is used to change the generator's settings for stimulating the CVN through the lead (*Figure 2*). The functional biological effects of CVN activation using VNS are defined by the various axons that traverse the nerve interface. Vagus nerve afferent activation centrally modulates efferent sympathetic and parasympathetic function centrally and has tonic and basal effects that decrease excess sympathetic activation and excessive release of norepinephrine. The summative effects of these modulations result peripherally in vasorelaxation through activation of the nitric oxide pathway.[7] Vagus nerve efferent activation causes anti-adrenergic effects both within the intrinsic cardiac nervous system and via pre-synaptic and post-synaptic interactions at the end terminus.[8] At the myocyte level, increases in acetylcholine from muscarinic receptors reduce oxidative stress, increase contractile function, improve calcium signalling function, and restore gene expression. At the same time, cholinergic trans-differentiation of sympathetic neurons occurs, providing a protective role against sympathetically mediated pathogenesis.[9]

VNS delivery, or 'dosing', comprises the combination of VNS intensity (including pulse amplitude, duration, and frequency), polarity, and duty cycle, which is a repeating cycle over time. Each duty cycle comprises a period of stimulation ('on-time') that begins the cycle, followed by a period of no stimulation ('off-time') to end the cycle, and is measured by dividing the duration of the on-time by the total cycle duration (i.e. on-time plus off-time). The mode of delivery may be closed loop or open loop. Closed-loop delivery occurs only in response to the detection of an external stimulus, whereas open-loop delivery is not gated by any external stimulus as a trigger for delivery (*Figure 3*).

Numerous pre-clinical and early phase human studies have tested the potential role of ART using VNS to improve HFrEF; however, changes in heart rate, heart rate variability, symptoms, and function in association with VNS have shown inconsistent results in larger clinical studies to date.[10] The reasons for the observed differences in the published data are unclear. We sought to compare the patient demographics and methodologies for VNS delivery and analysed the symptomatic and functional outcomes reported in the AutoNomic Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) Pilot,[11] Increase of Vagal Tone in Heart Failure (INOVATE-HF),[12] and Neural Cardiac Therapy for Heart Failure (NECTAR-HF)[13] studies to understand whether any of these might explain the differences for hypothesis generation.

