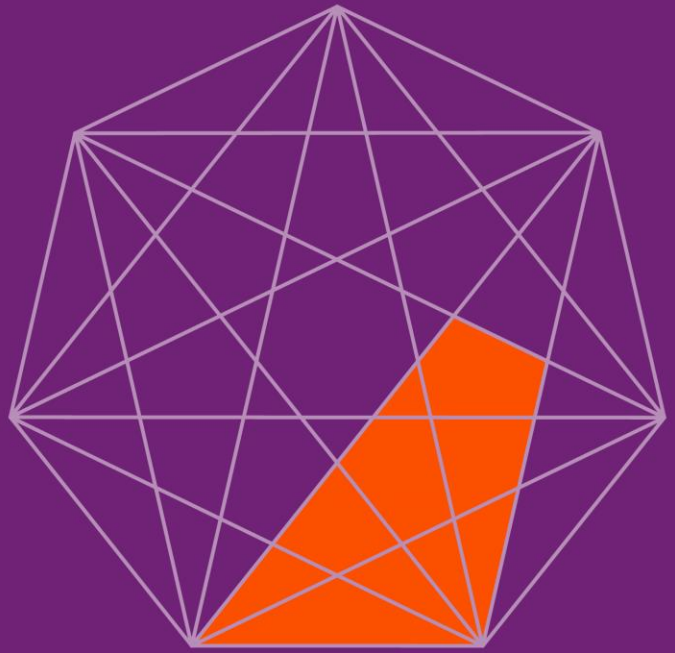

LivaNova Education Series:

Therapy for Heart Failure

“ART for the Heart”

LivaNova
Heart Failure

Safe Harbor

Certain statements in this presentation, other than purely historical information, are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). These statements include, but are not limited to, LivaNova's plans, objectives, strategies, financial performance and outlook, trends, the amount and timing of future cash distributions, prospects or future events and involve known and unknown risks that are difficult to predict. As a result, our actual financial results, performance, achievements or prospects may differ materially from those expressed or implied by these forward-looking statements. In some cases, you can identify forward-looking statements by the use of words such as "may," "could," "seek," "guidance," "predict," "potential," "likely," "believe," "will," "should," "expect," "anticipate," "estimate," "plan," "intend," "forecast," "foresee" or variations of these terms and similar expressions, or the negative of these terms or similar expressions. Such forward-looking statements are necessarily based on estimates and assumptions that, while considered reasonable by LivaNova and its management based on their knowledge and understanding of the business and industry, are inherently uncertain. These statements are not guarantees of future performance, and stockholders should not place undue reliance on forward-looking statements. There are a number of risks, uncertainties and other important factors, many of which are beyond our control, that could cause our actual results to differ materially from the forward-looking statements contained in this presentation, including the risks relating to the COVID-19 pandemic or settlement of litigation, as well as those described in the "Risk Factors" section of Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other documents filed from time to time with the United States Securities and Exchange Commission by LivaNova. All information in this presentation is as of the date of its release. The Company does not undertake or assume any obligation to update publicly any of the forward-looking statements in this presentation to reflect actual results, new information or future events, changes in assumptions or changes in other factors affecting forward-looking statements, except to the extent required by applicable law. If we update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements. We caution you not to place undue reliance on any forward-looking statements, which are made only as of the date of this presentation.

In this presentation, "LivaNova," "the Company," "we," "us" and "our" refer to LivaNova PLC and its consolidated subsidiaries.

LivaNova

Positioning LivaNova to Realize its Full Value

Consistently deliver growth, pipeline and profitability

Core Growth

Focus on portfolio optimization to support leadership positions in underserved markets

- Expand and enhance commercial initiatives for U.S. Epilepsy
- Forecast at least 30% ACS growth in 2020 and at least 20% in 2021

Pipeline Execution

Multiple existing and pipeline initiatives to accelerate growth

- Achieve key study milestones in RECOVER and ANTHEM HFrEF
- Continued progress on next generation Heart-Lung Machine

Operational Excellence

Drive margin expansion

- Expand Operating margin through cost discipline
- Drive improvement in free cash flow generation

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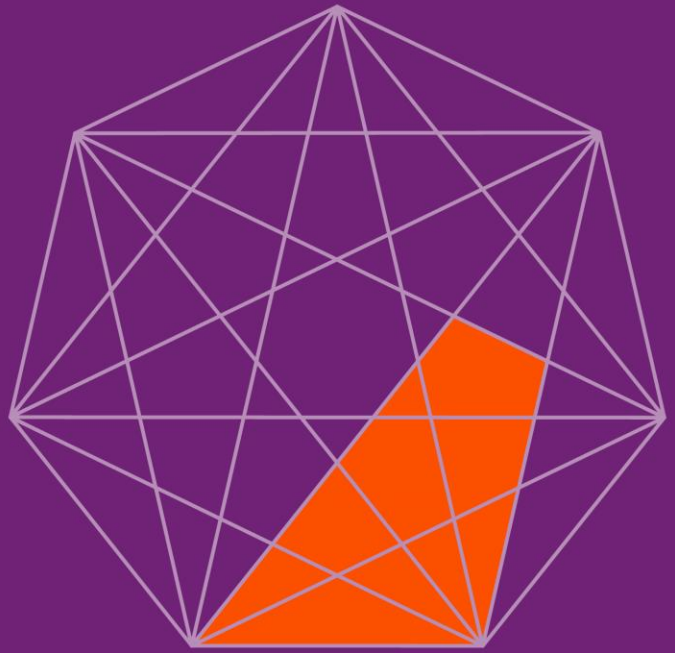


Autonomic Regulation Therapy for Heart Failure

"ART for the Heart"

