Endovascular Therapy in the Management of Hypertension

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- **Consultant/Advisory Board:** Boston Scientific, Medtronic Vascular, W.L. Gore, Philips Medical
- **Intellectual Property/Patents:** WL Gore
- **Research Grants:** The Medicines Company: International PI ENDOMAX Clinical Trial
- **Other:** Endowed Chair Cook Medical
Endovascular Rx for HTN

- Percutaneous Angioplasty and Stenting: Is there still a role?
- Renal Denervation
Disclosures

- Scientific Advisory Boards: Medtronic Vascular, Boston Scientific, St. Jude Medical, WL Gore, Philips Medical
- Steering Committee:
  - SYMPLICITY HTN 3 Trial
  - REDUCE HTN Trial
In 2000, 972 million (26%), of the adult population had hypertension.

By year 2025, 1.56 billion (29%) are projected to have hypertension.

Most of the expected increase will be in economically developing regions.

Despite Hypertension Treatment, Many Patients are Not Controlled

Established Market Economies (EME)

<table>
<thead>
<tr>
<th>Country</th>
<th>Study Year</th>
<th>Age Range</th>
<th>Aware (%)</th>
<th>Treated (%)</th>
<th>Controlled (%)</th>
<th>Controlled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1999-2000</td>
<td>18-80+</td>
<td>69</td>
<td>58</td>
<td>31</td>
<td>53</td>
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<tr>
<td>Canada</td>
<td>1986-1992</td>
<td>18-74</td>
<td>58</td>
<td>39</td>
<td>16</td>
<td>41</td>
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<tr>
<td>Spain</td>
<td>1990</td>
<td>35-64</td>
<td>45</td>
<td>32</td>
<td>5</td>
<td>16</td>
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<tr>
<td>England</td>
<td>1998</td>
<td>16-75</td>
<td>46</td>
<td>32</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Germany</td>
<td>1994-1995</td>
<td>25-74</td>
<td>60</td>
<td>35</td>
<td>12</td>
<td>34</td>
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<tr>
<td>Greece</td>
<td>1997</td>
<td>18-90</td>
<td>61</td>
<td>55</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>China*</td>
<td>2000-2001</td>
<td>35-74</td>
<td>45</td>
<td>28</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Japan</td>
<td>1980</td>
<td>30-74</td>
<td>−</td>
<td>55 (W)</td>
<td>36 (W)</td>
<td>65 (W)</td>
</tr>
</tbody>
</table>

M = men. W = women.

*Based on World Bank criteria used in this study, China was not considered an established market economy at time of publication.

Cardiovascular Mortality Risk Doubles With Each 20/10 mm Hg Increase in BP*

CV = cardiovascular; SBP = systolic blood pressure; DBP = diastolic blood pressure.

*In individuals aged 40 to 69 years (10-year study period), starting at BP 115/75 mm Hg.

Successful Treatment Confers Significant Benefit

Seminal Study on Morbidity in Hypertension

Early Veterans Administration cooperative study demonstrated a **96% reduction in CV events** over 18 months with the use of a triple antihypertensive regimen compared with placebo in patients with severe hypertension ($P<0.001$) (DBP 115 to 129 mm Hg)$^{1,2}$

DBP = diastolic blood pressure.

Central Sympathetic Drive in Hypertension

Sympathetic drive is elevated in multiple types of hypertension

s-MSNA = single-unit efferent sympathetic nerve activity.
LVH = left ventricular hypertrophy.
* $P < 0.05$ Compared with borderline hypertension.
† $P < 0.05$ Compared with white coat hypertension.
‡ $P < 0.05$ Compared with normal pressure.
§ $P < 0.05$ Compared with high-normal pressure.
¶ $P < 0.05$ Compared with essential hypertension–stage 1.
# $P < 0.05$ Compared with essential hypertension–stage 2/3.
Renal Nerves and the Sympathetic Nervous System

Efferent Sympathetics

Sympathetic signals from the CNS modulate the physiology of the kidneys

Afferent Renal Sympathetics

The kidney is a source of central sympathetic activity, sending signals to the CNS

Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia
Ideas and Associations

- Sympathetic nervous system controls blood pressure
- Intimate association between renal nerves and sympathetic nervous system
- What happens when renal nerves are denervated/removed?
Sympathectomy: An Early Surgical Precedent

Dr. Reginald H. Smithwick

Photo of Dr. Smithwick reproduced with permission from JAMA.
Surgical Sympathectomy in Essential Hypertension Provided Beneficial Effect on Survival

However, surgical sympathectomy was associated with significant morbidity.

