Rationale and study design of the INcrease Of Vagal TonE in Heart Failure study: INOVATE-HF

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Background Imbalance between the parasympathetic and sympathetic nervous systems is a recognized contributor to progression of chronic heart failure. Current therapy with beta adrenergic antagonists is designed to moderate the up-regulation of norepinephrine and sympathetic effects; however, to date, there are no therapies that specifically address the withdrawal of parasympathetic influences on cardiac function and structure.

Methods/Results In order to evaluate the impact of vagus nerve stimulation, an international multi-center randomized clinical trial (INOVATE-HF) has been designed to assess safety and efficacy of vagus nerve stimulation in symptomatic patients with heart failure on optimal medical therapy using the CardioFit System (BioControl Medical, Yehud, Israel). Up to 650 patients from 80 sites will be recruited and randomized in a 3:2 ratio to receive active treatment or standard optimal medical therapy. Inclusion criteria include left ventricular systolic dysfunction, the presence of New York Heart Association Class III symptoms, sinus rhythm, and QRS width less than 120 milliseconds. The study is powered to detect differences in the primary efficacy end point of all-cause mortality and heart failure hospitalization and 2 safety end points.

Conclusion Vagal nerve stimulation with CardioFit as a treatment for symptomatic heart failure is under active investigation as a novel approach to restore balance between the sympathetic and parasympathetic nervous systems. If shown to be safe and effective in decreasing heart failure events and mortality, this novel approach will impact the treatment paradigm for heart failure. (Am Heart J 2012;163:954-962.e1.)

The management of heart failure due to left ventricular systolic dysfunction remains a clinical challenge in the patient with advanced symptoms despite optimal medical and device therapy.1,2 A lack of progress in the development of new drug therapies3-7 has stimulated interest in new nonpharmacological approaches especially in patients without QRS prolongation for whom cardiac resynchronization therapy is not indicated.

One such approach, vagus nerve stimulation,8 addresses an important physiological abnormality that characterizes the heart failure state: an imbalance between the sympathetic and parasympathetic nervous systems.9 There is evidence that the combination of sympathetic up-regulation and parasympathetic withdrawal is associated with progressive ventricular remodeling, arrhythmia generation and disease progression. Although β-blockers can be used to modify the impact of elevated levels of norepinephrine and the effects of augmented sympathetic tone,10 the ability of drug therapy to influence parasympathetic function is limited,11 although low-dose digoxin may play a role.12,13 However, direct vagus nerve stimulation has now been evaluated in both pre clinical models14-16 and in a pilot study in patients with heart failure.17,18 Preliminary results suggest that patients may derive benefit in a variety of domains including quality of life, submaximal exercise capacity, and echocardiographic parameters.

As a consequence, a pivotal multicenter international clinical trial, the INOVATE-HF study, has been designed to address whether vagus nerve stimulation using a proprietary implantable system can change the natural history of patients with left ventricular ejection fractions less than 40% who have New York Heart Association (NYHA) Class III symptoms and a QRS duration of less than 120 milliseconds while on optimal medical therapy. The primary efficacy end point of INOVATE-HF will assess

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whether use of the device increases the time to first event defined by all-cause mortality or unplanned heart failure hospitalization.

**Mechanism of action of vagus nerve stimulation**

Neural control of the heart is exerted by the tonic interaction between the 2 limbs of the autonomic nervous system. Early studies focused on the electrical stability of the heart and arrhythmia generation in ischemia. Increasingly, interest has shifted to the role of sympathetic-parasympathetic imbalance in heart failure. Markers of vagal function, such as baroreceptor sensitivity and heart rate variability, are abnormal in the heart failure state. Research into the precise abnormality in the efferent limb of the parasympathetic nervous system has led to the observation that a primary site of attenuated vagal control on the heart occurs at the level of the parasympathetic ganglion. In addition, it appears that vagus nerve stimulation can modulate local inflammatory and nitric oxide-mediated responses, potentially important findings given the increasing acceptance that in inflammatory mediators may be more than ‘innocent bystanders’ in the pathophysiology of heart failure (Table I).

