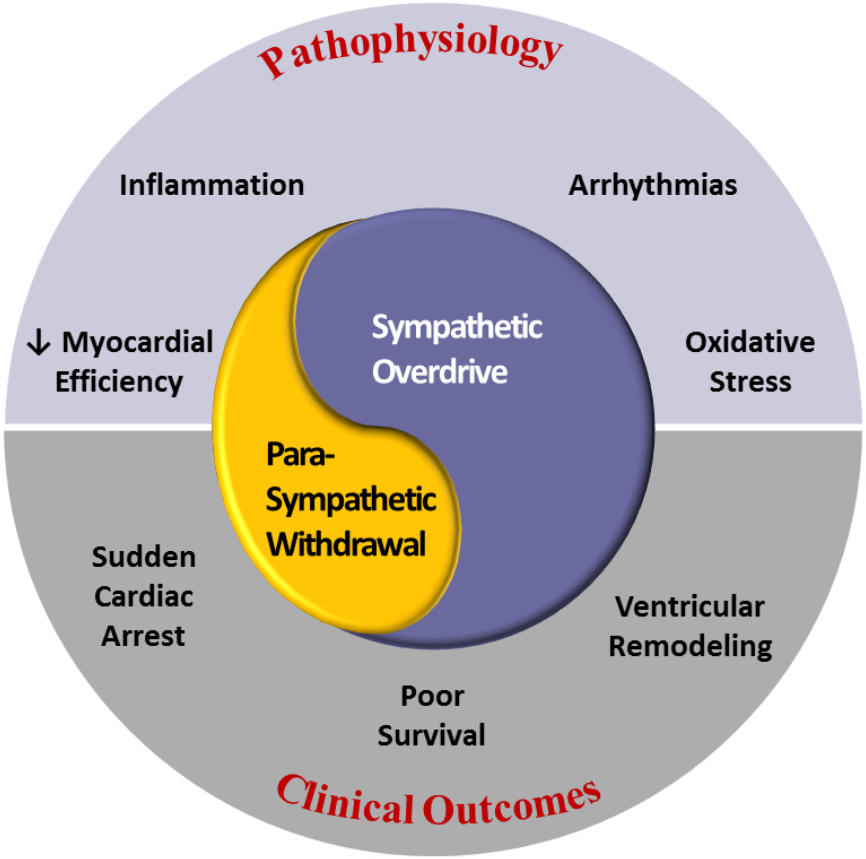
The Effect of Vagus Nerve Stimulation in Heart Failure: Primary Results of the INcrease Of VAgal TonE in chronic Heart Failure (INOVATE-HF) Trial

Michael R Gold, Brett J Berman, Martin Borggrefe, Sanja Djordjevic, P Milasinovic, Suresh Neelagaru, Peter J Schwartz, Randall C Starling, Paul J Hauptman, Spencer H Kubo, Randy A Lieberman, Goran Milasinovic, Dirk J van Veldhuisen, Douglas L Mann

*Dr. Gold and other members of this group have received consulting fees and/or research grants from BioControl Medical

A Key Feature of Heart Failure: Sympathovagal Imbalance

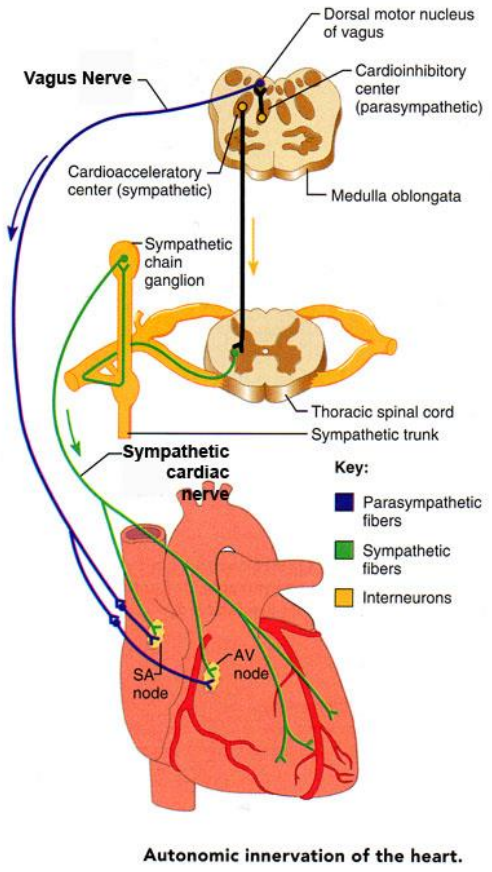
In patients with HF, there is imbalance between the parasympathetic and the sympathetic nervous systems[1-4]



