Baroreflex Activation Therapy Lowers Blood Pressure in Patients With Resistant Hypertension

Results From the Double-Blind, Randomized, Placebo-Controlled Rheos Pivotal Trial

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Objectives

We sought to determine the effect of baroreflex activation therapy (BAT) on systolic blood pressure (SBP) in patients with resistant hypertension.

Background

The Rheos Pivotal Trial evaluated BAT for resistant hypertension in a double-blind, randomized, prospective, multicenter, placebo-controlled Phase III clinical trial.

Methods

This was a double-blind randomized trial of 265 subjects with resistant hypertension implanted and subsequently randomized (2:1) 1 month after implantation. Subjects received either BAT (Group A) for the first 6 months or delayed BAT initiation following the 6-month visit (Group B). The 5 coprimary endpoints were:

1) acute SBP responder rate at 6 months; 2) sustained responder rate at 12 months; 3) procedure safety; 4) BAT safety; and 5) device safety.

Results

The trial showed significant benefit for the endpoints of sustained efficacy, BAT safety, and device safety. However, it did not meet the endpoints for acute responders or procedural safety. A protocol-specified ancillary analysis showed 42% (Group A) versus 24% (Group B) achieving SBP ≤140 mm Hg at 6 months (p = 0.005), with both groups achieving over 50% at 12 months, at which point Group B had received 6 months of BAT.

Conclusions

A clinically meaningful measure, those achieving a SBP of ≤140 mm Hg, yielded a significant difference between the groups. The weight of the overall evidence suggests that over the long-term, BAT can safely reduce SBP in patients with resistant hypertension. Future clinical trials will address the limitations of this study and further define the therapeutic benefit of BAT. (J Am Coll Cardiol 2011;58:765–73) © 2011 by the American College of Cardiology Foundation

Resistant hypertension (HTN) is defined as failure to achieve goal blood pressure (BP) (<140/90 mm Hg for most patients, <130/80 mm Hg for patients with diabetes or chronic kidney disease) when adhering to maximally tolerated doses of 3 appropriate antihypertensive drugs including a diuretic. Resistant HTN is frequently associated with comorbidities such as obesity, diabetes, and chronic kidney disease. Although the exact prevalence is unknown, studies indicate 20% to 30% of hypertensive patients have treatment-resistant HTN (1–3). Even with application of existing pharmacotherapies, the prevalence of resistant HTN is expected to increase in coming decades due to the aging of the population together with an increased burden of cardiovascular disease and obesity/metabolic syndrome.

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If left untreated, long-term HTN contributes to end-organ damage and mortality. The medical and social burdens of inadequately treated HTN have stimulated investigation of additional therapeutic options in patients with resistant HTN. Compensatory changes in sympathetic nervous system function are an important component of heart failure and primary HTN.

Decreased parasympathetic and increased sympathetic tone increase peripheral vascular resistance, reduce renal blood flow, and increase sodium retention, while impairing glucose handling and contributing to adverse cardiac and vascular remodeling (4). A new surgically implantable device for the treatment of resistant HTN (Rheos System, CVRx, Inc., Minneapolis, Minnesota) has been developed to administer baroreflex activation therapy (BAT) via electrical stimulation of the carotid baroreceptors. BAT modulates sympathovagal balance that is commonly deranged in patients with HTN as evidenced by recent findings that show BAT acutely reduced muscle sympathetic nerve activity (5) and increased parasympathetic activity (6). The current article presents results from the Rheos Pivotal Trial, a randomized, double-blind, placebo-controlled study in patients with resistant HTN.

Methods

Study design. The Rheos Pivotal Trial (NCT00442286) was a randomized, double-blind, parallel-design clinical trial designed to assess the efficacy and safety of the Rheos System in patients with resistant HTN as shown in Figure 1. The trial was approved by the Food and Drug Administration under an investigational device exemption. The institutional review board or ethics committee at each participating institution approved the protocol prior to the start of the trial, and all subjects provided written informed consent prior to any protocol-required procedures being conducted.