Bruce H. KenKnight, PhD
Vice President, New Ventures – HF Program

Marvin Konstam, MD – Clinical Perspective
Tufts Medical Center

LivaNova
Heart Failure

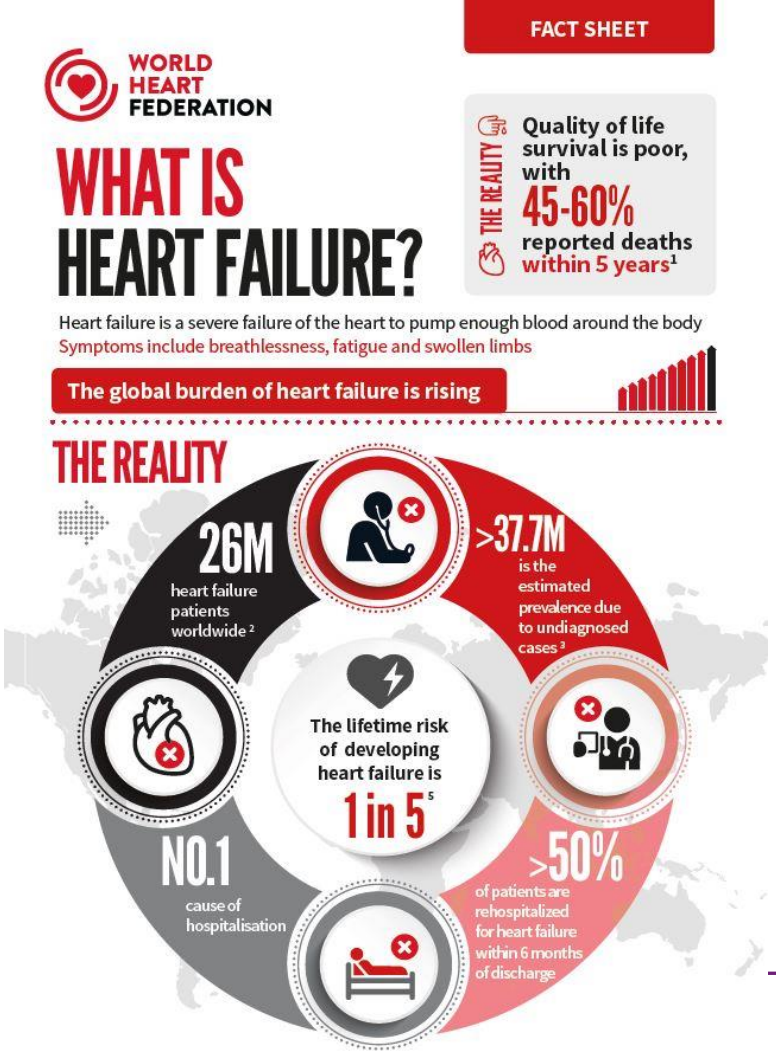
Agenda

Program

- Unmet in HF - growth opportunity
- Therapy and product development approach
- Therapy fundamentals
- Partnership with FDA and CMS
- Addressable market

Clinical Perspective

- Progression of HF
- Neuromodulation mechanisms
- Prior clinical evidence
- Pivotal Study design and implications
- Summary
- Discussion



Neuromodulation for HF Provides Substantial Strategic Growth Opportunity for LivaNova

- HF is a progressive syndrome characterized by compromised cardiovascular function, including heart pump function and blood flow
- Common symptoms include progressive fatigue, intolerance to physical activity, and fluid retention
- Progression of HF severity is linked to abnormal autonomic nervous system (unconscious) function
  - Symptoms ⇨ Hospitalizations ⇨ Death
- Neural modulation may improve neural regulation of cardiovascular function and thereby reduce symptoms, hospitalizations and improve quality of life and survival in patients with chronic HF

Focused on a Systematic Approach to our ART Program

- VITARIA® System delivers Autonomic Regulation Therapy (ART) via vagus nerve stimulation
- Supporting evidence[1-3] and strong collaboration with FDA led to design[4] and approval of ANTHEM Pivotal Study with FDA's *Breakthrough Technology* designation
- CMS's MCIT Rule provides immediate national coverage for VITARIA when authorized by FDA
- Multi-national, adaptive, randomized, controlled clinical trial underway
  - Good progress with enrollment and randomization
  - Regaining momentum post-COVID

FDA

CMS

Breakthrough Technology designation ☑

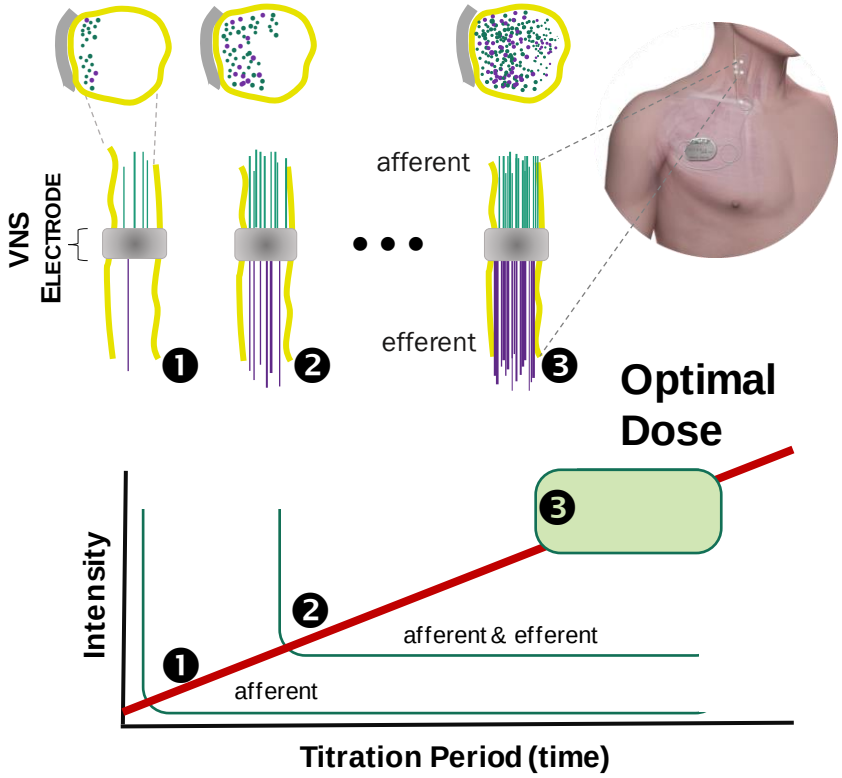
ANTHEM HFrEF Pivotal Study

LivaNova

Autonomic Regulation Therapy (ART)

How it works

- Electrical stimulation of **vagus nerve** with **specific intensity and temporal pattern** results in beneficial alteration of post-ganglionic signaling
- Neuromodulation targets are understood
  - Central & Peripheral
  - Ganglionic and Post-ganglionic
  - Activation (cholinergic) & Inhibition (adrenergic) of muscarinic (M_2) myocyte receptor systems
- Unique Approach: ART Dose is optimized in each patient by measuring real-time heart rate dynamics during ON-time compared to OFF-time[1]



Libbus I, et al *J Electrocardiol 2017*
Ardell JL, et al. *Am J Physiol Heart Circ Physiol* 2015
Ardell JL, et al. *J Physiol*. 2017

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ANTHEM Pivotal Study designed to accelerate evidence generation and FDA approval by bridging pre/post market

- Extensive pre-clinical research enabled new understanding of ART based on key fundamentals[1]

  anatomy • physiology • biophysics • engineering

- Initial clinical research yielded strong results[2,3]

  safety • efficacy • patient selection • titration • therapy dosing • durability of outcomes

- Partnership with FDA resulted in:
  - *"Breakthrough Technology"* designation
  - Novel study design including:
    - Adaptive sample size driven by pre-specified interim analyses
    - Endpoints accepted by HF specialists may result in rapid adoption of ART
    - Pre- to Post-Market transition

1. Ardell JL et al. *J Physiol* 2017;595.22:6887-6903
2. Premchand RK et al. *J Card Fail* 2016;22(8):639-42
3. Sharma K. et al. *International J Cardiol* 2020; 323:175-78

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Recent CMS Rule Automatically Provides National Coverage for VITARIA Upon PMA Approval

- Final Rule issued Jan 12, 2021
- *Medicare Coverage of Innovative Technology* (MCIT), for FDA-designated breakthrough medical devices
- Provides immediate national Medicare coverage upon FDA authorization for breakthrough devices for a period of 4 years (includes LivaNova VITARIA System)
- This new coverage pathway will offer beneficiaries nation-wide, predictable access to new, breakthrough devices to help improve their health outcomes