<table>
<thead>
<tr>
<th>Table I. Potential cellular and electrophysiological benefits of parasympathetic activation</th>
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<tbody>
<tr>
<td>Anti-inflammatory effects</td>
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<tr>
<td>Change in nitric oxide expression</td>
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<tr>
<td>Change in cytokine expression</td>
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<tr>
<td>Inhibition of the renin-angiotensin system</td>
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<tr>
<td>Improved baroreflex sensitivity</td>
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<tr>
<td>Reduced heart rate</td>
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<tr>
<td>Increased heart rate variability</td>
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<tr>
<td>Direct anti-arrhythmic effects</td>
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Changes normally seen following induced myocardial infarction, such as up-regulation of tumor necrosis factor-alpha and interleukin-6. These beneficial effects are promising though it is important to note that the precise parameters of nerve stimulation in these studies differ from the algorithm currently under evaluation in INOVATE-HF.

Results from a multi center European open label pilot trial involving 32 patients have been recently reported. Specifically, improvements in 6-minute hall walk distance, NYHA class and Quality of Life measurements were achieved. Left ventricular ejection fraction increased significantly from a mean of 22.3 ± 6.9 to 28.7 ± 8.4 at 6 months, as a result of a reduction in end systolic volume index. The positive effect of vagus nerve stimulation was sustained in the patients who were followed for 12 months. Importantly, these analyses have also provided valuable data on the approach for neurostimulation “dosing” and therapy titration while minimizing side effects of vagus nerve stimulation.

**Preclinical and pilot data**

With the use of preclinical animal models, direct vagus nerve stimulation has been tested under controlled circumstances. Studies by Sunagawa and colleagues demonstrated that stimulation of the vagus in rats following the development of heart failure within 14 days of experimentally induced myocardial infarction led to improvements in hemodynamic parameters and survival compared to sham-stimulated groups. In an ischemia-reperfusion rat model, stimulation reduces infarct size and both apoptotic and inflammatory reactions, and appears to protect against arrhythmia by preventing loss of connexin 43 induced by ischemia. In the canine infarct model, Sabbah et al demonstrated that direct vagus nerve stimulation leads to attenuation of both ventricular dilation and the typical phenotypic

**Study objectives and overall study design**

The INOVATE-HF study is an international, multi-center, randomized clinical trial designed to assess safety and efficacy of vagus nerve stimulation using the CardioFit System (BioControl Medical, Yehud, Israel) among patients with symptomatic heart failure who are already on optimal medical therapy. An overview of the study design is provided in Figure 3. The major components are the implant procedure, a period of optimization, and extended follow-up. The cohort randomized to the device undergoes the implant procedure within 21 days of randomization, followed by a wound check within 10 days. The procedure itself includes placement of the intracardiac lead into the right ventricle in standard fashion, longitudinal neck incision
at the mid cervical height akin to a carotid endarterectomy approach with exposure of the vagus nerve, selection of cuff size and careful placement of the cuff while flushing the wound and vagus nerve with saline, and subcutaneous placement of the stimulator. A fixation technique is used to ensure stability of the cuff position and the stimulation lead is tunneled to the pacemaker pocket and connected to the stimulator. Acute testing to confirm location of the cuff on the vagus nerve can be performed at this point. In order to increase uniformity of approach, each surgeon implanting the device undergoes off site training and implant of a device in an animal model.

After 1 month, the study subject undergoes multiple visits over a 4-week period, during which time adjustments are made in the stimulation parameters with a goal of achieving a current of 3.5 to 5.5 mA. The rate of change in current will be influenced by the presence or absence of symptoms including hoarseness and referred pain in the jaw. Therefore, the process of optimization is individualized and rigorously monitored. Study subjects randomized to standard of care have clinic visits and receive follow up calls from the study nurse according to a set schedule.

After the randomization and the optimization period, the clinical status of all subjects is evaluated at 3-month intervals through 18 months post implant. System parameters may be adjusted as needed during this period and onward. Subjects who experience a qualified end point event will be considered to have reached the primary efficacy end point, and their follow-up will continue as per the study plan. Subjects who do not meet primary end point criteria will also continue in the study and will be followed until the pre-specified number of events is accumulated or the study is closed. When the number of events required has been reached, all subjects will continue to be followed up every 6 months for safety until study closure. Following completion of the 18-month follow-up period, all subjects will be followed up in 6-month intervals for overall status. Serial echocardiograms, performance of 6-minute walk tests, and administration of health status questionnaires will occur at 3, 6, and 12 months after implant. Electrocardiograms and device interrogations will be performed every 3 months.