All three of these contemporary studies conformed to the principles outlined in the Declaration of Helsinki, and the study protocols were approved by local ethics committees at all of the study sites. All patients gave written informed consent translated into local languages.
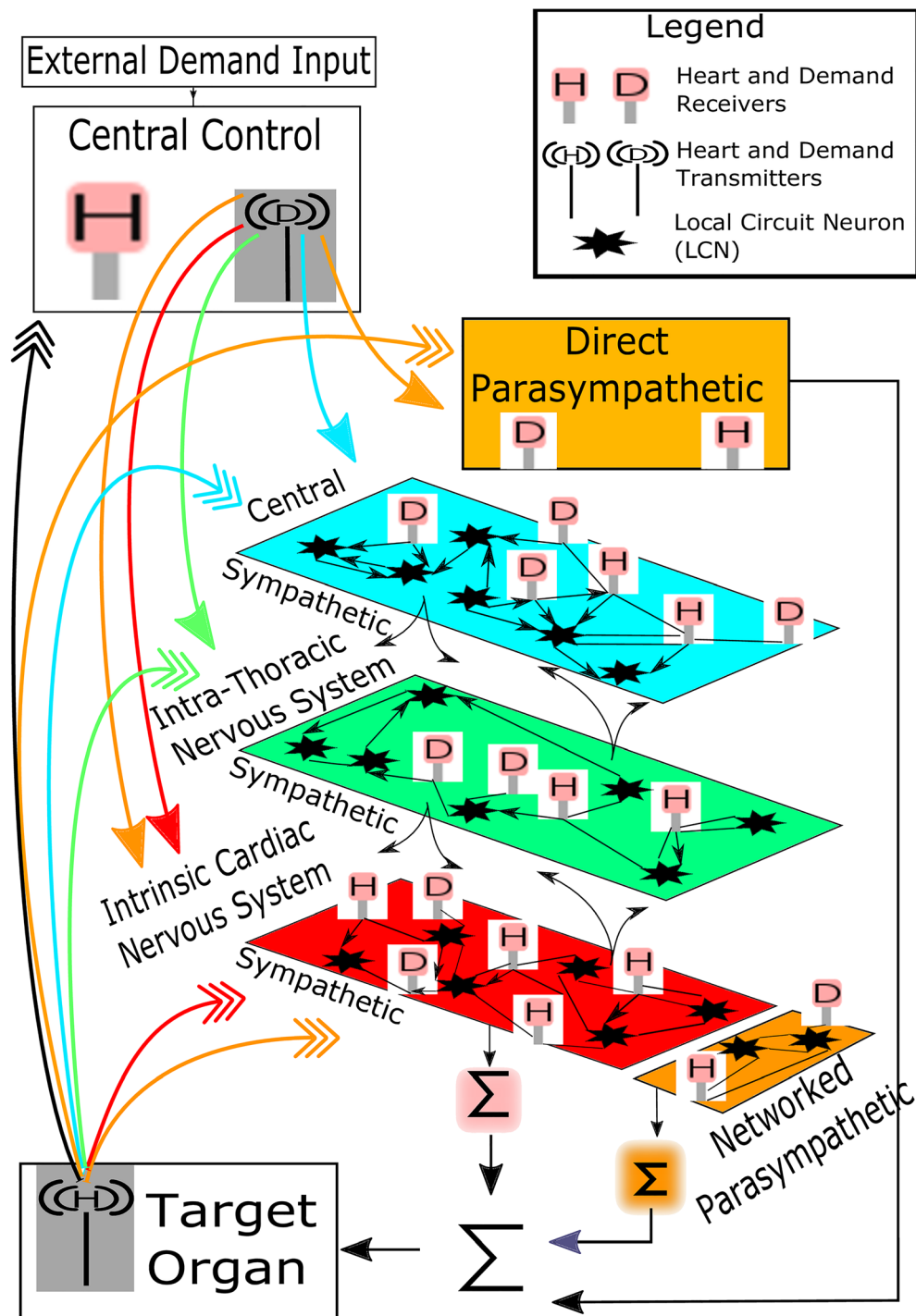
Methods

Information was obtained from peer-reviewed publications and the public domain for descriptive analysis. Because ANTHEM-HF was an uncontrolled trial, demographic data and clinical outcomes for the treatment arms in these three studies were used for comparisons. Descriptive statistics were utilized to summarize observed differences in proportions using Pearson's chi-square test, differences in mean values using Student's unpaired *t*-test, and differences in changes of mean values using two-sample *t*-tests with the Satterthwaite approximation for different variances.[14,15] Testing was performed at a significance level of 0.05. No adjustment was made for multiple comparisons. Given that only aggregate data and not individual patient-level data were available to the authors for INOVATE-HF and NECTAR-HF, statistical comparison between studies with respect to outcomes did not account for differences in baseline characteristics between the studies. Because of small sample sizes of these studies, no analysis was performed to assess non-inferiority of the ANTHEM-HF results to the results of the other studies.

Results

The study designs[4–6] and outcomes[11–13] of the ANTHEM-HF pilot, INOVATE-HF, and NECTAR-HF studies have been previously published.

Left ventricular ejection fraction (LVEF) $\leq$ 40% was required to enroll in ANTHEM-HF and INOVATE-HF and $\leq$35% in NECTAR-HF. New York Heart Association (NYHA) class 2 or 3 symptoms were required for entry into ANTHEM-HF and NECTAR-HF, and NYHA 3 class symptoms were required for INOVATE-HF. ANTHEM-HF randomized patients to VNS of the left vs. right CVN and did not include a control arm. INOVATE-HF and NECTAR-HF were randomized controlled

Figure 1 The intrinsic cardiac nervous system comprises sympathetic (Sympath) and parasympathetic (Parasym) efferent post-ganglionic neurons, local circuit neurons (LCN), and afferent (Aff.) neurons. The intrathoracic extracardiac nervous system is comprised of ganglia containing afferent neurons, LCN, and sympathetic efferent post-ganglionic neurons. Cardiovascular heart rate and demand inputs are conveyed centrally via dorsal root, nodose and petrosal ganglia subserving spinal cord (C-cervical, T-thoracic), brainstem, and higher centre reflexes for haemostatic maintenance. From Kember et al.[26] (with permission).