Patient population. The main enrollment criterion was resistant HTN defined as at least 1 outpatient, in-office, systolic blood pressure (SBP) ≥160 mm Hg with diastolic BP ≥80 mm Hg taken per protocol utilizing a standardized device described later in the text. This measurement was obtained following at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic. An ambulatory SBP ≥135 mm Hg for a 24-h average, obtained via a standardized protocol and assessed at a core laboratory, and an absence of clinically significant orthostatic BP changes were additional enrollment criteria. Forty-nine centers consented 590 subjects for screening between March 2007 and November 2009. The status of all subjects who consented to participate in the trial is shown in Figure 2. To account for an anticipated learning curve with the Rheos System implantation procedure, each enrollment center was allowed to implant up to 2 nonrandomized (open-label) subjects prior to enrolling subjects in the randomized portion of the trial. The main reasons for ineligibility were due to office SBP or 24-h ambulatory SBP below inclusion criteria, the presence of carotid stenosis, or the subject being an inappropriate surgical candidate as assessed by the vascular surgeon investigator. Of the 326 subjects eligible for implantation, 4 did not exhibit an acute testing response during surgery and, ultimately, were not implanted with the device. Two additional implanted subjects that should have been randomized had the device explanted prior to the randomization visit due to infection and thus were never randomized. A total of 265 subjects were randomized 2:1, 181 to Group A (immediate BAT) and 84 to Group B (BAT deferred until after Month 6). Three subjects (2 in Group A, 1 in Group B) met the emergency unblinding criteria of hypertensive emergency with confirmed diastolic BP of 120 mm Hg or greater with evidence of accelerated symptoms of end-organ damage and had their treatment assignment revealed prior to the 6-month visit.

Procedures. All eligible subjects were implanted with the Rheos System (CVRx) by a vascular, cardiothoracic, or neurosurgeon as previously described (7). The device consisted of a pulse generator and leads that were separately

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**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BAT</td>
<td>baroreflex activation therapy</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>DMC</td>
<td>data monitoring committee</td>
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<tr>
<td>HTN</td>
<td>hypertension</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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**Figure 1** Trial Schematic Showing the Visit Intervals During the 12-Month Blinded Follow-Up Period

Subjects were randomized 2:1 to Group A (device on) versus Group B (device off) during the first 6-month period.
tunneled subcutaneously to attach to each carotid sinus. Figure 3 provides an illustration of the implant site of the electrode and device. Once the device was activated 1 month post-implant, stimulation parameters were adjusted according to a protocol-defined algorithm to provide a gradual increase in baroreflex activation such that optimal therapy, including the option of bilateral or unilateral stimulation, was being provided by the fifth month after device activation. BAT was individually titrated within a protocol-defined set of parameters, and best practices were shared across centers. Subjects and investigators remained blinded to treatment until after the 12-month visit.

Field clinical engineers from the sponsor worked under the supervision of principal investigators and research coordinators to ensure that the device was programmed optimally for all patients in the study. These processes were done after best-practice methods had been determined from earlier clinical trials. All of this was done in an effort to minimize any intercenter differences in programming.

Out-patient office BP was assessed using a standardized, automated device (BpTRU, VSM Medtech Ltd., Vancouver, Canada) that was programmed to take 6 measurements at 1-min intervals and report the average of the last 5 of these measurements, which were taken with the investigator not in the room. In clinical testing, this method minimizes the “white coat” effect, and the results of these measurements compare well to daytime ambulatory BP (8). Blood pressure assessments were taken at a consistent time of day and within 4 to 6 h of the most recent dose of antihypertensive medication(s). As part of ongoing subject medical management, investigators were not prevented from changing antihypertensive medications during the course of the trial. All adverse events were reviewed and submitted for adjudication to an independent adverse events committee. Serious adverse events included death, life-threatening events, hospitalization or prolongation of a hospitalization, permanent functional or structural damage, or other medical events.

Endpoints. The Rheos Pivotal Trial was designed to demonstrate the efficacy and safety of the Rheos device via 5 pre-specified coprimary endpoints, 2 for efficacy and 3 for safety, as follows: 1) acute efficacy; 2) sustained efficacy; 3) procedural safety; 4) BAT safety; and 5) device safety.

The trial also had prespecified secondary endpoints for mean change in office SBP and a comparison of immediate versus deferred (delayed) BAT. The details of the primary and secondary endpoint analyses are given in the Statistical Analysis section that follows.