**Endpoints**

The INOVATE-HF study efficacy end points of heart failure hospitalization and all-cause mortality are considered the most objective and least subject to bias, given the inability to completely blind members of the care team or the study subjects even if study design involved implantation in all patients but activation in only some. In addition, this end point is a standard in contemporary heart failure trials. The mortality and heart failure hospitalization events are adjudicated based on prespecified definitions per a
charter developed by an experienced, independent Clinical Events Committee blinded to the randomized arm of the subject. The standard safety end points are designed to evaluate the magnitude of procedure and system-related complications associated with the implantation procedure.

Primary efficacy end point

The primary efficacy end point of the study is the composite of all-cause mortality or unplanned heart failure hospitalization equivalent using a time to first event analysis, as compared between the 2 study arms after the prespecified number of such events have been accumulated. The latter is defined by a HF event when the subject has signs and/or symptoms consistent with HF and (1) receives an augmented HF regimen with oral or intravenous medications during an in-hospital stay that includes a calendar date change or (2) receives intravenous decongestive therapy (including diuretics, vasodilators or inotropes) but that does not involve an inpatient hospital admission regardless of setting.

Primary safety end points

There are 2 co-primary safety end points: >75% freedom from procedure and system related complication events through 90 days post implant; comparison between the 2 study arms of time to first event of all-cause mortality or all-cause complications resulting in hospitalization (including complications contributing to prolongation of hospitalization, collectively referred to as “safety events”) during the follow-up of each study subject.

Secondary and additional end points

Six secondary efficacy end points will be tested according to a pre specified statistical gatekeeping procedure (Table II). Secondary safety end point data will also be evaluated comparatively at 6 and 12 months.
including all-cause mortality, cardiovascular mortality, serious adverse events and system- or procedure-related complications. Additional end points include time to first all-cause and first cardiovascular hospitalizations, number of days alive and out of hospital, NYHA functional class of the patient at 12 months, and echocardiographic core laboratory-measured changes in function and structure from baseline up to 12 months and changes in both the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EQ-5D. Although device-device interactions were not observed in the pilot study, the frequency and severity of arrhythmia events in subjects who are already implanted at baseline with an implantable cardioverter defibrillator (ICD) device, the overall number of shocks (appropriate or not) and anti-tachycardia pacing events, and the incidence of oversensing or inhibition of therapy (if any) will be evaluated by a core laboratory blinded to the patient at 12 months, and echocardiographic core laboratory.

In addition, in a subset of study subjects, several heart rate variability parameters (including the standard deviation of NN (beat to beat) intervals, the standard deviation of the average NN intervals calculated over short periods, the proportion of NN50 divided by total number of NNs, the square root of the mean squared difference of successive NNs) will be compared between baseline and 12 months post-randomization. Other limited analyses will be obtained comparing serum NT-ProBNP level at baseline, 6 months, and 12 months and cardiopulmonary exercise testing parameters such as peak VO2 at baseline and 6 months. These studies will help define the long-term impact of vagus nerve stimulation and provide supporting data on efficacy. In addition, other analyses, including examination of uvula deviation, change in peak respiratory flow volume on spirometry from baseline to 12 months, and the measurement of pancreatic polypeptide in a subset of the study patients may provide inferential data on long-term safety of cardiac nerve stimulation as well as its noncardiac impact.

No pathological studies of the vagus nerve are feasible in the clinical trial but histopathological studies27 and preliminary clinical data do not suggest that chronic stimulation leads to long term damage of the vagus nerve.18 Based on these observations, as well as studies by Agnew and McCreery,28 stimulation is provided intermittently (in a repetitive “on-off” cycle) with periods of “off stimulation” in an overall ‘duty cycle’ of 25% or less. These algorithms are believed to provide ample recovery time for the vagus nerve.

### Population under study

Based on pilot study experience, the INOVATE-HF study will enroll adult patients with NYHA Class III symptoms. Criteria such as distance on a 6-minute walk will help to further define the population as Class III. In addition, the left ventricular ejection fraction must be less than 40% and end-diastolic dimensions must be between 50 and 80 mm as determined by echocardiography at the participating site.

