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ORIGINAL INVESTIGATIONS

Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND This study demonstrated the safety and effectiveness of baroreflex activation therapy (BAT) in patients with heart failure with reduced ejection fraction (HFrEF).

OBJECTIVES The BeAT-HF (Baroreflex Activation Therapy for Heart Failure) trial was a multicenter, prospective, randomized, controlled trial; subjects were randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group).

METHODS Four patient cohorts were created from 408 randomized patients with HFrEF using the following enrollment criteria: current New York Heart Association (NYHA) functional class III or functional class II (patients who had a recent history of NYHA functional class III); ejection fraction ≤35%; stable medical management for ≥4 weeks; and no Class I indication for cardiac resynchronization therapy. Effectiveness endpoints were the change from baseline to 6 months in 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life (QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate (MANCE).

RESULTS Results from, timeline and rationale for, cohorts A, B, and C are presented in detail in the text. Cohort D, which represented the intended use population that reflected the U.S. Food and Drug Administration–approved instructions for use (enrollment criteria plus NT-proBNP <1,600 pg/ml), consisted of 245 patients followed-up for 6 months (120 in the BAT group and 125 in the control group). BAT was safe and significantly improved QOL, 6MHW, and NT-proBNP. In the BAT group versus the control group, QOL score decreased ($\Delta = -14.1$; 95% confidence interval [CI]: −19 to −9; $p < 0.001$), 6MHW distance increased ($\Delta = 60$ m; 95% CI: 40 to 80 m; $p < 0.001$), NT-proBNP decreased ($\Delta = -25\%$; 95% CI: −38% to −9%; $p = 0.004$), and the MANCE free rate was 97% (95% CI: 93% to 100%; $p < 0.001$).

CONCLUSIONS BAT was safe and significantly improved QOL, exercise capacity, and NT-proBNP. (Baroreflex Activation Therapy for Heart Failure [BeAT-HF]; NCT02627196) (J Am Coll Cardiol 2020;76:1–13) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MHW = 6-min hall walk distance

BAT = baroreflex activation therapy

CI = confidence interval

CRT = cardiac resynchronization therapy

EF = ejection fraction

FDA = U.S. Food and Drug Administration

HFrEF = heart failure with reduced ejection fraction

ITT = intention to treat

MANCE = major adverse neurological, cardiovascular-related device, procedure event-free rate

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

QOL = quality of life

Despite significant improvements in management, patients with heart failure with reduced ejection fraction (HFrEF) have reduced life expectancy, frequent heart failure hospitalizations, poor quality of life (QOL), and substantial limitations in exercise capacity (1,2). This is especially true for the ≥70% of patients with HFrEF who are ineligible for cardiac resynchronization therapy (CRT) (3). One novel treatment developed to fill this continuing unmet need is the use of an implantable device capable of producing cardiac autonomic modulation. Autonomic modulation has taken 3 general approaches: spinal cord stimulation; direct vagal stimulation; and carotid baroreflex activation therapy (BAT) (4–7). Results from spinal and vagal stimulation studies have been disappointing; none of the 3 randomized controlled trials that examined these methods resulted in significantly improved symptoms, reduced morbidity, or reduced mortality rates (4–6). We hypothesized that the decreased sympathetic and increased parasympathetic activity that resulted from BAT would improve heart failure symptoms in patients with HFrEF.

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The effects of BAT were examined in preclinical trials, a first-in-man, single-center trial, and in a moderate size, phase II, prospective, randomized multicenter controlled trial (7–18). These trials showed that BAT, which used afferent signaling to the brain via the carotid sinus nerve, reduced sympathetic and increased parasympathetic signaling that acted in aggregate to rebalance the autonomic input to the heart (8,16). In the phase II trial, BAT significantly decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP), increased 6-min hall walk distance (6MHW), improved the Minnesota Living With Heart Failure QOL score, and decreased the number of days hospitalized for heart failure after 6 months of treatment compared with control subjects who did not undergo implantation and received optimal medical management (7). These clinical benefits were pronounced in patients who were not treated with CRT (17). Follow-up data at 12 months post-treatment showed that these findings were durable (18). These data were used to design a phase III, prospective, randomized multicenter controlled clinical trial to evaluate the safety and effectiveness of BAT for HFrEF—the BeAT-HF (Baroreflex Activation Therapy for Heart Failure; NCT02627196) trial. The purpose of the BeAT-HF trial was to test the hypothesis that in patients with HFrEF, BAT safely and significantly improved patient-centered symptomatic endpoints of QOL and exercise capacity supported by objective evidence of a significant reduction of NT-proBNP.

METHODS

TRIAL DESIGN. BeAT-HF was a prospective, multicenter randomized 2-arm, parallel-group trial designed to develop valid scientific evidence for the safety and effectiveness of BAT with the BAROSTIM NEO system (CVRx, Minneapolis, Minnesota) in patients with HFrEF (19). The trial was designed by the Executive Steering Committee in collaboration with CVRx, Inc. and the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health through the Breakthrough Devices Program [a part of the 21st Century Cures Act (20) for medical devices] to provide a pathway that would potentially accelerate market access for promising technologies intended to treat chronically ill patients with severe unmet needs (21). The overall trial was designed to encompass 2 phases:

1. A pre-market phase that examined 3 primary effectiveness endpoints (6MHW, QOL, and NT-proBNP) and 1 safety endpoint (major adverse neurological or cardiovascular system or procedure-related event-free rate [MANCE]). Proof of effectiveness and safety using these endpoints led to an FDA-approved indication for BAT on August 16, 2019. The pre-market phase used an FDA-approved adaptive design and resulted in the