Symplicity Investigational Catheter Device

- Generator will automatically control RF energy delivery:
  - Power automatically ramped and maintained (5-8W)
  - Continuously monitors temperature and impedance
  - Automatically shuts off after 2 min or when either impedance or temperature exceed program limits
Renal Nerve Anatomy Allows a Catheter-Based Approach

- Standard interventional technique
- 4-6 two-minute treatments per artery
Six Month Post-Procedure Nerve Histology (Porcine Model)

- Nerve from untreated vessel: Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- Nerve from treated vessel: Periarterial nerve bundle has a hypercellular appearance and the perineurium has a thickened and fibrotic appearance.

The Symplicity HTN-1 Trial: Overview

- **Design**
  - Multicenter (19 sites in Europe, Australia, and the United States), non-randomized, open-label, proof-of-concept study

- **Population**
  - 153 patients with treatment-resistant hypertension

- **Treatment**
  - Endovascular catheter-based RDN using the Symplicity Renal Denervation System plus baseline antihypertensive medications

- **Duration**
  - 36 months (assessments at 1, 3, 6, 12, 18, 24, and 36 months)

- **Outcome Measures**
  - Primary efficacy measure: change in office BP
  - Primary safety measures: based on physical examination, basic blood chemistries, and anatomic assessment of renal vasculature

Changes in SBP and diastolic blood pressure (DBP) were significant at all time points; error bars represent 95% CIs.

Symplicity HTN-2 Trial: Overview

- **Design**
  - Multicenter (24 sites in Europe, Australia, and New Zealand), prospective, randomized, controlled study

- **Population**
  - 106 patients with treatment-resistant hypertension

- **Treatment**
  - Intervention group (endovascular catheter-based RDN with the Symplicity® Renal Denervation System™ plus baseline antihypertensive medications)
  - Control group (baseline antihypertensive medications alone)

- **Duration**
  - 6 months (for the primary endpoint) with follow-up to 3 years

- **Outcome Measures**
  - Primary endpoint: between-group changes in average office SBP from baseline to 6 months
  - Secondary endpoints: acute and chronic procedural safety, a composite cardiovascular endpoint, occurrence of ≥10 mm Hg SBP reductions, achievement of target SBP, change in 24-hour ambulatory BP, and change in home BP

Symplicity HTN-2 Trial: Office BP Reduction*

*P<0.005 for changes in SBP and DBP at all time points between Symplicity RDN and control groups; error bars represent 95% CIs.
Symplicity HTN-2 Trial: Chronic Safety

- No change in renal function

<table>
<thead>
<tr>
<th>△ Renal Function (baseline-6M)</th>
<th>Symplicity RDN Group</th>
<th>Control Group</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean eGFR ± SD (mL/min/1.73m²)</td>
<td>0.2 ± 11 (n=49)</td>
<td>0.9 ± 12 (n=51)</td>
<td>-0.7 (-5.4, 3.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean serum creatine ± SD (μmol/L)</td>
<td>0.2 ± 17.6 (n=49)</td>
<td>-1.1 ± 10.3 (n=51)</td>
<td>1.3 (-4.5, 7.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean cystatin-C ± SD (mg/L)</td>
<td>0.1 ± 0.2 (n=37)</td>
<td>0.0 ± 0.1 (n=40)</td>
<td>0.0 (0.0, 0.1)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Symplicity HTN-3: Overview

- **Design**
  - Multicenter (60 sites in the United States), prospective, randomized, blinded, controlled study

- **Population**
  - 530 patients with treatment-resistant hypertension

- **Treatment**
  - Treatment group (endovascular catheter-based RDN with the Symplicity® Renal Denervation System™ plus baseline antihypertensive medications)
  - Control group (sham procedure* plus baseline antihypertensive medications)

- **Primary Outcome Measures**
  - Change in office SBP from baseline to 6 months
  - Safety