CMS

Press release

CMS unleashes innovation to ensure our nation's seniors have access to the latest advancements

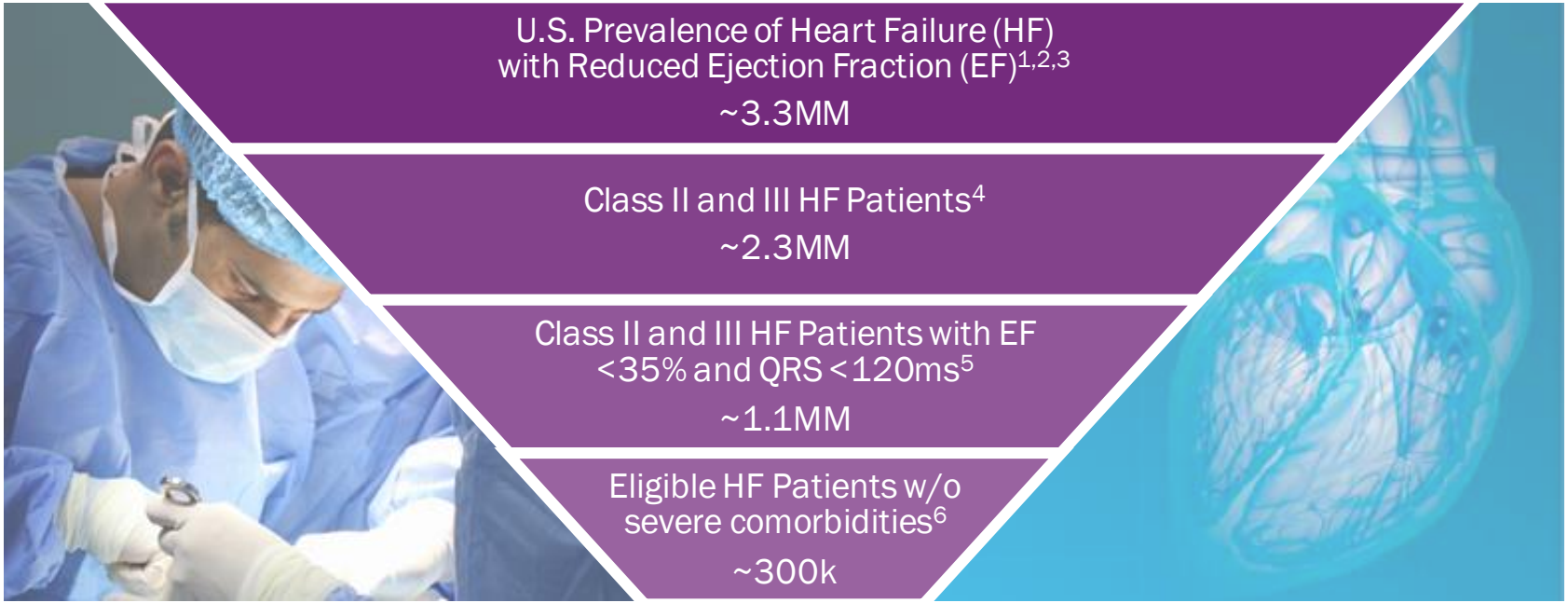
Jan 12, 2021 | Coverage, Initiatives

Today, the Centers for Medicare & Medicaid Services (CMS) issued a final rule that propels innovative technology so Medicare beneficiaries have access to the latest, most advanced devices. Today's action represents a step forward that will help smooth the Medicare coverage pathway for innovative products, resulting in faster access to new devices for America's seniors. This action delivers on CMS's Unleashing Innovation and Patients Over Paperwork Initiative.

https://www.cms.gov/newsroom/press-releases/cms-unleashes-innovation-ensure-our-nations-seniors-have-access-latest-advancements

LivaNova

VITARIA® for HFrEF – Addressable Market in US



[1] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2017. Accessed January 7, 2019.
[2] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–528.
[3] Jackson et al, Circ Heart Fail. 2018 National Burden of HF Events in US.
[4] Zhang et al. BMC Medical Informatics and Decision Making 2018, 18(Suppl 2):48 Discovering and Identifying NYHA classification from HER.
[5] Savarese et al, JACC, Heart Failure, Vol 7, No4, 2019, Ejection fraction change in heart failure.
[6] Bruch et al, Europace (2007) 9, 681–686, Prevalence and prognostic impact of co-morbidities in heart failure patients.

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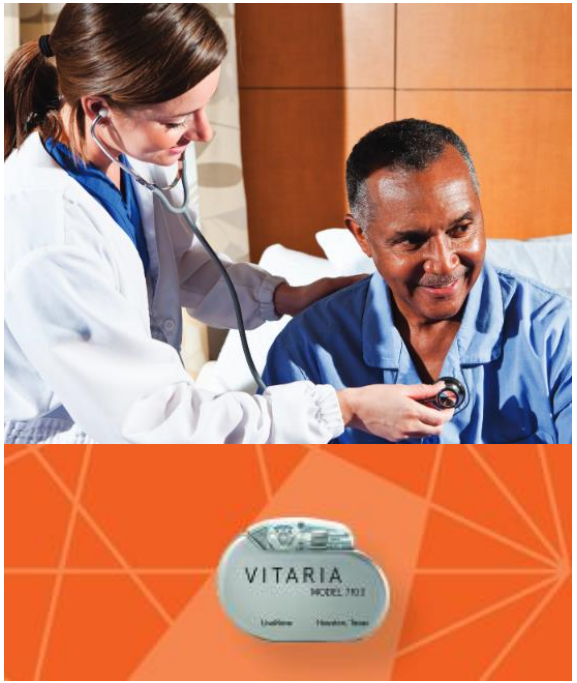
HF Program Provides Growth Opportunity for LivaNova

- Improving patient outcomes is **#1 priority for LivaNova**
- Market potential is large; prevalence and incidence pools continue to grow
- HF patients are receptive to implantable device technologies with compelling evidence of clinical benefit
- LivaNova is the world's leader in VNS technology and clinical experience
- ANTHEM Pivotal Study is based on the best, contemporary understanding of integrated neurophysiology and adaptive trial design methods
- Success in HF market has potential to transform LivaNova



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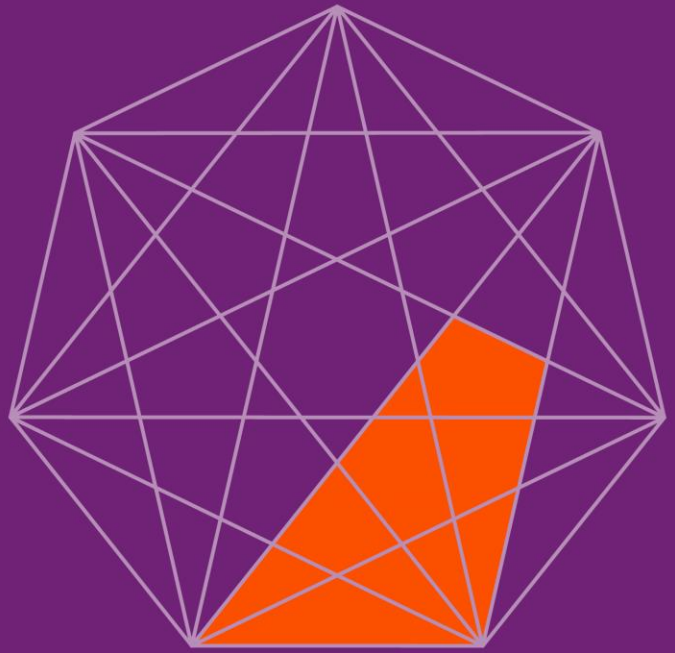