a consultant to CVRx; has received fees for being a member of the BeAT-HF trial executive steering committee; and has been a member of the Executive Committee of CVRx Barostim. Dr. Zannad has been a consultant to CVRx; and has received fees for being a member of the BeAT-HF trial executive steering committee. Mr. Rogers has been a consultant to CVRx. Ms. Galle is an employee of CVRx. Dr. Abraham has been a consultant to CVRx; and has received fees for being a member of the BeAT-HF Trial Executive Steering Committee.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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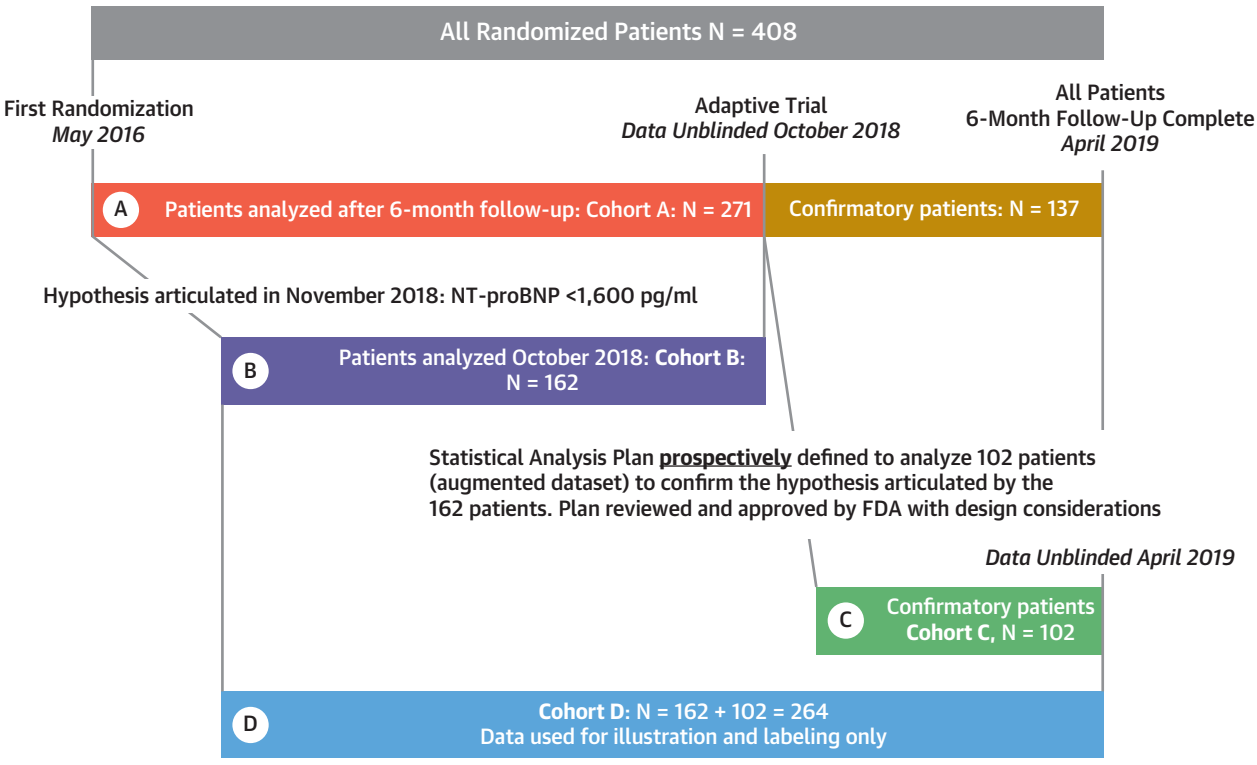
FIGURE 1 **BeAT-HF Trial Design Timeline**



Timeline and rationale for the development of the 4 cohorts of patients and the sequence of design decisions made in the BeAT-HF (Baroreflex Activation Therapy for Heart Failure) trial. The design decisions and statistical analysis plans were developed with interaction of the U.S. Food and Drug Administration (FDA) under the auspice of the Breakthrough Devices program. Sample sizes for each cohort are specified. Timeline dates are specified. NT-proBNP = N-terminal pro–B-type natriuretic peptide.

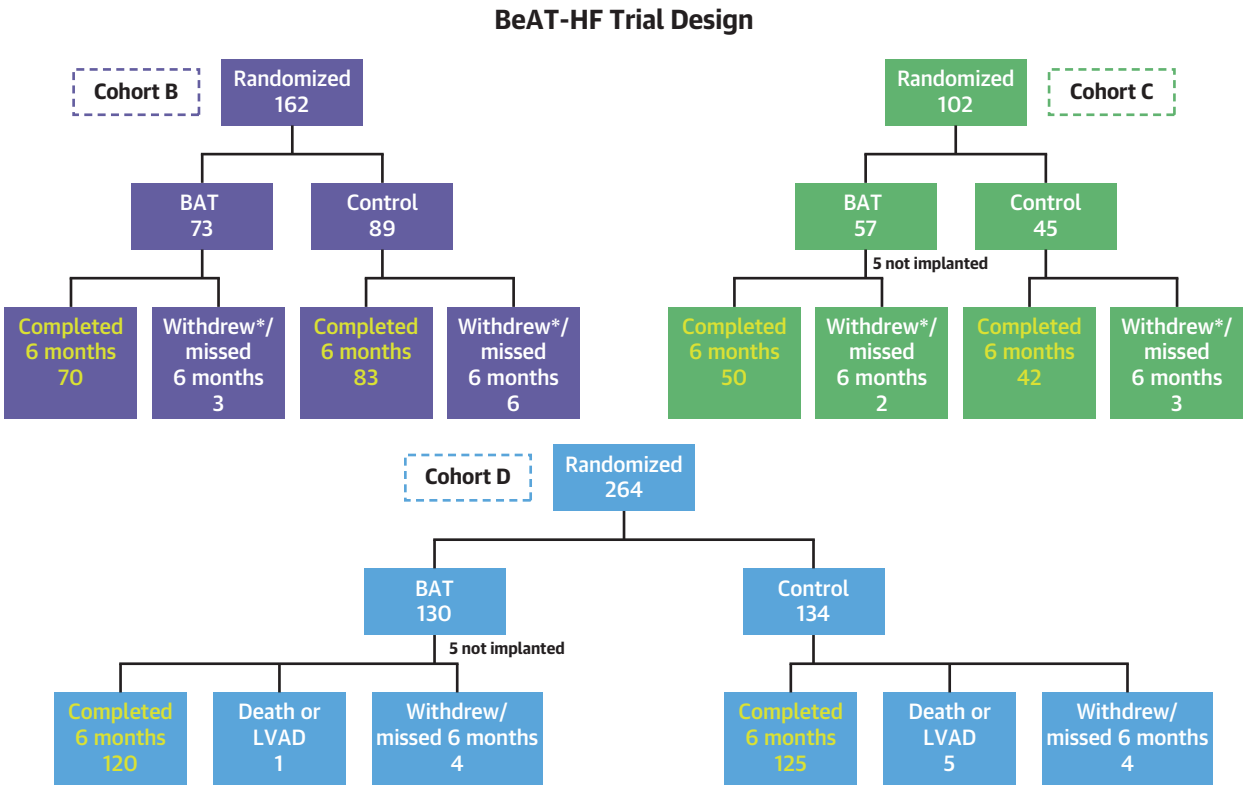
development of 4 study cohorts (cohorts A, B, C, and D) as defined in the following (Supplemental Figure 1).

