Supplemental Material

Data S1.

STUDY ORGANIZATION AND CONDUCT

This trial was sponsored by BackBeat Medical, an Orchestra BioMed company. The protocol, a synopsis of which is provided below, was designed by the investigators in collaboration with the sponsor. The protocol was approved by the ethics committee at each participating center, and all the patients provided written informed consent. The sponsor participated in site selection and management and in data analysis. Source documents of primary and secondary endpoints were 100% monitored to ensure integrity of the data. The principal investigators had unrestricted access to the data, wrote the manuscript, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

All collected data were confirmed by independent monitors. Blood tests, echocardiograms, 24-hours ambulatory blood pressure and 24-hour Holter recordings were evaluated by blinded core labs. Adverse events were reviewed by an independent events adjudication committee (EAC) which ascribed severity and device- and procedure-relatedness. An independent data safety monitoring board (DSMB) monitored aggregate safety data during the study. EAC and DSMB memberships are detailed below.

Data Safety Monitoring Board and Events Adjudication Committee

(Chair): Prof. Marc Klapholz, Chair, Department of Medicine Rutgers, New Jersey Medical School

Dr. Jose Dizon, Associate Professor of Medicine at CUMC, New York-Presbyterian/Columbia

Dr. Sam Hanon, Associate Professor of Medicine, Cardiology, The Mount Sinai Hospital

Non-voting statistician

Dr. Harold M Hastings, Division of Science, Mathematics and Computing, Bard College at Simon’s Rock, Great Barrington MA and Department of Physics and Astronomy, Hofstra University, Hempstead NY (Professor Emeritus)

List of Centers and Principal Investigators who screened patients

Country	City	Hospital	PI
Austria	Linz	Krankenhaus der Elisabethinen	Prof. Josef Aichinger
	Vienna	Medical University of Vienna, Vienna General Hospital	Prof. Thomas Pezawas
Belgium	Aalst	OLV Hospital Aalst	Dr. Riet Dierckx
Czech Republic	Prague	Na Homolce Hospital	Prof. Petr Neuzil
Hungary	Budapest	Semmelweis University Heart and Vascular Center	Prof. Bela Merkely
Latvia	Riga	P. Stradins Clinical University Hospital	Prof. Andrejs Erglis
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	Prof. Germanas Marinskis
Poland	Gdansk	Medical University of Gdansk	Prof. Krzysztof Narkiewicz
	Poznan	Szpital Kliniczny Przemiemienia Panskiego	Prof. Przemysław Mitkowski
	Szczecin	Pomeranian Medical University Hospital no. 2	Prof. Jaroslaw Kazmierczak
	Warsaw	I Katedra i Klinika Kardiologii Samodzielny Publiczny Centralny Szpital	Prof. Marcin Grabowski
	Zabrze	Silesian Center for Heart Diseases	Prof. Zbigniew Kalarus
UK	London	St. Thomas' Hospital	Prof. Aldo Rinaldi

Supplemental Methods

Methods for measuring blood pressure

Office blood pressure measurements were performed consistent with the Standard Joint National Committee VII, European Society of Hypertension and European Society of Cardiology recommendations.[1,2] Office blood pressure was based on the average of three measurements. Office blood pressures were measured using the automatic Omron blood pressure monitor (model number 705, Omron Corporation, Kyoto). All centers were provided with the devices to unify the measurements. If systolic blood pressure values were more than 15 mmHg apart on any pair of these readings, measurements were repeated, and the final value was based on the last three consecutive consistent (<15 mmHg differences) readings. 24-Hour ambulatory blood pressure monitoring tests were performed with an oscillometric Spacelabs 90207-1 monitor (Spacelabs Healthcare, Hertford, UK), with readings recorded every 10 minutes during the day (7am to 10pm) and every 20 minutes at night. Measurements were deemed acceptable if at least 30 readings during the day-time period and 9 readings during the night-time period were successfully recorded. One repeat of the 24-hour ambulatory measurement was permitted in case the number of readings did not meet specified minimum recordings.