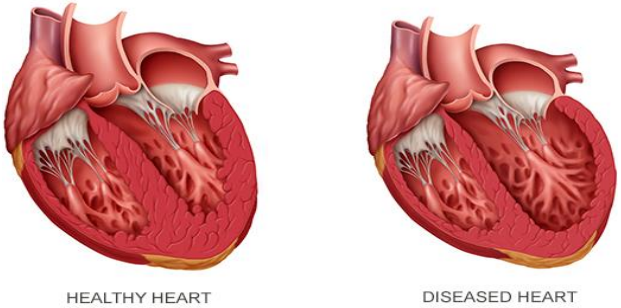
Clinical Perspectives

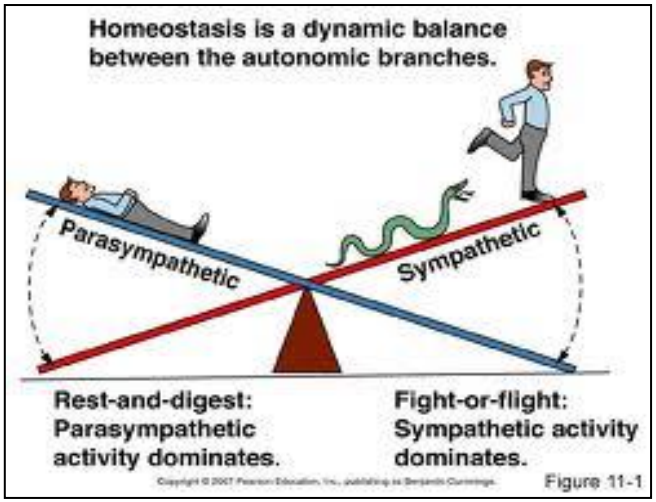
Dr. Marvin Konstam

LivaNova

Heart Failure

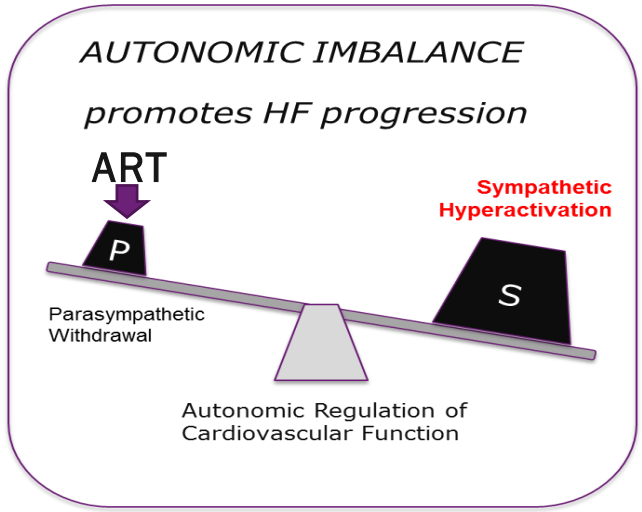
Prognosis for HF Patients Remains Poor Despite Drug Therapy





① HF progresses despite usual and customary care with Guideline-Directed Medical Therapy (GDMT)[1]

② Chronic heart failure is associated with and aggravated by autonomic dysregulation[2]



1. Yancy CW et al. ACC-AHA-HFSA Guidelines *J Card Fail* 2017
2. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877-883

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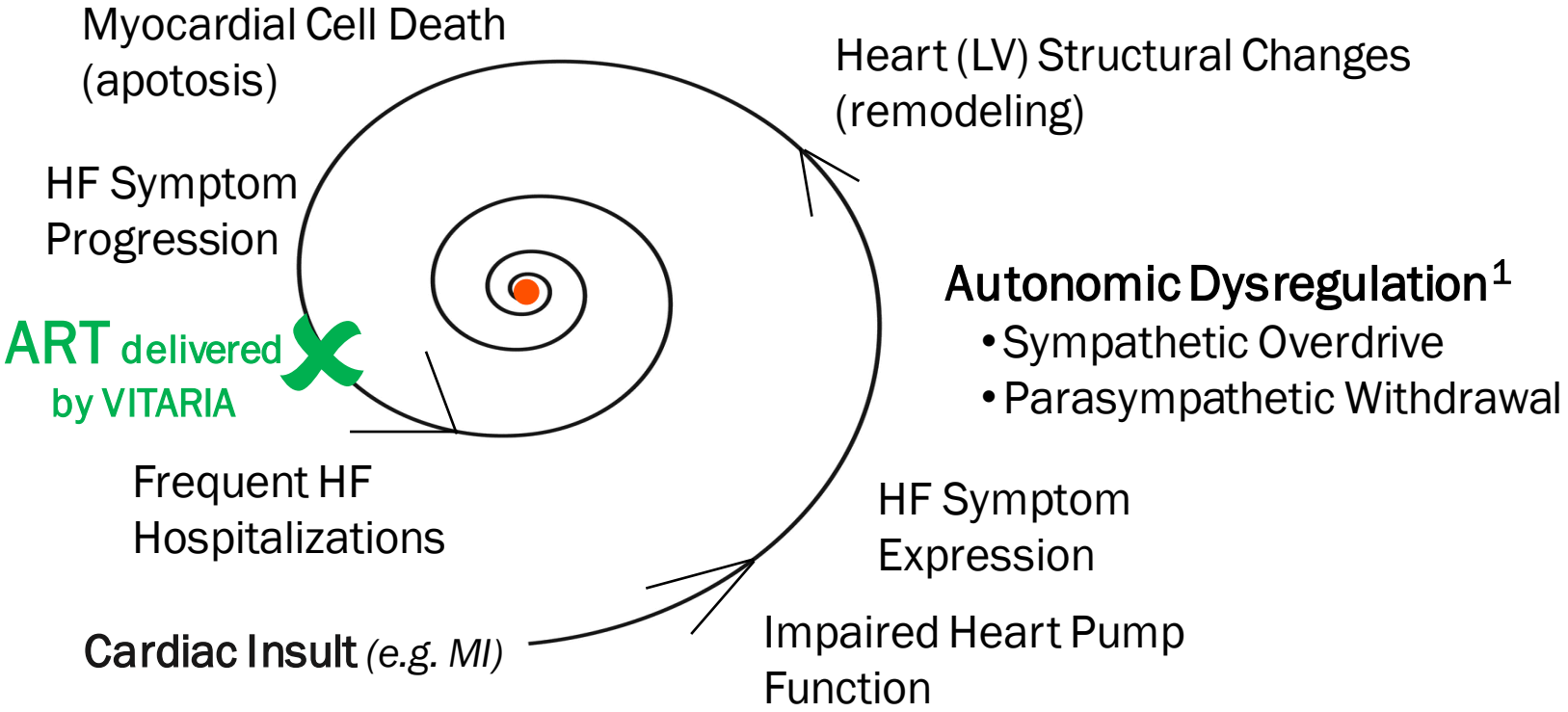
HF is a Progressive Condition[1]