1. Floras JS. JACC 2009;54:375-385
2. La Rovere MT, et al. Lancet 1998;351:484-484
3. Mortara A, et al. Circulation 1997;96:3450-3458
4. Schwartz PJ, et al. Circulation 1988;78:969-979

Cervical Vagus Nerve Stimulation (VNS) directly targets parasympathetic withdrawal

- Parasympathetic innervation of the heart is via the vagus nerve.
- In addition to atrial, SA node, and AV node innervation, parasympathetic post-ganglionic vagus nerve fibers course throughout the ventricles.[1]
- Hypothesis: Electrical pre-ganglionic cervical vagus nerve stimulation will help to reestablish diminished vagal tone in HF.[2]

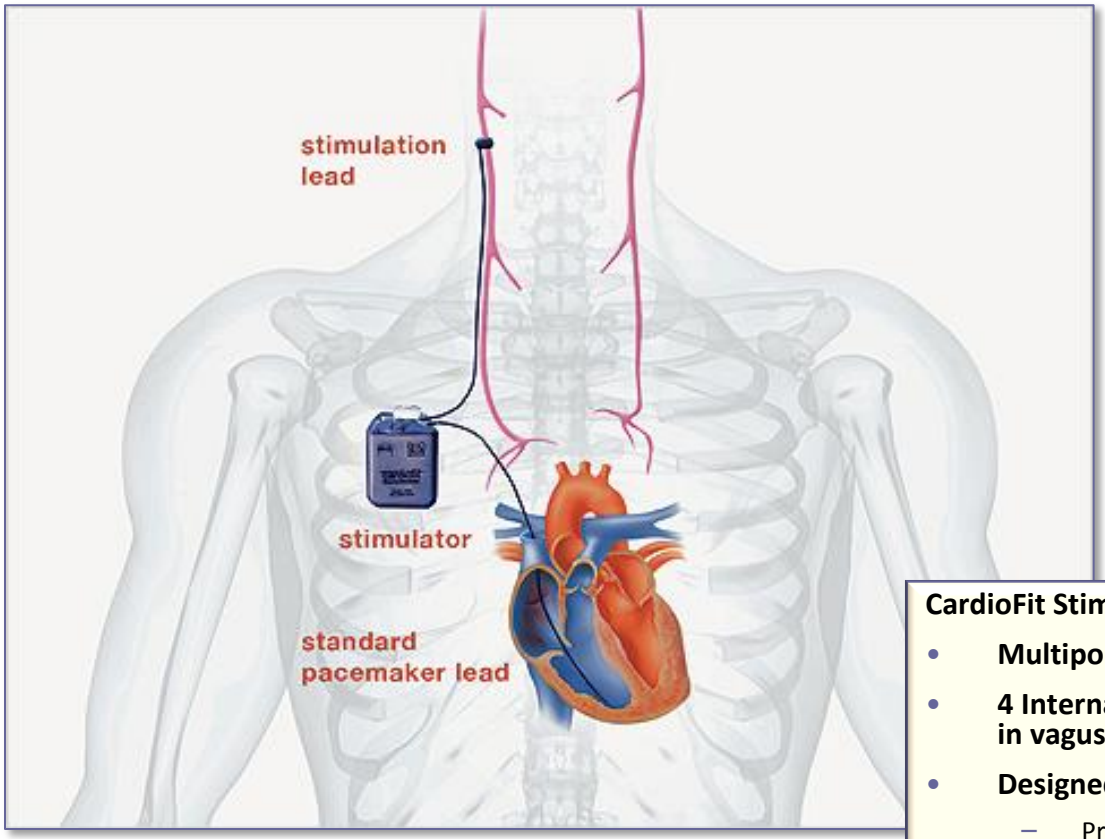


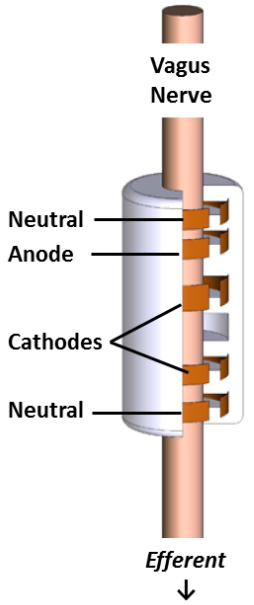
Autonomic innervation of the heart.