2. A post-market phase that will examine the effects of BAT on rates of heart failure hospitalization and cardiovascular mortality, and when successful, will seek an appropriately expanded FDA indication for BAT (Supplemental Figure 2).

PARTICIPANTS. Eligibility criteria for BeAT-HF were described in detail in a previous publication (19). Briefly, patients were included if they had New York Heart Association (NYHA) functional class III symptoms or functional class II (had a recent history of functional class III), a left ventricular ejection fraction (EF) of ≤35%, 6MHW distance of 150 to 400 m, and stable optimal medical management for ≥4 weeks. Patients who had an American Heart Association/American College of Cardiology Class I indication for CRT were excluded, and there were no restrictions for atrial fibrillation or atrial flutter. Initially, an additional eligibility criterion was the presence of an NT-proBNP >1,600 pg/ml in patients who did not have a previous heart failure hospitalization within the previous 12 months. This eligibility criterion was subsequently revised to exclude all patients with NT-proBNP >1,600 pg/ml. Patients were screened, enrolled, randomized, and all data were collected by study coordinators and staff in outpatient clinical study centers.

RANDOMIZATION. Patients who met all eligibility criteria with complete baseline measurements were randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group). Randomization schedules were created by an independent statistician using random permuted blocks and were stratified by site. Randomization assignments were obtained via the electronic data capture system after entering an intended device implantation date into this system. This date determined the timing of follow-up visits for those randomized to the control group. The actual implantation date

FIGURE 2 Disposition of Randomized Patients in Cohorts B, C, and D



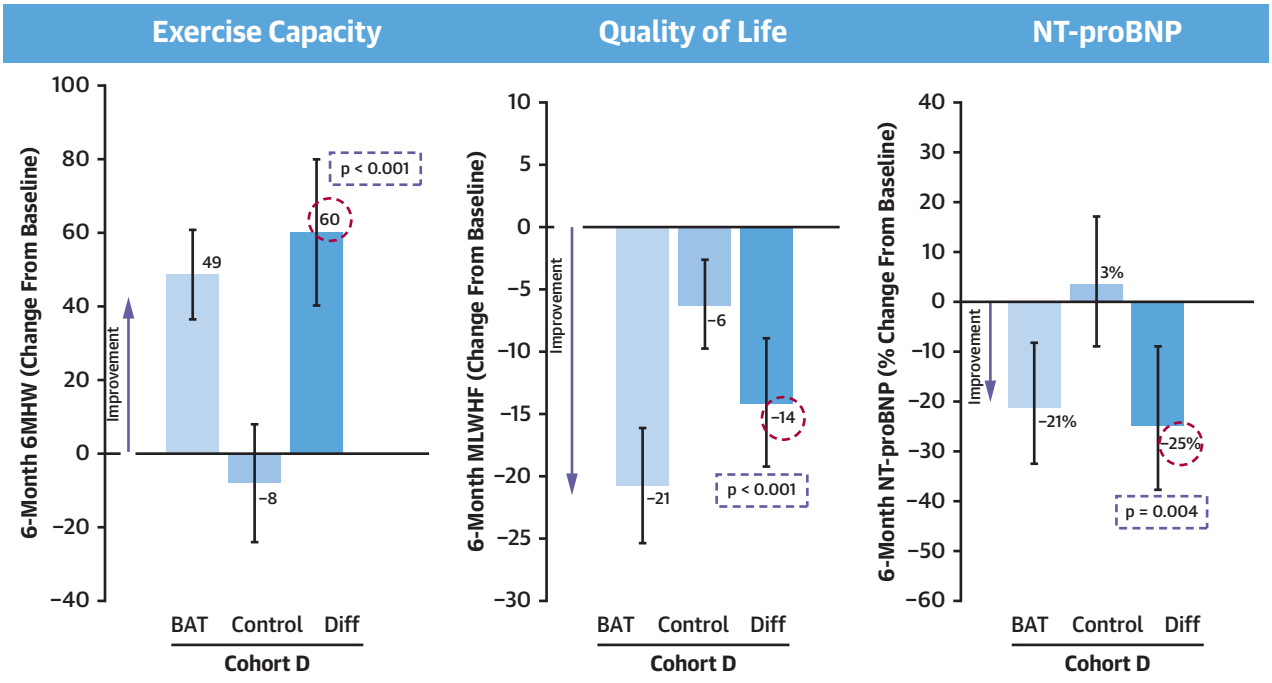
CONSORT diagrams for cohorts B, C, and D detail the number of patients randomized, the number assigned to baroreflex activation therapy (BAT) versus control groups, the number of patients that completed 6-month follow-up, and the number of patients excluded from the 6-month follow-up because of the number of deaths, left ventricular assist device (LVAD) implantations and heart transplantations, or because the patient withdrew from the study or missed the 6-month visit. *Includes death, LVAD, heart transplant.

determined the timing of follow-up visits for those randomized to the BAT group. Neither the patient nor the investigating team were blinded to the randomization allocation.

INTERVENTIONS. BAT was produced by placing a 2-mm electrode on the carotid sinus, connecting this electrode to a subcutaneously implanted pulse generator, and stimulating at an average device setting of 8.7-mA amplitude, 125-μs duration, and 40-pps frequency (Supplemental Table 1). Optimal medical management was defined as maximally tolerated guideline-directed management (1,2).

STATISTICAL METHODS. The pre-market phase sample size was planned to ensure at least 80% power for all 3 effectiveness endpoints and the safety endpoint (19). For continuous variables, statistics included mean ± SD and median (interquartile ranges). Categorical variables were summarized in frequency distributions. In data analyses, tables, and figures, an intention to treat (ITT) approach, a modified ITT "completers" approach for effectiveness endpoints, or a modified ITT "device implanted" approach for the safety endpoint were used. Tables and figures were annotated with the selection and the rationale for the specific approach used. The ITT approach included all patients randomized to the BAT group and the control group (**Figures 1 and 2**, Supplemental Figure 3). Patients included in the modified ITT completers approach fulfilled the following 3 criteria: they had a baseline value for all 3 efficacy endpoints (6MHW, QOL, NT-proBNP); they attended the 6-month visit; and they had at least 1 (but in some cases, not all) of the efficacy endpoints measured (**Figures 1 and 2**, Supplemental Figure 3). At the 6-month follow-up visit, a 6MHW assessment not attempted for cardiovascular reasons was considered as zero meters walked; a 6MHW assessment that was discontinued due to cardiovascular reasons was assessed as the total meters walked. However, if a patient refused to perform a 6MHW for non-cardiovascular reasons or if they refused to have

CENTRAL ILLUSTRATION **Phase III, Baroreflex Activation Therapy for Heart Failure Trial Top-Line Results**



Zile, M.R. et al. J Am Coll Cardiol. 2020;76(1):1–13.

