Presentation: Renal Denervation, Second Time is a Charm?

Speaker: Robert S. Schwartz, MD, FACC, FAHA, FSCAI
Senior Consulting Cardiologist, Minneapolis Heart Institute® at Abbott Northwestern Hospital; Medical Director – Professional Education, Minneapolis Heart Institute Foundation

Date: Monday, January 19, 2015, 7:00 – 8:00 AM
Location: ANW Education Building, Watson Room

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Describe renal denervation physiology and anatomy
2. Describe the Symplicity HTN-3 trial and its potential reasons for failure
3. Explain the importance of patient selection moving forward in renal denervation trials

ACCREDITATION
Physicians: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Allina Health and Minneapolis Heart Institute Foundation. Allina Health is accredited by the ACCME to provide continuing medical education for physicians.

Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses: This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.2 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

Others: Individuals representing other professional disciplines may submit course materials to their respective professional associations for 1.0 hours of continuing education credit.

DISCLOSURE STATEMENTS
Speaker(s): Robert S. Schwartz, MD has declared the following financial relationships: Boston Scientific research support.

Planning Committee: Dr. Michael Miedema and Eva Zewdie have declared that they do not have any conflicts of interest associated with the planning of this activity. Dr. Robert Schwartz declared the following relationships - stockholder: Cardiomind, Interface Biologics, Aritech, DSI/Transoma, InstyMeds, InterValve, Medtronic, Osprey Medical, Stout Medical, Tricardia LLC, CoAptus Inc, Augustine Biomedical; scientific advisory board: Abbott Laboratories, Boston Scientific, MEDRAD Inc, Thomas, McNerney & Partners, Cardiomind, Interface Biologics; options: BackBeat Medical, BioHeart, CHF Solutions; speakers bureau: Vital Images; consultant: Edwards LifeSciences.
Renal Denervation
Concept to Trial

MHI Grand Rounds
19 January 2015

Yale L. Wang, MD, FACC, FSCAI
ASH Hypertension Specialist
Minneapolis Heart Institute

Conflict of Interest Disclosures
None
Worldwide Prevalence of Hypertension Is Increasing


Epidemiology

- Affects nearly 78 million Americans
- Prevalence worldwide may be as high as one billion individuals
- Approximately 7.1 million deaths per year attributable to HTN
- Number one risk factor for death throughout the world
- Direct and indirect cost of hypertension in the US is approximately $70 billion dollars

NHANES
### Pharmacology - HTN

**Alpha-Blockers**
- Doxazosin (Cardura)
- Prazosin (Minipress)
- Terazosin (Hytrin)

**Beta-Blockers**
- Timolol and HCTZ (Timolide)
- Propranolol HCL and HCTZ (Inderide)
- Nadolol and bendroflumethiazide
- Metoprolol tartrate and HCTZ (Loperssor release (Inderide LA))
- Bisoprolol fumarate and HCTZ (Ziac)
- Atenolol and Chlorthalidone (Tenoretic)
- Acebutolol (Sectral)
- *Methyldopa (Aldomet)
- *Guanfacine HCL (Tenex)
- *Guanabenz acetate (Wytensin)
- *Clonidine HCL (Catapres)

**Combined Calcium Antagonists and ACEi**
- Lisinopril and HCTZ (Prinizide, Zestoretic)
- Enalapril maleate and HCTZ (Vaseretic)
- Captopril and HCTZ (Capozide)
- Benazepril HCL and HCTZ (Lotensin HCT)
- Amlodipine besylate and Benazepril HCL (Lotrel)
- Felodipine and enalapril maleate (Lexxel)
- Verapamil HCL and Trandolapril (Tarka)
- Diltiazem HCL and Enalapril maleate (Teczem)