trials that utilized VNS of the right CVN only. The recommendations for background HF therapy were similar for all three studies. Unless treatment was contraindicated or intolerable, patients were to receive beta-blockers, mineralocorticoid receptor antagonists (MRAs), digitalis, and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker

Figure 2 Open-loop vagal nerve stimulation (VNS) system to deliver autonomic regulation therapy (ANTHEM-HF, NECTAR-HF). For closed-loop VNS, implantation of an additional intracardiac lead was used synchronize VNS to R-wave sensing (INOVATE-HF; see text).
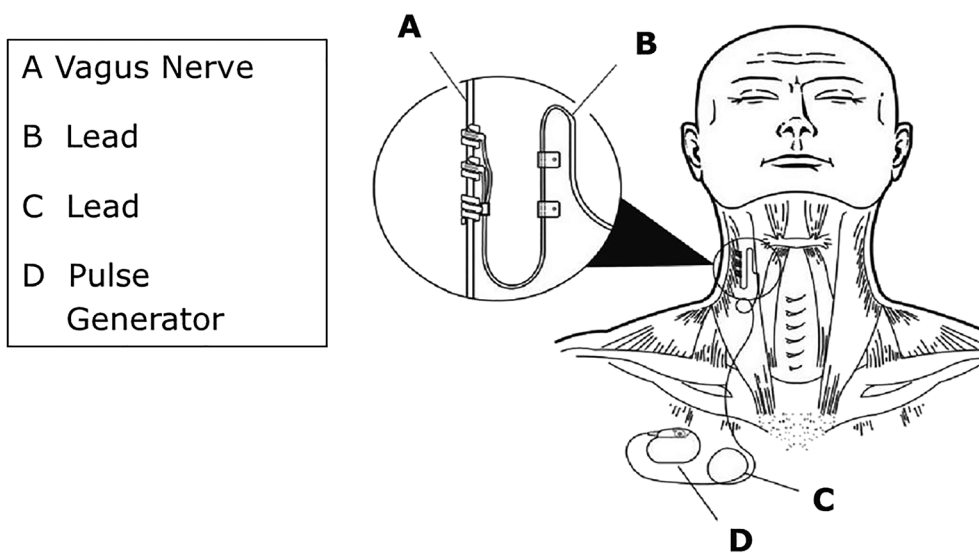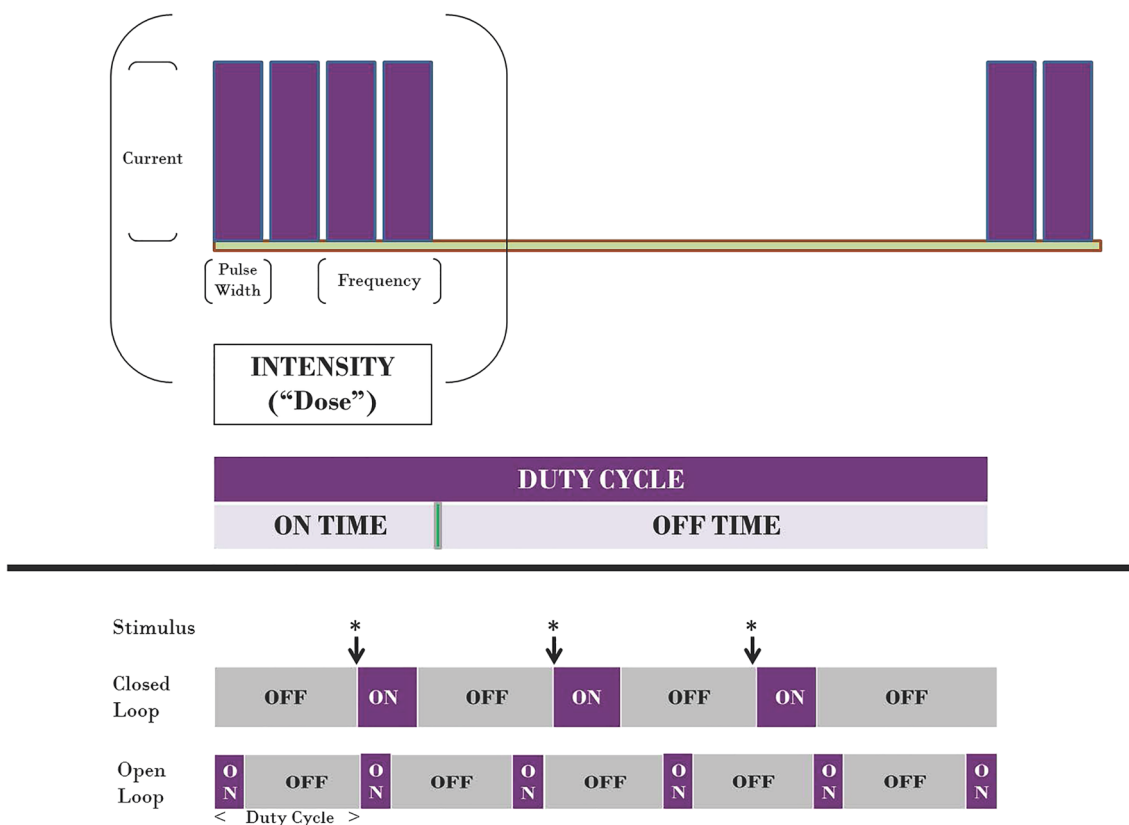
A Vagus Nerve

