ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3232

RESEARCH ARTICLE

Baroreflex activation therapy in patients with heart failure and a reduced ejection fraction: Long-term outcomes

Michael R. Zile[1]*, JoAnn Lindenfeld[2], Fred A. Weaver[3], Faiez Zannad[4], Elizabeth Galle[5], Tyson Rogers[6], and William T. Abraham[7]

[1]Medical University of South Carolina, Charleston, South Carolina and the Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, SC, USA; [2]Vanderbilt Heart and Vascular Institute, Nashville, TN, USA; [3]Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [4]Université de Lorraine, Inserm Centre d'Investigation, CHU de Nancy, Institute Lorrain du Coeur et des Vaisseaux, Nancy, France ; [5]CVRx, Inc., Minneapolis, MN, USA; [6]NAMSA, Inc., Minneapolis, MN, USA; and [7]Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA

Received 28 December 2023; revised 21 February 2024; accepted 21 March 2024

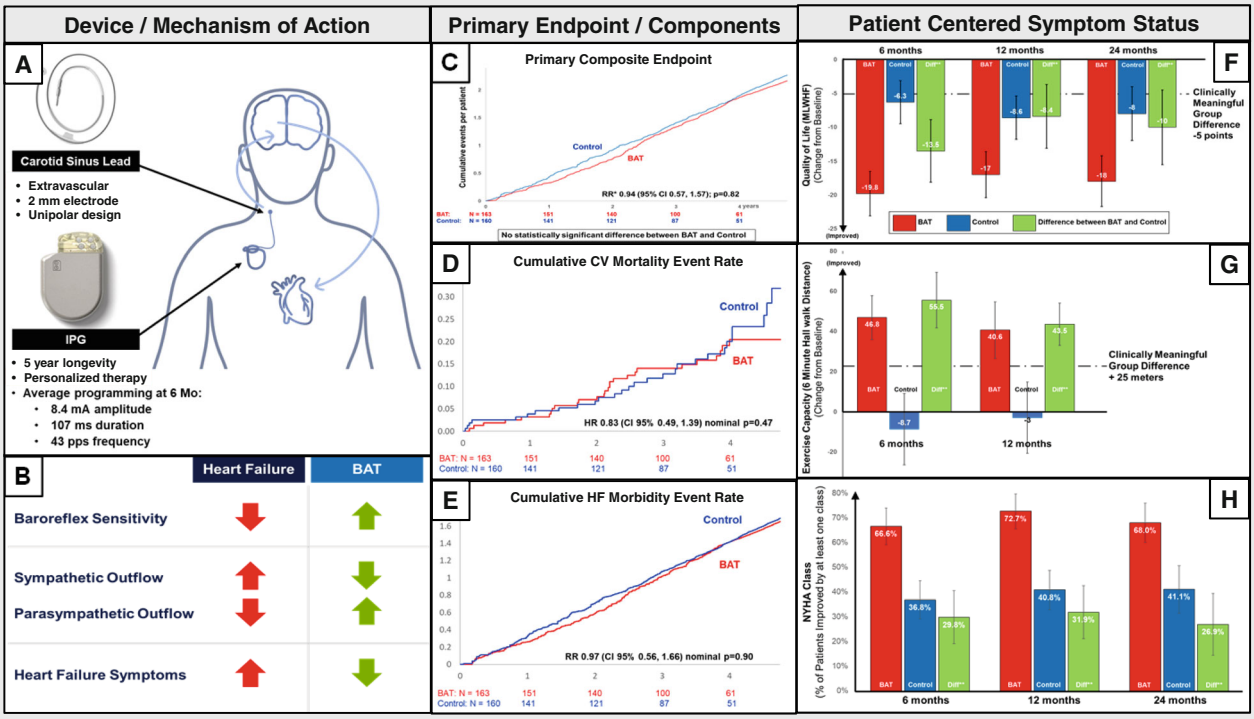
Aims Carotid baroreflex activation therapy (BAT) restores baroreflex sensitivity and modulates the imbalance in cardiac autonomic function in patients with heart failure with reduced ejection fraction (HFrEF). We tested the hypothesis that treatment with BAT significantly reduces cardiovascular mortality and heart failure morbidity and provides long-term safety and sustainable symptomatic improvement.

Methods and results BeAT-HF was a prospective, multicentre, randomized, two-arm, parallel-group, open-label, non-implanted control trial. New York Heart Association (NYHA) class III subjects, ejection fraction ≤35%, previous heart failure hospitalization or N-terminal pro-B-type natriuretic peptide (NT-proBNP) >400 pg/ml, no class I indication for cardiac resynchronization therapy and NT-proBNP <1600 pg/ml were randomized to BAT plus optimal medical management (BAT group) or optimal medical management alone (control). The primary endpoint was cardiovascular mortality and HF morbidity; additional pre-specified endpoints included durability of safety, quality of life (QOL), exercise capacity (6-min hall walk distance [6MHWD]), functional status (NYHA class), hierarchical composite win ratio, freedom from all-cause death, left ventricular assists device (LVAD) implantation, heart transplant. Overall, 323 patients had 332 primary events, median follow-up was 3.6 years/patient. Both primary endpoint (rate ratio 0.94, 95% confidence interval [CI] 0.57−1.57; $p = 0.82$) and components of the primary endpoints were not significantly different between BAT and control. The system- and procedure-related major adverse neurological and cardiovascular event-free rate remained 97% throughout the trial. Symptom improvement (QOL, 6MHWD, NYHA class, all nominal $p < 0.001$) in the BAT group was durable in time, sustainable in extent. Win ratio (1.26, 95% CI 1.02−1.58) and freedom from all-cause death, LVAD implantation, heart transplant (hazard ratio 0.66, 95% CI 0.43−1.01) favoured the BAT group but did not reach statistical significance.

Conclusion The BeAT-HF primary endpoint was neutral; however, BAT provided safe, effective, and sustainable improvements in HFrEF patient's functional status, 6MHWD and QOL.

*Corresponding author. Division of Cardiology, Department of Medicine, Medical University of South Carolina, Thurmond/Gazes, Room 323, 30 Courtenay Dr., Charleston, SC 29425, USA. Tel: +1 843 792-6866, Fax: +1 843 789-6850,
Email: zilem@musc.edu

Graphical Abstract



Summary of key evidence from the Post-Market Phase of the BeAT-HF trial. Device design (*A*), mechanism of action (*B*), primary endpoint (*C*) and the components of the primary endpoints (*D*,*E*), and long-term measures of symptomatic improvement (quality of life [*F*], 6-min hall walk distance [*G*], New York Heart Association [NYHA] class [*H*]). BAT, baroreflex activation therapy; CI, confidence interval; CV, cardiovascular; HF, heart failure; MLWHF, Minnesota Living With Heart Failure; RR, rate ratio.