Moderato device and CNT Description

The Moderato device and CNT therapy has been described in detail previously.[3] In brief, the CNT pacing sequence consists of 8-13 beats with a shorter AV delay followed by 1-3 beats with a longer AV delay. The CNT algorithm has atrial rate tracking, meaning that its rate automatically adjusts to an average of 4-to-5 beat/min above the native heart rate in patients whose heart rate is determined by the intrinsic atrial rate. The device connects to the heart with any commercially available IS-1 bipolar endocardial lead. An external device programmer allows clinicians to program device parameters and download diagnostic information. The device implantation or exchange procedures were performed according to local standard dual-chamber pacemaker implantation protocols; no special implantation instructions beyond those used for standard pacemakers were needed. A typical blood pressure response to activation of CNT pacing is shown in Fig. S1.

Efforts to Minimize Placebo and Hawthorne Effects

The nature of the Moderato system and the patient population to which it applies allowed for a novel study design to account for placebo and Hawthorne effects. Specifically, in addition to hypertension, all study subjects had a clinical indication for a pacemaker for treatment of bradyarrhythmia. Accordingly, patients could receive the device implant and be observed during a significant time period prior to randomization. In this manner, patients whose adherence with medical therapies or lifestyle behaviors resulted in improved control of blood pressure could be withdrawn from the study prior to randomization. This is not possible with other technologies whose putative anti-hypertensive effects are in effect at the moment of application. Indeed, Hawthorne effects have interfered with the ability to effectively quantify treatment effects in prior studies of renal denervation. Of the original 68 patients enrolled in our study, blood pressure fell below the study inclusion criterion in 21 (31%) during the initial 30-day observation period without any changes in prescribed therapies. Blood pressure also dropped in most subjects who remained in the study, but their final pre-randomization values were still in a range requiring additional treatment.

Exploratory Endpoints

A series of additional exploratory endpoints included between group differences in the change (from baseline to 6 months) of oSBP and diastolic blood pressure (DBP), average night-time SBP, average daytime SBP and 24-hour average DBP; the percentage of patients who had decreases in ambulatory blood pressure, the percentage of patients with a reduction of 5 mmHg or more in their ambulatory pressure and the percentage of patients having a super response of 10mmHg or more. Analyses of echocardiographic data focused on between-group differences in changes

of end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF). Analyses of blood test focused on changes of creatinine, BUN, eGFR.

Supplemental Results

Diastolic blood pressures

As detailed in Table 2 of the main text, aDBP in the randomized cohort averaged 73.3±6.8 mmHg and did not differ between control and treatment groups. Furthermore, aDBP did not change in either group during the follow-up period (Table S3).

Heart Rate

Average heart rate was assessed from 24-hour ambulatory blood pressure recordings and 24-hour Holter recordings. Results (detailed in Table S5 and S6) show a ~3-4 beat per minute higher heart rate in Treatment compared to Control, which is fully explainable by the atrial rate tracking feature of the IPG. This is an intrinsic feature of the CNT algorithm in order to ensure capture of both the atria and ventricles to achieve precise control of the AV interval.

Holter

Twenty-four hour Holter recordings were performed pre-randomization and at 6 months and were analyzed for ventricular and supraventricular arrhythmic burden. As detailed in Table S7, there was a very low overall arrhythmia burden which did not change significantly in either group.

Blood Sample Analysis

Blood sample analysis focused on changes in renal function. As detailed in Table S8, there were minimal changes in blood urea nitrogen, serum creatinine or estimated glomerular filtration rate (eGFR) over the 6-month study period in both Treatment and Control groups.

