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Vagus Nerve Stimulation for the Treatment of Heart Failure

The INOVATE-HF Trial

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ABSTRACT

BACKGROUND Heart failure (HF) is increasing in prevalence and is a major cause of morbidity and mortality despite advances in medical and device therapy. Autonomic imbalance, with excess sympathetic activation and decreased vagal tone, is an integral component of the pathophysiology of HF.

OBJECTIVES The INOVATE-HF (Increase of Vagal Tone in Heart Failure) trial assessed the safety and efficacy of vagal nerve stimulation (VNS) among patients with HF and a reduced ejection fraction.

METHODS INOVATE-HF was a multinational, randomized trial involving 85 centers including patients with chronic HF, New York Heart Association functional class III symptoms and ejection fraction ≤40%. Patients were assigned to device implantation to provide VNS (active) or continued medical therapy (control) in a 3:2 ratio. The primary efficacy endpoint was composite of death from any cause or first event for worsening HF.

RESULTS Patients (n = 707) were randomized and followed up for a mean of 16 months. The primary efficacy outcome occurred in 132 of 436 patients in the VNS group, compared to 70 of 271 in the control group (30.3% vs. 25.8%; hazard ratio: 1.14; 95% confidence interval: 0.86 to 1.53; p = 0.37). During the trial, the estimated annual mortality rates were 9.3% and 7.1%, respectively (p = 0.19). Quality of life, New York Heart Association functional class, and 6-min walking distance were favorably affected by VNS (p < 0.05), but left ventricular end-systolic volume index was not different (p = 0.49).

CONCLUSIONS VNS does not reduce the rate of death or HF events in chronic HF patients. (INcrease Of VAgal TonE in CHF [INOVATE-HF]; NCT01303718) (J Am Coll Cardiol 2016;68:149–58) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

EF = ejection fraction

HF = heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVESVi = left ventricular end-systolic volume index

NYHA = New York Heart Association functional class

VNS = vagus nerve stimulation

Heart failure (HF) remains an important public health problem that is increasing in incidence and prevalence (1–3). It is the leading cause of hospitalization in adults in the United States despite advances in the pharmacologic- and device-based therapies over the past several decades, and is still associated with a markedly reduced survival. Given the increasing burden of HF, there has been renewed effort towards finding innovative treatments; however, only a few new pharmacologic treatments have been shown effective for HF in the last 10 years (4–6). As a result, concomitant device therapy has received increasing attention in HF (7), and autonomic modulation is an important target (8–10). It has long been recognized that the autonomic nervous system becomes imbalanced in HF, with withdrawal of parasympathetic tone and increased activation of sympathetic nervous system (8–10). Beta blockers are a mainstay of current treatment and inhibit excess sympathetic stimulation. However, to date, pharmacologic interventions that increase parasympathetic tone and thus restore autonomic balance (11,12) are limited. In contrast, there are many device-based approaches under development that modulate autonomic activity (13,14), including vagus nerve stimulation (VNS) (15,16), spinal cord stimulation (17,18), and baroreceptor activation (19).

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VNS is the most-studied device-based therapy for autonomic modulation in HF. However, no pivotal study of VNS or other device-based autonomic modulation therapy has been performed to evaluate these therapies on clinical morbidity and mortality. Accordingly, the Increase of Vagal Tone in Heart Failure (INOVATE-HF) trial was undertaken to assess the impact of VNS in HF.

METHODS

STUDY DESIGN AND OVERSIGHT. The INOVATE-HF study was an international, randomized, open-label clinical trial. The trial was designed by the Steering Committee and sponsored by BioControl Medical (B.C.M.) Ltd. (Yehud, Israel). BioControl was responsible for trial execution and monitoring (20). The trial protocol was approved by the institutional review board at each participating center, and all patients provided written informed consent to participate. The study results were analyzed independently by North American Science Associates (NAMSA, Minneapolis, Minnesota). Details of the trial design have been published previously (20).

