Device Based Therapies for the Treatment of Resistant Hypertension: Baroreflex Stimulation

John D. Bisognano, MD PhD
Professor of Medicine / Cardiology
Director, ASH Comprehensive Hypertension Center
University of Rochester Medical Center
Rochester, New York
Baroreflex Activation Therapy (BAT)
The CVRx Rheos® System
CVRx Programmable Barostim Platform

Designed to *electronically activate* baroreceptors which signal the brain to orchestrate a multi-systemic response to address chronic, progressive diseases: hypertension, heart failure, arrhythmia…

**Autonomic Nervous System**
Reduce **Sympathetic** Activity
Enhance **Parasympathetic** Activity

- **HEART**: rate slows, to allow more time for heart to fill with blood, and reduce workload and energy demand
- **ARTERIES**: relax, making it easier for blood to flow through the body and reducing cardiac exertion
- **KIDNEYS**: reduce fluid in the body, lowering excessive blood pressure and workload on the heart
Ability to titrate device to meet individual patient need

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Volt</th>
<th>2 Volts</th>
<th>3 Volts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate bpm</td>
<td>71</td>
<td>56</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Blood Pressure mmHg</td>
<td>210 / 96</td>
<td>168 / 73</td>
<td>156 / 72</td>
<td>144 / 66</td>
</tr>
</tbody>
</table>

≈ 4 min
Rheos Hypertension Pivotal Trial Design

- **Trial Hypothesis:** Baroreflex Activation Therapy is Safe and Effective for the Treatment of Resistant Hypertension

- Prospective randomized double-blind trial
  - 322 subjects at 49 sites
  - 55 roll-in subjects / 265 randomized (2:1)

- Co-primary endpoints
  1. Short Term Acute Response
  2. Long Term Sustained Response
  3. Short Term Procedural Adverse Events
  4. Short Term Hypertension Therapy Adverse Events
  5. Long Term Device Adverse Events

<table>
<thead>
<tr>
<th>Implant N = 181</th>
<th>Randomization</th>
<th>6-Month Blinded Evaluation Period</th>
<th>6-Month Blinded Evaluation Period</th>
<th>Long-Term Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>Group A – Device ON</td>
<td>Group A – Device ON</td>
<td>Group A – Device ON</td>
<td>(months)</td>
</tr>
<tr>
<td>0</td>
<td>Group B – Device OFF</td>
<td>Group B – Device ON</td>
<td>Group B – Device ON</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>N = 84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key Inclusion Criteria

- Systolic Blood Pressure ≥ 160 mmHg
- Diastolic Blood Pressure ≥ 80 mmHg
- 24-hour Average Ambulatory Blood Pressure ≥ 135 mmHg
- At least one month of maximally tolerated therapy with at least three appropriate antihypertensive medications, including a diuretic
## Endpoint Summary

<table>
<thead>
<tr>
<th>Description</th>
<th>Timeframe</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Term Acute Efficacy</td>
<td>6 months</td>
<td>265</td>
<td>0.97</td>
</tr>
<tr>
<td>Long Term Sustained Efficacy</td>
<td>12 months</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Short Term Procedure Adverse Events</td>
<td>30 days</td>
<td>265</td>
<td>1.00</td>
</tr>
<tr>
<td>Short Term BAT Adverse Events</td>
<td>6 months</td>
<td>265</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long Term Device Adverse Events</td>
<td>12 months</td>
<td>265</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pre Specified Endpoint Analysis

% of Subjects at SBP ≤ 140 mmHg; Pre-implant SBP 176-179 mm Hg

- Month-6: Group A ON = 172, Group B OFF = 80; 42% vs 24%
  \( p = 0.005 \)

- Month-12: Group A ON = 171, Group B ON = 81; 53% vs 51%
  \( p = 0.70 \)
Barostim Pivotal Trial LV Remodeling

Rheos Study Demonstrated Left Ventricular Reverse Remodeling with BAT

- 60 Patients from Rheos study enrolled in echocardiography sub-study

- Study assessed changes in left ventricular mass index (LVMI) after 12 months of active therapy

- LVMI reduction is a strong indicator of effective heart failure therapy

- At 12 months of BAT, average reduction of LVMI was 15 g/m² (p < 0.01) to normal range

![Graph showing left ventricular mass index (LVMI) at baseline and 12 months](image)
Conclusions

• 3 primary endpoints achieved: long term efficacy, long term device safety, and short term therapy safety

• 2 primary endpoints not achieved: short term efficacy and procedure adverse events

• Weight of overall evidence suggests long term efficacy of BAT to reduce blood pressure in resistant hypertension

• These data justify further development of BAT
Statistical Separation at 12 months with Preservation of Circadian Rhythm

N=111 Paired
Minimally-Invasive System for Baroreflex Activation Therapy Chronically Reduces Blood Pressure: Initial Results From the Barostim neo™ Trial