MODERATO II STUDY SYNOPSIS

Study Title	**Clinical Evaluation of Safety and Effectiveness of the BackBeat Medical Moderato System in Patients with Hypertension: A Double-Blind Randomized Trial.**
Study code	CS-03 (Version 1.1, October 26, 2015)
Name of the Device	Moderato System
Intended Use	The Moderato System is indicated for patients with hypertension who also require a dual chamber pacemaker, in order to reduce their blood pressure.
Study Design	This will be a randomized, double-blind study in which patients are randomized to either a cohort that will receive active treatment with the Moderato System delivering hypertension therapy plus continued medical therapy or to a cohort that will have the Moderato System in pacemaker only mode and receive continued medical therapy.
Patient Population / Sample Size	A total of 50* subjects will be enrolled from up to 30 sites; a majority of sites will be from countries within the European Union. The maximum number of subjects enrolled per site will be 40. Patients who dropout during the "Run-In Phase" will be replaced.
Duration of the investigation	Each subject will be followed for approximately 7 months, consisting of a 1 month "Run-In Phase" after device implantation, followed by a 6-month observation period. It is expected to take approximately 20 months to recruit the subjects, so the total duration of the study will be approximately 20 + 7 = 27 months.
Study Rationale	Pacemaker technology is well established, with well-defined hardware, firmware and logic algorithms. The Moderato System leverages existing technology to deliver a novel pacing therapy to treat Hypertension (HTN). The device has undergone rigorous bench and preclinical animal testing to confirm its safety and performance and has been implanted in 35 patients in a pilot clinical study aimed to evaluate the safety and functionality of the system. Pilot study interim results indicate that the device functions as expected and suggest that there is a significant decrease in blood pressure in both ambulatory and office measurements after device activation. The goal of this study is to confirm the effects of the Moderato System on blood pressure in a controlled, randomized, double-blinded study. Hypertension (HTN) ultimately affects 1 in 3 adults in most cultures and is one of the most important factors contributing to cardiovascular morbidity and mortality. Medications are frequently effective in controlling blood pressure. However, >40% of HTN patients remain with unacceptably high blood pressure. Unacceptably high blood pressure is defined as systolic pressure >140 mmHg in the absence of other cardiovascular risk factors, or >130 mmHg in the presence of other risk factors. According to the United States National Heart, Lung and Blood Institute (NHLBI), about 69% of people presenting with their first heart attack, 77% presenting with their first stroke and 74% presenting with congestive heart failure have a systolic blood pressure higher than 140 mmHg. Cardiovascular risk doubles for every 10 mmHg increase in systolic blood pressure.

	Although there are several medications that are helpful in controlling blood pressure, one of their major limitations is the notoriously low rate of compliance. Thus, many medically responsive patients have high pressures simply because they do not take their medications. This is sometime due to unpleasant side effects. In addition, there are many patients who have persistently elevated blood pressure despite compliance with medical therapies. Accordingly, investigators have turned to alternate strategies to treat HTN, in particular device-based therapies. Percutaneous renal denervation is one example that, in early studies, achieved significant success in a population with medically refractory HTN (i.e., systolic pressure >160 mmHg despite the use of at least 3 antihypertensive drugs). Symplicity-3, a randomized, sham-controlled blinded study, however, revealed no significant difference between the renal denervation and sham groups (1). Another device therapy for hypertension utilizes Baroreflex Activation Therapy (BAT) to electrically stimulate the carotid sinus using an implanted pulse generator (Rheos). The Rheos pivotal trial (baroreceptor stimulation) enrolled 265 patients with a systolic BP >160mmHg and an average ambulatory BP >135mmHg (2); 42% of treated patients achieved blood pressure control during long-term follow-up (3). However, there was a 25% procedural complication event rate, an approximately 10% device-related complication event rate and a 13% device safety complication rate. Thus, additional treatments are needed. BackBeat Medical has developed a family of cardiac pacing algorithms that have been shown in pre-clinical studies to safely reduce blood pressure. They have also been shown to be safe and reduce blood pressure in acute studies performed in patients with HTN. Preliminary data from an ongoing long-term study in patients who require a pacemaker has also shown significant blood pressure-lowering effects with no adverse impact on cardiac function. These Cardiac Neuromodulation Therapy (CNT) pacing algorithms use standard dual-chamber pacing signals and involve alterations of the timing at which these signals are delivered. Accordingly, they have been incorporated as an added feature into a standard pacemaker that connects to the heart with standard, commercially available pacing leads. The present study will enrol subjects who have hypertension despite a stable anti-HTN medical regimen for greater than one month who either require implantation of a dual chamber pacemaker or have a pre-existing pacemaker that requires a pulse generator exchange. Subjects who require a new pacemaker implant or a pacemaker exchange will be exposed to the well-established risks of pacemaker implantation and pacing therapy, independent of whether they receive the Moderato System. Therefore, the risks associated with participating in this study and of using the Moderato System are restricted to those risks associated with use of the specific BackBeat-CNT therapy pacing algorithm. To enhance its safety profile, the BackBeat-CNT therapy pacing algorithm is programmed according to the needs of each individual subject and the therapy can be turned off at any time.
Description of System Components	1. Moderato IPG: A sterile Pacemaker that, in addition to standard pacemaker capabilities and features, also incorporates the BackBeat-CNT pacing algorithms to reduce blood pressure for use as a treatment for hypertension. 2. Any commercially available, IS-1 BI compatible, bipolar endocardial pacing leads; 3. Moderato Programmer: An external device programmer capable of communicating with the Moderato IPG through the skin to program device parameters.