Image from Human Anatomy & Physiology by Elaine N.Marieb 6th edition

1. Coote JH. J Physiol. 2013. 591(Pt 17):4073-85
2. Bibveski S, Dunlap ME. Heart Fail Rev. 2011. 16:129-35

CardioFit® System Components





CardioFit Stimulation Lead:

- **Multipolar recessed electrodes, coaxial lead, silicone body**
- **4 Internal CUFF diameter sizes to accommodate variability in vagus nerve:**
- **Designed for:**
  - Predominately unidirectional/efferent stimulation
  - B fiber stimulation which is important for cardiac response
  - Minimal current leakage to reduce side effects

CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use

Pre-Clinical and Pilot Study Evidence

- Pre-clinical studies:
  - VNS is associated with reverse remodeling in the presence of heart failure medical therapies[1]
  - Reverse remodeling persists despite fixed rate pacing[2]
  - VNS has possible antiarrhythmic benefit[3]
  - VNS is associated with reduction of inflammatory markers TNF-α and IL-6[4]

1. Sabbah HN, et al. Eur J Heart Fail 2007; 6 (Suppl. 1):114 (abstract)
2. Zhang Y, et al. Circ Heart Fail. 2009;2:692-699
3. Vanoli E, et al. . Circ Res. 1991;68:1471–1481
4. Gupta RC, et al. J Am Coll Cardiol. 2006;47:77A (abstract)

- Non-randomized Pilot Study:
  - 32 NYHA II-IV patient study in EU[1]
  - Most subjects improved by at least one NYHA class ($p<0.001$)
  - Improvements seen in 6MHW ($p=0.0014$) and QoL ($p=0.0001$)
  - Significant LVEF increase ($p=0.003$)
  - Results sustained to 2 years[2]

1. De Ferrari GM, et al. Eur Heart J. 2011;32(7):847-55
2. Dennert R, et al. Circulation. 2012;126(21, Suppl):A17001

INOVATE-HF Protocol Overview

- **Design:**
  - Prospective, Randomized, multi-national, Controlled
  - Open Label (device implant vs. OMT)
  - Intent to treat analysis, starts with randomization
- **Primary Endpoints:**
  - Efficacy: Time to first occurrence of *"unplanned heart failure hospitalization or all cause death"*
  - Safety:
    - 90 day system related complications
    - Comparative non inferiority endpoint (time to first all cause mortality or all cause complications through 1 year excluding events in first safety objective)

INOVATE-HF
INcrease Of VAgal TonE in Heart Failure

Key Screening inclusion/exclusion criteria

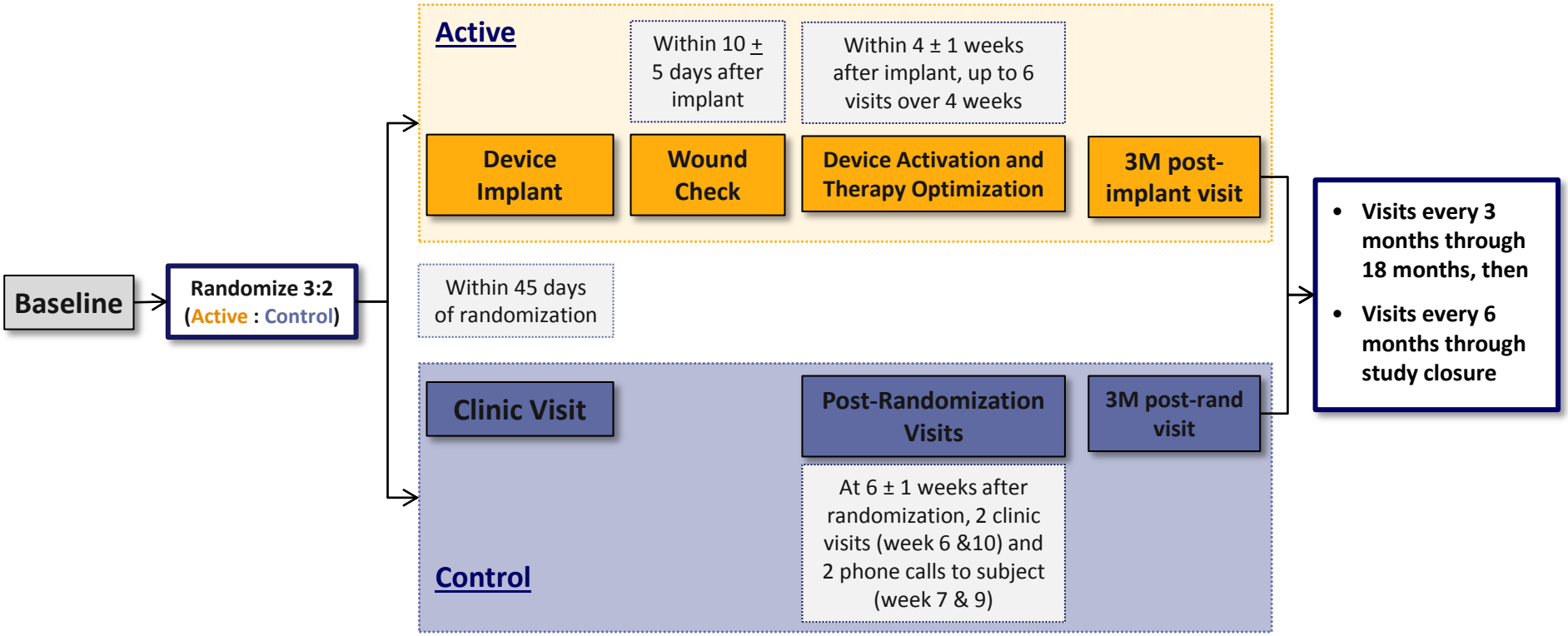
Key Inclusion:

