New Horizons

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Ablative Solutions, Inc.

   Founder, Co-Inventor, Stockholder, CEO

Abbott Vascular:

   Advisory Board Member, Grant Support

Boston Scientific:

   Grant Support
Post Symplicity HTN-3 Analysis Reveals Design Flaws and “Inadequate Denervation”*

**Conclusions from Report**

- Renal denervation will work if sufficient ablation/denervation is performed
  - 50% of patients did not receive the minimum of least 8 total ablations
- Adequate treatments (9-10 burns/artery) with RF requires vessel length of at least 4 -5 cm

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**Ablation number linked to ambulatory blood pressure fall**

**Number of renal-denervation ablations performed**

- N = 149 155 138 146 119 125 88 93 56 61 40 44 24 26 16 8 10

**Change in ambulatory systolic BP**

- Denervation
- Sham

**Note:** The SYMPPLICITY HTN-3 trial involved 535 patients with resistant hypertension.

**Source:** Dr. Kandzari

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* Cardiology news: **Renal denervation proceeds as U.S. trial’s flaws emerge**, Jun 23, 2014
Targeted (Adventitial) Chemical Neurolysis

PeriVascular Renal Denervation (PVRD™)

**Unique Mechanism**
- Renal nerves
- Micro-needles

**PVRD: Distinctive Features**
1. Controlled *perivascular* targeting to access deep nerve locations
2. Efficient, *simultaneous* delivery of neurolytic agent via micro-needles
3. Circumferential, axial, deep coverage achieved with single injection
4. Self-limited spread; adventitial space
5. No obstruction of blood flow
7. Essentially painless
8. No capital equipment
Chemical Neurolysis

- Inactivation of the neural structures by chemical agents

Use of Alcohol (dehydrated ethanol)

- The most common neurolytic agent
- FDA Grandfathered: “therapeutic neurolysis”

Multiple Mechanisms of Action

- Dehydration of target tissue
- Denaturation of target proteins
- Extraction of cellular lipids

Effects on Nerves

- Irreversible neuronal axon membrane damage
- Destruction of perineural sheath (“neurotmesis”)
Alcohol acts locally ⇒ no collateral damage

1. Micro volume (0.3-0.6 mL) directed to the perivascular space
2. Alcohol bio-activity reduced via dilution by extracellular fluid: self-limited spread
Designed For The Outpatient Cath Lab Setting

Performed under standard PCI sedation protocols

‘PCI like’ procedural time

No capital equipment
Lateral View
Angiographic and Neuro-Chemical
90-Day Follow-Up After EtOH (0.3 ml) PVRD

**Angiography**

**Neurochemistry***

<table>
<thead>
<tr>
<th>Pre-Rx</th>
<th>Rx</th>
<th>90-Day Post-Rx</th>
</tr>
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</table>

**Mean (SD) Renal Tissue Norepinephrine (ng/g)**

- **Control**: 10 animals
- **Rx**: 1 kidney, 6 measurements

*Control = 10 animals
*Rx = 1 kidney, 6 measurements
Alcohol-Mediated Renal Nerve Injury at 4 Weeks
Composite Surrogate Efficacy – 4 Independent Markers*

Observations
Excellent dose response across numerous surrogate markers of nerve damage

*Fischell, et al.; In Preparation
**Chemical Denervation Using Ethanol (EtOH) Depth + Circumferential Treatment -> Greater Denervation**

**Conclusion:** PVRD coverage is ~3-4 times the area covered by RF treatment

PVRD offers inherent Rx efficacy advantages over RF-based treatments

**Diagram:**
- **Human Artery Nerve Distribution**
  - RF
  - PVRD

<table>
<thead>
<tr>
<th>Number of Nerves</th>
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<tbody>
<tr>
<td>800</td>
</tr>
<tr>
<td>0 to &lt;0.5</td>
</tr>
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</table>