1. Yancy CW et al. ACC-AHA-HFSA Guidelines *J Card Fail* 2017
2. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877-883

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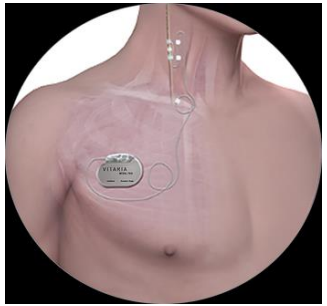
Adverse Effects of Autonomic Dysregulation

Adverse Effect	Reference
Tachycardia	*Exp Physiol* 2010;95:919-25; *Circ Heart Fail* 2009;2;692-99
Supraventricular and ventricular tachyarrhythmias	*Circulation* 2005;112:164-70; *IEEE Eng Med Biol* 2005;7:7072-75
Reduced coronary flow	*Cardiovasc Res* 2001;49:27-37
Increased oxidative stress	*Cardiovasc Res* 2008;77:713-21
Endothelial dysfunction	*Hypertension* 2016;68:1004-10
Reduced sympathetic responsiveness	Circ Heart Fail 2009;2:692-9
Renin-angiotensin system activation	*Clin Auton Res* 2019;29:231-43
Direct myocardial injury	*J Am Coll Cardiol* 2019;73:1189-1206
Adverse myocardial remodeling and fibrosis	*Am J Physiol Heart Circ* 2007;293: H2254-61
Apoptotic gene expression	*Eur J Heart Fail* 2007;6:114; *Circ Heart Fail* 2009;2;692-99
Immune system activation and inflammation	*J Clin Invest* 2007;117:289-96; *Nature* 2002;420:853–59

Autonomic Regulation Therapy (ART)

Central *(afferent)*



Peripheral *(efferent)*

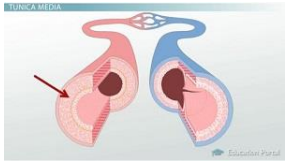
Autonomic Regulation Therapy

Integrated Reflex Control

↑ Parasympathetic *(muscarinic)*
↓ Sympathetic *(adrenergic)*

Central *(afferent)*

Peripheral *(efferent)*



ART
•
CV Regulation
•
Myocyte Receptor Systems
•
Cellular Metabolism
•
Gene Expression
•
Organ Function
•
Symptom Reduction & Survival Benefit

Cardiovasc Res 2001;49:27-37
Br J Pharmacol 1988;95:830-34
J Physiol 2009;587:3045-54
Circ 2004;109:120-124
J Card Fail 2010;16:689-99
Circ Heart Fail 2009;2:692-99
Eur J Heart Fail 2007;6:114
Cardiovasc Res 1983;17:50-60
Circ 2005;112:164-70
Cardiovasc Res 2008;77:713-21
J Mol Cell Cardiol 2010;49:234-44
Nature 2002;420:853-59

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ANTHEM Pilot Study Results

Concordance among data is encouraging [1,2,3]

	Baseline	12 Months	p-value	Proof of Feasibility	
LVEF (%)	33.2 ± 7.4	39.5 ± 10.4	<0.0005	Better LV Function	✓
NYHA Class (I/II/III/IV)	0/26/20/0	32/14/0/0	<0.0005	Improved Symptoms	✓
Quality of Life (MLHFQ Score)	39 ± 12	18 ± 9	<0.0005	Improved Symptoms	✓
HRV (SDNN, ms)	95 ± 29	109 ± 40	<0.01	Decreased Sympathetic Drive	✓
6 min walk (m)	288 ± 64	352 ± 62	<0.0005	Improved Function	✓

1. Premchand RK et al. *J Card Fail* 2016;22:639-42
2. Sharma K et al. *Int J Cardiol* 2021;323:175-78
3. Baseline and 12 Months n=46

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ANTHEM Pilot – Extended Follow-up Study

Therapy effects appear durable

	Baseline	12 Months	24 Months	30 Months	42 Months	p-value 0-42M
LVEF (%)	35.0 ± 6.9	42.6 ± 10.4	41.7 ± 10.0	44.8 ± 12.0	40.8 ± 12.5	0.005
LVESV (mL)	92.8 ± 31.3	77.6 ± 35.7	81.6 ± 35.6	82.4 ± 47.2	92.7 ± 51.2	NS
LVESD (mm)	48 ± 7.9	46 ± 7.0	47 ± 7.5	47 ± 10	46 ± 12	NS
NYHA Class (I/II/III/IV)	0/19/14/0	23/10/0/0	21/11/1/0	20/12/1/0	20/12/1/0	<0.0001
6MWD (m)	297 ± 62	354 ± 58	359 ± 47	367 ± 40	389 ± 70	<0.0001
MLHFQ score	38 ± 12	17 ± 9	21 ± 11	17 ± 9	10 ± 12	<0.0001
HRV (SDNN, ms)	96 ± 27	107 ± 32	112 ± 44	110 ± 30	107 ± 28	<0.025
Holter HR (bpm)	74 ± 10	75 ± 9	77 ± 10	76 ± 9	78 ± 11	NS

1. Sharma K et al. *Int J Cardiol* 2021;323:175-78. n=33 in at all time points

ANTHEM Pivotal Study Designed to Align with FDA's "*Breakthrough Devices Program*"

- *Breakthrough Devices Program*[1] improves FDA process for rapid evaluation and approval of major unmet medical needs involving debilitating diseases or conditions to protect and promote public health.
- LivaNova VITARIA System officially designated
- Benefits include: Interactive high-priority relationship with FDA regarding all discussions, IDE applications and marketing submissions
- ANTHEM Pivotal Study designed in collaboration with FDA and is based on best information regarding statistically-rigorous sample size adaptations, patient selection, and optimized therapy delivery

Breakthrough Devices Program

1. https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program
Breakthrough device program is currently under customary review by the incoming Presidential Administration

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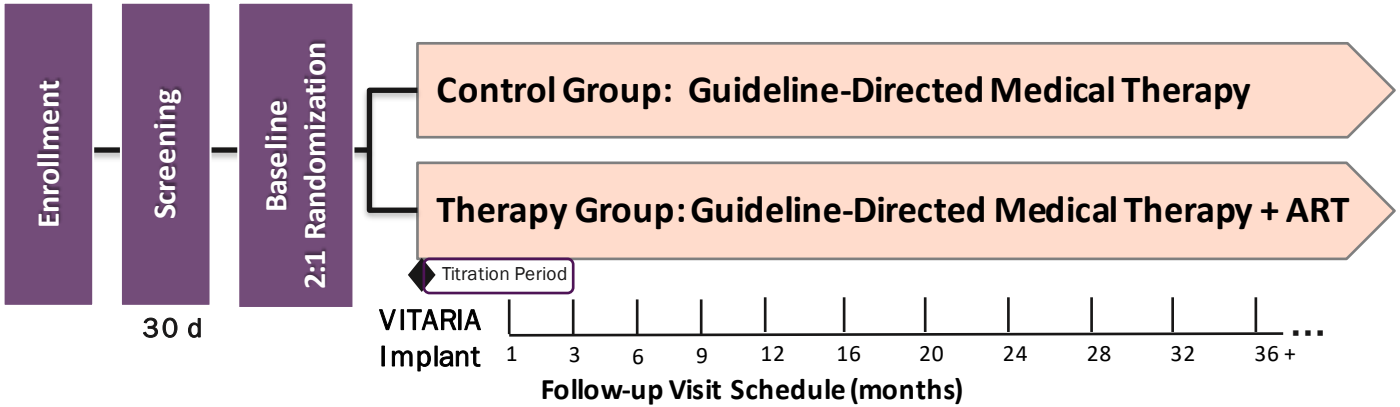
ANTHEM Pivotal Study Design