- Stable, NYHA class III on stable optimal medical therapy (ACE-I /ARB, beta blocker/CRT or other device therapy)
- LVEF ≤ 40% and LVEDD between 50 and 80 mm
- Predominately in sinus rhythm (unless subject has predominately paced rhythm)
- Subjects with CRT devices may be included in the trial provided they have had CRT for at least 12 months with continued NYHA III functional status (i.e. nonresponders)

Key Exclusion:

- 2nd or 3rd degree AV block or other pacemaker indication not treated with a pacemaker
- Chronic (permanent) atrial fibrillation in past 3 months or hospitalized due to AF in past 6 months
- Uncontrolled Diabetes Mellitus
- Severe renal or hepatic failure
- History of stroke or TIA within 3 months prior to enrollment, or significant neurological damage

Study Flowchart



Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, Van Veldhuisen DJ, Starling RC, Mann DL. Am Heart J. 2012 Jun;163(6):954-962.e1.

INOVATE-HF
INcrease Of VAgal TonE in Heart Failure

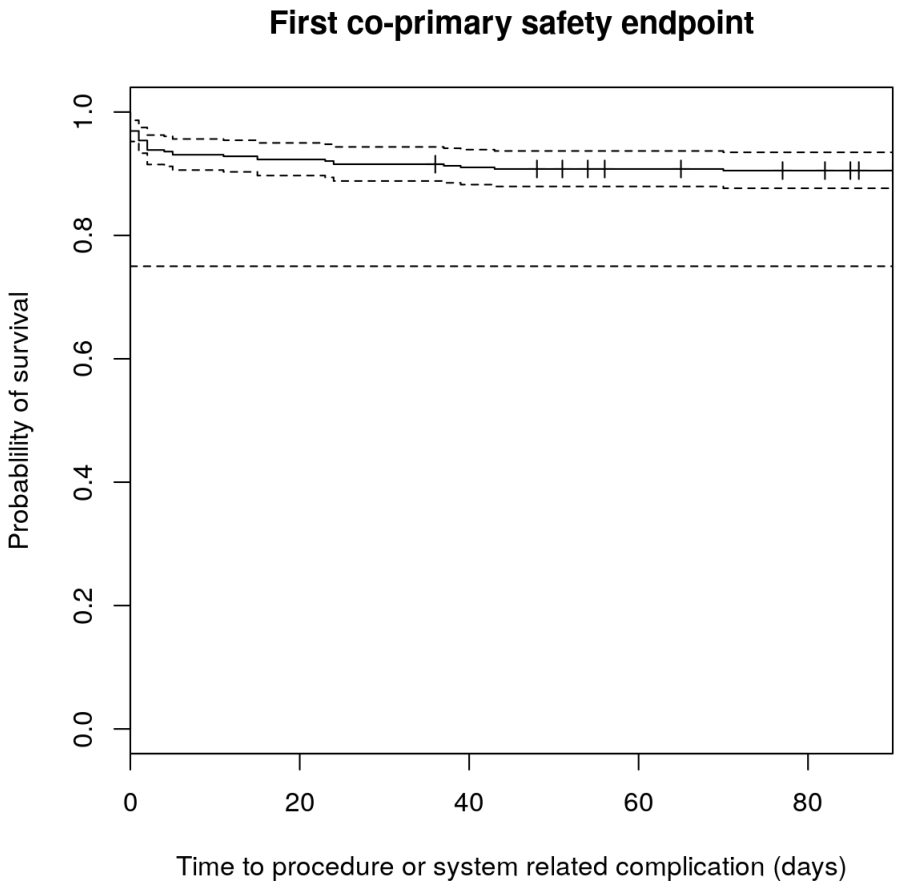
INOVATE-HF Baseline Demographics

Characteristic	Control Group N=271	Active Group N=436	p-value
Age (yr)	60.9±11.2	61.7±10.5	0.32
Gender (% Male)	219 (80.8%)	339 (77.8%)	0.38
Body mass index (kg/m^2)	30.6±6.4	30.4±6.1	0.68
Duration of heart failure (years)	7.07.7±5.73	7.64±6.59	0.22