**Combination Antihypertensives**
- Nisoldipine (Sular)
- Nifedipine (Procardia XL, Adalat CC)
- Isradipine (DynaCirc, CR)
- Felodipine (Plendil)
- Amlodipine (Norvasc)
- Verapamil (Isoptin SR, Calan SR, Covera HS, Dilacor XR, Tiazac)
- Mibefradil (Posicor)
- Diltiazem HCL (Cardiazem CD/SR, Verelan, Covera HS, Maxzide)
- Bepridil (Vasocor)
- Triamterene + HCTZ (Dyazide, Moduretic)
- *Triamterene (Dyrenium)
- *Spironolactone (Aldactone)
- *Amlodipine hydrochloride
- *Eplerenone (Inspra)
- *Alfuzosin hydrochloride
- *Valproic acid
- *Sildenafil (Viagra)
- *Amlodipine (Norvasc)

**Diuretics**
- Torsemide (Demadex)
- Ethacrynic acid (Edecrin)
- *Bumetanide (Bumex)

**Potassium sparing Diuretics**
- Indapamide (Lozol)
- *HCTZ (Esidrix, Hydrodiuril, Microzide)
- Chlorthiazide (Diuril)
- *Chlorthalidone (Hygroton)
- *Spironolactone + HCTZ
- *Aldactone + HCTZ
- *Midamar

**ACE Inhibitors (ACEi)**
- Captopril (Capoten)
- Lisinopril (Prinivil, Zestril)
- Fosinopril sodium (Monopril)
- Enalapril maleate (Vasotec)
- *Captopril (Capoten)
- *Ramipril (Altace)
- *Quinapril HCL (Accupril)
- Moexipril (Univasc)
- *Perindopril (Aceon)
- *Lisinopril (Prinivil, Zestril)

**Direct Renin Inhibitors**
- Aldosterone antagonists
- *Aliskiren (Tekturna)

**Non-Dihydropyridines**
- *Nifedipine (Procardia XL, Adalat CC)
- *Nicardipine (Cardene SR)
- *Isradipine (DynaCirc, CR)
- Felodipine (Plendil)
- Amlodipine (Norvasc)
- Verapamil (Isoptin SR, Calan SR, Covera HS, Dilacor XR, Tiazac)
- Mibefradil (Posicor)
- Diltiazem HCL (Cardiazem CD/SR, Verelan, Covera HS, Maxzide)
- Bepridil (Vasocor)
- Triamterene + HCTZ (Dyazide, Moduretic)
- *Triamterene (Dyrenium)
- *Spironolactone (Aldactone)
- *Amlodipine hydrochloride
- *Eplerenone (Inspra)
- *Alfuzosin hydrochloride
- *Valproic acid
- *Sildenafil (Viagra)
- *Amlodipine (Norvasc)

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### Definition of Resistant Hypertension

**Uncontrolled Hypertension**
- Includes all patients who lack BP control on treatment, including those on inadequate treatment regimens, those with poor adherence, those with undetected secondary hypertension, as well as those with true treatment resistance

**Resistant Hypertension**
- BP that remains above goal in spite of compliance with full doses of ≥3 antihypertensive medications of different classes; ideally, 1 of the 3 agents should be a diuretic
  - The treatment plan must include attention to lifestyle measures
- Includes those patients who achieve BP control but require ≥4 antihypertensive agents to do so

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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 2.
#\(^{P}<0.05\) Compared with essential hypertension–stage 3.

**Historical**

- **Cooperative study of renovascular hypertension**
- **Surgical Sympathectomy**
- **1st RCT showing benefit of Rx of HTN**
- **Nephrectomy for hypertension with a small kidney**
- **Central acting drugs, ganglion-blocking agents**
- **Urgent bilateral nephrectomy for treatment of resistant malignant hypertension**
- **ACE inhibitor Rx**
- **Ca++ blockers**
- **PTRA introduced**
- **Improved Surgery**
- **Prospective trials: Med Rx vs. Stent CORAL ASTRAL STAR RAVE**
- **ARB Rx**
- **Statin Rx**
- **Stents**
- **Radiofrequency ablation Symplicity 1 and 2 trials**