PATIENTS

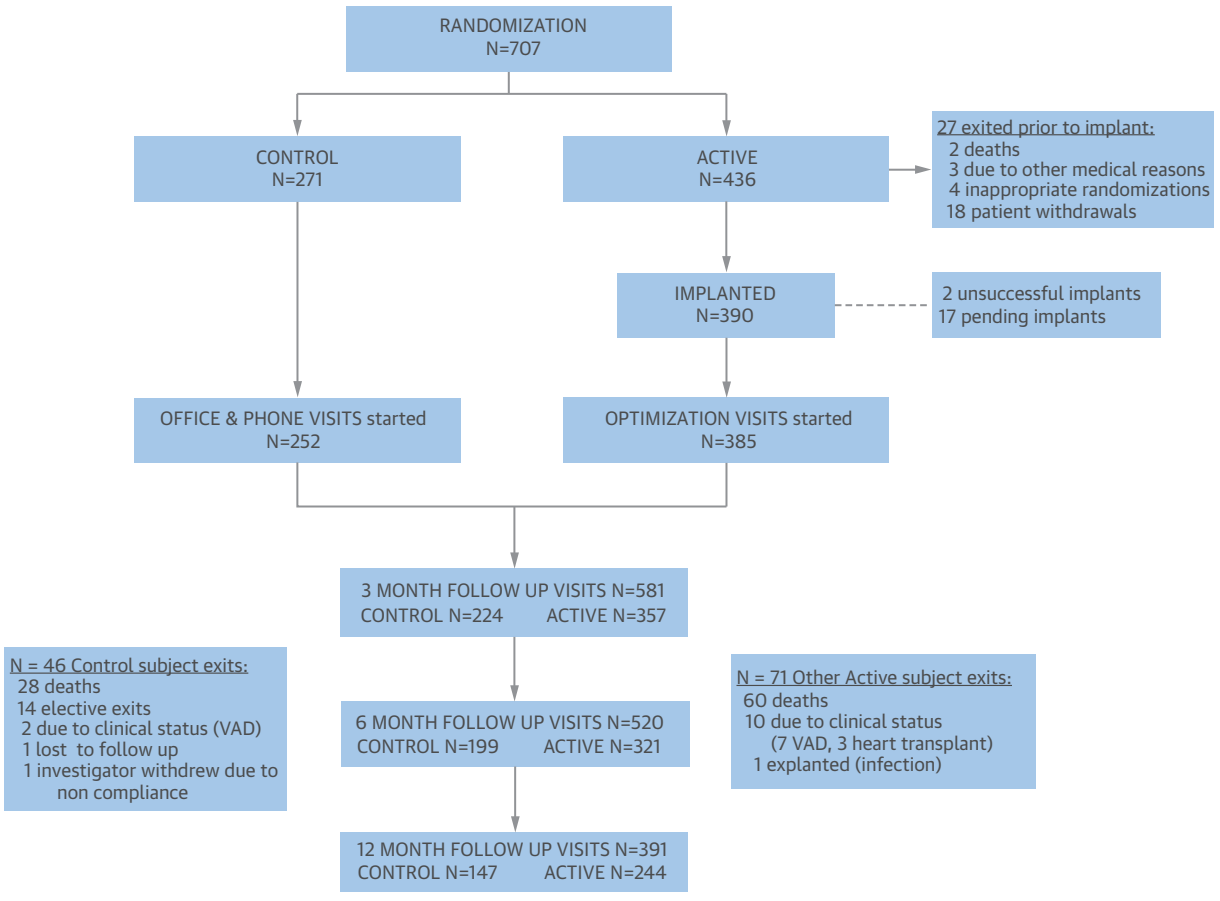
Eligible patients were 18 years of age or older, with New York Heart Association (NYHA) functional class III symptoms and on stable medical therapy recommended by current guidelines (1,3). Subjects were required to have a left ventricular ejection fraction (EF) ≤40% and a left ventricular end-diastolic diameter of 50 to 80 mm. The exclusion criteria included myocardial infarction or acute coronary syndrome in the preceding 30 days, cardiac surgery in the preceding 6 months, chronic atrial fibrillation, and severe liver or renal failure. Patient enrollment began in April 2011. An amendment to the protocol to allow patients with pre-existing cardiac resynchronization therapy (CRT) but persistent NYHA functional class III symptoms (i.e., nonresponders to CRT) was approved by regulatory authorities in August 2012 and such patients were enrolled from October 2012. Patients were randomly assigned in a 3:2 ratio to have implantation of the VNS system (active) in addition to continued medical therapy or medical therapy alone (control). Randomization was assigned electronically and stratified according to sex and presence of CRT.

VNS DEVICE IMPLANTATION. Patients randomized to VNS stimulation underwent implantation of a BioControl CardioFit system as previously described in detail (20). The procedure included placement of a standard transvenous lead into the right ventricle for sensing ventricular activation and a nerve stimulation cuff on the right vagus nerve. The leads were tunneled and connected to a pulse generator that was placed in the right infraclavicular space.

After a 1-month healing period, patients underwent multiple scheduled visits over a 4-week period, during which time the stimulation output was gradually increased with a goal of achieving current of 3.5 to 5.5 mA. In the control group, pre-planned study visits were also scheduled during this period so that the number of contacts with the study team could be roughly equivalent with the VNS group. Study visits in both groups were then performed every 3 months through 18 months and then every 6 months for the duration of the trial. At the 3-, 6-, and 12-months visits, echocardiography, 6-min hall walk, NYHA functional class assessment, and a quality-of-life questionnaire were performed in addition to routine evaluation. Echocardiographic measures were performed by a core lab, although this was not used for inclusion in the trial.