*The renal angiogram also acts as the sham procedure for patients in the control group. Data on file, Medtronic.
**Symplicity HTN-3 Trial: Study Design**

- **Initial Screening**
  - Home BP & Med Diary

- **Confirmatory Screening**
  - ABPM

- **Treatment**
  - Renal Angiogram

- **Control**
  - Home BP & Med Confirmation

- **Primary Endpoint**
  - 6M

- **Opportunity for cross over for control arm**

- **Key Points**
  - Patient and Research staff assessing BP are blinded to treatment status
  - No changes in medications for 6M
*Symplicity HTN-3 Trial: Inclusion Criteria*

- Average SBP ≥160mmHg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80 years

*Source: Data on file, Medtronic.*
Symplicity HTN-3 Trial: Antihypertensive Medications

At minimum, 3 antihypertensive medications must meet one or more of the following full dose criteria:

- Highest labeled dose according to medication’s labeling
- Highest usual dose per clinical guidelines (JNC-7)
- Highest tolerated dose
- Highest appropriate dose for the patient per the PI’s best clinical judgment
Symplicity HTN-3 Trial: Exclusion Criteria

- Hemodynamically or anatomically significant renal artery abnormalities or stenosis (>50%) or prior renal artery intervention
- eGFR < 45 mL/min/1.73m² (MDRD formula)
- In-patient hospitalization for HTN Crisis in past year
- 24 hour average ABPM SBP <135mm/Hg
- Type 1 diabetes mellitus
- Symptomatic orthostatic hypotension in past year
- Stenotic valvular heart disease for which ↓BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months
- Planned surgery or CV intervention within the next 6 months
- Known primary pulmonary HTN
- Known pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism
- Known alcohol or drug abuse
Symplicity HTN-3: Summary

- Office SBP ≥160mmHg
- ≥ 3 antihypertensive medications (one must be a diuretic)
- On stable, ≥ 3 full tolerated dose antihypertensive medication regimen for at least 2 weeks
- No significant renal insufficiency (eGFR < 45 mL/min)
- Meets inclusion/exclusion criteria by general medical review
- No known renal artery anatomy exclusion (i.e. dual renal arteries, known RA stenosis >50%)

**Until 6 month primary endpoint:**
- Patients must remain blinded
- No changes in medication unless medically necessary

After 6 mo endpoint, control patients can crossover if still meet all initial criteria
Summary

- Early trial for renal sympathetic denervation have shown great promise
  - Average decrease of SBP 20-30mmHg
- Positive results for Symplicity III should lead to FDA approval for use in United States
- Numerous approaches to sympathetic denervation being developed, and for other applications
Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint

January 9, 2014 6:00 AM CT

MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLECTICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

"SYMPLECTICITY HTN-3 met its primary safety endpoint related to the incidence of major adverse events one month following randomization and renal artery stenosis to six months," said Deepak L. Bhatt, M.D., M.P.H., executive director, Interventional Cardiovascular Programs, Brigham and Women's Hospital Heart and Vascular Center, professor of medicine, Harvard Medical School, and co-principal investigator of SYMPLECTICITY HTN-3. "Importantly, however, the trial did not meet its primary efficacy endpoint."
Multiple Technologies Studied
Significant Blood Pressure Reductions

* Vessix™ is an investigational device and not available for sale in the US.
# Renal Denervation Technologies