Follow-up Schedule	The details of the study flow are detailed in the protocol along with a flow diagram (Figure S2). After screening, the study will be conducted in two phases: a 4 weeks Run-In Phase and a 6-month Randomized Phase. **Pre-screening and Screening:** After signing an informed consent, subjects will be screened for blood pressure and hypertension treatments to determine eligibility. This will consist of an office visit to document medical therapies for hypertension (including drug name, daily dose and duration of treatment), to measure blood pressure and to obtain a 24-hour recording of ambulatory blood pressure. Subjects will also undergo an Echo study, blood samples will be collected and evaluated to determine GFR. ECG will be performed and, if applicable, the subject will undergo a pregnancy test. Subjects will be eligible for inclusion in the study if the average daytime (7AM to 10PM) ambulatory systolic pressure is ≥130 mmHg and an office blood pressure ≥140 mmHg. All subjects meeting this screening criterion and all other study inclusion/exclusion criteria (detailed below) will undergo implant of the Moderato IPG. **Run-In Period** Following implantation, the normal pacing functions of the device will be programmed as per the needs of the patient. The day of implantation will be considered Day 0 of the study from which the timing of future study visits will be determined. The patient will be seen in the office at the end of study week 3 and will have an office BP check, medical history and medications will be recorded, a 24 hour Holter to provide a baseline assessment of the amount of ambient ectopy, and a repeat 24-hour ambulatory blood pressure recording; this blood pressure will be considered the pre-randomization Baseline ambulatory blood pressure. Patients will be seen in the office at the end of study week 4, the results of the prior 24-hour ambulatory pressure recording will be reviewed. Patients will be eligible to move to the Randomized Phase of the study (detailed in the next section) if their average daytime (7AM-10PM) ambulatory systolic pressure is ≥125 mmHg. Patients eligible for randomization will undergo the final pre-randomization Baseline testing (echocardiogram, office blood pressure, blood tests) these tests will be used as the pre-randomization Baseline for evaluating the effect of BackBeat-CNT therapy on these tests. Patients who do not meet the criteria to be randomized will be followed according to the same study visit schedule as for randomized patients for 6 months and will be followed mainly for safety evaluation. These patients (the Non-Randomized Cohort), in collaboration with their primary physician, can choose to have the BackBeat-CNT hypertension treatment algorithm activated (e.g., if their office blood pressure is persistently elevated). However, efficacy results will not be included in the primary analysis of blood pressure effects. In addition, these patients will be replaced, so that a total of 170 patients enter the Randomized Phase of the study. **Randomized Phase** After the 4-week Run-In phase, all subjects eligible for the Randomized Phase will undergo a BackBeat-CNT therapy optimization procedure. This consists of measuring blood pressure while varying BackBeat-CNT therapy algorithm parameters to determine the parameters that provide the best therapy. Following this optimization procedure, patients will be randomized into one of two groups: Group 1 (active treatment group) will have continued medical therapy plus the BackBeat-CNT Therapy activated; Group 2 (control group) will continue with the standard