Keywords Baroreflex • Heart failure • Device • Autonomic nervous system • Randomized controlled trial

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is characterized by the presence of significant autonomic nervous system (ANS) dysfunction that includes decreased baroreflex sensitivity with increased sympathetic and decreased parasympathetic activation.[1–3] Autonomic dysfunction is a pivotal factor in the pathophysiology of the HF syndrome and likely contributes to the residual risk of increased morbidity and mortality that remains even with successful application of guideline-directed medical therapy (GDMT).[4,5] Despite HF therapy with all components of GDMT, significant autonomic dysfunction remains and constitutes a critical unmet need and a tangible target for the development of novel HFrEF therapy. Carotid baroreflex activation therapy (BAT) was developed to restore baroreflex sensitivity and modulate the imbalance in cardiac autonomic function present in patients with HFrEF. Previous studies have shown that BAT can improve baroreflex sensitivity, produce an afferent signal which the brain integrates into a balanced efferent signal that decreases sympathetic and increases parasympathetic tone[6,7] (*Graphical Abstract*). The pre-market phase of the BeAT-HF Trial (Baroreflex Activation Therapy for Heart Failure, ClinicalTrials.gov Identifier NCT02627196) demonstrated that treatment with BAT for 6 months was safe and significantly improved patient-centred symptomatic outcomes by increasing exercise capacity (60 m increase in 6-min hall walk distance [6MHWD]), improving quality of life (QOL; 14 point improvement in Minnesota Living With Heart Failure Questionnaire [MLWHFQ]), 25% decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP), and improving New York Heart Association (NYHA) class by 34%.[8] Based on these data, BAT was approved by the U.S. Food and Drug Administration (FDA) for the improvement of symptoms of HF for patients who remain symptomatic despite treatment with GDMT, are NYHA class III or II (with a recent history of class III), have a left ventricular ejection fraction ≤35%, a NT-proBNP <1600 pg/ml and excluding patients indicated for cardiac resynchronization therapy

(CRT) according to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines.[5]

However, whether BAT has an acceptable long-term safety profile, whether BAT can improve patient-centred symptomatic outcomes that are durable over time and sustainable in effect, and whether BAT alters mortality and morbidity have not been examined. The purposes of the post-market phase of BeAT-HF were: (i) to test the hypothesis that, in HFrEF patients, treatment with BAT significantly reduces cardiovascular (CV) mortality and HF morbidity, and (ii) to determine whether long-term effects on safety and improved patient-centred symptomatic outcomes are durable over time and sustainable in effect.

Methods

Trial design, oversight, eligibility criteria

Details regarding the BeAT-HF trial design, oversight and eligibility are described in a brief summary provided in online supplementary *Appendix S1* and the final FDA approved clinical investigation plan (revision G, 27 May 2022) and statistical analysis plan (revision E, 21 December 2022) are provided in online supplementary *Appendices S2* and *S3*.[9] The study complies with the Declaration of Helsinki, the locally appointed ethics committees have approved the research protocol and informed consent was obtained from the subjects (or their guardians).

Patients

The study cohort for the post-market phase of the BeAT-HF trial consisted of 323 patients, 264 patients from the pre-market phase and an additional 59 patients randomized between May 2019 and June 2020 during the post-market phase (*Figure 1*). Analyses included follow-up for all patients from randomization until last patient visit, which comprised 1036 patient-year of follow-up, with a median of 3.6 years of follow-up/patient. During this time period, the Clinical Events Committee (CEC) confirmed 332 primary events.

Primary endpoint

The primary endpoint was a composite of the rate of cardiovascular mortality and HF morbidity. CV mortality was defined as CV death (due to sudden death, HF, myocardial infarction, cerebrovascular accident, CV procedure, other cardiac death, other vascular death, or unknown; in short, deaths were considered CV unless a specific non-CV cause was identified). HF morbidity was defined as worsening HF events that led to a hospitalization or emergency room visit for worsening HF, implantation of a cardiac assist device or heart transplantation. Hospitalization was defined as a non-elective hospital stay (inpatient or observation) that resulted in at least one overnight stay. An emergency room visit was defined as a non-elective visit to the emergency room/department for urgent and immediate medical evaluation. A hospitalization or emergency room event for HF was defined as an event in which the patient was admitted for a primary diagnosis of HF and met the published 2014 ACC/AHA endpoint definition criteria[10,11] as described in the BeAT-HF CEC charter (see endpoint definitions in online supplementary *Appendix S1*). Recognizing the documentation required by the 2014 ACC/AHA/FDA/Clinical Data Interchange Standards Consortium endpoint definition criteria constrained the definition of HF morbidity described above, and following the experience in several recent trials, an expanded definition for a HF event was also applied in the examination of additional pre-specified endpoints (see endpoint definitions in online supplementary *Appendix S1*).

Additional pre-specified endpoints

Clinically relevant, pre-specified, additional endpoints were defined to provide a structure to evaluate the totality of the data while limiting the potential for a type I error inflation among non-primary endpoints. Durability of safety was assessed by measuring system- and procedure-related major adverse neurological and cardiovascular events (MANCE) throughout the length of the trial. Durability of improved patient-centred symptom status was assessed by quantifying the change from baseline to timed measurement points through 24 months in QOL (MLWHFQ) and functional status (NYHA class), and exercise capacity (6MHWD) assessed at 6- and 12-month follow-up. A hierarchical composite win-ratio analysis endpoint was defined with a five-level hierarchy: CV death, heart transplant or left ventricular assist device (LVAD) implantation, number of HF events (defined using the expanded definition of HF), number of expanded definition unscheduled clinic visits treated with intravenous diuretic, and change from baseline in MLWHFQ QOL at 12 months of $\geq$5 points (5 points was considered the minimal clinically relevant difference). Analyses were performed for specified time-to-event outcomes such as freedom from all-cause death, LVAD and heart transplant.

Statistical methods

Primary endpoint and components of primary endpoint

The primary endpoint was analysed using a negative binomial model for the count of primary endpoint events, including terminal and recurrent events, adjusted for number of HF hospitalizations in the 12 months prior to randomization and using an offset term to account for duration of follow-up. Differences between BAT and control were assessed as a rate ratio (RR). Follow-up was censored at terminal primary endpoint events, implantation of a device to deliver cardiac contractility modulation therapy, or time of last known follow-up. Components of the primary endpoint were additionally analysed using negative binomial analysis for recurrent HF morbidity events and Cox regression for CV mortality. For graphical presentation, cumulative number of events per patient was estimated as the product of the negative binomial event rate at the specified follow-up time multiplied by the follow-up time. This method was used to graph the primary endpoint and the HF morbidity endpoint. The CV mortality endpoint was graphed using the Kaplan–Meier (1- Kaplan–Meier estimate).

