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Vagus Nerve Stimulation for the Treatment of Heart Failure

The INOVATE-HF Trial

Michael R. Gold, MD, PhD,[a] Dirk J. Van Veldhuisen, MD, PhD,[b] Paul J. Hauptman, MD,[c] Martin Borggrefe, MD,[d] Spencer H. Kubo, MD,[e] Randy A. Lieberman, MD,[f] Goran Milasinovic, MD,[g] Brett J. Berman, MD,[h] Sanja Djordjevic, MD,[i] Suresh Neelagaru, MD,[j] Peter J. Schwartz, MD,[k] Randall C. Starling, MDs, MPH,[l] Douglas L. Mann, MD[m]

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.

From the [a]Cardiology Division, Medical University of South Carolina, Charleston, South Carolina; [b]Cardiovascular Division, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [c]Cardiology Division, Saint Louis University School of Medicine, St. Louis, Missouri; [d]1st Department of Medicine-Cardiology, University Medical Centre Mannheim, Mannheim, Germany, and DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Mannheim, Germany; [e]BioControl Medical, New Hope, Minnesota; [f]Detroit Medical Center, Detroit, Michigan; [g]Clinical Centre of Serbia, Belgrade, Serbia; [h]Chula Vista Cardiac Center, Chula Vista, California; [i]Clinical Hospital Center "Bezanijska Kosa," Belgrade, Serbia; [j]Lone Star Heart Center, Amarillo, Texas; [k]IRCCS Istituto Auxologico Italiano, Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Milan, Italy; [l]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; and the [m]Washington University School of Medicine, St. Louis, Missouri. Drs. Gold, Van Veldhuisen, Hauptman, Borggrefe, Lieberman, Milasinovic, Berman, Djordjevic, Neelagaru, Starling, and Mann received research grants for participation in the INOVATE-HF study. Dr. Gold is a consultant with BioControl Medical, Ltd. Dr. Van Veldhuisen is a member of the board with BioControl Medical, Ltd. Dr. Hauptman is a consultant and Steering Committee member with BioControl Medical, Ltd.; is a consultant with Sensible Medical, St. Jude Medical, Relypsa, and Covia; and has received grant support from NHLBI, Alynylam. Dr. Borggrefe is a consultant with BioControl Medical, Ltd., Impulse Dynamics, and Boston Scientific; and has received support from Impulse Dynamics, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. Dr. Kubo is a consultant with and Chief Medical Officer for BioControl Medical, Ltd. Dr. Lieberman is a consultant with Medtronic and St. Jude Medical; and is an investigator for BioControl Medical, Ltd. Dr. Neelagaru is a consultant with BioControl Medical, Ltd. Dr. Starling is a consultant with BioControl Medical, Ltd. Dr. Mann is a consultant with and a member of the Steering Committee for BioControl Medical, Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. P.K. Shah, MD, served as Guest Editor for this paper.

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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