OUTCOME MEASURES. The primary efficacy endpoint was the combination of death from any cause or first event attributed to worsening HF. An HF

FIGURE 1 Study Enrollment, Randomization, and Follow-Up



The distribution and status of patients in the 2 arms of the trial are depicted. After the 12-month visit, patients were followed every 3 months until 18 months, then every 6 months thereafter until study closure.

event occurred when the subject had signs or symptoms of worsening HF and received an augmented HF regimen for which a hospitalization was considered necessary, or if they received intravenous decongestive therapy in the absence of an inpatient hospitalization. All events were adjudicated based on pre-specified definitions per a charter developed by an independent clinical events committee. The first co-primary safety objective was to demonstrate >75% freedom from procedure and system-related complication through 90 days post-implantation (VNS group only) with 95% confidence. The second co-primary safety objective involved a comparison of time to first event of death or complications from any cause through 1 year between the 2 study arms.

The pre-specified secondary outcomes included the following measured at the 12-month visit: change in NYHA functional class, change in 6-min hall walk distance, echocardiographic core lab measured change in left ventricular end-systolic volume index (LVESVi) and changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

STATISTICAL ANALYSIS. The study size and duration were event driven. To provide at least 80% power, the study was designed to continue until the accumulation of 376 primary efficacy events and 437 second co-primary safety events. The analysis of the primary efficacy end point had 3 planned interim analyses for futility at 0.333, 0.556, and 0.778 of the total number of planned events (376). Baseline characteristics were summarized as means and SDs for continuous variables and as counts and percentages for categorical variables and were compared with the use of 2-sample Student *t* tests and chi-square (or

TABLE 1 Baseline Demographic and Clinical Characteristics According to Treatment Group

	Control Group (n = 271)	VNS Group (n = 436)	p Value
Age, yrs	60.9 ± 11.2	61.7 ± 10.5	0.32
Male	219 (80.8%)	339 (77.8%)	0.38
Duration of heart failure, yrs	7.07.7 ± 5.73	7.64 ± 6.59	0.22
Heart failure etiology (ischemic)	173 (63.8%)	255 (58.5%)	0.19
Type 2 diabetes	91 (33.6%)	167 (38.3%)	0.23
Creatinine, mg/dl	1.3 ± 0.5	1.2 ± 0.5	0.82
Heart rate, beats/min	71.4 ± 11.5	72.5 ± 12.2	0.20
QRS duration non-CRT subjects, ms	108.6 ± 21.1	111.2 ± 24.4	0.23
QRS duration ≥ 120, ms	130 (48.0%)	210 (48.2%)	1.00
6-min hall walk distance, m	317.0 ± 178.4	304.1 ± 111.5	0.29
Body mass index, kg/m^2	30.6 ± 6.4	30.4 ± 6.1	0.68
Blood pressure systolic, mm Hg	118.6 ± 18.5	117.7 ± 17.4	0.51
Blood pressure diastolic, mm Hg	72.5 ± 10.3	71.7 ± 10.9	0.33
Quality-of-life score (KCCQ score)	52.2 ± 21.8	51.6 ± 20.7	0.74
Left ventricular function			
Left ventricular ejection fraction, %	25.2 ± 7.3	23.9 ± 6.7	0.02
Left ventricular end systolic volume index	100.6 ± 40.5	106.0 ± 41.8	0.11
Left ventricular end diastolic volume index	131.7 ± 43.1	136.4 ± 44.6	0.19
Concomitant device			
CRT-pacer	5 (1.8%)	7 (1.6%)	1.00
CRT-defibrillator	90 (33.2%)	138 (31.7%)	0.73
Pacemaker	2 (0.7%)	4 (0.9%)	1.00
Defibrillator	127 (46.9%)	215 (49.3%)	0.58
Medication at baseline			
Beta-blocker use	251 (92.6%)	409 (93.8%)	0.56
ACE-I or ARB use	246 (90.8%)	383 (87.8%)	0.31
Aldosterone Antagonist use	163 (60.1%)	259 (59.4%)	0.94
Diuretic agent use	205 (75.6%)	336 (77.1%)	0.69

Values are mean ± SD or n (%). There were no significant between-group differences at baseline except for left ventricular ejection fraction (p = 0.02). Data were missing for the following characteristics: duration of heart failure (for 1 patient in the active group), creatinine (for 2 patients in the control group and for 1 patient in the active group), 6-min hall walk distance (for 2 patients in the control group and for 15 patients in the active group), quality-of-life score (KCCQ score) (for 1 patient in the control group and for 4 patients in the active group), left ventricular ejection fraction (for 28 patients in the control group and for 45 patients in the active group), left ventricular end systolic volume index (for 28 patients in the control group and for 45 patients in the active group), left ventricular end diastolic volume index (for 28 patients in the control group and for 44 patients in the active group).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; KCQC = Kansas City Cardiomyopathy Questionnaire; VNS = vagus nerve stimulation.