HF Etiology (Ischemic)	173 (63.8%)	255 (58.5%)	0.19
6-Min hall walk distance (m)	317.0±178.4	304.1±111.5	0.29
LVEF (%)	25.2±7.3	23.9±6.7	0.02
Heart rate (bpm)	71.4±11.5	72.5±12.2	0.20
Medication Therapy			
ACE-I or ARB use	246 (90.8%)	383 (88.2%)	0.31
Beta blocker use	251 (92.6%)	411 (94.7%)	0.56
Diuretic use	230 (84.9%)	365 (84.1%)	0.63
Aldosterone Antagonist use	159 (58.7%)	253 (58.3%)	0.56

Implant Data

- 407 of 409 attempted implants successful
  - 2 unsuccessful implants due to venous occlusions with inability to place RV lead
- 3 Adverse events during implant reported:
  - All events resolved and the subjects were implanted with the CardioFit system
    - Two subjects received IV medications for hypotension after anesthesia was administered and prior to implantation
    - One patient, after the RV lead was placed, developed VT/VF that was treated with ICD defibrillation and CPR
- No CardioFit and concomitant device interactions observed

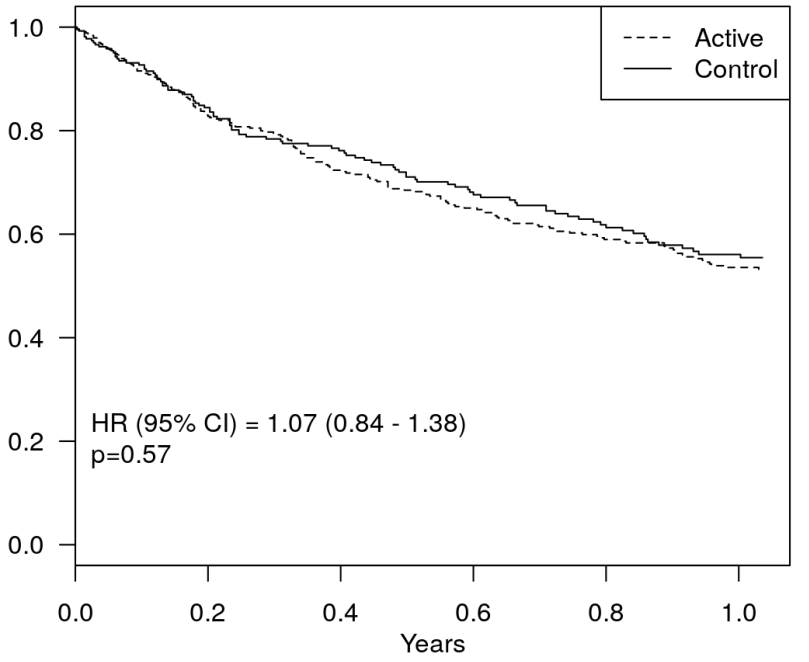
1st co-primary Safety



Objective Performance Criteria
LCB 75% (95% CI)

# pts with implant attempt	# pts with procedure related complications up to 90 days	# pts at risk at 90 days	% pts free of procedure related complications for 90 days (95 % CI)
392	37	341	90.6% (87.7% - 93.5%)