Statistical analysis. Per trial design assumptions, sample size was calculated to adequately power all coprimary endpoints. The sustained efficacy response endpoint re-
quired the largest total sample based on assumptions of 65% responders at Month 6 in Group A, yielding a needed sample size of 148 in Group A to attain 90% power to detect a sustained response at Month 12 of 80% with a 15% noninferiority margin. With this total sample size (148 in Group A and 74 in Group B to accommodate the 2:1 randomization), all other primary and secondary endpoints had at least 90% power. Prespecified analyses were performed according to a pre-established statistical analysis plan. Interim statistical analyses were performed at 6-month intervals for the data monitoring committee, which reviewed the results blinded to treatment group. After all subjects had been enrolled and implanted, and at a point when 95 subjects had not yet completed the 6-month visit, the DMC advised the sponsor that the trial was unlikely to attain significance for the acute efficacy analysis. The DMC recommended that all subjects be allowed to complete the 6-month visit in a blinded fashion.

Comparisons among randomized groups of clinical baseline and demographic data were performed with t tests for continuous variables and chi-square tests for categorical variables. Comparisons within patients were made with paired-sample t tests. Statistical analysis was performed parametrically and 2-sided using SAS version 9.2 statistical software (SAS Institute, Cary, North Carolina). An alpha level of 0.05 was used to denote statistical significance. Data are presented as mean ± SD of the mean unless otherwise noted.

**Primary endpoints.** The components of the primary endpoint included acute and sustained efficacy as well as procedural, BAT, and device safety. Since all coprimary endpoints had to be met in order to demonstrate overall efficacy and safety, no adjustment to the significance level was required to account for multiple tests of hypotheses. Efficacy analyses were conducted according to the principles of intention to treat, with unblinded and withdrawn subjects treated as failures. Only BP assessments made utilizing the BpTRU device per protocol and within the protocol-specified visit window were used. Change in BP was calculated using the average of the 5 measurements from the BpTRU device at each visit and Month 0 defined as the BP obtained at the randomization visit 1-month post-implant. Safety analyses were conducted using the assessment of the independent adverse events committee. All subjects in the randomized portion of the trial were included in the safety evaluation. For all safety evaluations, subjects were censored at the date of last known endpoint status.

**ACUTE EFFICACY.** Compare Group A versus Group B via a double-blind, randomized, parallel-group, super-superiority design for proportion of subjects that achieve at least a 10 mm Hg drop in SBP at Month 6 compared with Month 0, with a superiority margin of 20%.

**SUSTAINED EFFICACY.** Compare the sustained response in SBP Month 12 in Group A responders at Month 6 to an objective performance criterion of 65%. A sustained response to therapy required the reduction from Month 0 to Month 12 to be at least 10 mm Hg and to remain at least 50% of that seen at Month 6. For example, if a responder had a drop of 50 mm Hg from Month 0 to Month 6, then the reduction from Month 0 to Month 12 would have to be at least 25 mm Hg to qualify as a sustained response.

**PROCEDURAL SAFETY.** Compare the serious procedure- or system-related adverse event–free rate for events occurring within 30 days of implant to a pre-specified objective performance criterion of 82% based on historical literature on implantable cardioverter-defibrillators and pacemakers.

**BAT SAFETY.** Compare Group A versus Group B therapy-related adverse event–free rates via a double-blind, randomized, parallel-group, noninferiority design for therapy-related serious adverse events occurring between 30 days post-implant and the Month 6 visit. The noninferiority margin was 15%. Therapy-related adverse events included events attributable to therapy to treat resistant hypertension, including but not limited to serious adverse drug reactions, hypotension, bradycardia, hypertensive crisis requiring hospitalization, and extraneous stimulation.

**DEVICE SAFETY.** Compare the event-free rate for all major hypertension-related and serious device-related adverse events occurring between 30 days post-implant and the Month 12 visit, to a pre-specified objective performance criterion of 72% based on similar implantable devices such as defibrillators and resynchronization devices. Hypertension-related adverse events include fatal and nonfatal myocardial infarction (at least 2 of 3 standard criteria: typical chest pain, electrocardiogram changes, elevation of myocardial enzymes by more than 2-fold the upper normal limits), heart failure requiring hospitalization (at least 2 major or 1 major plus 2 minor Framingham criteria), fatal and nonfatal stroke (rapid onset of localized neurological deficit lasting ≥ 24 hours with computed tomography evidence), and renal failure requiring dialysis.

**Secondary endpoints. MEAN CHANGE IN SBP.** Compare Group A versus Group B via a double-blind, randomized, parallel-group, superiority design for mean change in SBP at Month 6 compared with Month 0.