Fisher exact) tests, respectively. The p values for time-to-event analyses, hazard ratios (HRs) for treatment effects, and 95% confidence intervals (CIs) calculated from Cox proportional hazards models. Interactions between treatment effects and subgroup levels were tested for in Cox models that included treatment and subgroup main effects and interaction terms. Time-to-event curves were estimated with the use of the Kaplan-Meier method. Changes in NYHA functional class from baseline to 12 months were analyzed with the use of an ordered logistic-regression model, providing a p value for difference between the control and VNS arms. The changes in secondary outcomes other than NYHA functional class were analyzed using 2 (VNS vs. control) by 2 (baseline vs. follow-up) repeated measures analysis of variance that included the treatment group by time interaction. All p values in the efficacy analysis were 2-sided. The p values were not adjusted for multiplicity or interim looks.

RESULTS

PATIENT ENROLLMENT AND FOLLOW-UP. Beginning in April 2011, patients were enrolled at 85 centers in the United States, Europe, and Israel. There were 707 subjects who underwent randomization (436 patients to VNS and 271 to control) (Figure 1). On December 15, 2015, the study was stopped by the Steering Committee on the recommendation of the independent Data and Safety Monitoring Board after the second planned interim analysis, on the basis of futility. At the date of study closure, the mean follow-up period was 16 months (range: 0.1 months to 52 months). The study-visit compliance rate among patients was 98%; a total of 3,521 of the 3,599 required study visits were completed.

PATIENT CHARACTERISTICS. The baseline characteristics of the patients who were randomized are shown in Table 1. This was a group of patients with chronic HF, with a mean duration of symptoms of approximately 7 years. The clinical characteristics were generally similar between groups, except that the left ventricular EF was lower in the VNS group. More than 80% of patients had cardiac implantable electronic devices, including approximately one-third with CRTs.

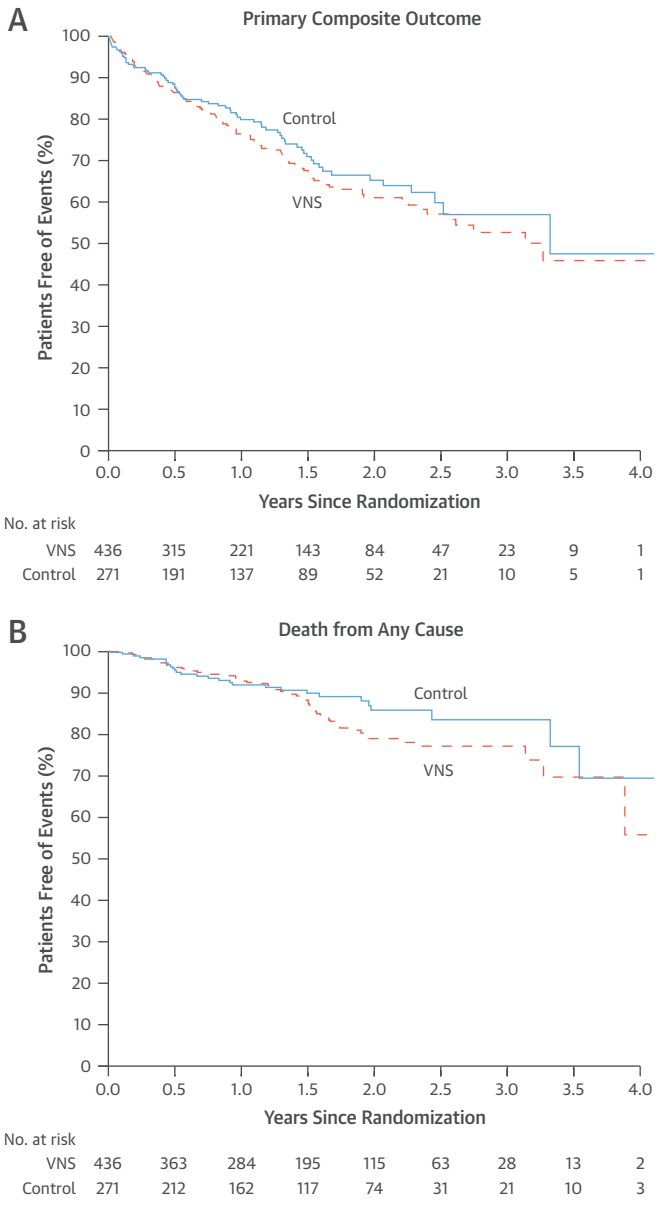
EFFICACY OUTCOMES. The mean stimulation current was 3.9 ± 1.0 mA at the 6-month follow-up visit, with 73% of patients achieving the goal of ≥3.5 mA. The primary efficacy endpoint, death from any cause or first event for worsening HF, occurred in 132 of 436 (30.3%) patients in the VNS group, as compared with 70 of 271 (25.8%) in the control group (HR with VNS, 1.14; 95% CI: 0.86 to 1.53; p = 0.37). The survival curves for the 2 groups are shown in Figure 2A. The composition of the 202 first primary endpoint events in this trial included 36 deaths, 155 HF hospitalizations, and 11 nonhospitalized HF events. Although only the first HF episode or death contributed to the composite endpoint, 53 patients had 2 events, 24 had 3 events, and 23 had 4 or more over the course of the study. During the trial, 62 VNS patients (14.2%) died compared with 28 control patients (10.3%) for estimated annual mortality rates of 9.3% and 7.1%, respectively (p = 0.19) (Figure 2B). The cause of death was adjudicated by the Clinical Events Committee, with no significant differences in the proportion of deaths between groups (Online Table 1).