**Crosstalk Between Renal Nerves and CNS**

- **↑ Neurohormones**
- **↑ Blood Pressure**
- **↑ Vasoconstriction**
- **↑ Contractility/Rate**
- **Amplifies central, or systemic, sympathetic outflow**
- **Kidney impairment, or dysfunction = ↑ afferent activity**
- **↓ RBF/GFR**
- **↑ Renin**
- **↑ Na+/Volume**
- **Ang II**
- **Aldo**

**Human Renal Sympathetic Nerve Distribution**

Atherton DS. et al Clinical Anatomy, 2011

**Renal Denervation by Ablation Therapy in a Porcine Model**

Serge Rousselle, TCT 2011
Six Month Post-Procedure Histology (Porcine Model)

Movat’s Pentachrome Stain

- An area of medial injury (yellow) is located between the arrows on the left. An enlargement of the boxed region is shown on the right.
  - Findings: minimal intimal thickening and minimal internal elastic lamina injury overlying areas of mild full thickness medial fibrosis (yellow [fibrosis] with green [proteoglycan deposition]) and adventitial fibrosis (yellow).


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

Flexible Tip (self-orienting)

Deflectable Shaft
**Symplicity RDN Global Clinical Program**

**Enrollment Complete / In Follow Up**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
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</thead>
<tbody>
<tr>
<td>Symplicity HTN-1</td>
<td>Series of Non-randomized Pilot Studies</td>
<td>n=153</td>
</tr>
<tr>
<td>Symplicity HTN-2</td>
<td>Randomized Controlled Trial (1:1) n = 106</td>
<td></td>
</tr>
<tr>
<td>Symplicity HTN-3</td>
<td>Randomized Controlled Trial (2:1), n=530</td>
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</table>

**Enrolling / Planning**

<table>
<thead>
<tr>
<th>Study</th>
<th>Feasibility Study</th>
<th>Prospective Registry</th>
<th>Participants</th>
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<tbody>
<tr>
<td>Symplicity HF</td>
<td></td>
<td></td>
<td>n=40</td>
</tr>
<tr>
<td>Global SYMPLICITY Registry</td>
<td></td>
<td></td>
<td>n=5,000</td>
</tr>
<tr>
<td>Symplicity HTN-Japan</td>
<td>Randomized Controlled Trial (1:1) n=100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symplicity HTN-4</td>
<td>Randomized Controlled Trial (2:1) n=530</td>
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</tr>
<tr>
<td>Symplicity HTN-India</td>
<td>Randomized Controlled Trial (1:1) n=40</td>
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</table>

**Symplicity Staged Evaluation in Hypertension and Beyond**

- **First-in-Man**
- **Series of Pilot Studies**
- **Symplicity HTN-2**
  - EU/AU Randomized Clinical Trial

**Symplicity HTN-1**

- **USA**
  - Symplicity HTN-3
    - US Randomized Clinical Trial (Presented March 2014 @ ACC)

**Other Areas of Research**

- Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

**Sources:**
**Results Recognized for Their Importance**

The Lancet

The Lancet. Published electronically on Nov 17, 2010.

**Initial Cohort – Reported in the Lancet 2009**
- First-in-man, non-randomized study conducted in Europe and Australia
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- All patients received bilateral renal denervation with the Symplicity Renal Denervation System
- Primary endpoint: change in office BP; 1, 3, 6, 9 and 12 months post-procedure

**Symplicity HTN-1 Investigators**

**Symplicity HTN-1**

The Lancet. 2009;373:1275-1281


**Expanded Cohort – Symplicity HTN-1:**
- Expanded cohort of patients (n=153) from 19 sites (US, Europe, and Australia)
  - 24 and 36-month follow-up of safety and effectiveness
Symplicity HTN-1 Trial: Key Inclusion/Exclusion Criteria*

**Inclusion Criteria**
- >18 years of age
- Elevated office systolic blood pressure (SBP) ≥160 mm Hg
- ≥3 antihypertensive medications (including 1 diuretic)

**Exclusion Criteria**
- Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m²
- Type 1 diabetes mellitus
- Known secondary cause of hypertension other than sleep apnea or chronic kidney disease
- Significant renovascular abnormalities

*Inclusion/exclusion criteria in the trial settings were stringent and conservative in order to ensure a homogenous population – in clinical practice, individual patient characteristics and physician judgment should guide patient selection.