**IMMEDIATE VERSUS DEFERRED BAT.** Compare Group A versus Group B via a randomized, blinded, parallel-group, noninferiority design for mean change in SBP at Month 12 compared with Month 0. Group A will have had therapy for 12 months whereas Group B will have had therapy for 6 months. The noninferiority margin was 7.5 mm Hg.

**Results**

**Patient cohort.** The 2 randomized groups were well matched for clinical baseline and demographic characteristics as shown in Table 1. Antihypertensive medications averaged 5.2 ± 1.7. Over 90% of patients were on a diuretic, and 27% of subjects were on a drug regimen that included...
A summary of the results from the 5 coprimary endpoints is presented in Table 2, and the details are discussed below in terms of efficacy and safety.

**Acute Efficacy.** The responder analysis at 6 months yielded 54% responders in Group A and 46% responders in Group B, which did not represent a significant difference with the 20% superiority margin (p = 0.97).

**Sustained Efficacy.** The sustained responder analysis yielded 88% of responders at 6 months, maintaining that response at 12 months per the protocol definition (p < 0.001).

**Secondary endpoints. Mean change in SBP.** Mean decrease in SBP at 6 months from Month 0 was 16 ± 29 mm Hg for Group A and 9 ± 29 mm Hg for Group B (p = 0.08).

**Immediate versus deferred BAT.** Mean decrease in SBP at 12 months from Month 0, at which point Group A had received 12 months of BAT and Group B had received 6 months of BAT, was 25 ± 32 mm Hg for Group A and 25 ± 31 mm Hg for Group B.

**Additional efficacy analyses.** An ancillary analysis was percentage of subjects attaining SBP ≤ 140 mm Hg at 6 and 12 months as shown in Figure 4. A significant difference is observed between the 2 groups at 6 months (p = 0.005), and no difference is observed at 12 months (p = 0.70) when both groups have received BAT for at least 6 months.

A post hoc analysis utilizing change from pre-implant rather than from Month 0 was performed due to the unexpected differences between the pre-implant and Month 0 SBP values and allows for more direct comparison to drug therapies and other therapies. Changes at 6 and 12 months from pre-implant are shown in Figure 5 and yielded a decrease in SBP of 26 ± 30 mm Hg for Group A and 17 ± 29 mm Hg for Group B (p = 0.03) at 6 months and a decrease of 35 ± 28 mm Hg for Group A and 33 ± 30 mm Hg for Group B (p = 0.57) at 12 months. At 12 months, the SBP of 81% of subjects had dropped at least 10 mm Hg from pre-implant. This responder group experienced an average SBP drop of 44 mm Hg, and 63% of these subjects reached SBP of ≤ 140 mm Hg.

### Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Race</th>
<th>Body mass index, kg/m²</th>
<th>Heart rate, beats/min</th>
<th>BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
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</tbody>
</table>

Values are absolute n (%) or mean ± SD. No significant differences were detected between the 2 groups.

ACE = angiotensin-converting enzyme; BP = blood pressure; CAD = coronary artery disease.

### Table 2 Summary of Coprimary Endpoints

<table>
<thead>
<tr>
<th>Endpoint Design</th>
<th>Timing</th>
<th>Type</th>
<th>Endpoint Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy endpoints</td>
<td>6 months</td>
<td>Super-superiority</td>
<td>[\alpha &gt; \alpha_g + 20%]</td>
</tr>
<tr>
<td>Sustained responder</td>
<td>12 months</td>
<td>OPC</td>
<td>[\alpha_{12\text{ Month}} \leq 65%]</td>
</tr>
<tr>
<td>Safety endpoints</td>
<td>30 days</td>
<td>OPC</td>
<td>[\alpha_{30\text{ days}} \leq 82%]</td>
</tr>
<tr>
<td>BAT</td>
<td>6 months</td>
<td>Noninferiority</td>
<td>[\alpha &gt; \alpha_g - 15%]</td>
</tr>
<tr>
<td>Device</td>
<td>12 months</td>
<td>OPC</td>
<td>[\alpha_{12\text{ Month}} &gt; 72%]</td>
</tr>
</tbody>
</table>

BAT = baroreflex activation therapy; CB = confidence bound; OPC = objective performance criterion.
Adverse events. GENERAL. There were a total of 7 deaths (4 occurring during the initial 12 months of follow-up and an additional 3 during long-term follow-up), of which none were related to either the procedure or the device. The causes of death were mainly due to the normal sequelae of long-term hypertension: 3 intracerebral hemorrhages; 2 cardiopulmonary arrests; 1 ruptured abdominal aortic aneurysm; and 1 drug overdose.