The pre-specified secondary endpoint analyses included the change from baseline of 4 parameters to be measured at the 12-month visit: 6-min hall walk distance, KCCQ quality-of-life score, NYHA functional class, and echocardiographic LVESVi. Of the 707 patients in the trial, there were 403 patients (57%) who were in the trial long enough to complete a 12-month follow-up visit; of these subjects, 391 (97%) completed this visit, although not all endpoints could be collected, for instance, due to technical quality of echocardiograms. The 6-min hall walk distance increased an average of 28.2 m in the VNS group whereas it decreased 4.6 m in the control group ($p < 0.01$). The KCCQ quality-of-life score increased an average of 11.2 points in the VNS group compared with 6.9 points in the control group ($p < 0.01$). The LVESVi decreased 5.4 ml/m^2 in the VNS group compared with a decrease of 2.8 ml/m^2 in the control group ($p = 0.49$). The results of these measurements are shown in **Figure 3**. Finally, the distribution of change of NYHA functional class differed with more patients improving in the VNS group ($p < 0.01$) (**Figure 4**). There were 520 patients (74% of the cohort) who completed the 6-month follow-up visit when these same endpoints were measured. These data are depicted in **Figures 3** and **4** and show similar results qualitatively to the 12-month data.

SUBGROUPS. The effects of treatment on 6 pre-specified subgroups for the primary efficacy composite outcome are shown in the **Central Illustration**. The only significant treatment by subgroup interaction was for sex with worse outcomes with VNS among female patients ($p = 0.03$). However, as expected, there were many differences in baseline characteristics between male and female patients. For instance, women were younger, more likely to have a nonischemic etiology of HF, smaller left ventricular volumes, and shorter QRS durations (Online Table 2). Given these differences in characteristics, a multivariate analysis of the primary efficacy endpoint was performed. This showed that sex was not an independent predictor of outcome ($p = 0.17$) (Online Table 3).

SAFETY. Among the 390 implanted patients, there were 46 complications in 37 patients by 90 days. The rate of freedom from procedure and system-related events was 90.6% (95% CI: 87.7% to 93.5%; $p < 0.01$ for excluding a rate ≤75%). Thus, this result met the first co-primary safety endpoint. The second co-primary endpoint was a comparison between groups of the composite endpoint of mortality of any-cause or all-cause complications. There was no difference between groups (HR with VNS: 1.07; 95% CI: 0.84 to 1.38; $p = 0.57$) (Online Figure 1).