Symplicity HTN-1: Significant, Sustained Blood Pressure Reductions to at Least Three Years*

<table>
<thead>
<tr>
<th>Time</th>
<th>Number of Patients</th>
<th>Change in Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>(n = 144)</td>
<td>-22</td>
</tr>
<tr>
<td>1 Year</td>
<td>(n = 132)</td>
<td>-27</td>
</tr>
<tr>
<td>2 Years</td>
<td>(n = 105)</td>
<td>-29</td>
</tr>
<tr>
<td>3 Years</td>
<td>(n = 34*)</td>
<td>-30</td>
</tr>
</tbody>
</table>

*Expanded results presented at the Transcatheter Cardiovascular Therapeutics Annual Meeting 2012 (Schlaich M).
Assessed for Eligibility (n=190)

Excluded During Screening, (n=84)
- BP < 160 at Baseline Visit (after 2-weeks of medication compliance confirmation) (n=36; 19%)
- Ineligible anatomy (n=30; 16%)
- Declined participation (n=10; 5%)
- Other exclusion criteria discovered after consent (n=8; 4%

Randomized (n=106)

Allocated to RDN
- n=52 Treated; n=49 Analyzable

Allocated to Control
- n=54 Control; n=51 Analyzable

Crossover
- n=46

6-month Per Protocol Post RDN (Crossover) n=35

12-month Post RDN
- n=47

30-month Post RDN
- n=37

6-month Per Protocol Post RDN (Crossover) n=33

30-month Post RDN (Crossover) n=7

*Expanded results presented at the American Society of Hypertension annual meeting 2013

Symplicity HTN-2 Patient Disposition 30M Post-RDN*

Symplicity HTN-2 Trial: 1-, 3-, and 6-Month 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.

Global SYMPLICITY Registry: Real-World Clinical Outcomes

Worldwide evaluation of the safety and efficacy of treatment with the Symplicity™ renal denervation system in real world uncontrolled hypertensive patients.

Consecutive patients treated in real world population: ~ 5000 patients

- 200 Global Sites
- Minimum 10% randomly assigned to 100% monitoring
- 30% monitoring to date

Follow-up schedule:
- 3mo
- 6mo
- 1yr
- 2yr
- 3yr
- 4yr
- 5yr

GREAT Registry N=1000

Korea Registry N=102

South Africa Registry N=400

Canada and Mexico N~3500

Rest of GSR

~ 5000 patients

Significant Reductions in Office BP for Patients with Uncontrolled Hypertension

3 Months

n=274

-13

-17

-18

-28

6 Months

n=220

-6

-8

-9

-28

n=36

-15

-18

-18

-16

n=135

n=114

n=17

*p=0.0002 for SBP BL ≥180 at 6 months

*p=0.0008 for DBP BL ≥180 at 6 months

*p=0.0001 all other groups

*Results Presented at EuroPCR 2013 annual meeting.
**Hypertension Devices**

- **Radiofrequency**
  - Medtronic Symplicity™
  - St. Jude EnLIGHTN™
  - BSC Vessix V2
  - Covidien-Maya OneShot

- **Ultrasound**
  - ReCor PARADISE®
  - CVRx® Barostim neo ™ System
  - Kona Medical

- **Injection**
  - Mercator Bullfrog®
  - Ablative Solutions (ethanol)

- **Baro-receptor Modulation**
  - (Guanethidine)
  - (Vincristine)

**REDUCE-HTN PMS – Interim Analysis**

**Significant Office Blood Pressure Reduction**

Mean reduction in office-based BP was -24.6/-10.3 mmHg at 6 months and significant reductions were sustained through 12 months.