#### Inclusion criteria

Key inclusion criteria are shown in Table III. Briefly, patients must have a diagnosis of chronic symptomatic heart failure, sinus rhythm and a QRS duration less than 120 milliseconds, without indications or plans for implantation of a CRT device. Presence of an ICD is acceptable in accordance with guidelines; however, patients are excluded if an elective ICD generator change is planned within 180 days. The mean heart rate with monitoring during wakeful hours must be between 65 and 110. Evidence of moderate but not severe exercise impairment must be present: patients should be able to walk 150 to 425 meters on a 6-minute walk test. The selection of a QRS duration less than 120 milliseconds is based on the goal to minimize cross over to cardiac resynchronization therapy during the study.

#### Exclusion criteria

Key exclusion criteria are shown in Table IV. Briefly, the key cardiovascular exclusions include pacemaker

### Table II. Efficacy end points

<table>
<thead>
<tr>
<th>Primary efficacy endpoint</th>
<th>Secondary efficacy endpoints</th>
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<tr>
<td>• Composite of all-cause mortality or unplanned heart failure hospitalization equivalent using a time to first event analysis</td>
<td>• Rate of unplanned heart failure hospitalization equivalents</td>
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<tr>
<td>• Mean improvement in LVESVi from baseline to 12 months</td>
<td>• Mean improvement in the summary KCCQ score from baseline to 12 months</td>
</tr>
<tr>
<td>• Mean improvement in 6-minute walk test from baseline to 12 months</td>
<td>• All-cause mortality and the number of unplanned heart failure hospitalization equivalents</td>
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<tr>
<td>• Rate of hospitalization-free days</td>
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### Table III. Key inclusion criteria

- Chronic symptomatic NYHA functional class III heart failure.
- Age ≥18 years.
- Rhythm should be sinus. Average daytime heart rate between 65 and 110 beat/min.
- On stable optimally uptitrated medical therapy recommended according to current guidelines as standard of care for heart failure treatment.
- LVEF <40% per site measurement within 1 month prior to enrollment.
- Physically capable and willing to perform repeated 6-minute walk tests associated with the study with baseline distance between 150 and 425 meters.
- QRS duration <120 milliseconds
- Left ventricular end diastolic diameter, per site measurement between 50 and 80 mm.
- The subject is a male or postmenopausal female. Females of childbearing age may be included if an acceptable contraception measure is used.
- Subject must sign an approved informed consent form and agree to attend all follow-up evaluations.
Table IV. Key exclusion criteria

| Acute myocardial infarction, variant angina pectoris, unstable angina or acute coronary syndrome in the previous 1 month. |
| Previous history of any stroke and/or neurologically significant transient ischemic attack. |
| Coronary artery bypass surgery, valve replacement or repair, aortic surgery or percutaneous coronary intervention in the prior 90 days or planned/anticipated within 180 days. |
| Heart failure due to acute myocarditis, restrictive cardiomyopathy, constrictive pericarditis or hemodynamically significant aortic valve insufficiency, aortic stenosis, or mitral valve stenosis. |
| Severe renal failure (creatinine level >3 mg/dL, 26.5 mmol/L) |
| Severe hepatic failure (transaminase level 4 times upper limit of normal, or total bilirubin level >1.8 mmol/dL). |
| Type I diabetes mellitus or type II diabetes mellitus with autonomic or sensory neuropathy or measured HbA1c within the preceding 60 days >8.0%. |
| Previous neck surgery (including for cerebrovascular disease or malignancy); previous radiation therapy of the neck. History of left neck surgery for other indications is allowed. |
| Current hypotension (systolic blood pressure <80 mm Hg). |
| Active peptic ulcer disease or history of upper gastrointestinal bleeding, or ulcer within 6 months. |
| Asthma, history of severe chronic obstructive pulmonary disease (eg, forced expiratory volume in one second <1.5 L), severe restrictive lung disease or oxygen dependency. |
| First-degree AV block with PR interval >240 milliseconds; second- or third-degree atrioventricular block; or pacemaker dependency. |
| Chronic atrial fibrillation or flutter in the previous 90 days, or hospitalization for atrial fibrillation due to clinical manifestations within 180 days. |
| Presence of sustained ventricular tachyarrhythmia with hemodynamic compromise, in the absence of implanted ICD; or planned elective ICD generator change within 180 days; use of unipolar sensing; or a minimal post-ventricular blanking period shorter than 135 milliseconds in all sensed leads. |
| Subject is currently a candidate for cardiac resynchronization device implantation or is anticipated to receive a cardiac resynchronization device within 180 days of randomization. |
| Congenital or acquired long QT syndrome. |
| Documented or suspected vaso-vagal syncope or vaso depressor syncope. |
| Use of class III anti-arrhythmic drugs within 3 months or calcium channel antagonists that affect sinoatrial node function including calcium-channel blockers, such as diltiazem and the sinus nodal slowing agent ivabradine which is available in Europe. |
| In addition, due to concerns about neuropathy and its impact on the efficacy of neural stimulation, patients with type I diabetes or type II diabetes who are being treated for an autonomic or sensory neuropathy or who have a markedly elevated HbA1c values are excluded. Due to the potential need to manipulate the right carotid artery during implantation, patients with carotid artery disease cannot be enrolled. In addition, patients with elevated body mass index above 38.0 are excluded due to concerns about perioperative risk and the multiple etiologies for dyspnea in this population. |