Additional pre-specified endpoints

System- or procedure-related MANCE-free rate was analysed with the Clopper–Pearson exact binomial method and compared to the pre-market phase 85% one-sided performance goal. Change from baseline of symptomatic endpoints were compared between BAT and control using a generalized estimating equation repeated measurement model adjusted for baseline measurement. The hierarchical composite win-ratio analysis endpoint was analysed using the Finkelstein–Schoenfeld method. Time-to-event endpoints were analysed using the Kaplan–Meier method and Cox proportional hazards.

The primary endpoint was assessed at three interim analyses and a final analysis with pre-defined group sequential boundaries to control

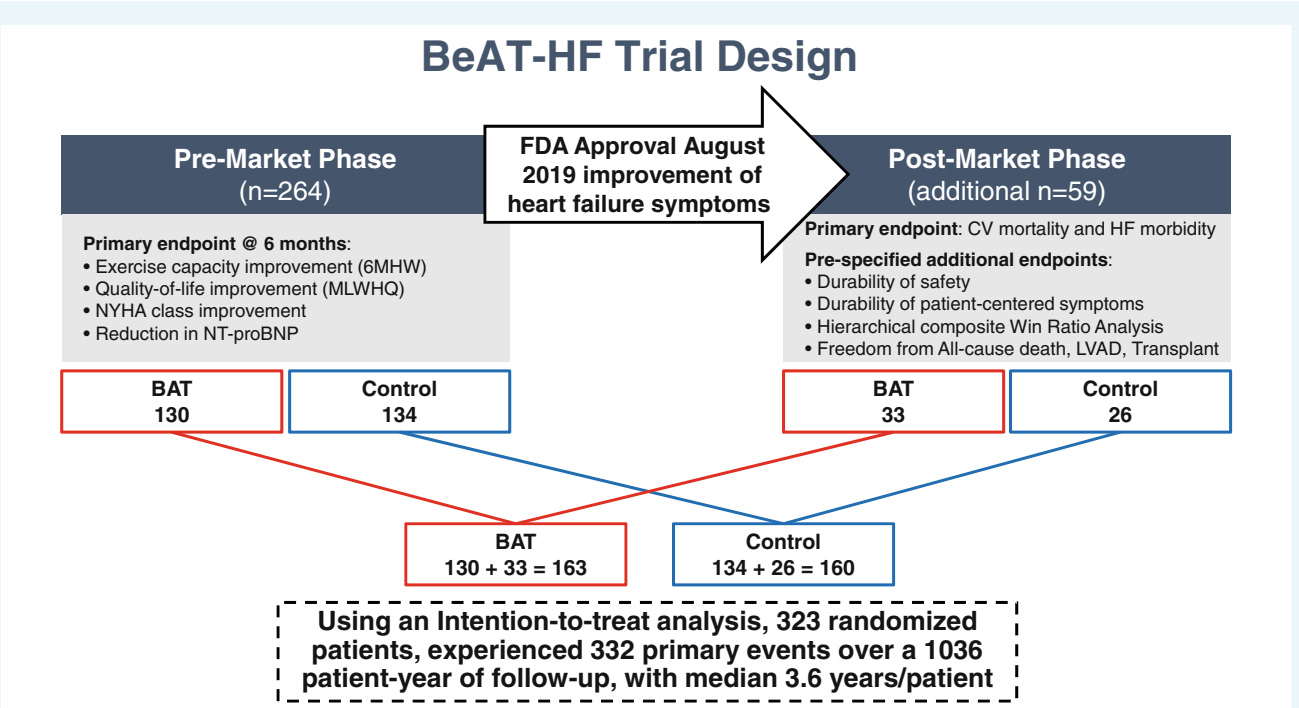


Figure 1 BeAT-HF trial design and summary of key evidence. BeAT-HF trial was performed in two phases: pre-market phase and post-market phase. 6MHW, 6-min hall walk; BAT, baroreflex activation therapy; CV, cardiovascular; FDA, Food and Drug Administration; HF, heart failure; LVAD, left ventricular assist device; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

type I error to less than 5%. Analysis of all pre-specified secondary endpoints was performed using nominal two-sided 95% confidence intervals (CI) and *p*-values, as pre-specified in the statistical analysis plan without adjustment for multiple comparisons. While pre-specified, these secondary endpoints are exploratory. Statistical analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Sample size estimate

The post-market phase was event-driven with collection of at least 320 primary endpoint events planned to provide 86% power to detect a 35% reduction in the rate of primary endpoint events in BAT versus control subjects.

Analysis population

Analyses were planned for a modified intention-to-treat (ITT) population. Due to modified ITT subjects having identical follow-up to the ITT population, the primary endpoint analysis was performed in the ITT population.

Results

Baseline characteristics and heart failure treatments

Baseline clinical characteristics and comorbidities (*Table 1*) demonstrate that patients randomized to BeAT-HF had characteristics and comorbidities typical of NYHA class III HFrEF. The treatment regimens (*Table 1*) reflected the GDMT that had a class I guideline recommendation at the time subject randomization occurred (from 2016 to 2020).

Primary endpoint and components of the primary endpoint

The primary endpoint results are presented in *Figure 2A*, plotted as the cumulative number of primary endpoint events per patient at a given time, and compared over the entire follow-up period using a RR. In the BAT group, the crude event rate was 32.5 per 100 years with 177 events during 544 patient-years at risk. In the control group, the crude event rate was 31.5 per 100 years with 155 events during 492 patient-years at risk. In the overall follow-up, negative binomial rates were estimated as 0.46 (95% CI 0.32–0.65) per year in the BAT group versus 0.48 (95% CI 0.33–0.70) per year in the control group. There was no significant difference between BAT and control (RR 0.94, 95% CI 0.57–1.57; $p = 0.82$).

The cumulative CV mortality event rate calculated using the Kaplan–Meier method for time-to-first CV terminal event, and compared using a hazard ratio (HR), is shown in *Figure 2B*. In the BAT group, the crude event rate was 5.0 per 100 years with 27 events during 544 patient-years at risk. In the control group, the crude event rate was 5.9 per 100 years with 29 events during 492 patient-years at risk. There was no significant difference between BAT and control (HR 0.83, 95% CI 0.49–1.39; nominal $p = 0.47$).