Cohort D, representing the intended use group that reflects the U.S. Food and Drug Administration–approved instructions for use, was followed for 6 months. Baroreflex activation therapy (BAT) increased 6-min hall walk (6MHW) distance, improved quality-of-life score using the Minnesota Living With Heart Failure questionnaire (MLWHF), and decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP). Diff = difference in the change from baseline to 6 months in effectiveness endpoint in the BAT group versus the control group.

blood drawn for a NT-proBNP assessment, they were excluded from the completers analysis (these exceptions are described in the Results section). Randomized patients who did not have the BAT device implanted, patients who died, patients who had a left ventricular assist device or transplantation, or who withdrew or missed the 6-month visit were excluded from the completers analysis. This modified ITT completers approach was the primary analyses method applied to each of the 3 effectiveness endpoint outcomes. The safety analysis used a modified ITT device implanted approach (**Figures 1 and 2**, Supplemental Figure 3). Patients who did not have a BAT device implanted were excluded from the safety analysis (these exceptions are described in the Results section). Statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, North Carolina).

To demonstrate the safety of BAT, the event-free rate of all system- and procedure-related MANCE events that occurred within 6 months after BAT implantation was examined. The event-free rate was compared using an exact binomial test with a 1-sided alpha of 0.05 to a performance criteria of 85%, which was derived from a target event-free rate of 95% adjusted by a 10% safety margin.

Effectiveness endpoints were examined using an analysis of covariance linear regression model that included treatment group and the baseline value as a continuous covariate, compared the mean improvement from baseline to 6 months in the BAT group versus the control group, and evaluated for superiority based on a 1-sided alpha of 0.025. The mean change in NT-proBNP was examined on the log10 scale, and using an inverse transformation, was interpreted as a comparison of the percentage change in NT-proBNP at 6 months from baseline. NT-proBNP measurement was performed by a central core laboratory.

The BeAT-HF trial was reviewed and approved by each site's individual institutional review board.

RESULTS

For clarity and focus, top-line results in the intended use population that reflects the FDA-approved

instructions for use are presented. Then, the timeline and rationale that led to the development of the 4 study cohorts are presented.

TOP-LINE RESULTS. Cohort D, which represented the intended use population that reflects the FDA-approved instructions for use (enrollment criteria plus NT-proBNP <1,600 pg/ml) consisted of 245 patients followed for 6 months (120 in the BAT group and 125 in the control group). BAT was safe and significantly improved QOL, 6MHW, and NT-proBNP (**Central Illustration**). In the BAT group versus the control group, QOL score decreased ($\Delta = -14.1$; 95% confidence interval [CI]: −19 to −9; $p < 0.001$), 6MHW distance increased ($\Delta = 60$ m; 95% CI: 40 to 80 m; $p < 0.001$), NT-proBNP decreased ($\Delta = -25\%$; 95% CI: −38% to −9%; $p = 0.004$), and the MANCE-free rate was 97% (95% CI: 93% to 100%; $p < 0.001$).

DEVELOPMENT OF 4 PATIENT COHORTS USING BREAKTHROUGH DEVICES PROGRAM. Timeline. Between April 2016 and October 2018, 408 patients were randomized (**Figure 1**). In October 2018, 271 of these 408 patients had been followed for 6 months and had baseline and 6-month data. Their data were made available to (and therefore, "unblinded" to) the sponsor and the executive committee at the time of analysis as pre-specified by the protocol and constituted cohort A. Subsequently, the results were presented at scientific meetings and were reported to the FDA based solely on the unblinded dataset. The patients in the BeAT-HF trial although not blinded to treatment group, remain blinded to their own individual data. Furthermore, the sponsor, the executive committee, the patients, and the sites remain blinded to the adjudicated mortality and heart failure hospitalization data, divided by treatment assignment. In November 2018, post hoc analyses resulted in the hypothesis-generating cohort B, which consisted of 162 of the 271 patients with an NT-proBNP <1,600 pg/ml. At that time, there were 137 of the original 408 randomized patients who had not completed their 6-month follow-up; therefore, their 6-month endpoint data had not yet been collected. In March 2019, the FDA approved a revised statistical analysis plan that prospectively defined 102 of 137 patients with an NT-proBNP <1,600 pg/ml as an augmented dataset (cohort C) designated to confirm the hypothesis articulated by the results of cohort B. In April 2019, cohort C data were made available to (and therefore, unblinded to) the sponsor and the executive committee at the time of analysis as pre-specified by the statistical analysis plan. Subsequently, results were presented at scientific meetings and were reported to the FDA based solely on the unblinded dataset. The patients in the BeAT-HF trial, although not blinded to treatment group, remain blinded to their own individual data. Furthermore, the sponsor, the executive committee, the patients, and the sites remained blinded to the adjudicated mortality and heart failure hospitalization data, divided by treatment assignment. Cohort D, which consisted of the combined data from cohorts B and C, was used for illustration and labeling. On August 16, 2019, based on the totality of the data in the 4 cohorts, the FDA approved BAT for the intended use population defined in cohort D. Baseline NT-proBNP level, as measured by a core laboratory, was the sole reason for excluding subjects from the intended use population.

Rationale. Cohort A consisted of the first 271 patients (of 408 randomized) who had been followed for up to 6 months, and, as the protocol pre-specified, whose data were made available (data were unblinded) to the sponsor and executive steering committee and analyzed in October 2018 (Supplemental Figure 1). Three primary effectiveness endpoints and 1 primary safety endpoint were examined in the 239 (of 271) patients (completers approach) who had both baseline and 6-month data (Supplemental Figure 3). Three of the 4 primary endpoints were positive. The safety endpoint (device implanted approach) of the MANCE-free rate (MANCE-free rate: 94% (109 of 116 patients) exceeded the performance criteria of 85%, with $p = 0.002$). BAT resulted in a highly significant >13-point improvement in the QOL score compared with that in the control group (Supplemental Figure 4). The 6MHW distance increased by 48 m in the BAT group compared with that in the control group. However, there were no statistically significant changes in NT-proBNP. The effects of BAT on NT-proBNP in cohort A of this phase III trial stood in sharp contrast to the highly significant 35% reduction in NT-proBNP ($p = 0.03$) observed in the phase II trial (17).

