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

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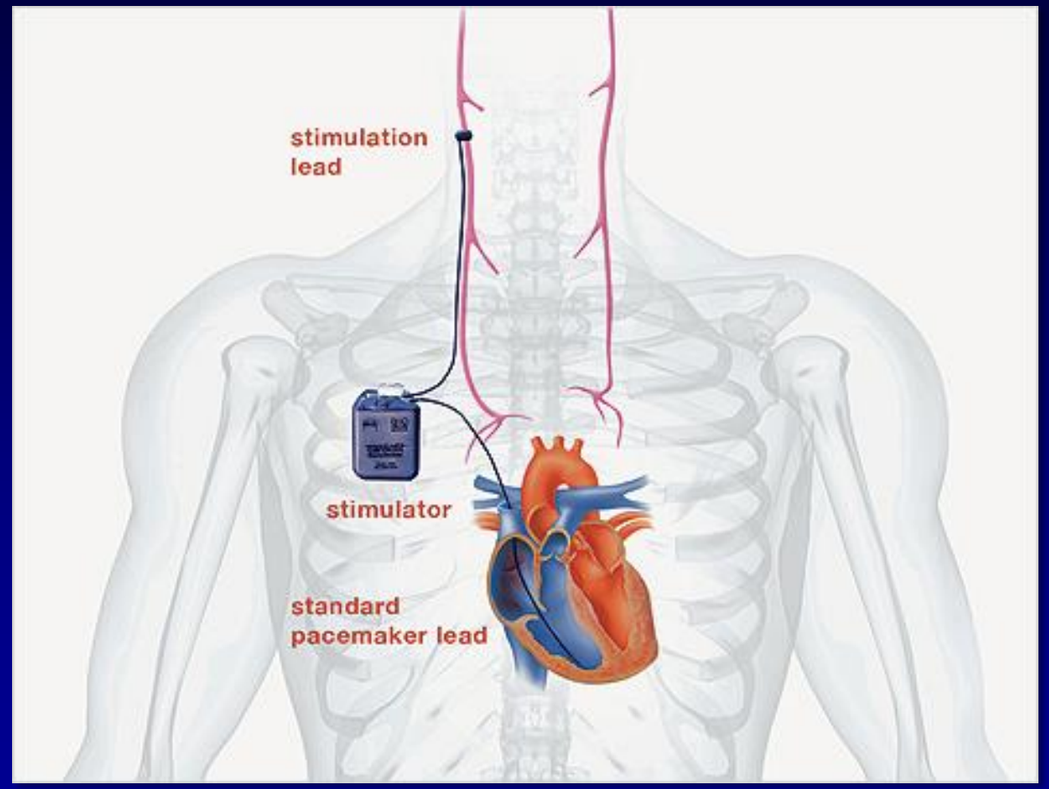
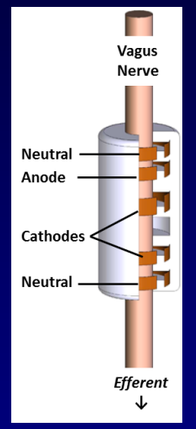
CardioFit® System Components
Vagal Nerve Stimulation:

Hypothesis: Autonomic modulation with increased parasympathetic and decreased sympathetic tone will improve HF outcomes





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**

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)

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)

Key Inclusion:

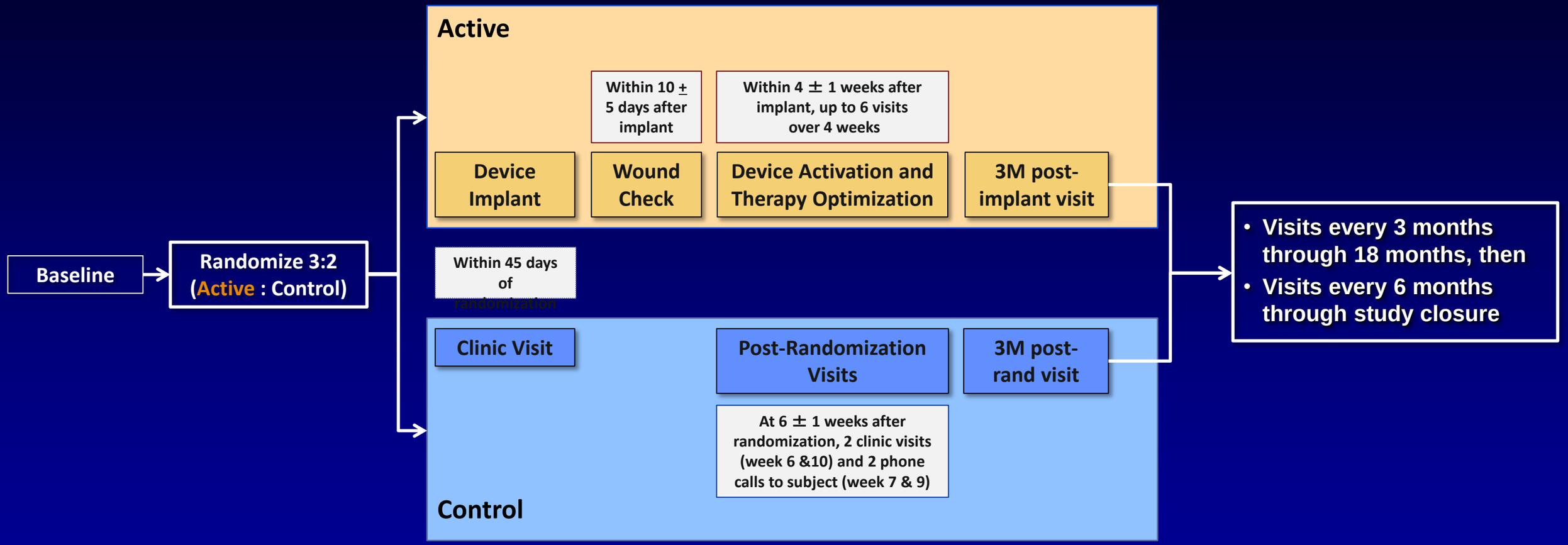
Stable, NYHA class III on stable optimal medical therapy (ACE-I /ARB, beta blocker/CRT or other device therapy)