- **1 Month (n=142)**: -22.7 systolic, -13.6 diastolic
- **3 Months (n=144)**: -20.6 systolic, -10.0 diastolic
- **6 Months (n=139)**: -24.6 systolic, -10.3 diastolic
- **12 Months (n=41)**: -29.6 systolic, -12.0 diastolic

*P<.0001 for each timepoint vs baseline

Error bars represent 95% confidence bounds

BP=blood pressure

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Cardiovascular Grand Rounds, 1/19/15
Minneapolis Heart Institute® at Abbott Northwestern Hospital
Office BP Reduction from Baseline

REDUCE:
Office Systolic Blood Pressure
(93% Responder Rate)
The OneShot™ System is a balloon-based RF system using a mounted spiral electrode with a unique feature of irrigation of the vessel lumen during treatment. The non-compliant balloon is inflated under low pressure (1 atm) in the renal artery. The electrode delivers RF energy to ablate adjacent nerve bundles with a single 2-minute treatment. A first in man feasibility study to evaluate the OneShot™ System was performed. These are the six month data for the RHAS (Renal Hypertension Ablation System) trial.

Eligible patients had:
- Office systolic blood pressure (SBP) ≥160 mmHg or ≥150 if diabetic
- A drug regimen that included two or more antihypertensive medications, including a diuretic
- Renal artery diameters 4-7 mm

Endpoints:
- Primary: to deliver RF energy using the OneShot™ RF Balloon Catheter into each renal artery
- Secondary: Office blood pressure and procedure time

Procedural Variables Median (Interquartile Range)
- Median OneShot™ System procedure time (min)* 20.0 (16.0, 24.8)
- Median tool procedure time (min) 15.0 (10.5, 23.0)
- Median fluoroscopy time (min) 7.0 (5.0, 10.0)

Median contrast volume used (mL) 134.0 (98.0, 168.0)

*Comparable median Symplicity™ RDN System procedure time: 38 min from initiation to completion of radiofrequency delivery (Source: Lancet, 2009; 373:1275-1281)

In the RHAS trial the OneShot™ RF Balloon Catheter produced in the 8 treated patients a substantial and significant reduction in the office SBP (-34, p=0.004) that improved over time. There were no significant complications. Only 2 minutes of treatment are required on each side, so the procedure is shorter and therefore less painful than some technologies.

**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

*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

Main Differences
- ABPM
- Sham-blinded study

Patient and Research staff assessing BP are blinded to treatment status
No changes in medications for 6M
Follow-up to 5 years

SYMPLECTITY HTN-3

Are you booking your ticket to Phoenix? 😊
Go colts!
Uh maybe you should hold on a sec
"In God we trust; all others must bring data."

W. Edwards Deming
A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhattacharya, M.D., M.P.H., David E. Kandzari, M.D., William W. O’Neill, M.D., Ralph D’Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Mingjui Liu, Ph.D., Laura Mauri, M.D., Manuela Negrova, M.D., Sidney A. Cohon, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Roche-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLECTICITY HTN-3 Investigators

Symplicity HTN-3

Figure 1. Primary Efficacy End Point.
A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The bars indicate standard deviations.

Figure 2. Secondary Efficacy End Point.
A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The bars indicate standard deviations.
Procedural Variability - Correlation with # of ablations and Correlation with 4-quadrant ablation pattern

David E. Kandzari et al. EuroPCR 2014

4 quadrant ablation pattern

Critical Neuro-Anatomical Differences: Normal vs. Chronic Hypertensive Patient

1. Sympathetic nerve proliferation
2. Much deeper nerve location

Nervous System
Renal artery

Normal Patient
Chronic Hypertensive Patient

Courtesy G. Sangiovanni
Relationship Between Office SBP Changes and Number of Ablations Attempted for Combined* RDN Subjects at 6 Months