**Randomization and baseline testing**

INOVATE-HF will randomize up to 650 patients from 80 sites in the United States and Europe. The study subjects are dynamically allocated to the study groups. Where possible, a secure on-line Interactive Wireless Randomization System is being utilized. Two principles of allocation are employed and adjust for the 3:2 overall proportion among the study arms and for gender and presence of ICD for equal distribution between the arms based on enrollment.

Baseline evaluations include a comprehensive medical history and physical exam, carotid study, Holter recording, uvula deviation and gag reflex testing, peak flow testing via spirometry, echocardiography, performance of a 6-minute walk test, administration of the KCCQ and EQ-5D, and in substudies the measurement of serum pancreatic polypeptide and biomarker levels.

**Statistical design**

**Analysis**

The primary efficacy end point will be compared between groups using a log-rank test, under the intention-to-treat principle. The formal hypothesis test examines whether the hazard rate is significantly improved for the treatment group at a one-sided 0.025 α level.
The safety end point of freedom from procedure and system-related events at 90 days post implant in the treatment group will be compared to a performance goal of 0.75; the end point will be considered successful if the lower bound of the 2-sided 95% CI for the proportion free from procedure or system-related events at 90 days is above 0.75 (demonstrating that the event free rate is significantly greater than 75%). This figure is based on a literature review of objective performance criteria for prior active implantable cardiovascular device studies and discussions with the relevant regulatory authorities.

The second safety end point of time to first all-cause complication resulting in hospitalization or contributing to prolongation of hospitalization or all-cause mortality will be tested at a one-sided 0.025 α level using a proportional hazards model. The formal hypothesis compares the non-inferiority of the device to usual care based on a null hypothesis for the negative log hazard ratio of −0.3472. At 1 year, this would correspond to a 12.5% lower event rate in favor of the usual care arm. Both safety end points must be met for the trial to be successful.

An independent data and safety monitoring board has been established to perform review of the data including events as adjudicated by the clinical events committee.

Sample size assumptions and calculations

The study size and duration is event driven. To provide at least 80% power, the study will continue until the accumulation of 376 primary efficacy events and 437 secondary primary safety events and either the 600th randomized subject is followed up at least 1 year or each patient is followed up to a maximum of 4.5 years. A total of 650 randomized subjects, randomized in a 3:2 ratio (active: control) is expected to satisfy these requirements based on assumptions regarding accrual and event rates. Specifically, the analysis of the primary efficacy end point is an analysis of the time to first unplanned heart failure hospitalization, or all cause mortality with 3 planned interim analyses for futility at 0.333, 0.556, and 0.778 of the total number of planned events (376). A dropout hazard rate of 1.5%/year was foreseen in both the treatment and control group (similar rate to the treatment groups in earlier device trials). The control hazard rate was assumed to be 0.52 and is based upon review of event rates (hospitalization or death) in studies of patients who are in equivalent status to the intended patient population in the CardioFit study, including, for example, NYHA class III and low ejection fraction. Hazard rate curves from the following studies were used (in addition to events derived from the CardioFit pilot): COMPASS, CARE-HF, EVEREST, and COMET.

Type I error control/interim analysis

Because both the primary efficacy and the 2 co-primary safety end points must be attained in order to have a successful trial, there is no type I error inflation due to multiple testing of end points. Interim monitoring of the trial will be performed based on a beta spending function and conditional power-based futility monitoring.