B Lead

C Lead

D Pulse
    Generator

Figure 3 Vagal nerve stimulation delivery includes its intensity (also called 'dose'; a combination of pulse amplitude, pulse frequency, and pulse duration) and duty cycle.

as background pharmacological treatment per guideline-directed medical therapy (GDMT).

Table 1 summarizes treatment arm demographics by study. When compared with patients in INOVATE-HF and NECTAR-HF, patients in ANTHEM-HF were younger and had a lower body mass index and a higher baseline heart rate. Fewer patients were in NYHA Class 3. Baseline systolic blood pressure was lower than in INOVATE-HF and trended lower than in NECTAR-HF. There was a trend towards more beta-blocker use in ANTHEM-HF when compared with the other two studies. More patients in ANTHEM-HF received MRAs than in INOVATE-HF, and there tended to be more patients who received MRAs than in NECTAR-HF.

In ANTHEM-HF, the mean baseline LVEF was higher than in INOVATE-HF, which required a lower baseline LVEF for study entry, and there was no difference when compared with the mean baseline LVEF in NECTAR-HF. The baseline 6-min walk distance tended to be lower in ANTHEM-HF than in INOVATE-HF. Six-minute walk tests were not performed in NECTAR-HF.

Figure 4 illustrates how VNS was delivered, and *Table 2* summarizes similarities and differences in VNS delivery by study. Up-titration of VNS intensity was attempted in all three studies. VNS delivery in ANTHEM-HF and NECTAR-HF was open loop and was configured to direct stimulation in an afferent direction towards the CNS and in an efferent direction towards peripheral neural targets. In NECTAR-HF, VNS was delivered at 20 Hz, which caused off-target adverse effects that limited VNS up-titration in a majority of patients.[13] In

ANTHEM-HF, VNS was delivered at 10 Hz and was well tolerated. Up-titration occurred in all patients in ANTHEM-HF until autonomic modulation was confirmed by a change in heart rate dynamics.[16]

In contrast, VNS delivery was closed loop in INOVATE-HF, which required the adjunct implantation of a right ventricular intracardiac lead in order to synchronize VNS delivery to R-wave sensing.[12] VNS was programmed using a timing schedule that allowed no more than three pulses of VNS following at most 25% of detected R waves.[17,18] This resulted in a pulse frequency of 1–2 Hz, which was much lower than the pulse frequencies used in ANTHEM-HF or NECTAR-HF. VNS in INOVATE-HF also differed in being aimed preferentially at peripheral neural targets, using an asymmetric pulse delivery consisting of an initial high-amplitude anodal phase to induce afferent electrophysiologic conduction block followed by a low-amplitude cathodic phase to induce efferent electrophysiologic conduction. The current amplitude of the cathodic phase was 5% of the current amplitude of the anodic phase.[12,18]