The cumulative HF morbidity event rate, plotted as the cumulative number of recurrent HF morbidity events per patient at a

Table 1 Baseline characteristics and heart failure treatments

Parameters	BAT ($n = 163$)	Control ($n = 160$)
Age at screening (years)	63 ± 11	63 ± 10
Female sex	28 (17.2%)	35 (21.9%)
Race		
White	120 (73.6%)	116 (72.5%)
Black or African American	29 (17.8%)	24 (15.0%)
Asian	3 (1.8%)	2 (1.3%)
Other/unknown	11 (6.7%)	18 (11.3%)
SBP (mmHg)	120 ± 16	121 ± 16
DBP (mmHg)	74 ± 10	73 ± 10
HR (bpm)	75 ± 10	75 ± 11
BMI (kg/m^2)	31 ± 5	31 ± 5
eGFR (ml/min/1.73 m^2)	62.5 ± 16.3	61.1 ± 18.9
NYHA class III	155 (95.1%)	151 (94.4%)
LVEF (%)	27 ± 6	28 ± 6
6-min hall walk distance (m)	314 ± 66	300 ± 71
Quality of life	53 ± 24	51 ± 24
NT-proBNP (pg/ml)	736 (474–1057)	704 (442–1044)
LBBB	4 (2.5%)	2 (1.3%)
At least one HF hospitalization	66 (40.5%)	79 (49.4%)
Number of HF hospitalizations	0.6 ± 0.9	0.7 ± 0.8
Coronary heart disease		
Coronary artery disease	104 (63.8%)	107 (66.9%)
Myocardial infarction	89 (54.6%)	97 (60.6%)
CABG	35 (21.5%)	44 (27.5%)
PCI	72 (44.2%)	72 (45.0%)
Cardiac arrhythmia		
Bradycardia	19 (11.7%)	18 (11.3%)
Tachycardia	54 (33.1%)	56 (35.0%)
Atrial fibrillation	53 (32.5%)	66 (41.3%)
Stroke or TIA	29 (17.8%)	37 (23.1%)
Chronic kidney disease	45 (27.6%)	43 (26.9%)
Diabetes		
Type I	0 (0.0%)	2 (1.3%)
Type II	74 (45.4%)	80 (50.0%)
Number of medications	4.0 ± 1.3	4.1 ± 1.5
ACE-I/ARB/ARNI	143 (88%)	129 (81%)
ARNI	57 (35%)	43 (27%)
Beta-blocker	152 (93%)	147 (92%)
MRA	74 (45%)	64 (40%)
SGLT2i	1 (0.6%)	0 (0%)
Diuretic	138 (85%)	139 (87%)
Ivabradine	4 (2.5%)	9 (5.6%)
ICD	125 (77%)	127 (79%)
Pacemaker (non-ICD)	3 (1.8%)	2 (1.3%)
CRT	4 (2.5%)	5 (3.1%)
Other cardiac device (e.g. CardioMEMS)	8 (4.9%)	4 (2.5%)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BAT, baroreceptor activation therapy; BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TIA, transient ischaemic attack.

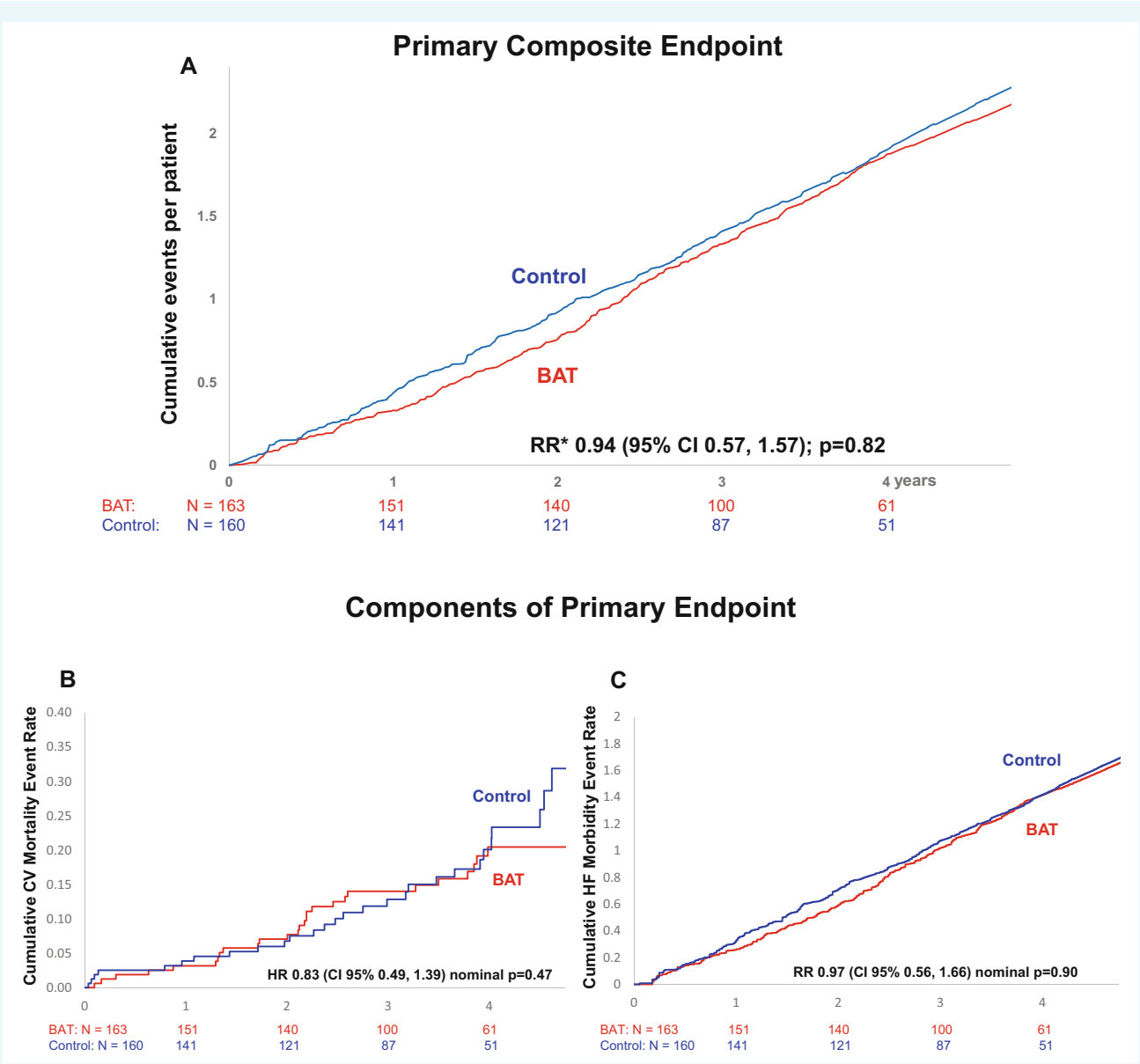


Figure 2 Primary composite endpoint and components of the primary endpoint. (*A*) Primary composite endpoint. Cumulative primary events per patient. No significant difference between the baroreflex activation therapy (BAT) and control group. (*B*) Cumulative cardiovascular (CV) mortality event rate. No significant difference between BAT and control. (*C*) Cumulative heart failure (HF) morbidity event rate. No significant difference between BAT and control. CI, confidence interval; HR, hazard ratio; RR, rate ratio.

given time and compared over the entire follow-up period using a RR, is shown in *Figure 2C*. In the BAT group, the crude event rate was 27.5 per 100 years and 150 events during 544 patient-years at risk. In the control group, the crude event rate was 25.6 per 100 years with 126 events during 492 patient-years at risk. In the overall follow-up, negative binomial rates were estimated as 0.35 (95% CI 0.24–0.51) per year in the BAT group versus 0.36 (95% CI 0.24–0.53) per year in the control group. There were no significant differences between BAT and control (RR 0.97, 95% CI 0.56–1.66; nominal $p = 0.90$).