David E. Kandzari et al. EuroPCR 2014
Operator Experience in GSR

- 189 operators did 1,000 procedures

59% of interventionists performed >15 RDN procedures

Medication Changes During Trial

- ~40% (n = 211) of trial subjects required medication changes between baseline and primary efficacy endpoint assessment:
  - 69% of first medication changes were medically necessary
  - 121 patients had a med change due to an adverse event
  - 80 patients had a med change due to a drug side-effect
  - ~69% were changes in drugs at maximally-tolerated dose

David E. Kandzari et al. EuroPCR 2014
Multivariate Predictors of Systolic Blood Pressure Change at 6 Months

<table>
<thead>
<tr>
<th>Control</th>
<th>Positive Predictors</th>
<th>Negative Predictors</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td></td>
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<td>Baseline Office SBP at ≥180</td>
<td>0.064</td>
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<tr>
<td>-12.003</td>
<td>Alpha-1 blocker use</td>
<td></td>
<td>0.044</td>
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<tr>
<td>-11.975</td>
<td>African American race</td>
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<td>0.003</td>
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<td>-8.004</td>
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<td>0.005</td>
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<table>
<thead>
<tr>
<th>RDN</th>
<th>Positive Predictors</th>
<th>Negative Predictors</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Baseline Office SBP at ≥180</td>
<td>0.0001</td>
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<tr>
<td>-14.311</td>
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<tr>
<td>-9.774</td>
<td>Aldosterone Antagonist</td>
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<td>0.002</td>
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<tr>
<td>Total Number of Attempts</td>
<td>-0.936</td>
<td></td>
<td>0.04</td>
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</table>

Kandzari TCT 2014
Univariate $P < 0.2$ required to enter the model

Why Did SYMPLICITY HTN-3 Fail?
Possible Interpretations

- Renal nerve ablation does not work
- Statistical power was not sufficient
- Renal nerve ablation was not properly performed
- Patients were not stabilized medically
- Patients were medically overtreated
- The wrong patient population was treated
- Other factors
The Sympathetic Nervous System in Control of the Circulation

J.T. Shepherd and P.M. Vanhoutte 1979

What Now Rob?
Renal Denervation – Fact or Fancy?
1/19/2015
MHI Grand Rounds

Robert S. Schwartz, MD, FACC

Introduction

- HTN-3 was a ‘wakeup call’
- Careful look into methods, study populations, and analysis should be done
- Visit by BSx Fall 2013
- Wished desire to understand Non-Response
Monopolar

- Symplicity 1-electrode Monopolar

Bipolar

- Vessix-BSx Bipolar-Multi electrode
**REDUCE-HTN**

- Prospective, non-randomized, single arm, multicenter study evaluating Vessix™ RDN
- Resistant hypertension
- Office-based SBP ≥ 160 mm Hg
- While on ≥ 3 medications (including diuretic)
- Maximally tolerated doses.

**Typical Case**

![Blood Pressure Graph](image.png)
REDUCE-HTN
148 patients

Office Blood Pressure Reduction

Mean Blood Pressure Change from Baseline (mmHg)

1 Month 3 Months 6 Months 12 Months 18 Months
n = 172 n = 144 n = 143 n = 133 n = 51
Systolic Diastolic Systolic Diastolic Systolic Diastolic Systolic Diastolic Systolic Diastolic

-22.7 -10.0 -20.6 -8.2 -24.5 -10.3 -23.8 -10.0 -30.2

P < 0.0001 for each timepoint vs baseline
Error bars represent 95% confidence bounds

REDUCE-HTN

✓ Response Definition > 10 mmHg at 6 mos
✓ What Causes Non-Response?
✓ BSx Scientists came to MHI
REDUCE-HTN

✓ First thoughts
✓ Renal Artery Atherosclerosis?