Six months after completion of titration, heart rate decreased significantly, and standard deviation in normal-to-normal R-R intervals (SDNN) increased significantly in ANTHEM-HF.[11] Heart rate and SDNN were reported to be unchanged in INOVATE-HF and NECTAR-HF.[12,13,22] Comparisons of available data for symptomatic and functional outcomes are summarized in *Figure 5*. When NECTAR-HF and ANTHEM-HF were compared, greater improvements in heart

Table 1 Summary of treatment arm demographics by study

	ANTHEM-HF $N = 60$	INOVATE-HF $N = 436$	Difference[a] [95% CI]	P^a	NECTAR-HF $N = 63$	Difference[b] [95% CI]	P^b
Age (years)	52 ± 12	62 ± 10	−10 [−12.2, −7.8]	<0.0001	60 ± 12	−8 [−12.2, −3.7]	0.0003
Male gender (%)	87	78	9 [−2.4, 16.6]	0.11	89	2 [−10, 14]	0.73
Ischaemic HF (% Patients)	75	59	16 [3, 26]	<0.02	70	5 [−10, 20]	0.5
NYHA 1/2/3/4 (%)	0/57/43/0	0/0/100/0	57[c] [44, 69][c]	<0.0001[c]	0/12/88/0	45[c] [29, 58][c]	<0.0001[c]
Body mass index (kg/m^2)	24 ± 4	30 ± 6	−6 [−7.6, −4.4]	<0.0001	29 ± 6	−5 [−6.8, −3.2]	<0.0001
Systolic BP (mm Hg)	113 ± 15	118 ± 17	−5 [−9.1, −0.8]	<0.02	118 ± 17	−5 [−10.7, 0.7]	<0.09
Heart rate (bpm)	78 ± 10	73 ± 12	5 [1.8, 8.1]	0.0022	68 ± 13	10 [5.8, 14.2]	<0.0001
LVEF (%)	32 ± 7	24 ± 7	8 [6.1, 9.8]	<0.0001	31 ± 6	−1 [−3.3, 1.3]	0.396
6-min walk distance (m)	287 ± 66	304 ± 111	−17 [−46, 12]	0.247	Unavailable	-	-
Beta-blockers (%)	100	94	6 [−0.3, 8.6]	0.052	94	6 [−1, 15]	0.055
ACEi or ARB (%)	85	88	−3 [−14, 5]	0.5	NR	-	-
MRA (%)	75	59	16 [3, 26]	<0.02	68	7 [−9, 22]	0.39
CRT (%)	0	2	-	-	0	-	-
CRT-D (%)	0	33	-	-	5	30[c] [21, 36][c]	<0.0001[c]
ICD (%)	0	47	-	-	51	24[d] [12, 37][d]	<0.0001[d]
Pacemaker (%)	0	1	-	-	NR	-	-

ACEi, angiotensin converting enzyme inhibitor; BP, blood pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NR, not reported; NYHA, New York Heart Association.