FIGURE 2 Kaplan-Meier Estimates of Primary-Outcome Events

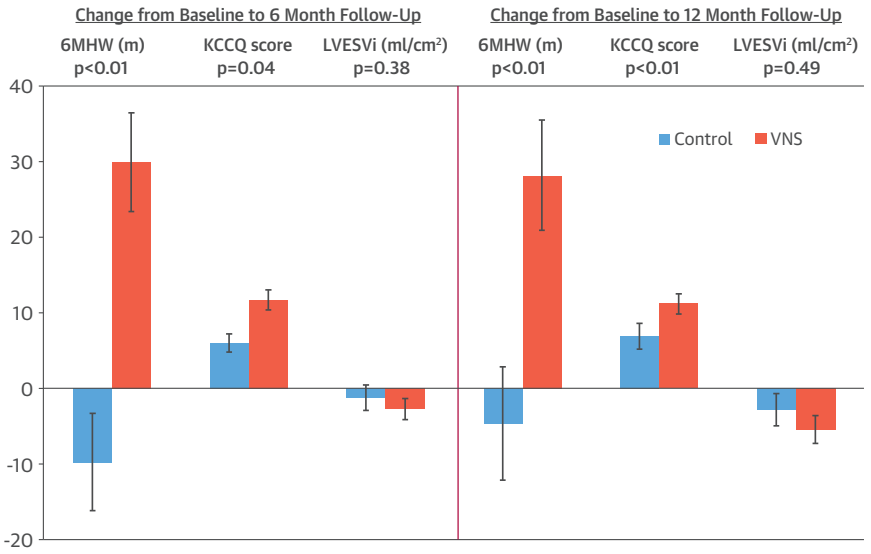


(A) The Kaplan-Meier curves for the composite outcome of death from any cause or a worsening heart failure event. **(B)** The Kaplan-Meier curves for death from any cause.

DISCUSSION

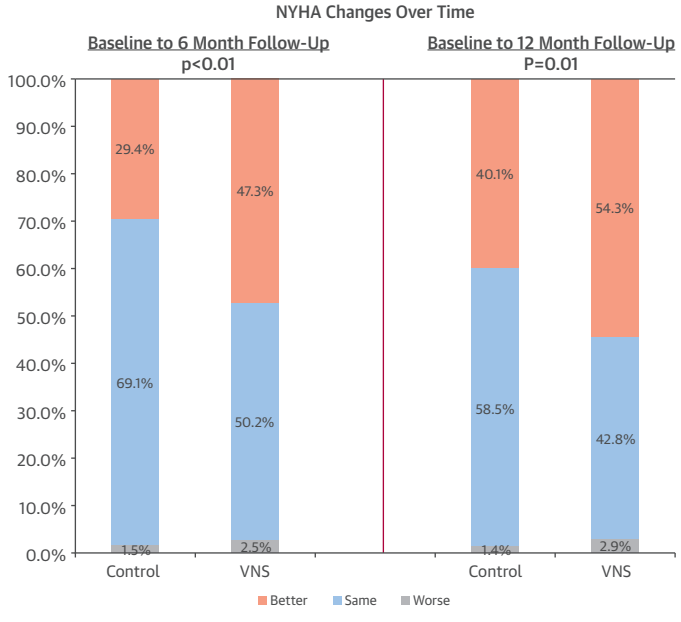
INOVATE-HF is the first adequately powered, pivotal study to assess the effect of device-based autonomic modulation on outcome parameters in patients with HF with a reduced EF. The primary results of this study show that VNS was not effective for reducing the rate of death from any cause or HF events.

FIGURE 3 Secondary Endpoints at 6 and 12 Months



Data shown are mean ± standard error of the mean. KCCQ = Kansas City Cardiomyopathy Questionnaire; LVESVi = left ventricular end-systolic volume index; VNS = vagus nerve stimulation; other abbreviation as in Figure 1.

FIGURE 4 Change of New York Heart Association Functional Class From Baseline at 6 Months and 12 Months