REDUCE-HTN

✓ ? Renal Artery Atherosclerosis
✓ BSC Funded a Research Study
✓ CTA in all patients
✓ Send us CTAs from study
✓ Blind to Response-NonResponse
Early Findings

- The RDN as delivered by the BSx-Vessix technology works well.
- Effects of the BSx-Vessix System become evident as early as 2-weeks post procedure and maintain this efficacy.

**OSBP and ODBP over Time (SD)**

- **Week vs OSBP Mean**
- **Week vs ODBP Mean**

Cardiovascular Grand Rounds, 1/19/15
Minneapolis Heart Institute® at Abbott Northwestern Hospital
REDUCE-HTN

✔ ? Renal Artery Atherosclerosis
✔ CTA RESULTS in 12 patients

ZERO Atherosclerosis

Corollary: Variability Reduction

Enables Using the MEAN to reduce Variability
Questions Answered by Analysis

Is Absolute Blood Pressure Reduction the Best Endpoint?

Continuous Change (eg HTN-3) vs Categorical (eg ‘Responder vs Non-Responder’)

Is a Fractional Change of use? 
(\( \delta \ P/\text{Baseline} \ P \))

Physiology: Endpoints

The Absolute Blood Pressure Reduction is Proportional to the Baseline Blood Pressure
Regression: Baseline SBP vs Change postop

**Physiology: Endpoints**

- What should we use for endpoints?
- SBP and DBP are comparable
- Categorical and Change uncertain
- Fractional interesting, probably not necessary
REDUCE-HTN

✓ Observation:
✓ Accessory Renal Arteries quite prevalent

Accessory Renal Arteries markedly over-represented
REDUCE HTN CT Subset

52% Accessory Artery Prevalence
23-30% General Population Prevalence

Questions:
Is this an artifact of CT Imaging?
Or is it a feature of the resistant HTN population?
Accessory Renal Arteries in NORMALS

✓ Thanks to David Caye
✓ 58 Subjects with MHI CTA of Kidneys
✓ Possible Renal Transplant donors
✓ Healthy, no DM, HTN, CAD, PAD, etc

REDUCE HTN CT Subset

52% Accessory Artery Prevalence
23% General Population Prevalence

Questions: Now with an Answer
Is this an artifact of CT Imaging?
Transplant Donor Population
33 %
MHI Analysis

Response Rate
Patients with
Solitary Renal Arteries

87%

Response Rate
Patients with
Accessory Renal Arteries

64%

Table 4
RDN response rate for patients with accessory and solitary arteries

<table>
<thead>
<tr>
<th>Count</th>
<th>All Accessory</th>
<th>Accessory Untreated</th>
<th>Accessory Treated</th>
<th>Accessory Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (n=41)</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Non-Response (n=17)</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total (n=58)</td>
<td>36</td>
<td>20</td>
<td>14</td>
<td>24</td>
</tr>
</tbody>
</table>

Of 13 NR, 9 (69%) had Accessory Renal Art
Only 4 of 24 Solitary are Nonresponders

16%

<table>
<thead>
<tr>
<th>Patient</th>
<th>Value</th>
<th>Solitary</th>
<th>#</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-011</td>
<td>-50.13</td>
<td>Solitary</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>25-020</td>
<td>-41.73</td>
<td>Solitary</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>25-017</td>
<td>-40.67</td>
<td>Solitary</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>05-011</td>
<td>-37.22</td>
<td>Solitary</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>25-009</td>
<td>-34.72</td>
<td>Solitary</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>10-014</td>
<td>-34.60</td>
<td>Solitary</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>09-001</td>
<td>-34.48</td>
<td>Solitary</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>25-012</td>
<td>-32.50</td>
<td>Solitary</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>25-010</td>
<td>-24.89</td>
<td>Solitary</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>05-001</td>
<td>-18.05</td>
<td>Solitary</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>29-004</td>
<td>-14.07</td>
<td>Solitary</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>05-008</td>
<td>-12.94</td>
<td>Solitary</td>
<td>12</td>
<td>37</td>
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<tr>
<td>12-010</td>
<td>-12.13</td>
<td>Solitary</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>12-012</td>
<td>-8.53</td>
<td>Solitary</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>27-005</td>
<td>-6.00</td>
<td>Solitary</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>