An analysis conducted to understand the differences in the NT-proBNP results between the 2 trials suggested that the main difference was the added eligibility requirement in the phase III BeAT-HF trial of a NT-proBNP that was >1,600 pg/ml in patients without a previous heart failure hospitalization. This eligibility criterion was originally added to enhance the population for morbid and mortal events necessary for success in the post-market phase. However, there are several facts that now indicate that this was an "over-enhancement." For example, recent randomized control trials, such as CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), I-Preserve (Irbesartan in Heart Failure with Preserved

TABLE 1 Baseline Demographic Characteristics and Treatment for Cohort D

	Control (n = 134)	BAT (n = 130)	Total (N = 264)	p Value
Race				
Asian	1.5	2.3	1.9	0.680
Black or African American	15.0	18.0	17.0	0.510
White	72.0	75.0	73.0	0.677
Other/Unknown	12.0	4.6	8.3	0.044
Female	22.0	18.0	20.0	0.542
Age at screening, yrs	63 ± 10	62 ± 11	62 ± 11	0.614
Age ≥65 yrs	43.0	42.0	42.0	0.804
Body mass index, kg/m^2	31 ± 5	31 ± 5	31 ± 5	0.699
Systolic blood pressure, mm Hg	121 ± 16	120 ± 17	121 ± 16	0.385
Diastolic blood pressure, mm Hg	73 ± 10	73 ± 10	73 ± 10	0.618
Heart rate, beats/min	75 ± 11	75 ± 10	75 ± 11	0.864
eGFR at screening	61.9 ± 19.5	63.6 ± 16.8	62.7 ± 18.2	0.430
Core lab NT-proBNP, pg/ml*	765 (479–1,052)	731 (475–1,021)	743 (477–1,031)	0.786
NYHA functional class III	95.0	93.0	94.0	0.614
6-min walk, m	294 ± 73	316 ± 68	305 ± 71	0.015
Quality of life	52 ± 24	53 ± 24	53 ± 24	0.800
LV ejection fraction, %	28 ± 6	27 ± 7	27 ± 6	0.192
QRS interval at screening	110.5 ± 25.6	108.9 ± 17.6	109.7 ± 22.0	0.545
Left bundle branch block	0.7	2.3	1.5	0.365
AF (screening ECG)	10.0	9.2	9.5	1.000
AF (medical history)	43.0	29.0	36.0	0.029
Paroxysmal AF	28.0	19.0	24.0	0.086
Permanent AF	2.2	3.8	3.0	0.495
Persistent AF	11.0	5.4	8.3	0.118
At least 1 HF hospitalization	51.0	42.0	46.0	0.140
No. of HF hospitalizations	0.7 ± 0.8	0.6 ± 1.0	0.6 ± 0.9	0.815
No. of medications	4.1 ± 1.4	3.9 ± 1.2	4.0 ± 1.3	0.228
ACE inhibitor/ARB	59.0	58.0	58.0	0.901
ARNI (sacubitril/valsartan)	26.0	32.0	29.0	0.344
ACE/ARB/ARNI	84.0	88.0	86.0	0.372
Beta-blocker	95.0	95.0	95.0	1.000
Digitalis	16.0	16.0	16.0	1.000
Diuretic	87.0	85.0	86.0	0.596
Ivabradine	4.5	2.3	3.4	0.501
MRA	42.0	48.0	45.0	0.322
ICD	79.0	78.0	78.0	0.881

Values are %, mean ± SD, or median (interquartile range). *Results reported as median (interquartile range), analysis used the intention-to-treat approach.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; BAT = baroreceptor activation therapy; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV= left ventricular; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

Systolic Function), and TOPCAT (Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function), suggested that there might be a greater response to heart failure therapies in patients with a lower NT-proBNP (22-24). In cohort A of BeAT-HF, patients with NT-proBNP ≥1,600 pg/ml had more advanced heart failure as evidenced by the fact that they were older, had a lower left ventricular EF, a shorter 6MHW distance, and a higher number of previous HF hospitalizations than patients with NT-proBNP <1,600 pg/ml (Supplemental Table 2). In addition, a sensitivity analysis was performed using NT-proBNP values from <1,000 to <2,000 pg/ml that showed similar results at each value of NT-proBNP (Supplemental Table 3). The value of 1,600 pg/ml was chosen because it was the value originally chosen for the NT-proBNP eligibility criterion in the initial protocol; it represented approximately two-thirds of the patients in cohort A. Therefore, an intended use population of patients with HFrEF with an NT-proBNP <1,600 pg/ml was defined, which consisted of 162 of the 271 patients in cohort A, and was designated cohort B (**Figure 1**). In cohort B, BAT resulted in a MANCE-free rate of 97%, a 12-point improvement in the QOL score, a 65-m increase in 6MHW distance, and an 18% reduction in NT-proBNP. Based on these