Additional pre-specified endpoints

Durability of safety

System- or procedure-related MANCE occurred in five subjects within 30 days of BAT implantation. There was a durable safety profile with a MANCE-free rate of 97% (154 of 159 subjects implanted), nominal $p < 0.001$ for the comparison to the MANCE-free performance goal of 85%. The five related MANCE events were two infections that required explant, right neck pain that required lead repositioning, a stroke, and a decompensation of HF that required hospitalization. All resolved with no residual effect except the stroke, where no follow-up was deemed necessary.

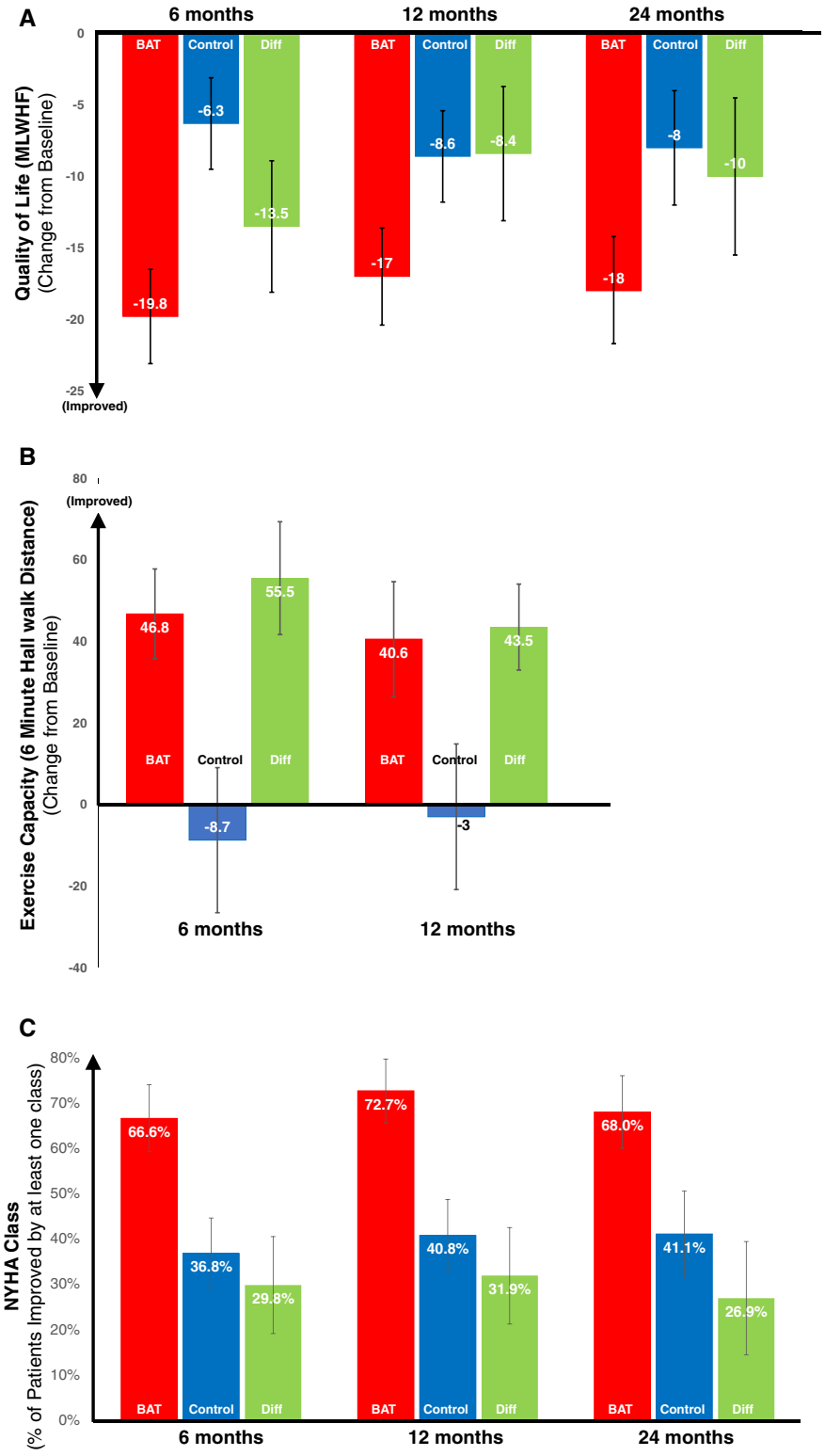


Figure 3 Improvement in patient symptom status. (*A*) Change in quality of life score (Minnesota Living With Heart Failure [MLWHF] Questionnaire). (*B*) Change in 6-min hall walk distance. (*C*) Change in functional status (percent of patients improved by at least one New York Heart Association [NYHA] class) at each time point was significantly improved in the baroreceptor activation therapy (BAT) group versus control (nominal *p*-values <0.001 for each time point).

Durability of patient-centred symptoms

The change in QOL score (using the MLWHFQ) from baseline to 6, 12, 24 months are presented in *Figure 3A*. Clinically meaningful group difference is −5 points. The estimated between group differences were −13.5 (95% CI −18.1 to −8.9) at 6 months, −8.4 (95% CI −13.1 to −3.7) at 12 months, and −10.0 (95% CI −15.5 to −4.5) at 24 months. The nominal *p*-values were < 0.001 for between-group differences at all time points. The extent to which BAT improved the QOL score compared to control was similar at each time point.

The change in exercise capacity (using the 6MHWD) from baseline to 6 and 12 months is presented in *Figure 3B*. Clinically meaningful group difference is +25 m. The estimated between-group differences were 55.5 (95% CI 37.7–73.3) at 6 months and 43.5 (95% CI 25.7–61.4) at 12 months. The nominal *p*-values were < 0.001 for between-group differences at all time points. The extent to which BAT improved 6MHWD compared to control was similar at each time point.

The change in functional status (using percent of patients improved by at least one NYHA class) from baseline to 6, 12, 24 months are presented in *Figure 3C*. The estimated between-group differences were 29.8 (95% CI 19.1–40.5) at 6 months, 31.9 (95% CI 21.2–42.5) at 12 months, and 26.9 (95% CI 14.4–39.4) at 24 months. The nominal *p*-values were < 0.001 for between-group differences at all time points. The extent to which BAT improved the NYHA class compared to control was similar at each time point.

For the symptomatic endpoints, an interaction test between treatment and time was performed to determine whether the treatment difference varied by time versus was consistent at all time points. The interaction test was not significant for QOL, 6MHWD, or NYHA class (all $p \geq 0.05$); therefore, there were no significant differences in effect size across time points.