	pacing regimen and continued medical therapy. Both the patients and the physicians will be blinded to group assignment. At each center, there will be one "unblended" physician who will handle all pacemaker evaluations and treatments. Patients in both groups will be seen at 1, 3, and 6 months post randomization and will undergo a review of the interim medical history, an office measurement of BP (each visit), echocardiograms (at 1 and 6 months), blood tests including ANP and BNP (at 1 and 6 months) and a 24-hour ambulatory blood pressure recording (at 1 and 6 months). An ECG and Holter monitor recording will also be performed at the 6 month visit post-randomization. The study will be considered complete for the primary endpoint after all randomized subjects have completed the 6-month follow-up tests. At the end of the 6-month BackBeat-CNT Therapy period (post randomization), subjects in Group 1 (the active group) will have the option to continue with the BackBeat-CNT therapy activated; subjects in Group 1 opting for active treatment will have office visits at months 12, 18 and 24 post randomization. Subjects in Group 2 (the control group) will have the option to have the BackBeat-CNT therapy activated; patients opting for active treatment will be followed at 1, 3 and 6 months post activation (months 7, 9 and 12 post randomization) and every 6 months thereafter for a total of 2 years. At the 1, 3 and 6 months post activation (months 7, 9 and 12 post randomization), subjects who were in group 2 will repeat the tests and evaluations as described under the visits 1, 3, and 6 months post randomization. Subjects in the Non-Randomized Cohort who have opted to activate the BackBeat-CNT treatment algorithm will be seen at 1, 3, 6, 12, 18 and 24 months with the same tests as the study patients. Non-randomized Cohort subjects who do not have active treatment or subjects in groups 1 or 2 who decide not to activate the BackBeat-CNT treatment at the end of the 6-month post randomization visit will be followed every 6 months through a total of 2 years follow-up for the interrogation of the Moderato pacemaker and modification of the standard pacemaker parameters in case needed.
Inclusion Criteria	**1)** Subject is ≥ 18 years of age **2)** Subject requires the implant or replacement of a dual chamber pacemaker **3)** Subject has stable (for prior 1 month) hypertension treatment with at least 1 antihypertensive drug, which is anticipated to be able to be maintained without changes for 7 months. **4)** Subject has an average day-time (7AM to 10PM) ambulatory systolic blood pressure of ≥ 130mmHg and office systolic blood pressure ≥140 mmHg **5)** Subject lives in the proximity of the study center, which will permit compliance with study visits for at least 7 months.
Exclusion Criteria	**1)** Subject has a known secondary cause of HTN **2)** Subject with average ambulatory or office systolic BP >195 mmHg **3)** Subject has permanent atrial fibrillation

	4) Subject has a history of significant paroxysmal atrial fibrillation/flutter burden (defined as >25% of beats). Fibrillation/flutter burden will be determined by pacemaker interrogation (for those already having a pre-existing pacemaker) or, otherwise, by patient history. **5)** Subject has ejection fraction <50% **6)** Subject has symptoms of heart failure, NYHA Class II or greater **7)** Subject has hypertrophic cardiomyopathy, restrictive cardiomyopathy or interventricular septal thickness ≥15 mm **8)** Subject is on dialysis **9)** Subject has estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m² **10)** Subject has prior neurological events (stroke or TIA) within the past year or an event at any prior time that has resulted in residual neurologic deficit **11)** Subject has known carotid artery disease **12)** Subject has known autonomic dysfunction **13)** Subject has a history of clinically significant untreated ventricular tachyarrhythmia or has experienced sudden death **14)** Subject has had previous active device-based treatment for hypertension **15)** Subject has an existing implant, other than a pacemaker that needs replacing **16)** Subject is pregnant or has the possibility of becoming pregnant during the conduct of the study and is not willing to use a means of contraception during the study. **17)** Subject cannot or is unwilling to provide informed consent.
Analysis of Clinical Effectiveness	The Moderato System will be considered to be effective if the mean change of the average 24-hour ambulatory systolic blood pressure (6 months' average – pre-randomization Baseline average) in the active treatment group (Group 1) is significantly greater than the mean change (6 month average – Pre-randomization Baseline average) in the control group (Group 2) (Note: The Baseline pre-randomization 24-hour blood pressure is the mean ambulatory blood pressure measured at the 3 week visit during the Run-In Phase.)
Safety	The Moderato System will be considered safe if the rate of major adverse cardiac events [including: heart failure, clinically significant arrhythmias (e.g., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke, heart failure and renal failure and/ or other related safety events that result in death] does not differ between groups.
Other Analyses	Changes in the following parameters will be analyzed (6 months versus pre-randomization [Baseline]) and compared between groups using descriptive statistics to provide additional information about the safety and effectiveness of the therapy: • Holter recording to confirm proper functioning of the BackBeat-CNT treatment algorithm and to assess changes in the incidence of ventricular and supraventricular events • Average day-time blood pressures from 24-hour ambulatory monitoring • Average night-time blood pressures from 24-hour ambulatory monitoring • Office systolic and diastolic blood pressure measurements • Echocardiograms: Ejection fraction, left ventricular end-diastolic and end-systolic volumes • Blood tests: ANP, BNP, Creatinine • Overall type and rate of adverse events

*Note: the original protocol called for 170 patients and was designed as a pivotal study with sample size based on results from a prior unblinded study. However, it was decided that results from the first 50 patients would be analyzed to provide a better assessment of the rate of safety events and changes of blood pressure (particularly in the blinded control group) for more accurate estimation of sample size for the pivotal study powered for both safety and efficacy.