<table>
<thead>
<tr>
<th></th>
<th>MDT Symplicity</th>
<th>MDT Spyral</th>
<th>STJ EnligHTN</th>
<th>Covidien OneShot</th>
<th>ReCor Paradise</th>
<th>J&amp;J Renlane</th>
<th>BSC Vessix</th>
<th>Terumo Iberis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheter Design</strong></td>
<td>Catheter; 1 electrode</td>
<td>Pigtail catheter; 4 electrodes</td>
<td>Basket; 4 electrodes</td>
<td>Balloon catheter; helical electrode and cooling</td>
<td>Balloon catheter; internal cooling</td>
<td>Pigtail catheter; 5 electrodes; Irrigation</td>
<td>Balloon catheter; 4-8 electrodes</td>
<td>Catheter; 1 electrode</td>
</tr>
<tr>
<td><strong>Balloon</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Guidewire</strong></td>
<td>No</td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Ultrasound</td>
<td>Monopolar RF</td>
<td>Bipolar RF</td>
<td>Monopolar RF</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>8W</td>
<td>6.5W</td>
<td>8W</td>
<td>25W</td>
<td>~12W</td>
<td>Unknown</td>
<td>~1W</td>
<td>Max 8W</td>
</tr>
<tr>
<td><strong>Energy Delivery Time</strong></td>
<td>2 min.</td>
<td>60 sec</td>
<td>60 sec</td>
<td>2 min.</td>
<td>10 sec.</td>
<td>Unknown</td>
<td>30 sec.</td>
<td></td>
</tr>
<tr>
<td><strong>Total Treatment Time</strong></td>
<td>16 - 24 min.</td>
<td>2 - 4 min.</td>
<td>2 - 4 min.</td>
<td>4 min</td>
<td>~1 min.</td>
<td>Unknown</td>
<td>1 - 2 min.</td>
<td>16 min. minimum</td>
</tr>
</tbody>
</table>

None of these devices are available for sale in the US. *Vessix™ is an investigational device and not available for sale in the US. Medtronic Website, March 2013; Zeller, T. LINC 2014; Covidien (Maya) Presentation; Ormiston et al. EuroInterv. 2013; Worthley, S. EuroPCR 2013; The ReCor Device, Weil, TRENDS Frankfurt 2013; Sievert, Live Case, TRENDS, Frankfurt 2013; LINC 2013, Live Case ReCor; Mahfoud, RHC 2014; Honton, B. EuroInterv. 2014 Apr.

*All cited trademarks are the property of their respective owners. CAUTION: The law restricts these devices to sale by or on the order of a physician. Indications, contraindications, warnings and instructions for use can be found in the product labeling supplied with each device. Information for the use only in countries with applicable health authority product registrations.*
SYMPLICITY HTN-3 (April 2014)
Safety and Efficacy

Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th>Major Event Rate (MAE)</th>
<th>Renal Denervation (N=364)</th>
<th>Sham Procedure (N=171)</th>
<th>Difference [95% CI]</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4% (5/361)</td>
<td>0.6% (1/171)</td>
<td>0.8% [-0.9%, 2.5%]</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Speculations on SYMPLICITY HTN-3
Failed Efficacy Results

Operator Experience

Patient Demographics

Medication Changes or Adherence

Hawthorne Effect

Catheter Design

Trial Design/Conduct

Placebo Effect

Regression to the Mean

Symplicity-HTN 3 Response
Disillusioned Community

U.S. and European heart docs want to put the kibosh on renal denervation devices
April 10, 2014 | By Emily Wasserman

Medical device companies with renal denervation platforms are facing yet another obstacle, as U.S. and European heart doctors are calling for a decrease or halt in the use of the devices to treat high blood pressure.

The physicians’ opinions stem from troubling trial data that was presented at the American College of Cardiology (ACC) annual meeting on March 29, which showed that Medtronic’s (SMDT) Symplicity renal denervation device failed to lower blood pressure more than a sham procedure in a 364-patient study. The company’s renal denervation devices are available in more than 80 countries but are not approved in the U.S.

Dr. Steven Nissen, head of cardiology at the Cleveland Clinic, told Reuters that sales should be suspended for all renal denervation products, not just Medtronic’s device. "You (now) have a trial with no evidence it works," he said.
Renal Denervation in Europe
Pre and Post Symplicity HTN-3 Results

RDN Cases in Europe

Q4 2013

Q1 2014

Q2 2014

Failure to meet primary endpoint announcement 9-January

Primary Endpoint results release 29-March

40% Decline in procedure volume from Q4 to Q1

50% Decline in procedure volume from Q1 to Q2

Boston Scientific Internal Data analysis, 2014.
SJM: EnligHTN
Renal Artery Ablation Catheter

- Multi-electrode catheter
  - 4 radiopaque electrodes, monopolar
- Deflectable tip
- Two basket sizes:
  - 16 mm length; 6 mm expansion
  - 18 mm length; 8 mm expansion
  - Good for arteries 4-8mm
- 8F guide compatible
- Ablation time 90 sec per electrode
Vessix Vascular
V2 Renal Denervation System