The remainder of the abbreviations are described in the text and the other tables. NN ± NN = mean ± standard deviation.
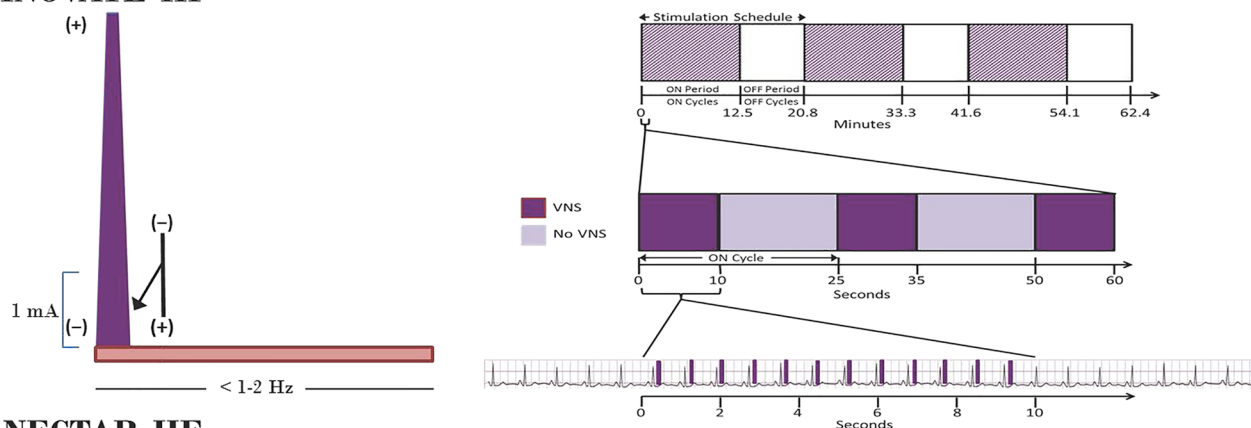[a]ANTHEM-HF vs. INOVATE-HF.
[b]ANTHEM-HF vs. NECTAR-HF, with the exception of differences in electrical device implantations before randomization. [c]Percentage of patients in NYHA 3.
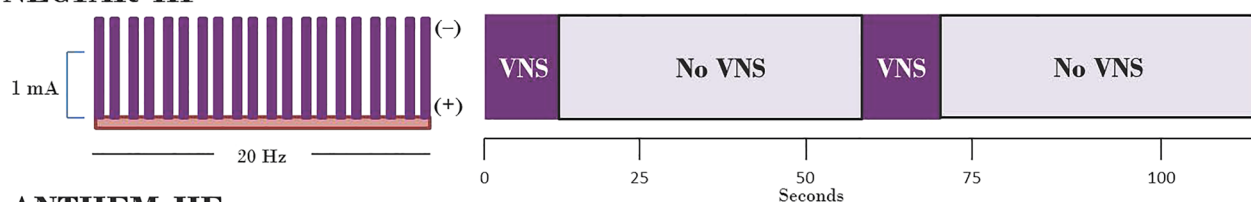[c]INOVATE-HF vs. NECTAR-HF (any CRT).
[d]INOVATE-HF vs. NECTAR-HF (any cardioverter-defibrillator therapy).

Figure 4 Differences in vagal nerve stimulation polarity, pulse frequency, and stimulation schedules across studies. A very complex repetitive schedule of stimulation was utilized in increase of vagal tone in heart failure, as illustrated here and described in the text.
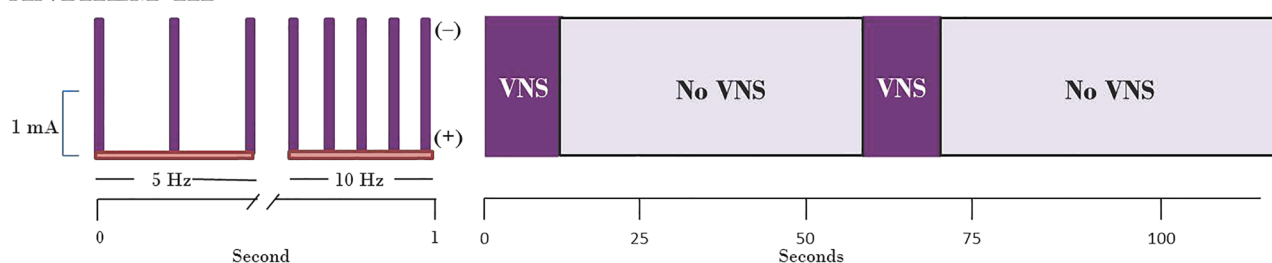