Adaptive, multi-national, open-label, randomized, controlled

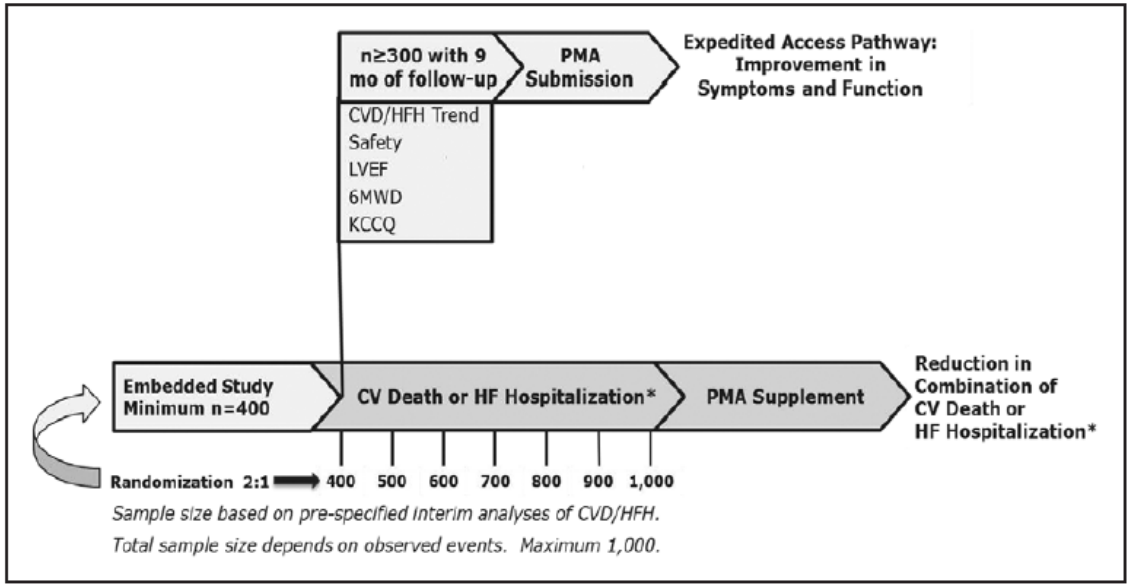


- Key Inclusion Criteria; selects for symptomatic patients likely to have outcome events
  - stable GDMT for ≥4 weeks, symptomatic
  - NYHA class III or class II if hospitalized for HF within the previous 12 months
  - LVEF ≤ 35%, LVEDD <8.0 cm
  - NT-proBNP ≥800 pg/mL and 6-minute walk distance (6MWD) of 150 to 450 meters, limited by HF symptoms
- Key Characteristics
  - Adaptive sample size selection based on pre-specified assessment of adjudicated Primary Events
  - Primary Outcome: time-first-event, HF Hosp or CV death
  - Novel design utilizes embedded study to provide data for both pre-market and post-market regulatory submissions
    - improved symptoms and function (PMA), and
    - reduction of morbidity and mortality (PMA Supplement)

1. Konstam MA et al. ANTHEM-HFrEF Pivotal Study Design. Circulation: Heart Failure. 2019

ANTHEM Pivotal Study Design

FDA's Breakthrough Devices Program provides expedited pathway



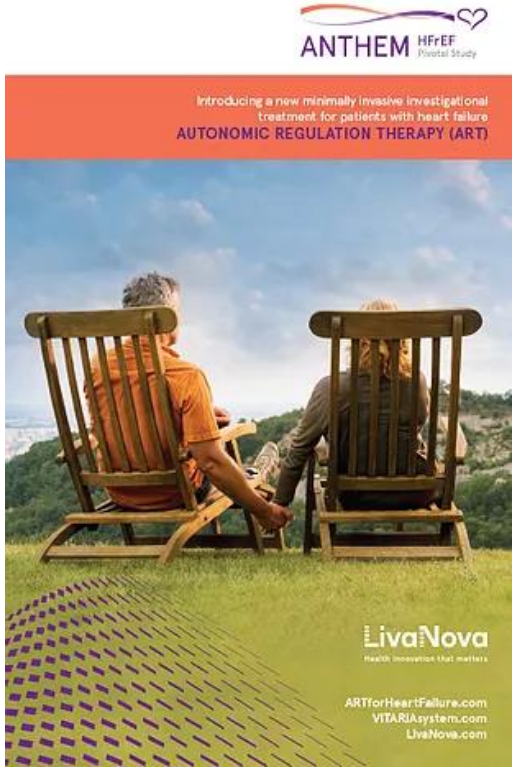
- Bayesian, adaptive design determines most appropriate sample size selection
- Stratification for:
  - Region
  - 6-min walk
  - ±Heart Transplant Site
  - ±ICD/CRT recipient
- Interim Analyses of embedded trial provides PMA pathway for improved symptoms and function
- Early stopping for expected Success or Futility

Konstam MA, et al., The ANTHEM-HFrEF Pivotal Study Design. *Circ Heart Fail* 2019

ART = Autonomic Regulation Therapy; GDMT = Guideline-directed Medical Therapy (drugs)
CVD = Cardiovascular death; HFH = HF hospitalization; LVEF = LV ejection fraction;
6MWD = 6 min walk distance; KCCQ = Kansas City Cardiovascular Questionnaire (QoL)

Summary – Clinical Perspectives

- Therapeutic target has strong scientific basis
- Patients with chronic HF need adjunctive treatment options
- ANTHEM Pivotal informed by results of previous trials
  - Study committee members have reviewed and validated the therapeutic approach and study design
  - Site Investigators and staff are committed to trial execution
  - LivaNova has strong, experienced Team executing the trial
- Strong clinical outcomes data will be used to support PMA
  - statistically significant and clinically meaningful changes
- Strong clinical outcomes will facilitate:
  - inclusion of ART indication in published HF management Guidelines, and
  - promote adoption of ART by HF Specialists