Table S1. Study Schedule of Visits and Tests.

			All visits after implantation have a window of±1 week						
			Run-In Period			Randomized Phase			Post-Study**
	Pre-Screening	Screening	Moderato IPG Implant	3 Wk F/U	4 Wk F/U	+1 Mo F/U	+3 Mo F/U	+6 Mo F/U	Post-Study F/U: every 6 Months through 2 years
Informed Consent	X								
Office Visit / Medical History		X		X	X	X	X	X	X
Medications		X		X	X	X	X	X	X
Office Blood Pressure Check		X		X	X	X	X	X	X
Electrocardiogram		X						X	
Pregnancy test (if applicable)		X							
24 Hour Holter Monitor				X				X	
24 Hour Ambulatory Blood Pressure Monitor		X		X	X	X		X	
Eligibility Determination		X			X				
Echocardiogram		X*			X▲	X▲		X▲	X▲
Blood tests		X			X	X		X	
Basic chemistry panel and hematology		X			X	X		X	
Estimated GFR		X *			X	X		X	
MR pro ANP and NT Pro BNP		X			X	X		X	
Moderato IPG Implant			X						
Randomization and BackBeat-CNT Therapy optimization					X				
Moderato IPG interrogation				X	X	X[a]	X[a]	X[a]	X[a]
Adverse Events (as needed)		X	X	X	X	X	X	X	X

**Subjects in the control arm who agree to be activated with the Moderato-CNT therapy at the end of the study (+6 months F/U) will repeat the F/U schedule of +1 month to + 6 months in the post study and every 6 months through 2 years

*) GFR and Echocardiography will be also evaluated by the institution for the determination of the inclusion/exclusion criteria.

▲) Echocardiography will be done twice, with Moderato-CNT therapy ON and OFF

[a]) Moderato-CNT Therapy optimization as required

Table S2. Summary of ambulatory and office diastolic blood pressure at the follow-up time points.

	Ambulatory Diastolic BP				Office Diastolic BP			
	Pre-Randomization	+1 Day	+1 Month	+6 Months	Pre-Randomization	+1 Month	+3 Months	+6 Months
Treatment	74.0±6.9	71.9±6.9	74.3±8.4	73.2±5.4	83.0±10.8	83.3±9.6	79.0±9.2	82.1±9.3
Control	72.6±6.7	72.5±8.0	71.1±7.0	70.7±6.9	81.6±12.4	79.6±11.2	80.3±11.8	80.8±8.5
Difference	1.4	0.58	3.1	2.5	1.34	3.7	-1.3	1.2
p-value	0.670	0.800	0.179	0.178	0.693	0.227	0.684	0.643

Treatment/Control values are mean±SD.

Table S3. Summary of adverse events.

Subject	Group	EVENT
A	Control	Anemia
B	Control	Unstable angina leading to RCA stent
		Metastatic prostate cancer
C	Control	Pneumonia
D	Control	Atrial fibrillation requiring cardioversion
		Hyponatremia
		Gastroenteritis
		Dislocated RV pacing lead

Table S4. Heart rate based on Holter analysis.

		Week 3 Pre-Randomization	+6 Months	Change +6M–W3
Treatment	Mean	74.00	76.81	2.81
	SD	9.70	10.52	7.55
	N	26	26	26
Control	Mean	71.19	70.65	-1.05
	SD	9.16	8.60	4.44
	N	21	20	20

Table S5. Heart rate based on ambulatory blood pressure monitor results.

		Baseline	Week 3	+1 Day	+1 Month	+6 Months	Change +1D–W3	Change +1M–W3	Change +6M–W3
Treatment	Mean	64.13	69.57	74.85	73.10	72.63	4.92	3.53	3.06
	SD	8.02	9.50	9.43	8.46	10.14	4.33	6.06	6.63
	N	25	26	25	26	26	25	26	26
Control	Mean	64.69	68.43	68.26	69.46	67.70	0.24	1.04	-1.59
	SD	12.48	8.46	9.24	9.10	7.80	2.83	2.93	4.19
	N	21	21	20	21	19	20	21	19

Table S6. **Holter monitor analysis of ventricular and supraventricular arrhythmia burden. No significant difference noted between treatment and control groups**.