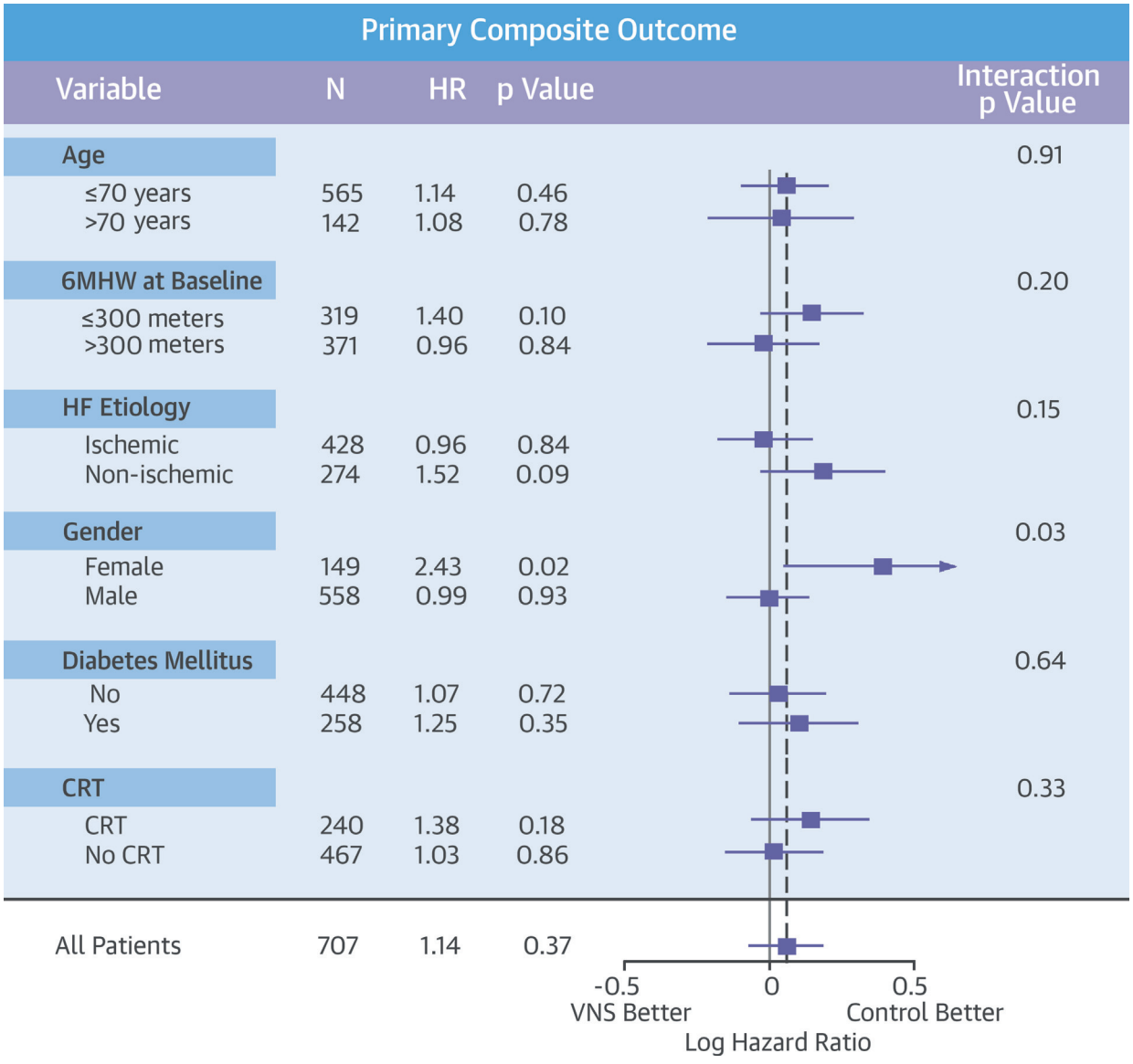


Paired data for the VNS and control groups at baseline and at 6-month follow-up (N = 317 for VNS, N = 194 for control) are shown on the left. The paired data at 12 months (N = 243 for VNS, N = 142 for control), which was a predefined secondary endpoint, are shown on the right. Data were missing at 6 months for 4 VNS and 5 control patients, and at 12 months for 1 VNS and 5 control patients. Abbreviation as in Figure 3.

Moreover, VNS did not promote reverse remodeling in this population. In contrast to the lack of benefit for reducing clinical events, there were significant improvements in 6-min hall walk duration, NYHA functional class, and quality-of-life measures.

It is well established that autonomic imbalance is an important component of the adverse pathophysiologic changes associated with chronic HF, so this has been a target of many new therapies (21–23). VNS is the best studied of such therapies (13–15). It has been used for many years for the treatment of epilepsy (24) and depression, and long-term safety and tolerability are well established. However, in comparison to the well-known effects of the sympathetic nervous system, the role of the parasympathetic nervous system in the pathophysiology of HF is less well understood. Preclinical studies demonstrated the benefit of VNS to reduce mortality, improve cardiac function, and decrease inflammation in a variety of animal models of HF (8–10). Indeed, the anti-inflammatory effects of VNS after ischemia and reperfusion injury are accompanied by a reduction in the number of macrophages and apoptotic cells that is paralleled by decreased levels of circulating pro-inflammatory cytokines (25). This has been referred to as the "cholinergic anti-inflammatory reflex" (26). The potential deleterious effects of VNS in the heart include

CENTRAL ILLUSTRATION **Vagus Nerve Stimulation in Heart Failure: Univariate Predictors of Primary Outcome Events**



Gold, M.R. et al. J Am Coll Cardiol. 2016;68(2):149-58.

Forest plots of the pre-specified subgroups are shown. 6MHW = 6-min hall walk; CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio; int. p = interaction p value for each pair of subgroups.

bradycardia, as well as potential negative inotropic effects mediated through the M2 muscarinic receptor.