2nd co-primary Safety



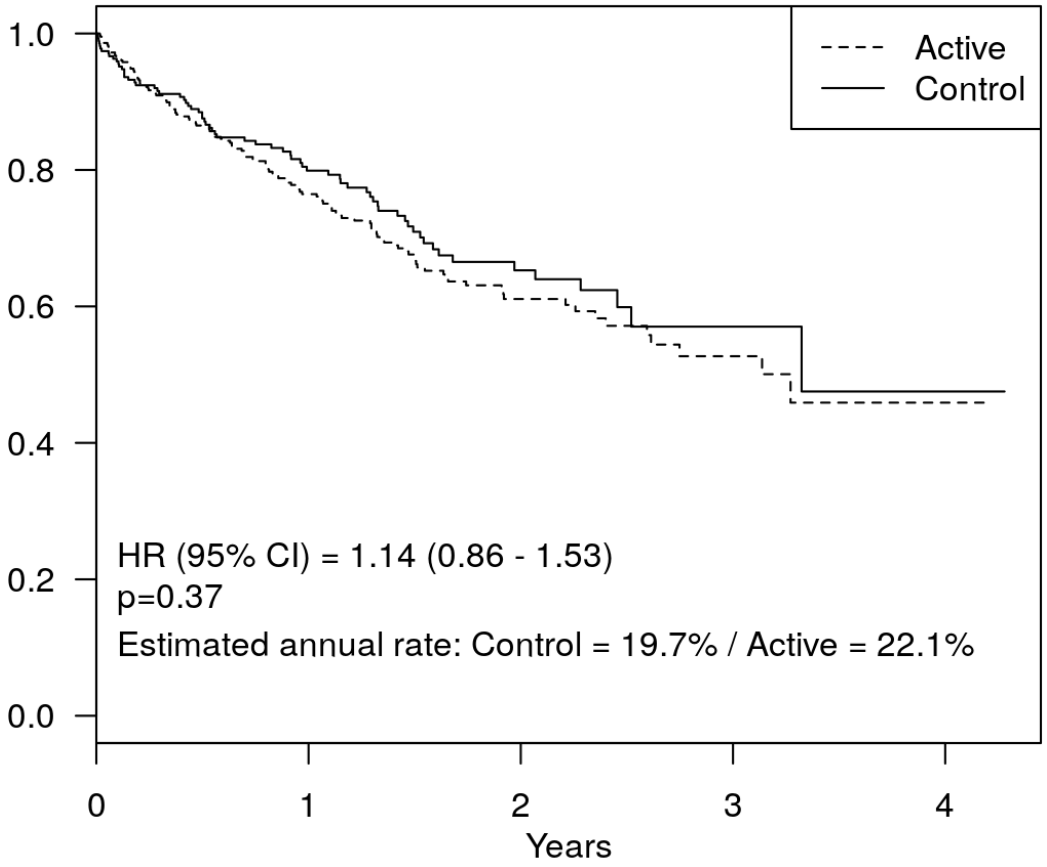
No. at risk			
Active	435	243	153
Control	269	151	89

Outcome	Control Group (# pts)	Active Group (# pts)	Hazard Ratio (95% CI)	p-Value
Complications post 90 days or All cause death	206 (98, 36.2%)	416 (175, 40.1%)	1.07 (0.84 - 1.38)	0.57