- Balloon catheter with Bipolar RF electrodes
- Low pressure (<3 atm)
- 68°C
- Simultaneous energy delivery to all electrodes
- Treatment time 30 seconds
- 1 watt max
- 3-7 mm renal arteries
Vessix™ Renal Denervation System

- Balloon-based technology
  - 4 - 7 mm diameters
- Helical pattern of bipolar RF electrodes
- All electrodes are activated simultaneously
- 30 second treatment time
- Temperature-control algorithm for energy delivery at 68° C
- One button operation
- 7F compatible (Vessix Reduce™ Catheter)

*Vessix™ is an investigational device and not available for sale in the US.*
Vessix™ Renal Denervation System

Custom-Built for Renal Denervation

Precise access
Shapes and atraumatic tip
Designed to facilitate smooth Renal artery access

Optimized torque
Braided shaft for efficient torque response and control

Designed for Vessix Reduce™ Catheter

* Vessix™ is an investigational device and not available for sale in the US.
Vessix™ System bipolar energy delivery illustrated in thermal gel*

Treatment zones visible after bipolar electrode activation in thermal gel*

Consistent lesion size and pattern

*Bench tests results for illustration only.
Vessix™ is an investigational device and not available for sale in the US.
**Vessix™ System Bipolar RF on a Balloon**

Bipolar RF vs. Monopolar

**Bipolar RF**
- Localized energy delivery from positive to negative poles; no grounding pad
- No need for cooling
- Reduced impact of treatment variability
- Low energy of ~1W delivered

**Monopolar RF**
- Energy dispersed through the body; terminates in grounding pad
- Cooled via blood flow and/or irrigation
- Increased impact of treatment variability
- Higher energy required

*Vessix™ is an investigational device and not available for sale in the US.*
Lesion size variability significantly less for Vessix™ vs. Symplicity

Swine model results not necessarily indicative of clinical performance.
Vessix™ is an investigational device and not available for sale in the US.
Renal Denervation with injury depth of 3-4mm

Efficacy comparable to surgical denervation

Swine model results not necessarily indicative of clinical performance.
Vessix™ is an investigational device and not available for sale in the US.
Vessix Preclinical Studies (Swine)
Nerve Morphology at 7 days

**Affected Nerves (7 days)**

- **One treatment per artery**
- **Full artery-length treatment**

<table>
<thead>
<tr>
<th>Susceptible Nerves</th>
<th>Chronic/Reactive</th>
<th>Necrotic</th>
<th>Degenerative</th>
<th>No changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>16%</td>
<td>29%</td>
<td>44%</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>15%</td>
<td>33%</td>
<td>22%</td>
<td>4%</td>
<td>39%</td>
</tr>
<tr>
<td>59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Full artery-length treatment, 7 days**:  
  - 72% of nerves were within the treatment zone or outside of treatment zone but affected (66% for single treatment)  
  - 59% of nerves within treatment zones were necrotic or had chronic/reactive changes

**Tyrosine Hydroxylase Staining (7 days)**

- Untreated
- Radiofrequency-treated

- Tyrosine hydroxylase intensity reduced in 90% of nerves, including nerves without radiofrequency-related changes

Swine model results not necessarily indicative of clinical performance.
Vessix™ is an investigational device and not available for sale in the US.
Renal Denervation Preclinical Program

Preclinical Study Timeline

2010 – 2014

Feasibility Studies

Sep 2010 – Aug 2011

Iterative Development:\(^1\)
- Various RF balloon catheter designs
- Various treatment algorithms

Vessix™ Renal Denervation System

2011
- GLP Safety Study 28, 60, 90 days
- Safety and Efficacy Studies 7, 14, 28, and 90 days

2012
- GLP Safety Study 180 day

Vessix Reduce™ Renal Denervation System

2013
- Safety and Efficacy Studies 7, 28 days

2013-2014
- GLP Safety Study 28, 90, 180 days

>180 swine studied


Vessix™ is an investigational device and not available for sale in the US.
Vessix™ System Bipolar RF on a Balloon

Treatment of the full artery length

- RF treatment can be tailored to length of the artery landing zone
- Electrodes that are unapposed to vessel wall are automatically deactivated

* Vessix™ is an investigational device and not available for sale in the US.
Treatment with Vessix at 68° C for 30 sec yielded renal norepinephrine reductions across multiple studies.