Table 2 Summary of vagal nerve stimulation delivery by study

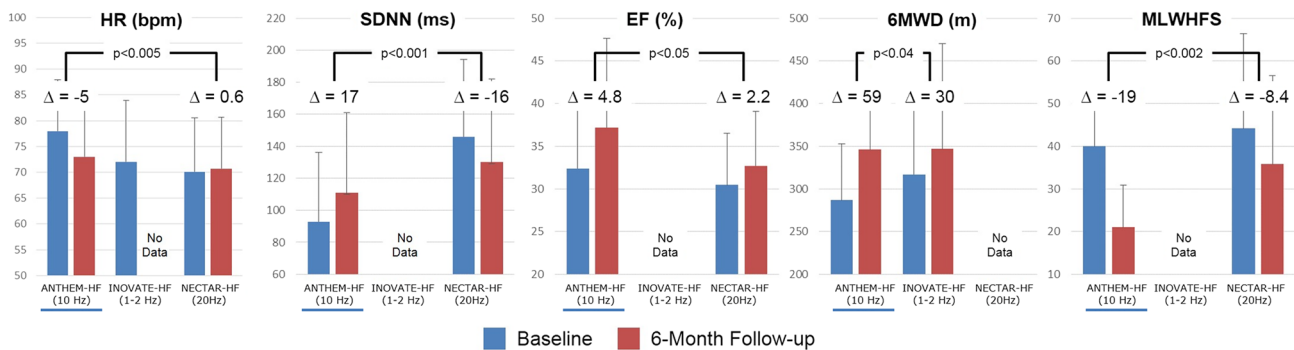|	ANTHEM-HF	INOVATE-HF	NECTAR-HF
Neural target	Central/peripheral	peripheral	Central/peripheral
Delivery site	Left or right CVN	Right CVN	Right CVN
Delivery intensity			
Amplitude (milliamperes)	2.0 ± 0.6^a	3.9 ± 1.0^a	1.4 ± 0.8^a
Frequency (Hz)	10	$1–2^b$	20
Duration (ms)	250	500	300
Electrode polarity (cathode)	Caudal	Cephalad	Caudal
Duty cycle	23%	25%	17%
On-time/off time (s)	18/62	Variable	10/50
Mode of delivery	Open loop /cyclic	Closed loop /intermittent	Open loop / intermittent

CVN, cervical vagus nerve; a=mean ± standard deviation; b=range
The remainder of the abbreviations are described in the text and the other tables.

rate, SDNN, LVEF, and Minnesota Living with Heart Failure (MLWHF) questionnaire mean score were observed in ANTHEM-HF. When INOVATE-HF and ANTHEM-HF were compared, a greater improvement in 6-min walk distance was observed in ANTHEM-HF.

Discussion

In this post-hoc analysis, differences in some patient demographics were observed across the three studies. The GDMT administered in ANTHEM-HF compared favorably with the

GDMT administered in INOVATE-HF, NECTAR-HF, and has also compared favorably with other contemporary studies of novel HF therapies for patients with HFrEF.[19]

The methodologies used for VNS in ANTHEM-HF, INOVATE-HF, and NECTAR-HF differed considerably in their neurologic targets, technology platforms, the mode and delivery of VNS for ART, and the responses in heart rate and heart rate variability that occurred in association with VNS.[10,20,21] INOVATE-HF was a multinational, randomized, controlled study of high amplitude, low-frequency VNS plus GDMT vs. GDMT alone in 707 patients with chronic HF, NYHA 3 symptoms, and ejection fraction ≤ 40%. VNS delivery aimed preferentially at peripheral neural targets using closed-loop, low-frequency, asymmetric pulses and was not associated with any long-term change in mean heart rate or heart rate variability. The primary efficacy endpoint of a composite of death or HF hospitalization occurred more often in the VNS group than in the control group but was not significantly different. Improvements occurred in the secondary endpoint outcomes of NYHA class, Kansas City Cardiomyopathy Questionnaire mean score, and 6-min walk distance.[12]

NECTAR-HF was a multicentre, randomized, sham-controlled study of low-amplitude, high-frequency VNS plus GDMT, vs. GDMT alone, in 96 patients with chronic HF, NYHA Class 2 or 3, and ejection fraction ≤ 35%. The study investigators reported that side effects (e.g. neck pain and coughing) associated with a pulse frequency of 20 Hz limited titration to low stimulation amplitudes and resulted in no significant long-term reduction of heart rate or increase in heart rate variability. Whereas there were significant improvements in MLWHF mean score, Short Form Health Survey, and NYHA class after 6 months of follow-up, VNS did not reduce the primary efficacy endpoint, LV end-systolic diameter, or other secondary echocardiographic measures.[13] A follow-up NECTAR-HF report presented results after 18 months of VNS in 96 patients with the aim of evaluating long-term efficacy of VNS at 20 Hz.