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 stable and optimal programming for at least 3 months

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 Baseline Demographics

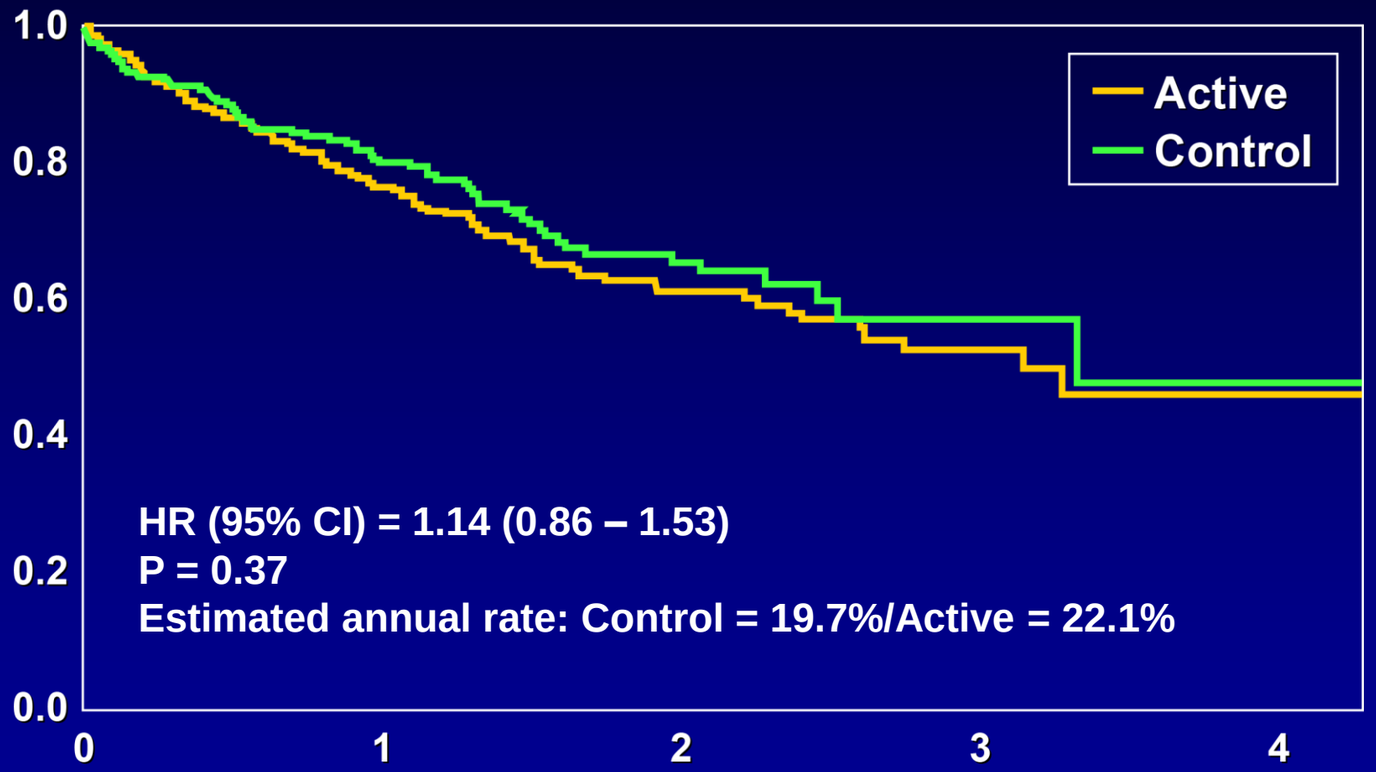
Characteristic	Control Group N=271	Active Group N=436	p-value
Age (yr)	60.9±11.2	61.7±10.5	0.32
Gender (% Male)	219 (80.8%)	339 (77.8%)	0.38
Body mass index (kg/m^2)	30.6±6.4	30.4±6.1	0.68
Duration of heart failure (days)	2578.7±2090.2	2790.9±2406.4	0.22
NYHA class III	173 (63.8%)	255 (58.5%)	0.19
6-Min 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

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

Time to first occurrence of ***"unplanned heart failure hospitalization or all cause death"***



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

INOVATE-HF Summary

- VNS has an acceptable safety profile and is well tolerated long term
- 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

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