- Trend toward greater norepinephrine reduction with full artery-length treatment versus one treatment per artery.

Swine model results not necessarily indicative of clinical performance.

Vessix™ is an investigational device and not available for sale in the US.
Vessix Preclinical Studies (Swine)
Vascular Safety through 180 days

Vascular Response

- At 30 days, endothelial cell confluence on 81% of flow surface but not completely confluent on remainder (worst case shown)
- Complete endothelial cell confluence on 100%

Endothelial Cell Coverage

Swine model results not necessarily indicative of clinical performance.
Vessix™ is an investigational device and not available for sale in the US.
Significant Office Blood Pressure Reductions Over Time

- Preliminary 18 month data show sustained significant office-based blood pressure reductions ($P < .0001$)

Mean BP Change from Baseline (mmHg)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>N</th>
<th>Mean BP Change</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month (N=142)</td>
<td></td>
<td>-10.0</td>
<td>-22.7</td>
<td></td>
</tr>
<tr>
<td>3 Months (N=144)</td>
<td></td>
<td>-8.2</td>
<td>-20.6</td>
<td></td>
</tr>
<tr>
<td>6 Months (N=143)</td>
<td></td>
<td>-10.3</td>
<td>-24.5</td>
<td></td>
</tr>
<tr>
<td>12 Months (N=133)</td>
<td></td>
<td>-10.0</td>
<td>-23.6</td>
<td></td>
</tr>
<tr>
<td>18 Months (N=51)</td>
<td></td>
<td>-12.7</td>
<td>-30.2</td>
<td></td>
</tr>
</tbody>
</table>

$P < .0001$ for each timepoint vs baseline.
Error bars represent 95% confidence bounds.
**Blood Pressure Response**

- 84% had a clinically meaningful response (ie, reduction >5 mmHg)\(^1\) based on office systolic blood pressure at 18 months.

<table>
<thead>
<tr>
<th>Change in Office Systolic BP from Baseline</th>
<th>6 Months (N=143)</th>
<th>12 Months (N=133)</th>
<th>18 Months (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reduction</td>
<td>10%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Reduction &lt;5 mmHg</td>
<td>5%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Reduction 5-10 mmHg</td>
<td>9%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Reduction &gt;10 mmHg</td>
<td>76%</td>
<td>78%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Schofer, J. PCR 2014.
Ability to Customize Treatment
Ultrasound: Record Medical

- Ultrasound transducer mounted inside of a 6 F balloon catheter
- Ultrasound creates heat within the surrounding structures and tissue
- Cooled water in the balloon protects the endothelium against heat
ApexNano Therapeutics

- Nano particles (~ 100 Nanometer)
  - Paramagnetic core with polymeric coating
  - Neurotoxin (Botox B)
  - Biodegradable
- Particles are injected into the renal artery and pulled into the artery wall by a magnetic field
- Two possible mechanisms
  - Heat generated by the magnetic field
  - Botox released by the particles
- Animal trials end of 2012
Bullfrog® Micro-Infusion Catheter

- Low pressure balloon (2 atm)
- Deploys microneedle into the adventitia
- Allows drug delivery to renal sympathetic nerve sheath
- Catheters available for >2 mm arteries

- No perivascular hemorrhagic events in >200 pigs or 39 human cases
- FDA 510(k)-cleared
Guanethididine

Specificity to Sympathetic Nerves

20x view of renal perivascular nerve fascicles, H&E stain

Control renal adventitial nerve fascicles

24 hours after adventitial guanethididine: injured interstitial nerve fascicles with buildup of hypereosinophilic coagulum

Kirk P. Seward, Mercator MedSystems, TRenD 2011
Radiation: Best Medical Int.