Discussion

During the last 30 years, experimental and clinical evidence has accumulated indicating that depressed vagal reflexes are associated with both increased arrhythmic risk and overall cardiac mortality; impaired vagal reflexes predict increases in mortality in patients with heart failure and following myocardial infarction; and augmentation of vagal activity, either by electrical stimulation or by exercise training may reduce arrhythmic and total cardiac mortality.

These data have prompted initial attempts to assess the feasibility, safety, and possibly outcome effects of direct vagal stimulation in patients with heart failure and underlie the rationale for the INOVATE-HF study which is designed to test the hypothesis that chronic stimulation synchronized to the heart rate, using a novel vagus nerve stimulator, will prolong the time to first event (mortality or unplanned heart failure hospitalization equivalent) among patients who have functional limitations, left ventricular dilation, and impaired systolic function despite optimal medical therapy. Key exclusion criteria include a QRS duration of >120 milliseconds, mean daytime heart rate less than 65 or greater than 110 beat/min, and the presence of atrial fibrillation or recent hospitalization for atrial fibrillation. Substudies will provide greater insights into the precise mechanism of action of vagus nerve stimulation. The study is also devised to evaluate safety given the invasive nature of the implant procedure. The first patient was enrolled in April 2011, and the study is expected to reach full enrollment in less than 5 years.

Limitations: The trial randomizes patients with heart failure within a relatively narrow spectrum. It is conceivable that a therapeutic response can be achieved in patients with lesser or greater degrees of heart failure and/or with longer QRS durations. Furthermore, the estimates of probabilities for the primary efficacy analysis were based on a review of the heart failure literature and the results of the CardioFit for Heart Failure pilot study, and are therefore approximate. In addition, while a rigorous training protocol has been established for each investigative site prior to the site’s first randomization, we cannot discount the possibility of a “learning curve.” Nevertheless, the pilot study provides reassurance about morbidity associated with implantation and 2 safety end points have been selected to maximize subject protection.

Summary

INOVATE-HF is the first large multi center phase III study of vagus nerve stimulation for the treatment of symptomatic heart failure and represents a novel
approach to re-establish balance between the sympathetic and parasympathetic limbs of the autonomic nervous systems in patients with heart failure. If proven effective and safe, the system including the stimulator is envisioned to be synergistic with existing medical therapy and potentially adaptable into current ICD technology.

Disclosures
The INOVATE-HF study is funded by BioControl Medical Ltd, Yehud, Israel.

All the authors have received honoraria as members of the Steering Committee (PJS, MRG, MB, DJV, RS and DLM) or Scientific Advisory Board (PJS). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Dr Hauptman reports consulting for BioControl Medical and CardioMEMS Inc.
Dr Schwartz reports consulting for BioControl Medical.
Dr Gold reports research funding, consulting and/or honoraria from Medtronic, Boston Scientific, St Jude’s and Sorin.
Dr Borggrefe reports consulting for BioControl Medical.
Dr Van Veldhuisen reports consulting for BioControl Medical.
Dr Starling reports consulting for BioControl Medical, research funding and honoraria as a member of an advisory committee from Medtronic and research funding as site PI for the Echo CRT study sponsored by Biotronik.
Dr Mann reports consulting for BioControl Medical.

References


Appendix. Technological Considerations

The CardioFit system (BioControl Medical Ltd) is comprised of a stimulation lead with cuff placed over the right vagus nerve via a standard carotid endarterectomy approach; a standard intracardiac sensing electrode placed in the right ventricle which enables suppression of nerve stimulation when heart rate falls below a predetermined value; an implantable stimulator to which the stimulation and sensing leads connect via a 2-port connector; and an external testing device and portable physician programmer with proprietary software (as shown in Figures 1 and 2). The CardioFit system is designed to provide vagus nerve stimulation to patients with heart failure based on sensed ventricular impulses via $R$ wave measurement using the sensing lead. In addition, the following parameters can be programmed to provide vagus nerve stimulation therapy: current level (in mA), pulse width (in milliseconds), on and off cycle times (seconds), number of pulses per heart beat, and upper and lower heart rate thresholds for therapy delivery. Most of these parameters are preset; the focus during optimization of stimulation is the gradual increase of the current level rather than the manipulation of the other parameters.

The cuff contains a multi contact bipolar electrode that may preferentially stimulate cardiac parasympathetic fibers in a unidirectional fashion. The design of the cuff, which is available in multiple sizes depending on the size of the vagus nerve, also minimizes leakage of current into surrounding tissue.

Supplementary Reference