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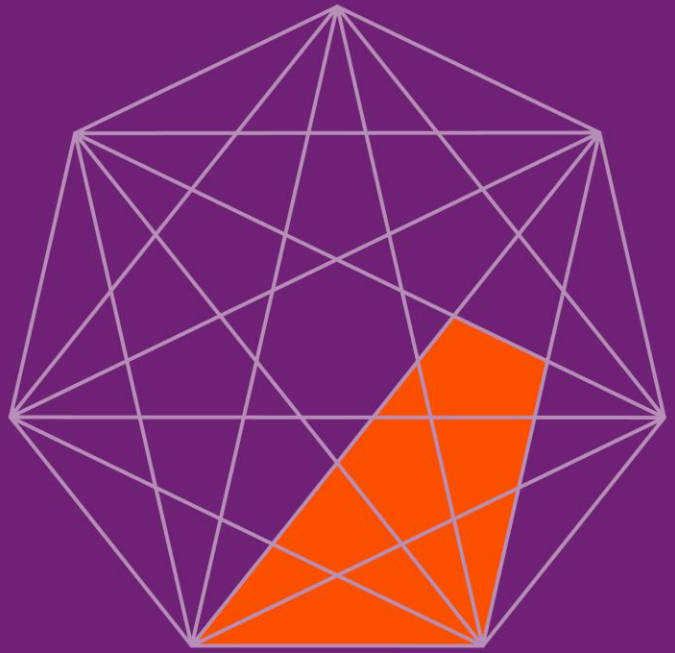

Discussion

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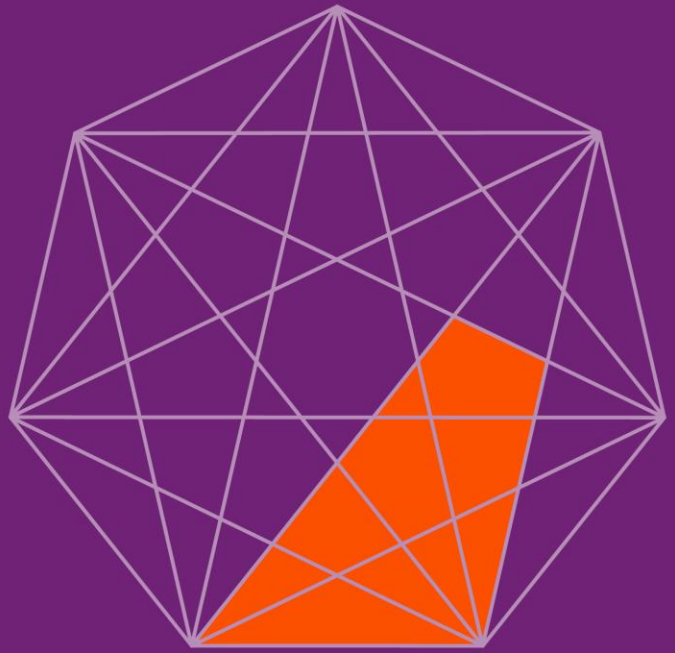

Appendix

LivaNova
Heart Failure

Publications

Citation (abbreviated)	Topic	Message
Hadaya J, Ardell JL. Autonomic Modulation for Cardiovascular Disease. *Frontiers in Physiology* Dec 2020	Review	Dysfunction of the autonomic nervous system is implicated in pathogenesis of cardiovascular disease. Neuromodulation has emerged as treatment approach to attenuate disease progression
Anand IS, et al. Baseline NT-proBNP and Responsiveness to Vagus Nerve Stimulation in Patients with Heart Failure and Reduced Ejection Fraction. *Int J Cardiol Heart Vasc* 2020	Differentiation	The VITARIA stimulation lead has demonstrated excellent long-term performance, with a low rate of complications and failures
Anand IS, et al. Long-Term Lead Performance for Vagus Nerve Stimulation: Low Rate of Complications and Failures. *NeuroRegulation* 2020	Differentiation	The VITARIA stimulation lead has demonstrated excellent long-term performance, with a low rate of complications and failures
Anand IS, et al. Comparison of Symptomatic and Functional Responses to Vagus Nerve Stimulation in ANTHEM-HF, INOVATE-HF, and NECTAR-HF. *ESC Heart Fail* 2020	Differentiation	Compared to contemporary studies of ART in heart failure patients, the ANTHEM-HF pilot study demonstrates effective autonomic engagement resulting in significantly greater improvement in cardiac function and heart failure symptoms
Anand IS, et al. Neuromodulation for Drug-Refractory Epilepsy and Chronic Heart Failure: Targets, Delivery, Composition, and Titration. *Int J Neurol Neurother* 2019	Differentiation	There are significant differences between delivery of ART in heart failure patients and therapy delivery of VNS in epilepsy patients, and ART has been tailored to heart failure patients

Publications

Citation (abbreviated)	Topic	Message
Konstam MA, et al. Impact of Autonomic Regulation Therapy in Patients with Heart Failure: The ANTHEM-HFrEF Pivotal Study Design. *Circ Heart Fail* 2019	Pivotal Study Design based on FDA's *Breakthrough Device Program*	The ANTHEM-HFrEF pivotal study is a randomized, controlled, adaptive study of up to 1000 heart failure patients, designed to evaluate the safety and efficacy of ART in patients with heart failure with reduced ejection fraction
Premchand RK, et al. Background Pharmacological Therapy in the ANTHEM-HF Pilot Study: Comparison to Contemporary Trials of Novel Heart Failure Therapies. *ESC Heart Fail* 2019	Differentiation	The background pharmacological therapy that patients received in the ANTHEM-HF pilot study is similar to the pharmacological therapy received by heart failure patients in other contemporary trials
Annoni EM, et al. Chronic low-level vagus nerve stimulation improves long-term survival in salt-sensitive hypertensive rats. *Front Physiol* 2019	Safety Mechanisms	In rats with chronic hypertension, chronic ART results in a significant improvement in long-term survival
Libbus I, et al. Electrical interaction between implantable vagus nerve stimulation device and implantable cardiac rhythm management device. *Conf Proc IEEE Eng Med Biol Soc* 2018	Safety Reliability	There is no risk of device interaction between an ART device and a concurrently implanted cardiac rhythm management device
Lee SW, et al. Stochastic vagus nerve stimulation affects acute heart rate dynamics in rats. *PLoS One* 2018	Optimization	ART delivery with novel stimulation parameters shows that heart rate and heart rate variability responses can be finely modulated

Publications

Citation (abbreviated)	Topic	Message
DiCarlo LA, et al. Autonomic regulation therapy to enhance myocardial function in heart failure patients: the ANTHEM-HFpEF study. *ESC Heart Fail* 2018	Study design	The ANTHEM-HF pilot study was designed to evaluate the safety and feasibility of ART in patients with heart failure with preserved ejection fraction
Libbus I, et al. Quantitative evaluation of heartbeat interval time series using Poincaré analysis reveals distinct patterns of heart rate dynamics during cycles of vagus nerve stimulation in patients with heart failure. *J Electrocardiol 2017*	Optimization	In the ANTHEM-HF pilot study, ART induces a distinct pattern of heart rate response during stimulation on-time, which can be revealed using Poincaré analysis
Beaumont E, et al. Cervical vagus nerve stimulation augments spontaneous discharge in second- and higher-order sensory neurons in the rat nucleus of the solitary tract. *Am J Physiol Heart Circ Physiol* 2017	Safety Mechanisms	ART acutely elevates neuronal activity in the medial nucleus of the solitary tract, suggesting that centrally-mediated afferent mechanisms may be responsible for therapy efficacy
Carlson GM, et al. Novel Method to Assess Intrinsic Heart Rate Recovery in Ambulatory ECG Recordings Tracks Cardioprotective Effects of Chronic Autonomic Regulation Therapy in Patients Enrolled in ANTHEM-HF Study. *Ann Noninvasive Electrocardiol* 2017	Optimization Mechanisms Differentiation	In the ANTHEM-HF pilot study, an analysis of intrinsic heart rate recovery demonstrated that chronic ART is associated with cardioprotective improvement in heart rate dynamics