Ultrasound
  Recor Medical
  CardioSonic
  Sound Interventions
  Kona
Radiation
  Best Medical Int.
• External ultrasound
• tracks target and delivers ablative ultrasound energy
• 1st Generation: Utilizes an intravascular catheter to assist external system in targeting and tracking appropriate segment
• 2nd Generation: Fully non-invasive system utilizing ultrasound for targeting / tracking
1. Transducer positioned posterior

2. Catheter placed in renal artery to assist targeting, tracking

3. Ultrasound energy delivered to renal nerves

4. Energy field ablates renal nerves without damaging artery
Conclusions

- Sympathetic denervation has generated great interest in treatment of resistant hypertension
- Important Clinical Trials are underway, complex and challenging
- Sympathetic denervation may have benefit in diabetes, sleep apnea, CHF
- Currently 8 devices have CE mark, but…
- Over 1000 patents issued on techniques and methods
- But…..
WHAT ABOUT RENAL ANGIOPLASTY AND STENTING?
Renal Stenting: anatomy and function
Renovascular Hypertension

- Atherosclerotic disease
  - Aortic plaque
  - Primary renal stenosis
  - Greater than 80% stenosis
  - Severe hypertension or deteriorating renal function
- Fibromuscular dysplasia
  - Can be an incidental finding in normotensive and hypertensive patients
  - Younger women (less than 30)
  - Recent onset, no family history, change in pattern of HTN
- Focal, unilateral, renal aneurysms
CORAL
Subgroup Analyses

CV + Renal Death

Stroke

Myocardial Infarction

Heart Failure

Progressive Renal Insufficiency

Renal Replacement

P=ns

P=ns

P=ns

P=ns

P=ns

P=ns

C. Cooper, AHA 2013
Initial Right Renal Arteriogram
Right renal PTA, 6mm x 2cm
Post init
Repeat PTA: proximal right renal artery, 6mm x 2cm
Completion right renal arteriogram
Endovascular RX for FMD

- Angioplasty alone is treatment of choice
- Post procedural imaging often not ‘perfect’
- Healing of the site over time
- Look for focal webs
- Results are long lasting, with restenosis rare
- Stenting generally not necessary
- Intimal fibroplasia may require stents
Case Example

BP and Renal Function at Baseline

24h-ambulatory BP:
Mean: 184/91mmHg,
Min. 145/77mmHg,
Max. 239/115mmHg
Case Example
Baseline Angiography

F.K. *21.10.1923
24h-ambulatory BP:
Mean: 110/61 mmHg,
Min. 82/37 mmHg,
Max. 139/85 mmHg
Revascularization of RAS
Blood Pressure Control – RCT‘s prior to ASTRAL

Nordman et al., Am J Med 2003;114:44-50
49% of patients < 70% diameter stenosis by visual estimation
ASTRAL - PLOT OF SCR OVER TIME

Primary Endpoint at 2 years

P = 0.06

**Primary Endpoint – Event-Free Survival**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent + Medical</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% stenosis (<em>core lab</em>)</td>
<td>67.3 ± 11.4</td>
<td>66.9 ± 11.9</td>
</tr>
<tr>
<td>% stenosis (<em>investigator</em>)</td>
<td>72.5 ± 14.6</td>
<td>74.3 ± 13.1</td>
</tr>
</tbody>
</table>

**Stent plus medical therapy**

- **Stent + Medical Therapy** 35.1%
- **Medical Therapy** 35.8%
- HR 0.94 [0.76-1.17], p =0.58
Identifying Significant Renal Artery Stenosis

Pressure gradient
- De Bruyne et al JACC 2006

Resistance index
- Zeller et al. CCI 2008

Renal Frame Count
- Mahmud E et al. JACC Cardiovasc Int. 2008;1:286
Conclusions

- Hypertension remains an important area of interest for endovascular therapy, especially for those who have resistant hypertension.
- Hypertension continues to be a contributing factor to adverse CV events, AMI, Stroke, Amputation.
- Clinical trials in this area are complex and difficult to control for the many variables.
Conclusions

- Renal Angioplasty and Stenting is an important therapy in correctly selected patients
  - Critical RAS, abnormal renal function, uncontrollable HTN
  - Studies do not support first line therapy
  - Some have concluded *erroneously* that there is no role for PTRA and stenting
  - Treatment of choice for appropriate FMD patients
- Renal Denervation
  - Effective in some patients
  - More studies to determine appropriate patients who might benefit