Parameter			Week 3	+6 Months	Change +6M – W3
TREATMENT	**SVE**	Mean±SD	0.92±2.3	0.49±0.9	-0.44±2.5
		Median (IQR)	0.06 (0.01, 0.46)	0.01 (0.01, 0.61)	-0.01 (-0.14, 0.05)
	PVC	Mean±SD	0.85±2.2	0.70±1.5	-0.16±1.6
		Median (IQR)	0.13 (0.04, 0.43)	0.1 (0.02, 0.39)	-0.01 (-0.16, 0.12)
CONTROL	**SVE**	Mean±SD	0.38±0.9	0.82±2.3	0.42±2.5
		Median (IQR)	0.01 (0.00, 0.13)	0.02 (0.01, 0.31)	0.00 (-0.05, 0.02)
	PVC	Mean±SD	1.04±3.0	0.27±0.46	-0.82±3.1
		Median (IQR)	0.14 (0.02, 0.63)	0.13 (0.02, 0.28)	0.00 (-0.39, 0.06)

IQR, interquartile range; SVE, percentage of all beats that are supraventricular ectopic beats; PVC, percentage of all beats that are premature ventricular contractions.

Table S7. Blood tests related to renal function.

	Blood tests	baseline	Week 4	+1 Month	+6 Months	Change +1M – W4	Change +6M – W4
Treatment	BUN (mmol/l)	5.8±1.6	6.0±1.7	6.1±1.5	6.3±1.2	0.10±1.3	0.29±1.3
	Creatinine (μmol/l)	77.5±16.4	76.7±12.8	81.2±15.6	82.7±20.5	3.9±12.0	5.9±17.9
	eGFR (ml/min/1.73m²)	80.5±19.1	79.0±16.9	76.0±18.0	75.3±22.1	-2.7±13.7	-3.7±16.0
Control	BUN (mmol/l)	7.2±3.7	6.9±2.2	6.9±2.3	6.6±2.0	0.11±1.1	-0.41±1.8
	Creatinine (μmol/l)	97.4±24.5	92.6±20.5	92.1±20.5	94.3±19.6	0.5±7.0	2.3±15.2
	eGFR (ml/min/1.73m²)	65.4±20.6	68.1±19.3	68.8±17.3	66.8±21.0	-0.71±6.8	-1.8±9.6

Values are mean±SD.

Figure S1. Study design and randomization scheme.