Mathias-Christoph Brandt¹, Rolf Wachter², Joachim Beige³, Hermann Haller⁴, Uta Hoppe¹, Eric Lovett⁵, Jill Schafer⁶ Abraham Kroon⁷

¹Paracelsus Medical University Salzburg, Salzburg Austria; ²University of Gottingen, Gottingen, Germany; ³University of Leipzig, Leipzig, Germany; ⁴Medizinische Hochschule Hannover, Hannover, Germany; ⁵CVRx, Inc, Minneapolis, MN; ⁶Integra Group, Minneapolis, MN; ⁷University Hospital Maastricht and Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands

CAUTION: The Rheos® System is an investigational device and is limited by Federal (or United States) law to investigational use.
Note: The Barostim neo™ is CE Mark approved, but is not yet available in the US
2nd Generation Platform

1st Generation

2nd Generation
Programmable Barostim neo Platform

Designed to electronically activate baroreceptors which signal the brain to orchestrate a multi-systemic response

The system includes three components:

- **Implantable Pulse Generator (IPG) Device**: Inserted under collar bone and provides control and delivery of activation energy through Carotid Sinus Lead
- **Carotid Sinus Lead**: One thin lead wire placed at either Carotid Artery and connected to the IPG conducts activation energy from the Barostim neo device to the baroreceptors
- **Programmer System**: External device used to program and adjust the therapy non-invasively

The system is minimally invasive and highly adaptable:

- Single-side incision
- Wirelessly monitored and controlled at physician’s office
- Therapy can be adjusted to meet each patient’s individual needs as they change over time, providing personalized treatment and avoiding issues of non-compliance
XR-1 Verification Trial in Hypertension

- Excluding first 2 implants/site, implant time = 1:37 ± 0:29
- Rheos implant time ~3 hrs (mapping time ~1.25 hours)

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<tr>
<th>Variable</th>
<th>N</th>
<th>Mean ± SD or N (%)</th>
</tr>
</thead>
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<tr>
<td>Procedure Time (hours)</td>
<td>30</td>
<td>1:47 ± 0:28</td>
</tr>
<tr>
<td>Mapping Time (hours)</td>
<td>30</td>
<td>0:44 ± 0:28</td>
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Procedure Details

- Excluding first 2 implants at sites, implant time averaged 1:37 ± 0:29
- Rheos average implant time about 3 hours, with average mapping about 1.25 hours

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Barostim $neo^TM$ vs. Rheos Efficacy

Change in Systolic BP (mmHg)

-26

Barostim $neo$ System

Unilateral

Rheos System

Bilateral

3 Months BAT

6 Months BAT

Source: CVRx Data File
Barostim: neo™ Demonstrates Equivalent Efficacy

Unilateral Barostim neo™ Efficacy Results

<table>
<thead>
<tr>
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<th>Systolic</th>
<th>Diastolic</th>
<th>Heart Rate</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>172 ± 20 mmHg</td>
<td>100 ± 14 mmHg</td>
<td>75 ± 14 bpm</td>
</tr>
<tr>
<td>Change in BP &amp; HR (mmHg &amp; bpm)</td>
<td>[Diagram showing changes]</td>
<td>[Diagram showing changes]</td>
<td>[Diagram showing changes]</td>
</tr>
</tbody>
</table>

- Systolic: [Diagram showing changes]
  - Month 3: *
  - Month 6: *
- Diastolic: [Diagram showing changes]
  - Month 3: *
  - Month 6: *
- Heart Rate: [Diagram showing changes]

N = 30

p-value < .001

Procedural Improvements

- Single electrode (vs. two multi-pronged electrodes)
- Patient positioning
- Shorter procedure time and hospital stay (1 hour and 1 day vs. 3 hours and 2 days)
- Substantially improved safety profile

Product Improvements

- Significantly smaller lead design
- Longer battery life
- Lower cost of goods
Baseline BP, HR by History (Hx) of Renal Nerve Ablation (RNA)

Baseline BP or HR (mmHg or bpm)

- Hx RNA (N=6)
- No Hx RNA (N=24)

SBP

DBP

HR

*
Response at 6 mo by History (Hx) of Renal Nerve Ablation (RNA)

Change in BP or HR (mmHg or bpm)

-35
-30
-25
-20
-15
-10
-5
0
SBP DBP HR

Hx RNA (N=6)
No Hx RNA (N=24)
Conclusions

Barostim *neo*™ system

- Maintains the anti-hypertensive efficacy of its predecessor
  - 26 mm Hg reduction in systolic BP at 6 months
  - SBP reduction consistent with Rheos, which has demonstrated long-term sustained benefit

- Simplifies implant procedure

- Greatly improves safety profile
  - 90% subjects free from 30d event
  - 97% subjects free from long-term events

- Provides viable treatment option for patients in whom prior renal nerve ablation failed to control blood pressure
Ability to show results specific to device activations
Ability to show results specific to device activations