Hierarchical composite win ratio

The win ratio for the hierarchical composite endpoint was 1.26 (95% CI 1.02–1.58) which favored the BAT group with 26% more wins in BAT versus control and a nominal *p*-value of 0.04 (*Figure 4*). Among all pairwise comparisons, 53.1% were wins for BAT versus 42.1% for control, with <5% of the comparisons resulting in a tie. *Figure 4* also lists the BAT wins, ties, control wins for each of the five hierarchical categories: CV mortality, LVAD and heart transplant; HF event using the expanded definition of HF, the number of unscheduled clinic visits with intravenous diuretic using the expanded definition for HF, and change in MLWHFQ at 12 months ≥5 points. The contribution that each category made to the final win ratio is also listed. Each category contributed substantively to the win ratio analysis of the hierarchical composite.

Freedom from all-cause death, left ventricular assist device implantation, and heart transplant

Kaplan–Meier estimates of freedom from all-cause death, LVAD implantation and heart transplant are displayed in *Figure 5*. In the BAT group, the crude event rate was 7.0 per 100 years with 38 events during 544 patient-years at risk. In the control group, the crude event rate was 10.4 per 100 years with 51 events during 492 patient-years at risk. The HR was 0.66 (95% CI 0.43–1.01), representing a relative risk reduction of 34% in the BAT group compared with the control group. This difference trended toward the BAT group with a nominal *p*-value of 0.054 that did not reach statistical significance. Using the Altman–Andersen HR method,[12] the absolute risk reduction was estimated as 9.6% at 4 years.

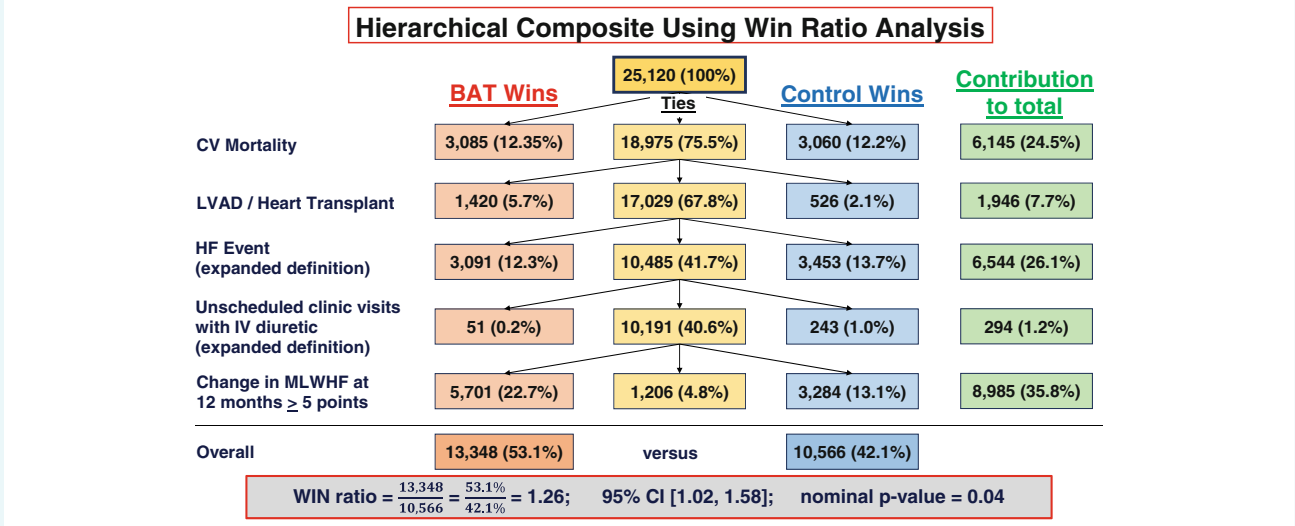


Figure 4 Hierarchical composite using win-ratio analysis. The hierarchical structure applied to the BeAT-HF data used a five level composite (see text for details) and the Finkelstein–Schoenfeld statistical method. The win ratio of 1.26 favoured the baroreceptor activation therapy (BAT) group with 26% more wins in BAT versus control. CI, confidence interval; CV, cardiovascular; HF, heart failure; IV, intravenous; LVAD, left ventricular assist device; MLWHF, Minnesota Living With Heart Failure.

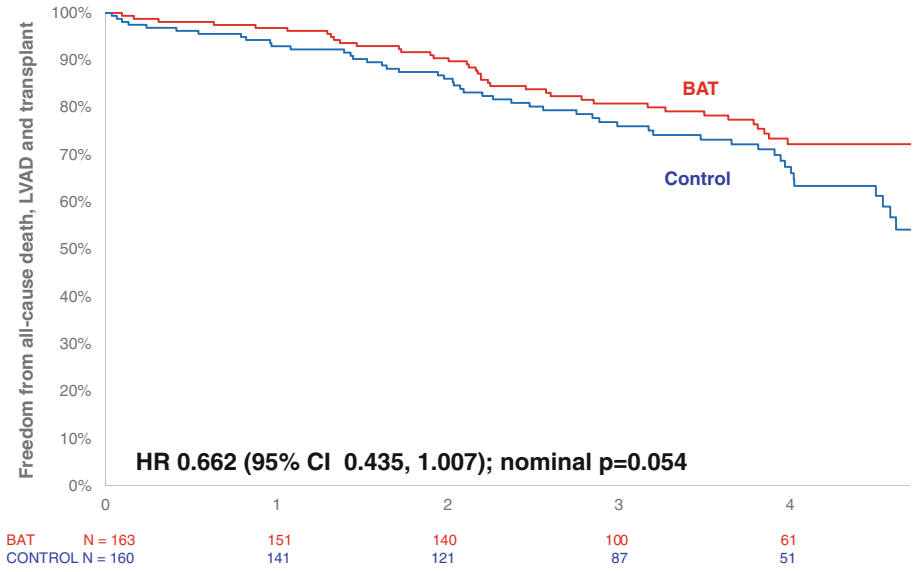


Figure 5 Freedom from all-cause death, left ventricular assist device (LVAD) implantation, and heart transplant. Baroreceptor activation therapy (BAT) resulted in a 34% reduction in relative risk. CI, confidence interval; HR, hazard ratio.

Online supplementary *Appendix S1*, *Table S1* delineates the number of non-CV deaths by organ system that occurred in the BAT versus the control group. Clearly, however, the sample sizes are too small to make any statistical conclusions about differences between the BAT and control group frequencies in these categories. Total non-CV deaths were 6 (3.8% of patients at risk) in BAT versus 12 (7.5% of patients at risk) in control; HR between arms is 0.44 (95% CI 0.16–1.16) in the BAT versus control.

Subgroup analysis

The effects of BAT on measured outcomes compared to controls was not altered by heart rate, sex, age, or estimated glomerular filtration rate. This was true for safety, mortality, morbidity, and all of the symptomatic endpoints. The improvement in 6MHWD, QOL, NYHA class in the BAT versus control group was consistent across heart rate, age, sex, and estimated glomerular filtration rate.