Based on the encouraging results noted previously, a number of clinical studies of VNS were initiated (27). A nonrandomized pilot study of 32 patients implanted with the CardioFit system as used in the present study showed improved quality of life and left ventricular (LV) systolic function which was maintained over long-term follow-up (14). More recently, 2 randomized trials of 6-month duration were performed using other VNS systems. NECTAR-HF (NEuroCardiac TherApy foR Heart Failure Study) (15) was a double-blinded, randomized study of 96 patients that compared VNS to medical therapy. The

primary endpoint of the trial was the change in LV end-systolic diameter, which did not improve with VNS. However, there was a significant improvement in quality of life. ANTHEM-HF (Autonomic Neural regulation THerapy to Enhance Myocardial function in Heart Failure) (16) was an open-label study of 60 patients randomized to right- or left-sided VNS. Both arms of this study showed significantly improved echocardiographic measures of reverse remodeling.

The INOVATE-HF study adds importantly to our knowledge of VNS therapy. Patients were followed for up to 4.3 years with a mean follow-up 16 months, compared with the short-term follow-up (6 months) of other randomized trials of VNS. The long-term treatment with chronic VNS in HF patients appears to be safe, and it is consistent with the safety profile of VNS for other indications. Finally, we chose efficacy endpoints (mortality and HF events) which have been used in many seminal pivotal HF trials. Despite improvements in quality of life and functional status, VNS did not improve these "hard" outcomes.

STUDY LIMITATIONS. One limitation of the study design is the lack of blinding and a sham control group. However, VNS often leads to minor side effects so that it is not possible to ensure patient blinding. For instance, the NECTAR-HF study, which is the only VNS trial with an implanted and unstimulated control group, blinding was not successful (15). In the active group receiving VNS, 77.2% of patients believed they were in the active arm compared with 7.0% who believed they were in the control arm (blinding index = 0.70). Further, the use of sham implants is more appropriate when the follow-up period is short so that the control patients can be crossed over to active treatment (28). INOVATE-HF was designed to evaluate long-term outcomes and it was believed to be inappropriate to expose the control group to the risks of implantation but leaving the device inactive for periods that could be several years.

We previously hypothesized (13,29) that the average stimulation current may have been inadequate (or too low) to achieve a response with VNS in the NECTAR-HF trial (15) (1.4 mA) and may have blunted the response in ANTHEM-HF (16) (2.0 mA). Although higher currents were achieved with the cuff electrode used in the present study, this hypothesis was not supported by our study as the primary outcome did not improve with VNS.

The improved 6-min hall walk distance, NYHA functional class, and quality-of-life scores with VNS in the present study may potentially be interesting, and these measures have been associated with favorable outcome in patients with HF (30). However, these findings must be interpreted with caution given that they were secondary endpoints and may be subject to bias. Whether these outcomes are due to a "placebo" effect in an unblinded trial or true benefits of VNS will require further study. However, it is noteworthy that quality of life (albeit assessed with a different questionnaire) was also improved with VNS in NECTAR-HF (15). The failure of VNS to reduce the primary composite endpoint coupled with the nonsignificant effect on LVESVi in our trial is consistent with other HF therapies which show a clear association between clinical outcomes and reverse LV remodeling. Specifically, HF hospitalization rates and mortality typically improve when LV remodeling occurs with therapy (31,32).

The subgroup analyses of this trial showed only 1 significant interaction, with a worse outcome in female patients. Although this may be a concerning result, the marked difference in clinical characteristics may account for the observed findings as supported by the multivariate analysis. Further analysis will be needed to assess if subgroups can be identified that appear to benefit or be harmed by VNS, which will help generate hypotheses for further study. However, all subgroup analyses must be interpreted cautiously even if pre-defined, as they are underpowered statistically.

The mixed results from INOVATE-HF and previous VNS studies (14–16) has also been noted with other device therapies in HF such as spinal cord stimulation (17,18). This probably illustrates the complexity of autonomic modulation with many different factors that may affect outcomes, including trial design, stimulation parameter (such as site, frequency, and intensity), and patient population under study (13,33).

CONCLUSIONS

The INOVATE-HF trial was the first large, randomized trial of device-based autonomic modulation in HF. The results of the study show that VNS did not improve the risk of death or HF events among patients with HF and a reduced LVEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: VNS was shown in pre-clinical and small observational studies to improve heart function, quality of life, and exercise capacity.

COMPETENCY IN MEDICAL KNOWLEDGE 2: VNS improved quality of life, functional status, and 6-min walk time in chronic HF but it did not promote reverse remodeling.

TRANSLATIONAL OUTLOOK: Further study is needed to determine if specific subgroups or stimulation protocols benefit or are harmed by VNS. Moreover, additional research is needed to determine the optimal delivery of this therapy, including site, frequency, and strength of stimulation.

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KEY WORDS autonomic modulation, clinical trials, heart failure, outcomes, vagus nerve stimulation

APPENDIX For a list of the centers and their principal investigators and the study committees as well as supplemental figure and tables, please see the online version of this article.