**Net area covered by PVRD = 50-100 mm$$^2$$**

*Virmani, TCT 2012*

**Net area covered by RF = 20-30 mm$$^2$$**

*Fischell et al, EuroIntervention, 2013*
RF (Symplicity) vs. Peregrine Porcine Model at 3 Months

**RF Symplicity Modest Arc and Depth**
Nerve Injury + Medial Necrosis

Ablation CSA – 4.3 mm²

Media Necrotic

Ablation CSA 11.4 mm²

**Alcohol (0.6 ml) Injection Circumferential**
Nerve Injury Without Medial Injury

Ablation CSA – 58.7 mm²

Media Healthy

Ablation CSA – 46.3 mm²

Morphometry performed by Virmani, et al. CV Path
Clinical Strategy
Stepwise Progress to Validate Technology

First-Human-Use Study (Paraguay)
Safety, procedural feasibility
(n= 18)

CE Mark Study (Poland)
Single-arm treatment study
Pre/post arterial imaging
ABPM as criterion
Strict medication compliance
(n= 20)

Two-Arm Pilot Study RCT with Sham Control (US)
(n= 240)

Enrollment Complete

Met all primary endpoints

Favorable outcomes

Enrollment underway (n=5)

Data to be used for CE Mark, US IDE submission
First Human Use

Artery: Pretreatment

Artery: 6 mos Post Treatment

Artery: Post-Treatment

Peregrine Introduction

Guide Tube Engagement

Needle Engagement
Advantage of Peregrine: Treatment of Challenging Anatomy (Short Stem Artery)

Target Artery: Pretreatment

Artery: Short Length (9.8 mm)

Guide Tube Engagement

Artery: 6 mo Post-Treatment

Artery: 10 min Post-Treatment

Needles Injecting
Sustained OBP Lowering Despite Significant Reduction in Medication

### Patient 03

**HTN Medications**
- Baseline: 4
- Month 3: 2
- Month 6: 2

**BP Change (mmHg)**
- **Systolic**
  - Baseline: 204
  - 1 Month: 200
  - 3 Months: 167
  - 6 Months: 147
- **Diastolic**
  - Baseline: 111
  - 1 Month: 101
  - 3 Months: 92
  - 6 Months: 66

### Patient 08

**HTN Medications**
- Baseline: 3
- Month 3: 1
- Month 6: 1

**BP Change (mmHg)**
- **Systolic**
  - Baseline: 160
  - 1 Month: 103
  - 3 Months: 108
  - 6 Months: 112
- **Diastolic**
  - Baseline: 75
  - 1 Month: 75
  - 3 Months: 82
  - 6 Months: 74

SYMPLECTICITY I Trial average BP meds 5.2 (baseline) increased to 5.6 at follow-up
## Primary Endpoint: Procedural Safety

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Procedures</th>
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<tbody>
<tr>
<td>Alcohol Successfully Delivered to the intended Areas</td>
<td>100% (38/38)</td>
</tr>
<tr>
<td>Procedure Completed As Intended</td>
<td>100% (38/38)</td>
</tr>
<tr>
<td>Problems Encountered with the Peregrine Infusion Catheter</td>
<td>0% (0/38)</td>
</tr>
<tr>
<td>Procedural Adverse Events</td>
<td>0% (0/38)</td>
</tr>
<tr>
<td>Device Deficiency</td>
<td>0% (0/38)</td>
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Renal denervation remains a promising and potentially disruptive technology for the treatment of hypertension, CHF and possibly other conditions.

The failure of Symplicity HTN 3 may be primarily related to a failure to consistently and adequately denervate, and not a failure of “renal denervation.”

Chemical renal denervation (PVRD) with very low doses of alcohol is a promising means of creating complete (deep and circumferential) and predictable renal sympathetic denervation, with essentially no anatomical limitations, pain or vessel wall injury.

This technology may prove to have significant advantages over “energy-based” denervation. Further Clinical trials ongoing.
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