FIGURE 3 Effectiveness Endpoints for Cohorts B, C, and D

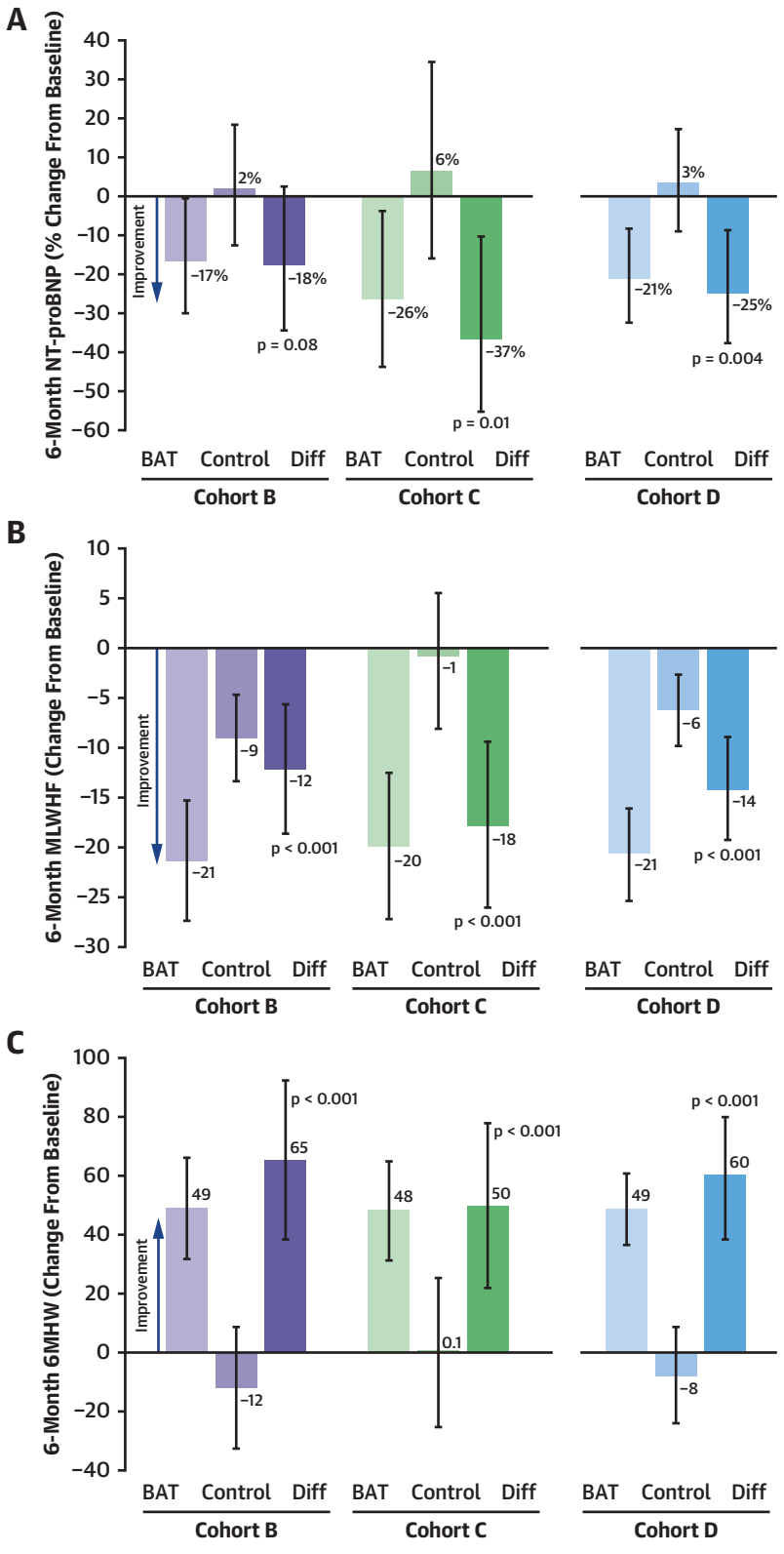


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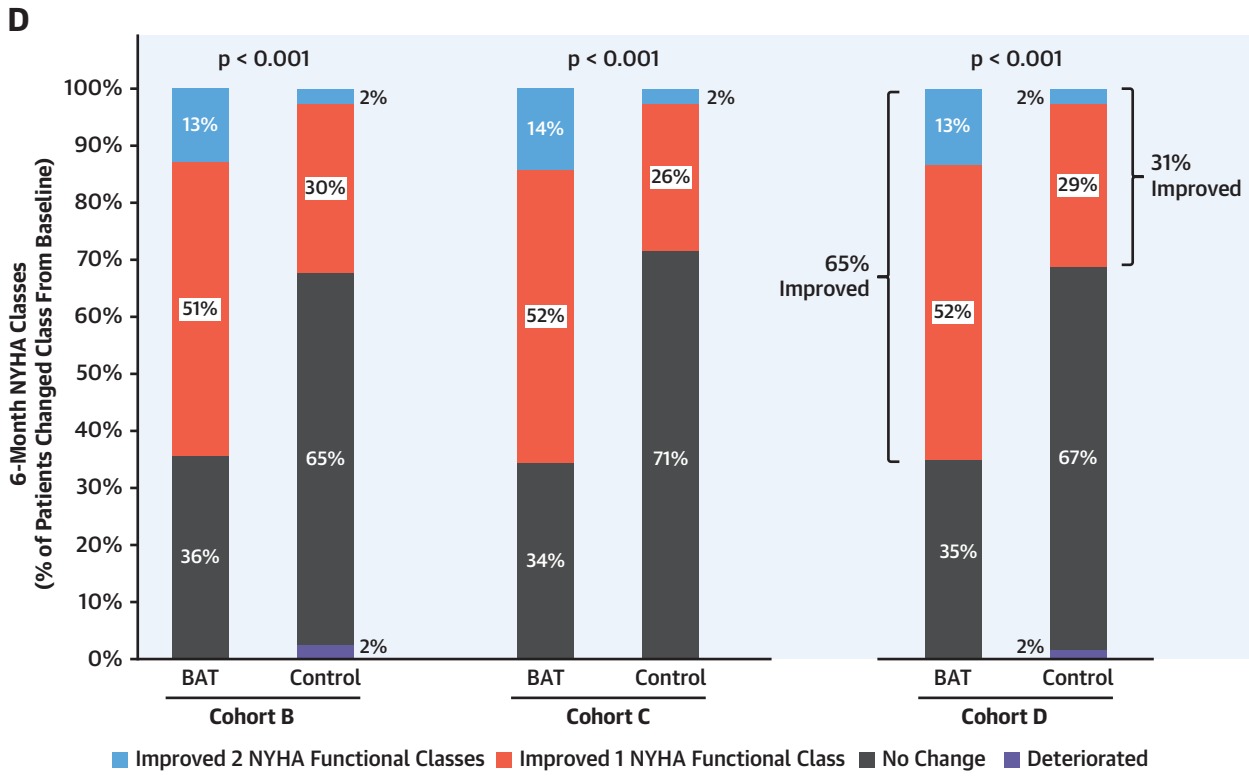
FIGURE 3 Continued



(A) In each of the 3 cohorts presented, cohort B **(purple)**, cohort C **(green)**, and cohort D **(blue)**, BAT decreased NT-proBNP compared with the control group. Data are mean ± 95% confidence interval (CI), all differences analyzed using Log10 transformation NT-proBNP by analysis of covariance (ANCOVA) adjusted for baseline values. **(B)** In each of the 3 cohorts presented, cohort B **(purple)**, cohort C **(green)**, and cohort D **(blue)**, BAT improved quality-of-life score using the Minnesota Living With Heart Failure questionnaire (MLWHF) compared with the control group. Data are mean ± 95% CI, all differences analyzed by ANCOVA adjusted for baseline values. **(C)** In each of the 3 cohorts presented, cohort B **(purple)**, cohort C **(green)**, and cohort D **(blue)**, BAT increased the 6-min hall walk (6MHW) distance compared with the control group. Data are mean ± 95% CI, all differences analyzed by ANCOVA adjusted for baseline values. **(D)** In each of the 3 cohorts presented, cohort B **(left columns)**, cohort C **(middle columns)**, and cohort D **(right columns)**, BAT decreased New York Heart Association (NYHA) functional class and improved functional capacity compared with the control group. Diff = difference in the change from baseline to 6 months in effectiveness endpoint in the BAT group versus the control group; other abbreviation as in Figure 1.

hypothesis-generating data, the FDA approved a prospective statistical analysis plan for the remaining 137 randomized patients in whom 6-month endpoint data had not yet occurred (patients had not yet reached the 6-month visit). These 137 patients constituted an augmented dataset to confirm the findings in cohort B. Of these 137 patients, 102 had an NT-proBNP <1,600 pg/ml and were designated cohort C. The full intended use population, consisting of cohort B plus cohort C, was designated as cohort D and consisted of 264 patients. The rest of this section focuses on data from cohorts B, C, and D for simplicity and clarity.