Primary safety endpoints. The results of the coprimary endpoints are summarized in Table 2, and the most common adverse events that occurred for each endpoint during the trial are shown in Table 3.
Table 3  Summary of Adverse Events

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural</td>
<td>68</td>
<td>25.5%</td>
</tr>
<tr>
<td>Surgical complication</td>
<td>13</td>
<td>4.8%</td>
</tr>
<tr>
<td>Nerve injury with residual deficit</td>
<td>13</td>
<td>4.8%</td>
</tr>
<tr>
<td>Transient nerve injury</td>
<td>12</td>
<td>4.4%</td>
</tr>
<tr>
<td>Respiratory complication</td>
<td>7</td>
<td>2.6%</td>
</tr>
<tr>
<td>Wound complication</td>
<td>7</td>
<td>2.6%</td>
</tr>
<tr>
<td>BAT</td>
<td>33</td>
<td>12.8%</td>
</tr>
<tr>
<td>Hypertensive crisis (Group A)</td>
<td>9</td>
<td>5.0%</td>
</tr>
<tr>
<td>Hypertensive crisis (Group B)</td>
<td>7</td>
<td>8.3%</td>
</tr>
<tr>
<td>Device</td>
<td>34</td>
<td>12.8%</td>
</tr>
<tr>
<td>Hypertension-related stroke</td>
<td>6</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Values are n (%).

**Procedural Safety.** Procedure safety yielded an event-free rate of 74.8% with a 95% 1-sided lower confidence interval bound of 70.5%, which is less than the pre-specified objective performance criterion of 82% ($p = 1.00$). The majority of these events are related to the carotid sinus lead placement and involved transient (4.4%) or permanent nerve injury (4.8% with some residual effect) that occurred at the time of implant. Additionally, there were 4.8% of subjects with a general surgical complication and 2.6% with either a respiratory complaint or a wound complication following implant. All other events occurred at a rate of less than 2%. The majority (76%) of procedure-related adverse events resolved completely. There were no procedure-related deaths.

**BAT Safety.** BAT safety yielded a therapy-related event-free rate in Group A of 91.7% and in Group B of 89.3% ($p < 0.001$). The only event occurring at a rate of greater than 2% in either group was for hypertensive emergency, with 40% reduction in rate of hypertensive events in Group A.

**Device Safety.** Device safety yielded an event-free rate of 87.2% with a 95% 1-sided lower confidence interval bound of 83.8%, which exceeded the pre-specified objective performance criterion of 72% ($p < 0.001$). The only event occurring at a rate of greater than 2% was for hypertension-related stroke at 2.3%.

**Discussion**

The Rheos Pivotal Trial was the first large-scale, double-blind, randomized, placebo-controlled device trial in patients with resistant HTN. The trial did not meet 2 of the 5 pre-specified coprimary endpoints in the short-term safety and the short-term efficacy analyses. In addition, the pre-specified coprimary endpoint for sustained efficacy as designed may not provide the best evidence for the long-term efficacy of BAT. However, as compared with pre-implant values, mean reductions in SBP of up to 35 mm Hg were observed at the Month 12 time point in all subjects participating in the trial. Additionally, over 50% of subjects were able to achieve a SBP of $\leq 140$ mm Hg with BAT. The observation that during the initial 6 months of the trial, the subjects receiving BAT experienced a 40% reduction in rate of serious adverse events for hypertensive urgency highlights an important aspect to the potential utility profile of BAT.

The SBP reductions observed with BAT in this trial are comparable to the results of the DEBuT (Device Based Therapy) feasibility study in which SBP was reduced from 180 mm Hg by 30 mm Hg after 12 months of BAT in 26 subjects (9). In addition, it is important to note that the reductions observed within this study following 6 months of treatment with BAT are comparable across the 2 randomized groups and the 45 subjects from the open-label arm (10), with reductions of 26, 33, and 33 mm Hg from pre-implant for Group A, Group B, and open-label, respectively. This magnitude of SBP reduction has the potential to significantly reduce the impact of cardiovascular disease. A recent meta-analysis concluded that a 30 mm Hg drop in SBP among hypertensive patients results in 60% to 75% reduction in the incidence of stroke and a 50% to 60% reduction in the incidence of myocardial infarction and sudden cardiac death (11). Likewise, the proportion of patients achieving SBP $\leq 140$ mm Hg was 42%, 51%, and 53% in Group A, Group B, and open-label (10), respectively, after 6 months of BAT. Considering the average pre-implant SBP of this cohort and the intensive medical therapy applied throughout the trial, the rate of reaching SBP $\leq 140$ mm Hg is noteworthy and of greater clinical significance than an arbitrarily defined reduction in SBP.