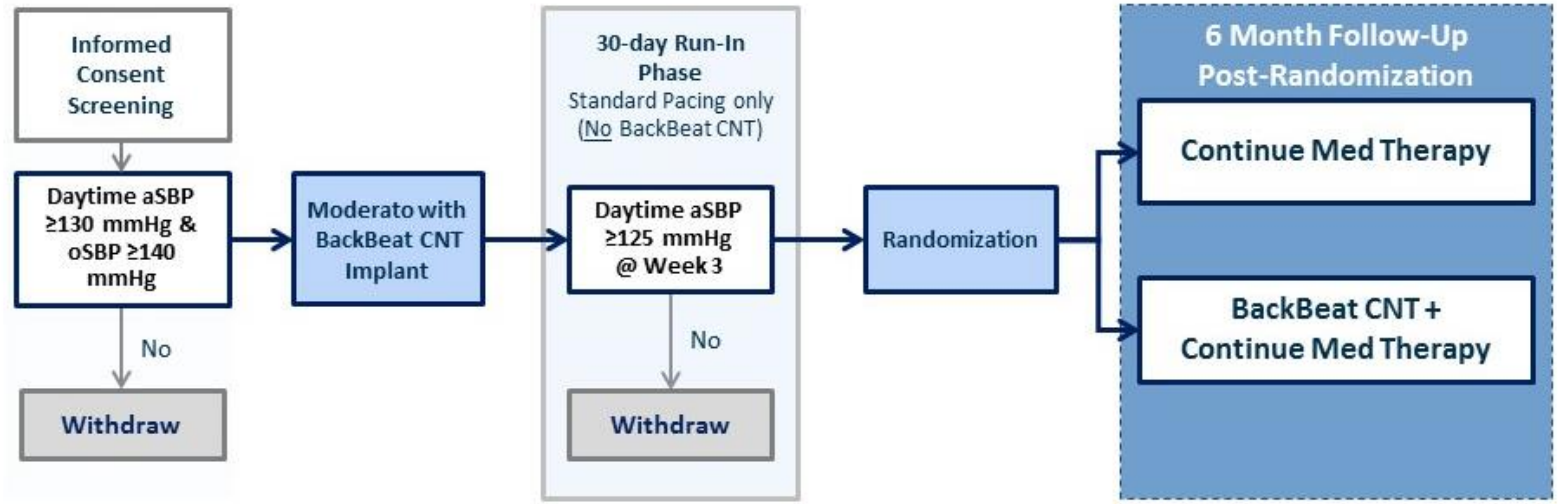

Figure S2. Red dots show systolic blood pressure (SBP) on each beat; sinusoidal variation due to respiration. Cardiac Neuromodulation therapy (CNT) pacing initiated as indicated by the bar. SBP on short AV delay paced beats drops significantly. SBP increases on the two beats with longer AV delays (red arrows) and then drops significantly with resumption of short AV delay pacing. When CNT pacing is suspended, blood pressure increases gradually back towards the original baseline, suggesting that total peripheral resistance was decreased during the period on CNT pacing through modulation of autonomic nervous system activity by SBP variations.

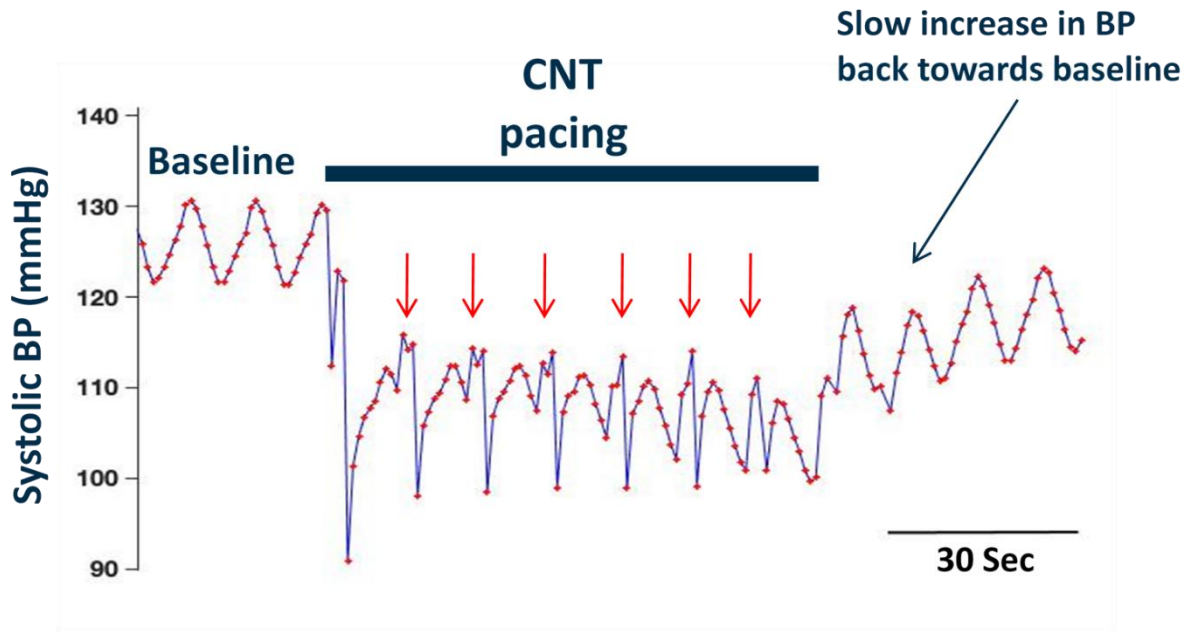

Figure S3. Fan plots showing changes in ambulatory systolic blood pressure (aSBP) from pre-randomization (week 3) in treatment and control groups. In this "responders' analysis", orange lines show instances when aSBP increased compared to pre-randomization; grey lines show instances when aSBP decreased.