PARTICIPANT FLOW. In cohort D (Figure 2) in the BAT group, 5 patients withdrew before device implantation because they died (n = 1), withdrew consent (n = 1), or study enrollment and/or implantations were not completed (n = 3). After implantation, 1 subject died, 2 withdrew from the trial, and 2 missed the 6-month follow up, which left 120 patients in the BAT group for the 6-month effectiveness endpoint analysis. In the control group, 3 patients died, 2 received a left ventricular assist device, and 4 missed the 6-month follow-up, which left 125 patients in the control group for the 6-month effectiveness endpoint analysis. Subject disposition data for cohorts A, B, and C are presented in Figure 2 and Supplemental Figure 3.

For cohort D, efficacy analyses are shown in the Central Illustration and Supplemental Table 4. The QOL data were available for all 120 patients in the BAT group and 125 patients in the control group who completed 6-month follow-up and fulfilled the completer analysis criteria described in the following.

Two patients in the BAT group and 5 patients in the control group refused to perform the 6MHW because of noncardiovascular issues, which left 118 patients in the BAT group and 120 patients in the control group for the completer analysis. For NT-proBNP, 2 patients in the control group refused to allow NT-proBNP to be drawn, which left 120 patients in the BAT group and 123 patients in the control group for the completer analysis.

BASELINE DEMOGRAPHIC CHARACTERISTICS AND TREATMENT DATA. In cohort D, the intended use population, the initial 6MHW distance was shorter ($p = 0.015$) and a history of atrial fibrillation was more common ($p = 0.029$) in the control group compared with the BAT group (**Table 1**). The results of 6MHW, QOL, and NT-proBNP endpoints were adjusted for these observed imbalances in baseline characteristics. Examination of baseline therapies indicated that patients in both the BAT and control groups were well treated for HFrEF. Approximately 90% were treated with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker or an angiotensin receptor-neprilysin inhibitor, 95% were treated with a beta-blocker, and almost 80% had an implantable cardioverter-defibrillator. There were no significant treatment differences at baseline between the BAT and control groups. Baseline data for cohorts A, B, and C are shown in Supplemental Tables 5 to 7, and baseline data for all randomized patients are shown in Supplemental Table 8.

EFFECTIVENESS OUTCOMES IN COHORTS B, C, AND D. In cohort D, compared with the control group, treatment with BAT resulted in a statistically and clinically significant 25% greater reduction in NT-proBNP (inverse transformed $\Delta = -25\%$; 95% CI: −38% to −9%; $p = 0.004$) (**Figure 3A**, Supplemental Table 4). BAT reduced NT-proBNP in both cohorts B and C, with a 37% reduction in cohort C (significant at the $p = 0.01$ level).

In cohort D, BAT led to significantly greater improvement in QOL, which improved by 14 points more than that in the control group ($\Delta = -14$; 95% CI: −19 to −9; $p < 0.001$) (**Figure 3B**, Supplemental Table 4). Similar results were seen in cohorts B and C.

BAT improved functional capacity as assessed by 6MHW distance more than that in the control group. In cohort D, there was a 60-m greater increase in 6MHW distance in the BAT group versus that in the control group ($\Delta = 60$; 95% CI: 40 to 80; $p < 0.001$) (**Figure 3C**, Supplemental Table 4). The improvements were consistent in cohorts B and C.

The results of 6MHW, QOL, and NT-proBNP endpoints in cohort D remained statistically significant after adjusting for observed imbalances in baseline characteristics using a propensity score analysis. A worst-case analysis did not significantly change the reported results.

SAFETY OUTCOMES. In cohort D, the MANCE-free rate exceeded the performance criteria of 85% with 121 of 125 patients who underwent implantation who were event free (event-free rate: 97%; 95% 1-sided CI: 93% to 100.0%; $p < 0.001$) (Supplemental Table 9). A system or procedure-related serious adverse event occurred in 7 patients who underwent BAT within 30 days post-implantation (event-free rate: 94%; 95% 1-sided CI: 90% to 100.0%). There were no additional system- and procedure-related serious adverse events between 30 and 180 days post-implantations (Supplemental Tables 10 and 11). Similar results were seen in cohorts B and C.

ANCILLARY ANALYSIS. During the 6-month follow-up, there was a significant difference in medical management between the 2 arms, with a disproportionately higher number of medications added in the control group (Supplemental Table 12). Patients in the control group were more likely to have a new class of drugs added (36 [29%] in the control group vs. 21 [18%] in the BAT group; $\Delta = 11\%$; 95% CI: 1% to 22%; $p = 0.049$) and were more likely to have a new angiotensin receptor-neprilysin inhibitor added (20 [16%] in the control group vs. 5 (4%) in the BAT group; $\Delta = 12\%$; 95% CI: 4% to 19%; $p = 0.003$). BAT improved the EuroQol-5 Dimensions (EQ-5D) index by a net difference of $\Delta = 0.10$ (95% CI: 0.07 to 0.14; $p < 0.001$). BAT improved NYHA functional class (78 [65%] in the BAT group vs. 39 [31%] in the control group; $\Delta = 34\%$; 95% CI: 22% to 46%; $p < 0.001$ (**Figure 3D**). BAT reduced the rate of cardiovascular serious adverse events (non–heart failure-related events or non-cardiovascular death) by 51% (events per patient-year; 0.101 in the BAT group vs. 0.206 in the control group; relative rate reduction: 0.51; 95% CI: 0.10 to 0.73; $p = 0.023$) (Supplemental Table 13). There were no significant differences in blood pressure or heart rate (Supplemental Table 14).

In the 144 of 408 randomized patients that had a NT-proBNP >1,600 pg/ml, BAT did not have a statistically significant improvement on 6MHW distance or NT-proBNP but did improve QOL score compared with that in the control group.

DISCUSSION

To our knowledge, BeAT-HF is the first successful pivotal, prospective, phase III trial of a device-based neuromodulation approach for the treatment of patients with HFrEF. Data in this trial support the

following novel conclusions: 1) BAT is safe in patients with HFrEF; 2) BAT significantly improves patient-centered symptomatic endpoints of the QOL score, exercise capacity, and functional status; 3) these results are supported by objective evidence of significant improvement of NT-proBNP; and 4) these significant differences in treatment effect were observed despite a disproportionate increase in the number of medications in the control group.