Publications

Citation (abbreviated)	Topic	Message
Ardell JL, et al. Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. *J Physiol*. 2017	Optimization Mechanisms Differentiation	Integrated neurophysiological response to VNS revealed optimal intensity level where functional effects of afferent and efferent signals are balanced
Hanna P, et al. Cardiac neuroanatomy - Imaging nerves to define functional control. *Auton Neurosci* 2017	Mechanisms	Special imaging techniques reveal anatomic detail specific to the functional effects of nerves involved in cardiovascular regulation
Beaumont E, et al. Vagus nerve stimulation mitigates intrinsic cardiac neuronal remodeling and cardiac hypertrophy induced by chronic pressure overload in guinea pig. *Am J Physiol Heart Circ Physiol* 2016	Safety Efficacy Mechanisms	Chronic ART prevents remodeling of the intrinsic cardiac nervous system and cardiac myocytes that occur in response to chronic hypertension
Nearing BD, et al. Acute autonomic engagement assessed by heart rate dynamics during vagus nerve stimulation in patients with heart failure in the ANTHEM-HF trial. *J Cardiovasc Electrophysiol* 2016	Optimization Mechanisms Differentiation	In the ANTHEM-HF pilot study, ART induces an acute heart rate response that can be measured, and that demonstrates autonomic engagement
Lee SW, et al. Chronic cyclic vagus nerve stimulation has beneficial electrophysiological effects on healthy hearts in the absence of autonomic imbalance. *Physiol Rep* 2016	Safety Efficacy Mechanisms	Chronic ART reduces ventricular arrhythmia susceptibility in normal animals, demonstrating that therapeutic benefits do not require pre-existing autonomic imbalance

Publications

Citation (abbreviated)	Topic	Message
Premchand RK, et al. Extended follow-up of patients with heart failure receiving autonomic regulation therapy in the ANTHEM-HF study. *J Card Fail* 2016	Safety Efficacy Reliability Mechanisms	The ANTHEM-HF pilot study demonstrated that chronic ART is safe and feasible, and is associated with a significant improvement in cardiac function and reduction in heart failure symptoms at 12 months
Libbus I, et al. Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in heart failure patients enrolled in the ANTHEM-HF study. *Heart Rhythm* 2016	Mechanisms	In the ANTHEM-HF pilot study, chronic ART reduces T-wave alternans, a measure of cardiac arrhythmia vulnerability, and improves baroreflex sensitivity in heart failure patients
Shivkumar K, et al. Cardiac autonomic control in health and disease. *J Physiol* 2016	Mechanisms	Autonomic control of cardiovascular function is complex; autonomic dysregulation is associated with expression of maladaptive phenotypes and disease progression
Beaumont E, et al. Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling postmyocardial infarction. *Am J Physiol Heart Circ Physiol* 2015	Mechanisms	Chronic ART prevents remodeling of the intrinsic cardiac nervous system and cardiac myocytes that occur following a myocardial infarction
Ardell JL, et al. Central-peripheral neural network interactions evoked by vagus nerve stimulation: functional consequences on control of cardiac function. *Am J Physiol Heart Circ Physiol* 2015	Optimization Mechanisms	Optimal patterns of VNS are derived from integrated neurophysiology of nested reflex arcs acting in the neurocardiac axis

Publications

Citation (abbreviated)	Topic	Message
Buckley U, et al. Autonomic Regulation Therapy in Heart Failure. *Heart Fail Rep* 2015	Mechanisms Optimization	Autonomic Regulation Therapy (ART) is enabled by specific forms of neuromodulation involving central and peripheral elements of the autonomic nervous system
Ardell JL, et al. Neurocardiology: Structure-based Function. *Compr Physiol* 2016	Mechanisms	The heart and brain are inextricably linked by neural signaling pathways that are organized in specific ways
Ardell JL, et al. Translational neurocardiology: preclinical models and cardioneural integrative aspects. *J Physiol* 2016	Mechanisms Optimization	Multiple preclinical models have been used to improve knowledge of neurocardiolog. Autonomic nervous system function is based on nested-hierarchy of reflex arcs; an integrated neurophysiological approach is critically important
Annoni EM, et al. Intermittent electrical stimulation of the right cervical vagus nerve in salt-sensitive hypertensive rats: effects on blood pressure, arrhythmias and ventricular electrophysiology. *Physiol Rep* 2015	Optimization Mechanisms	Chronic ART is associated with improvement in blood pressure and reduction in cardiac arrhythmias in hypertensive rats
Premchand RK, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: Results of the ANTHEM-HF trial. *J Card Fail* 2014	Safety Feasibility Efficacy Reliability	The ANTHEM-HF pilot study demonstrated that chronic ART is safe and feasible, and is associated with a significant improvement in cardiac function and reduction in heart failure symptoms at 6 months

Publications

Citation (abbreviated)	Topic	Message
Buckley U, et al. Autonomic Regulation Therapy in Heart Failure. *Heart Fail Rep* 2015	Mechanisms Optimization	Autonomic Regulation Therapy (ART) is enabled by specific forms of neuromodulation involving central and peripheral elements of the autonomic nervous system
Shinlapawittayatorn K, et al. Vagus nerve stimulation initiated late during ischemia, but not reperfusion, exerts cardioprotection via amelioration of cardiac mitochondrial dysfunction. *Heart Rhythm* 2014	Safety Mechanisms	Acute ART provides significant cardioprotective effects during coronary artery occlusion, but not during reperfusion, suggesting the importance of therapy initiation timing.
Kember G, et al. Vagal nerve stimulation therapy: what is being stimulated? *Plos One* 2014	Mechanisms	The vagal axon is just a biological conductor of signal; the critical structures in which neuromodulation is occurring are located centrally (brainstem) and peripherally (intrinsic cardiac nervous system ganglia)
DiCarlo LA, et al. Autonomic regulation therapy for the improvement of left ventricular function and heart failure symptoms: The ANTHEM-HF Study. *J Card Fail* 2013	Pilot Study design	The ANTHEM-HF pilot study was designed to evaluate the safety and feasibility of ART in patients with heart failure with reduced ejection fraction
Shinlapawittayatorn K, et al. Low-amplitude, left vagus nerve stimulation significantly attenuates ventricular dysfunction and infarct size through prevention of mitochondrial dysfunction during acute ischemia-reperfusion injury. *Heart Rhythm* 2013	Safety Mechanisms	Acute ART provides significant protective effects following an acute myocardial infarction, significantly reducing infarct size, improving ventricular function, and decreasing ventricular fibrillation episodes