DSMB Review of 2nd Interim Analysis

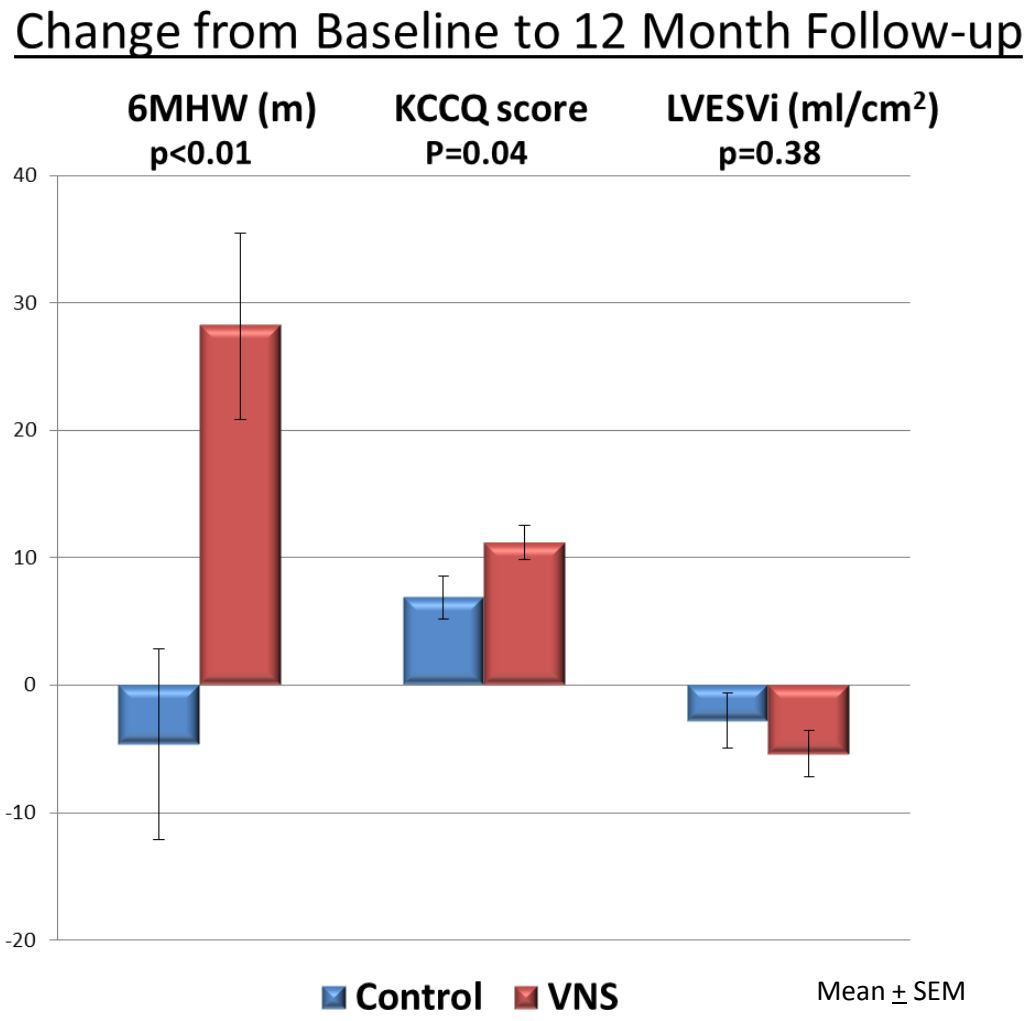
- Both safety objectives were considered acceptable
- Futility border had been crossed for primary efficacy endpoint
- DSMB recommended stopping the study due to futility
- Study closure by Steering Committee occurred on 15 December 2015