Discussion

Data obtained during the post-market phase of the BeAT-HF trial indicated that treatment with BAT did not result in a significant difference in the primary endpoint, or either of the individual components (CV mortality and HF morbidity) of the primary endpoint compared with control. However, both long-term measures of safety and symptomatic improvement favoured the BAT group, were durable over time, and sustainable in the extent of their effects. Based on the totality of the data presented in the post-market phase of the BeAT-HF trial, FDA revised indications for use labeling on 26 December 2023 as follows: 'Barostim is indicated for patients who are NYHA class III or class II (who had a recent history of class III) despite treatment with GDMT (medications and devices), have a left ventricular ejection fraction of ≤35%, and a NT-proBNP <1600 pg/ml. Barostim delivers BAT for improvement of patients' HF functional status, 6MHWD, and QOL'.

Baroreflex activation therapy added to existing treatment for NYHA class III heart failure with reduced ejection fraction

Patients in BeAT-HF were treated with the GDMT that was recommended by the guidelines at the time each patient was randomized including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists. BeAT-HF subjects were treated with remarkably high frequency of these three GDMT classes and implantable cardioverter-defibrillators. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) were not approved until after the completion of randomization. Even with four pillar GDMT, there remains a significant residual risk of mortality, morbidity and symptomatic disability.[13,14] Patients with NYHA class III HFrEF who continue to have symptoms that impact life quality and remain significantly disabled, have few additional choices. LVAD and heart transplant have limited availability and application. Short- and long-term inotropic treatment clearly improves symptoms but comes at the cost of reduced survival. Uniquely, add on treatment with BAT has a durable/sustainable improvement in QOL, exercise capacity, and functional status without an associated change in survival and without the complication rates of LVAD and transplant. We acknowledge that BAT was not examined in BeAT-HF in the presence of SGLT2i and

that SGLT2i therapy could reduce HF morbidity and mortality; however, existing SGLT2i studies that have found the effects of SGLT2i on symptomatic endpoints such as QOL (measured by the Kansas City Cardiomyopathy Questionnaire) are limited.[13,14] Examined in the context of current available therapy, BAT successfully addresses the unmet need for treatment of patients with HFrEF who are NYHA class III (or recently class II) with an ejection fraction ≤35% and NT-proBNP <1600 pg/ml, that remain symptomatic despite treatment with GDMT (medications and devices).

Baroreflex activation therapy versus other methods that alter autonomic nervous system homeostasis

The majority of efforts to modulate autonomic function in patients with HF have focused on implantable device-based treatments such as baroreceptor activation, vagal stimulation, and spinal cord stimulation.[15–18] Other therapies that may alter the ANS that have been tested in randomized clinical trials (RCTs) include renal and splanchnic artery denervation.[19,20] Based on some encouraging data from the INOVATE-HF (Increase in Vagal Tone in Heart Failure) trial,[15] vagal stimulation therapy trials remain in progress, specifically ANTHEM-HF (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure).[17] In the INOVATE-HF trial, vagal stimulation did not alter all-cause mortality, HF hospitalization, or left ventricular end-systolic volume; however, 6MHWD and Kansas City Cardiomyopathy Questionnaire scores were improved at 6 and 12 months of treatment.[15] To date, only BAT has received approval from regulatory agencies for use in patients with HF. In addition, BAT has significant design advantages and advantages with respect to mechanisms of action compared with the above mentioned ANS modulation devices. BAT is totally extravascular, directly alters baroreceptor sensitivity, provides a balanced modulation of ANS with both decreased sympathetic and increased parasympathetic signalling, and can provide individual patient-dependent therapy by modulation of therapy intensity (*Graphical Abstract*).

Endpoint choices

The choices made in the design of RCTs, particularly those related to the selection of the primary and additional study endpoints, are influenced by a number of factors. These factors include issues related to regulatory agencies, payers, patient preference and therapy mechanism of action. While the effects of treatment on morbidity and mortality remain a central concern, study endpoints that allow development of an in-depth understanding of the totality of the data, and study endpoints that provide insight into patient-centred symptomatic endpoints are becoming pivotal to product development. The hierarchical composite win-ratio analysis is one example.

When the primary endpoint used in a RCT is a composite of CV mortality and HF morbidity, only a limited percentage of patients contribute events to the endpoint. In BeAT-HF, only 40% of the randomized patients experienced a CV death or HF morbidity event and contributed to the primary endpoint. In contrast, using a hierarchical composite win-ratio analysis endpoint, 100% of patients contribute to the endpoint. In addition, a win-ratio design facilitates a composite structure that combines morbidity and mortality endpoints and patient-centred symptomatic endpoints in a hierarchical structure that sequentially examines each component. These factors are also relevant to the limited sample size that characterizes device studies in which morbidity and mortality events may be underpowered as individual endpoints. These advantages underlie the choice to use a hierarchical composite win-ratio analysis as the primary endpoint in a number of recently completed and currently ongoing RCTs, and to include the win ratio as a pre-specified additional endpoint as was done in BeAT-HF.[21–23]

Study limitations

BeAT-HF was an unblinded study with a non-implanted control. This design decision constitutes one important limitation, particularly as it relates to a differential placebo effect in the control versus BAT group. Based on data provided in the current study, we cannot rule out the presence of a persistent placebo effect (in the BAT device group) that could have contributed to the differences seen between the control and BAT groups in the patient-centred symptomatic endpoints. Future studies with BAT are planned that will use a double-blind, implanted control design that will address this limitation.

The sample size in BeAT-HF was likely to be underpowered for at least the CV mortality endpoint of the composite endpoint. It is for this and other reasons that freedom from all-cause death, LVAD and heart transplant was also examined. In addition, the entrance criteria (particularly NT-proBNP <1600 pg/ml) may have limited the expected number of mortal and morbid events.

BeAT-HF focused exclusively on patients with HFrEF. Given the BAT mechanism of action and given the fact that autonomic dysfunction is present in all patients with chronic HF, there is every reason to anticipate that BAT would have salutary effects on patients with HF and mildly reduced and preserved ejection fraction.[24–26] These studies are currently being planned.

Conclusions

Baroreflex activation therapy did not result in a significant difference in the composite primary endpoint, CV mortality and HF morbidity, or the individual components of the primary endpoints compared with control. However, both long-term measures of safety and symptomatic improvement favoured the BAT group, were durable over time, and sustainable in the extent of their effects. In addition, results of the all-cause mortality and the hierarchical win-ratio analyses favoured the BAT group. The totality of evidence obtained during the post-market phase of the BeAT-HF trial indicated that BAT provided safe, effective, and sustainable improvements in HFrEF patient's functional status, 6MHWD and QOL.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

Funding

CVRx, Inc., Minneapolis, Minnesota, ClinicalTrials.gov Identifier: NCT02627196.