Although the long-term safety profile was favourable, no improvement in the efficacy endpoints was seen with the VNS dose that was delivered. A detailed analysis demonstrated that in the majority of patients, the VNS protocol used in that study generated no significant change in parameters of heart rate variability indicative of autonomic modulation.[22]

The ANTHEM-HF pilot study was a multicentre uncontrolled study that randomized 60 patients with HFrEF to VNS of the right or the left CVN. VNS delivery using 10 Hz, and titration based upon confirmation of autonomic engagement using changes in heart rate dynamics as a biomarker, was associated with significant improvements from baseline in mean heart rate, heart rate variability (SDNN), LVEF, 6-min walk distance, and MLWHF mean score.[11,16]

While VNS in ANTHEM-HF was associated with greater improvements in symptoms and function when compared with VNS in INOVATE-HF and NECTAR-HF; any conclusions that may be drawn should be considered hypothesis generating. Data from the treatment arms was compared across three studies because the ANTHEM-HF pilot study was an uncontrolled study. It is possible that the improvements in symptoms and function that were seen may not have been solely attributable to ART alone or could have occurred due to a Hawthorne effect, especially in the more subjective assessments.

It is noteworthy that titration of VNS delivery ANTHEM-HF resulted in an acute change in heart rate dynamics, and a long-term decrease in heart rate and increase in heart rate variability were observed only in that study. It is also encouraging that the overall direction of change that occurred in symptoms and function after 6 months has also continued in a cohort of ANTHEM-HF patients after 12, 24, and 42 months of VNS.[23,24] Further study is underway in a randomized controlled trial with these considerations in mind. The ongoing ANTHEM-HFrEF pivotal study is a multinational, multicentre, randomized controlled trial evaluating the use

of ART in addition to GDMT to improve symptomatic and functional outcomes and to decrease morbidity and mortality.[3]

Conclusions

HFrEF is associated with sympatho-vagal imbalance consisting of sustained sympathetic hyperactivation and withdrawal of parasympathetic tone.[25] Clinical studies that have administered VNS to deliver ART to patients with HFrEF have reported disparate responses in symptoms and function. In a post-hoc analysis of the treatment arms of the ANTHEM-HF pilot, INOVATE-HF, and NECTAR-HF studies, some differences in patient demographics were observed and could have influenced the respective outcomes of these three studies. There were also considerable differences in the technology platforms, neural targets, and delivery methods for VNS, and these may have also had an important role in the relative magnitudes of response to VNS that were observed in heart rate, heart rate variability, symptoms, and function across these studies. Further study is underway in a randomized controlled trial with these considerations in mind.

Conflict of interests

D.G. is a biostatistician and employee of Cardiovascular Clinical Studies Foundation LLC (CCSF), the contract research organization (CRO) that has been contracted by LivaNova for ANTHEM-HFrEF pivotal study operations. J.U. is contracted to CCSF as a cardiovascular consultant. J.M. is contracted to CCSF for statistical consultation. M.K. is contracted to CCSF and LivaNova, respectively, as a cardiovascular consultant. J.A. is contracted to LivaNova as a neuro-cardiology consultant. J.B., H.K., M.K., D.M., J.P., J.T., and J.U. are contracted to LivaNova as members of the ANTHEM-HFrEF pivotal study steering committee. I.L. and L.D. are employees and shareholders of LivaNova, USA Incorporated.

Author contributions

No medical writer was used. All authors contributed to the writing of this manuscript, had full access to all of the data that were used for this analysis, and agreed to submit this manuscript for publication. Co-author involvement was as follows: I.A., M.K., J.U., J.B., H.K., J.P., J.T., and D.M. (interpretation and writing), J.A. (interpretation, figures, and writing), D.G. and J.M. (analysis, interpretation, and writing), I.L. (data collection, figures, and writing), L.D. (data collection, figures, and writing).

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