GENERALIZABILITY. Substantial advances in the management of patients with HFrEF have resulted in improvements in symptoms and reductions in morbidity and mortality (1,2,25,26). Despite these improvements, the burden of debilitating symptoms, reduced exercise tolerance, and increased morbidity and mortality remain high (1,2). In addition, compliance with complex medical regimens, comorbidity-induced limitations of drug categories and doses, and limited indications for devices remain challenges to successful management of HFrEF. Thus, there is a substantial and persistent unmet need for the development of novel and complementary therapies in HFrEF. Data from the BeAT-HF trial suggested that for patients in NYHA functional class III (or patients in NYHA functional class II who had a recent history of NYHA functional class III) with HFrEF, who had EF ≤35%, NT-proBNP <1,600 pg/ml, and who did not have a Class I indication for CRT, BAT would fill an unmet need. Based on the totality of the data (**Central Illustration**) from the BeAT-HF trial, the FDA approved BAT (BAROSTIM NEO System, CVRx) on August 16, 2019 with the following instruction for use: "The BAROSTIM NEO® System is indicated for the improvement of symptoms of heart failure-quality of life, six-minute hall walk and functional status, for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA functional class III or functional class II (who had a recent history of functional class III), have a left ventricular ejection fraction ≤35%, a NT-proBNP <1,600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines."

PREVIOUS STUDIES OF NEUROMODULATION IN HFrEF. Autonomic modulation for the treatment of HFrEF has taken 3 general approaches: spinal cord stimulation, direct vagal stimulation, and carotid BAT (4–7). Results from spinal and vagal stimulation studies have been disappointing. Vagal stimulation in the INOVATE-HF (INcrease Of VAgal TonE in CHF) trial did increase 6MHW and Kansas City Cardiomyopathy Questionnaire QOL scores. However, vagal stimulation did not result in significant improvements in objective endpoints of decreased end-systolic volume, reduced heart failure hospitalizations, or cardiovascular mortality in either INOVATE-HF or NECTAR-HF (Neural Cardiac Therapy for Heart Failure) trials (5,6). In contrast, in the BeAT-HF trial, BAT improved 6MHW, QOL and NT-proBNP. The BeAT-HF trial did not assess left ventricular structure or function; the post-market phase will assess morbidity and mortality. Preclinical and early mechanistic clinical studies that used BAT suggested that because carotid baroreceptor stimulation resulted in an afferent signal processed in the brain, a balanced reduction in sympathetic activity, coupled with an increase in parasympathetic activity, was achieved (8–16). This rebalancing of the abnormal sympathetic and/or parasympathetic tone in HFrEF is a novel aspect of BAT.

TRIAL DESIGN AND PERFORMANCE. Several aspects of the BeAT-HF trial design and performance were novel and were optimized through collaboration with the FDA's Center for Devices and Radiological Health under the recently approved Breakthrough Devices Program (20,21). The design and performance of pivotal trials aimed at obtaining U.S. regulatory approval and favorable reimbursement designation for new device therapies in HFrEF posed several challenges. These included the need to exceed the effectiveness of current guideline-directed medical management, a task made more difficult by continuing advances in medical management and better adherence to treatment guidelines; the fiscal constraint in trial size imposed by device studies compared with drug studies; and the costs associated with these trial designs. In recognition of these challenges, the FDA initially issued guidance on an Expedited Access Pathway program that subsequently became the Breakthrough Devices Program, a part of the 21st Century Cures Act (20,21) for medical devices. In June 2015, FDA designated Barostim NEO as a Breakthrough Device and prioritized its review process, consistent with the Section 515B of the FD&C Act (21 U.S.C. 360e-3).

Data from the pre-market phase of the BeAT-HF trial were used to examine safety and effectiveness of BAT (interactive and adaptive design described in detail in a previous publication [19]). As a result, data from cohort B with NT-proBNP <1,600 pg/ml was validated by a concurrently performed cohort C that demonstrated a highly statistically and clinically significant improvement in the patients who received BAT versus control patients in each of the 3 effectiveness endpoints. The totality of the evidence in cohort D that consisted of the intended use

population provided substantial support for the effectiveness of BAT.

TRIAL LIMITATIONS AND FUTURE DIRECTIONS. The BeAT-HF trial pre-market phase did not examine morbidity and mortality or change in cardiovascular structure or function endpoints. Data from previous studies suggested that the BAT-induced reduction in the NT-proBNP data of 25% made it highly probable that morbidity and mortality would also be reduced, and that structural and functional remodeling would occur with BAT (27–29). For example, in the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) trial, morbidity and mortality were reduced when NT-proBNP fell by as little as 10%, regardless of the treatment groups (sacubitril/valsartan vs. enalapril) (28). The GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial (29) suggested that reduction in NT-proBNP from >1,000 to <1,000 pg/ml was associated with a significant improvement in left ventricular systolic function (increased EF) and left ventricular remodeling (reduced left ventricular end-diastolic volume). However, all these specific endpoints will require additional studies. Heart failure hospitalization and cardiovascular mortality rates will be examined in the post-market phase (19) of BeAT-HF. Enrollment will continue as initially planned until a total of 480 patients have been randomized. The post-market phase is intended to expand the indication of use to reduction of heart failure hospitalizations and cardiovascular mortality (19). This post-market phase will be achieved when 320 mortal and morbid events have occurred. A supplemental pre-market approval will then be submitted to the FDA.

BeAT-HF was not a blinded trial. The control group did not have an implanted BAT device. It was clearly acknowledged that 6MHW, QOL, NYHA functional class might be subject to placebo effects. This is why the NT-proBNP data served a pivotal role in supporting the results of these patient-centered symptomatic endpoints.

CONCLUSIONS

BAT is safe, improved the patient-centered symptomatic endpoints of QOL score, exercise capacity, and functional status, and significantly decreased NT-proBNP in patients with NYHA functional class III (or patients with NYHA functional class II who had a recent history of NYHA functional class III), EF ≤35%, NT-proBNP <1,600 pg/ml, and who did not have a Class I indication for CRT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFrEF is commonly accompanied by autonomic imbalance, characterized by increased sympathetic and decreased parasympathetic signaling. Afferent baroreflex activation through electrical stimulation of the carotid sinus nerve reduces sympathetic and augments parasympathetic tone, rebalancing cardiac autonomic innervation, improving functional and neurohormonal status.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the impact of baroreflex activation therapy on the frequency of hospitalization and mortality, and identify patients with HFrEF most likely to gain lasting benefit from this type of intervention.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.