The results of 2 other trials of similar patient populations with resistant HTN have recently been published, providing some perspective for BAT-related SBP reduction (12,13). Six months following renal denervation, 46 patients showed a reduction of $32 \pm 23$ mm Hg (baseline SBP: 178 mm Hg on 5.2 medications) with 39% reaching a SBP $\leq 140$ mm Hg (12). After 14 weeks of treatment with an endothelin type A–selective receptor antagonist, 364 patients showed a reduction of $15 \pm 14$ mm Hg (baseline SBP: 151 mm Hg with 36% of patients on $\geq 4$ medications) with 48% reaching goal SBP (13).

Although the implant procedure safety did not meet the pre-specified 82% event-free objective performance criterion based on historic implant safety of implantable cardioverter-defibrillators, the adverse event profile compares favorably with results from endarterectomy trials, which are more like the dissection for the Rheos procedure in the carotid region. For example, the North American Symptomatic Carotid Endarterectomy trial reported 8.6% cranial nerve injury and 9.3% wound complications for unilateral procedures (14). A recent literature review reports rates of cranial nerve injuries in 10 carotid endarterectomy trials published since 2000 to be in the range of 2.2% to 59% (15). It is not surprising that nerve injury was the main contributor to the event rate as the carotid sinus region is richly innervated. Residual effects were generally modest,
including localized numbness, dysphonia, and dysphagia. It is interesting to note that, when optimized, the majority of subjects (~75%) were programmed to a unilateral pathway. This suggests that the complexity and duration of the implant procedure could be reduced by performing unilateral implants, thereby reducing the likelihood of nerve injury and other procedure-related safety issues.

The experimental design required assumptions that could not be verified a priori due to the novelty of the device and the patient population being studied. For example, the trial assumed a standard deviation of 15 mm Hg in the reduction of SBP from Month 0 to Month 6, whereas the observed standard deviation of the difference exceeded 27 mm Hg. In addition, the reduction in SBP in Group B was larger than anticipated during the first 6 months of the trial. The high variability and reduction in Group B could be explained by several factors. Although the BpTRU device was used with an averaging technique shown to correlate with ambulatory BP (8), BP readings were taken 4 to 6 h post-medication rather than at trough, and the protocol contained no restrictions on dosing of or changes to antihypertensive medication. In addition, the trial design did not have a run-in period during screening to allow for several qualifying BP measurements to be made on separate days, which might have helped to reduce variability and lessen the false-positive rate. Finally, the dichotomized responder analysis in which SBP was measured only once at 2 instances of time was particularly vulnerable to excess variability with the change measured from Month 0 (1 month post-implant), a point at which each subject was at a different stage of recovery. Because the design could not take into account the full range of confounding factors associated with excess variability, Hawthorne effect, and placebo effect, further clarification of these issues is not possible.

**Perspectives.** BAT was evaluated in a large, diverse, heterogeneous sample of patients with resistant HTN. Clinically significant and sustained SBP reductions were observed, and the BAT and device adverse event-free rates exceeded pre-specified objective performance criteria, thereby providing additional evidence for safety and efficacy of BAT. BAT reduced SBP despite intensive ongoing medical therapy. At enrollment, subjects were taking more than 5 medications on average. The spectrum of medical therapies included the full range of standard-of-care drugs with an emphasis on calcium channel blockers, renin-angiotensin system inhibitors, and diuretic therapy. Ninety-one percent of subjects were on beta-blockers and/or sympatholytic agents. Device programming was titratable and programmable by time of day, which is particularly advantageous in the context of offering a chronotherapeutic approach to hypertension management. Ultimately, BAT allowed a large percentage of difficult-to-treat patients to achieve SBP ≤140 mm Hg. Shortcomings of the trial design precluded 2 of the 5 pre-specified primary endpoints from attaining statistical significance.

Future clinical trials will address the limitations of this study and further define the therapeutic benefit of BAT. New technology for delivering BAT that involves a less invasive implant procedure has been developed by CVRx and is currently undergoing confirmatory study in Europe.

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**REFERENCES**


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