Primary Efficacy Endpoint

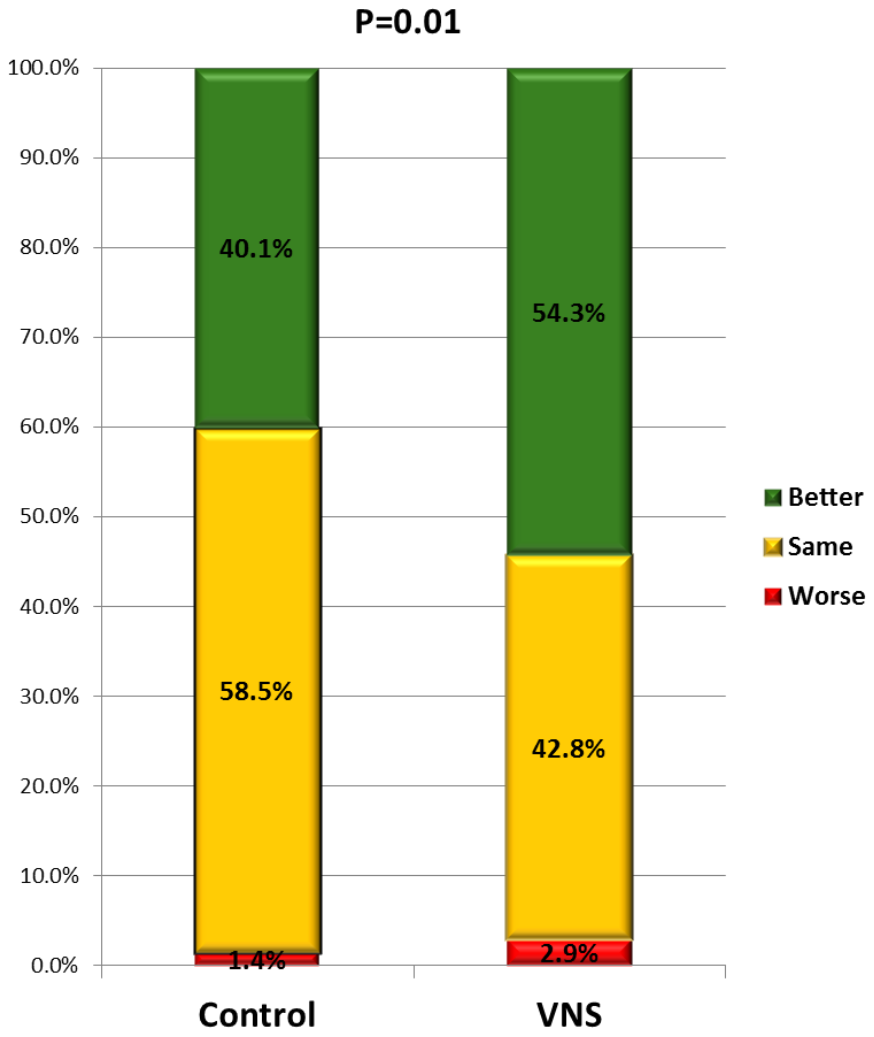


No. at risk					
Active	436	221	84	23	1
Control	271	137	52	10	1

Secondary Endpoints



Change in NYHA (Baseline to 12 Months)

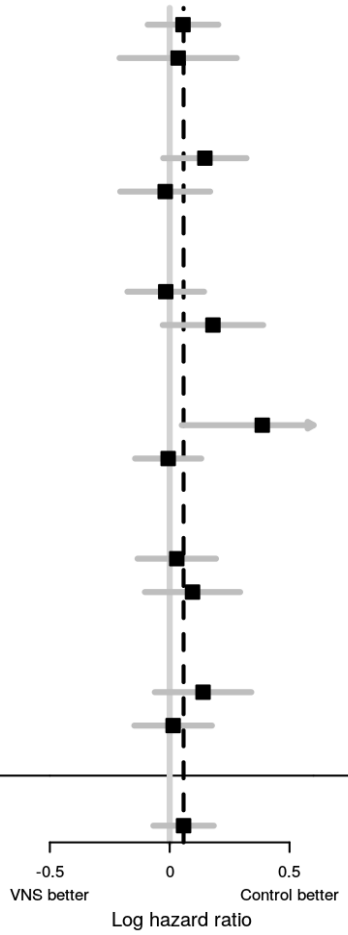


Echo Parameters

Variable	Control Baseline	Control Followup	Active Baseline	Active Followup	Difference between groups	p-value
12 month	Mean±SD (N)	Mean±SD (N)	Mean±SD (N)	Mean±SD (N)	Mean±SE	
LVEF (%)	25.9±7.4 (110)	26.8±8.3 (110)	23.9±7.2 (204)	24.7±7.1 (204)	0.0±0.7	0.97
LVESV (ml)	204.2±86.5 (110)	196.8±87.4 (110)	228.4±98.6 (204)	217.3±99.3 (204)	-3.7±5.9	0.55
LVEDV (ml)	269.1±92.4 (110)	261.3±91.2 (110)	292.4±104.8 (205)	281.3±107.8 (205)	-3.3±6.2	0.61

Univariate Analysis of Pre-specified Subgroups

Variable	N	HR	p	int. p
Age				0.91
<=70	565	1.14	0.46	
>70	142	1.08	0.78	
6MHW at baseline				0.20
<=300	319	1.40	0.10	
>300	371	0.96	0.84	
HF etiology				0.15
Ischemic	428	0.96	0.84	
Non-ischemic	274	1.52	0.09	
Gender				0.03
Female	149	2.43	0.02	
Male	558	0.99	0.93	
Diabetes Mellitus				0.64
No	448	1.07	0.72	
Yes	258	1.25	0.35	
CRT				0.33
CRT	240	1.38	0.18	
no CRT	467	1.03	0.86	
All patients	707	1.14	0.37	



Multivariate analysis of the primary efficacy endpoint showed that gender was not an independent predictor of outcome (p=0.17)

INOVATE-HF Summary

- VNS has an acceptable safety profile and is well tolerated long term
- However, this therapy did not reduce the incidence of HF events or all-cause mortality among patients with NYHA III functional status and a reduced ejection fraction
- Positive trends were noted in NYHA class, exercise capacity (6MWT) and QOL measures (KCCQ)
- There were no significant difference in echocardiographic measures between groups