Conflict of interest: M.R.Z. serves as a consultant to Abbott, Boston Scientific, Boehringer Ingelheim, CVRx, Corvia, Edwards, EBR, Lilly, Medtronic, Merck, Novartis, Vectorious, and V Wave. J.L. has received research grants from AstraZeneca, Sensible Medical, and Volumetrix and is a consultant for Abbott, Alleviant Medical, AstraZeneca, Boehringer Ingelheim, Boston Scientific, CVRx, Edwards, Impulse Dynamics, Medtronic, Merck, V Wave, and Whiteswell. F.A.W. serves as consultants to CVRx. F.Z. serves as consultant to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, Novo Nordisk, and Vifor Fresenius. E.G. is an employee of CVRx. T.R. is an employee NAMSA and serves as consultant to CVRx. W.T.A. serves as consultant to Boehringer Ingelheim, CVRx, Impulse Dynamics, Sensible Medical, Vectorious, V-Wave, and Zoll Respicardia.

References

1. Floras JS. Sympathetic nervous system activation in human heart failure: Clinical implications of an updated model. *J Am Coll Cardiol* 2009;**54**:375–385. https://doi.org/10.1016/j.jacc.2009.03.061
2. Creager MA, Creager SJ. Arterial baroreflex regulation of blood pressure in patients with congestive heart failure. *J Am Coll Cardiol* 1994;**23**:401–405. https://doi.org/10.1016/0735-1097(94)90427-8
3. Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, *et al.* Arterial baroreflex modulation of heart rate in chronic heart failure: Clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997;**96**:3450–3458. https://doi.org/10.1161/01.cir.96.10.3450
4. Giannoni A, Gentile F, Buoncristiani F, Borrelli C, Sciarrone P, Spiesshoefer J, *et al.* Chemoreflex and baroreflex sensitivity hold a strong prognostic value in chronic heart failure. *JACC Heart Fail* 2022;**10**:662–676. https://doi.org/10.1016/j.jchf.2022.02.006
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
6. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, *et al.* Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: A proof-of-concept study. *Eur J Heart Fail* 2014;**16**:977–983. https://doi.org/10.1002/ejhf.138
7. Wustmann K, Kucera JP, Scheffers I, Mohaupt M, Kroon AA, de Leeuw PW, *et al.* Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension. *Hypertension* 2009;**54**:530–536. https://doi.org/10.1161/HYPERTENSIONAHA.109.134023
8. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, *et al.* Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:1–13. https://doi.org/10.1016/j.jacc.2020.05.015
9. An Act to accelerate the discovery, development, and delivery of 21st century cures, and for other purposes. Public Law 114–255 – Dec. 13, 2016, 130 STAT. 1033 114th Congress. https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf
10. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, *et al.* 2014 ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol* 2015;**66**:403–469. https://doi.org/10.1016/j.jacc.2014.12.018
11. Abraham WT, Psotka MA, Fiuzat M, Filippatos G, Lindenfeld JA, Mehran R, *et al.* Standardized definitions for evaluation of heart failure therapies: Scientific expert panel from the Heart Failure Collaboratory and Academic Research Consortium. *Eur J Heart Fail* 2020;**22**:2175–2186. https://doi.org/10.1002/ejhf.2018
12. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**:1492–1495. https://doi.org/10.1136/bmj.319.7223.1492
13. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.*; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424. https://doi.org/10.1056/NEJMoa2022190
14. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.*; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
15. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, *et al.* Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF trial. *J Am Coll Cardiol* 2016;**68**:149–158. https://doi.org/10.1016/j.jacc.2016.03.525
16. De Ferrari GM, Stolen C, Tuinenburg AE, Wright DJ, Brugada J, Butter C, *et al.* Long-term vagal stimulation for heart failure: Eighteen month results from the NEural cardiac TherApy foR Heart Failure (NECTAR-HF) trial. *Int J Cardiol* 2017;**244**:229–234. https://doi.org/10.1016/j.ijcard.2017.06.036
17. Konstam MA, Udelson JE, Butler J, Klein HU, Parker JD, Teerlink JR, *et al.*; ANTHEM-HFrEF Investigators and Coordinators. Impact of autonomic regulation therapy in patients with heart failure: ANTHEM-HFrEF Pivotal study design. *Circ Heart Fail* 2019;**12**:e005879. https://doi.org/10.1161/CIRCHEARTFAILURE.119.005879
18. Zipes DP, Neuzil P, Theres H, Caraway D, Mann DL, Mannheimer C, *et al.* Determining the feasibility of spinal cord neuromodulation for the treatment of chronic systolic heart failure: The DEFEAT-HF study. *JACC Heart Fail* 2016;**4**:129–136. https://doi.org/10.1016/j.jchf.2015.10.006
19. Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, *et al.*; RADIANCE II Investigators and Collaborators. Endovascular ultrasound renal denervation to treat hypertension: The RADIANCE II randomized clinical trial. *JAMA* 2023;**329**:651–661. https://doi.org/10.1001/jama.2023.0713
20. ClinicalTrials.gov. Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF (Rebalance-HF). NCT04592445. https://clinicaltrials.gov/study/NCT04592445 Accessed 30 March 2024.
21. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, *et al.*; REDUCE LAP-HF II Investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): A randomised, multicentre, blinded, sham-controlled trial. *Lancet* 2022;**399**:1130–1140. https://doi.org/10.1016/S0140-6736(22)00016-2
22. Berwanger O, Pfeffer M, Claggett B, Jering KS, Maggioni AP, Steg PG, *et al.* Sacubitril/valsartan versus ramipril for patients with acute myocardial infarction: Win-ratio analysis of the PARADISE-MI trial. *Eur J Heart Fail* 2022;**24**:1918–1927. https://doi.org/10.1002/ejhf.2663
23. ClinicalTrials.gov. Reducing Lung Congestion Symptoms in Advanced Heart Failure (RELIEVE-HF). NCT03499236. https://clinicaltrials.gov/study/NCT03499236 Accessed 30 March 2024.
24. Bunsawat K, Ratchford SM, Alpenglow JK, Ryan JJ, Richardson RS, Wray DW. Direct assessment of muscle sympathetic nerve activity during exercise in heart failure with preserved ejection fraction: A case report. *J Card Fail* 2021;**27**:114–116. https://doi.org/10.1016/j.cardfail.2020.11.001
25. Badrov MB, Tobushi T, Notarius CF, Keys E, Floras JS. In heart failure with preserved ejection fraction muscle sympathetic nerve activity is augmented At rest and during exercise. *J Card Fail* 2024;**30**:P245–P246. https://doi.org/10.1016/j.cardfail.2023.10.305
26. Badrov MB, Mak S, Floras JS. Cardiovascular autonomic disturbances in heart failure with preserved ejection fraction. *Can J Cardiol* 2021;**37**:609–620. https://doi.org/10.1016/j.cjca.2020.12.006