Overview

Moreover, Treatment of Accessory RA associated with higher response rate

71% (10/14)
Accessory Renal Arteries are associated with:

- A Diminished therapeutic response
- These Kidneys have Larger Renal Mass
- Smaller Main Renal Arteries
- Low Renal Mass Perfused/Artery area (gm Kidney/mm² artery area)

Findings to Date

Accessory renal arteries are markedly more prevalent in the hypertensive RDN patients than healthy renal donors, (59% vs 32%)
Accessory renal arteries are markedly more prevalent in the hypertensive RDN patients than healthy renal donors, (59\% vs 32\%).

RDN overall response rate 71\%

Patients with at least one accessory vessel have a lower response rate to RDN than those without accessory vessels.
Findings to Date

Of all non-response patients, 76% had accessory arteries.

In patients with accessory arteries, 14 accessory vessels were treated by RDN

Of non-responders with accessory arteries, 69% had untreated accessory arteries.

Added Analytic Update

REDUCE HTN CT Subset
### REDUCE HTN CT Subset

**58 patients**

- Sensitivity: 76%
- Specificity: 56%
- Positive Predictive Value: 38%
- Negative Predictive Value: 87%
- Accuracy: 62%

### Treating Accessory Arteries

**45 patients**

In patients where all accessory arteries were treated the response rate was **82%**
Treating Accessory Arteries

45 patients

In patients where accessory arteries were *untreated* the response rate was

55%

Failure (Nonresponse) Rate by Accessory Arteries Treated

18%

45%

All Treated

Not all Treated
Multivariate analysis showed the strongest correlate of failure was accessory renal artery presence.

And the strongest correlate of success was accessory renal artery treatment.

Are Accessory Renal Arteries Associated with Resistant Hypertension?
Renin-Dependent Hypertension Caused by Nonfocal Stenotic Aberrant Renal Arteries: Proof of a New Syndrome
David C. Kem, Daniel F. Lyons, James Wenzl, Donald Halverstadt and Xichun Yu

Hypertension. 2005;46:380-385; originally published online June 20, 2005;
doi: 10.1161/01.HYP.0000171852.25749.5b
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Nephrology beyond JASN

Accessory Renal Arteries—Mostly, But Not Always, Innocuous
Kem D.C., Lyons D.F., Wenzl J., Halverstadt D., Yu X.

Since the classical observation of Harry Goldblatt (1), hypertension resulting from renal ischemia has become an established paradigm to explain several forms of hypertension. The closest human counterparts to the experimental model of Goldblatt are the various forms of renal artery stenosis. Systemic or atherosclerotic. The clinical diagnosis is based on the combination of an activated renin-angiotensin system and morphologic evidence of a hemodynamically relevant arterial stenosis, ideally supplemented by evidence of deficient renal perfusion (2-4). Accessory renal arteries have been known since the early days of human anatomy. It has been reported that they occur in 2% of individuals (5) and originate mostly directly from the aorta (6). Their frequency reflects the complexity of the anastomoses of the kidneys. They represent vestiges of the urogenital sinus.
Kidney Volume/Mass and Renal Artery Cross Sectional Area

Total Kidney Mass is Statistically Larger in Kidneys with Accessory Vessels
BUT Main Renal Artery Area is SMALLER!

And mass/vessel Area Main Renal A is LARGER!
Kidney Volume/Mass and Renal Artery Cross Sectional Area

Anatomy, Function, or Both??

A Very Interesting Case.....

67 yo Man with Hypertension and ASO
Clinical Trial Perspectives and Implications for Trial Design 2015

Clinical Trial Design

- Awareness of Accessory Arteries
- Systemic Blood Draw ARR (Aldo/RAA)
- Treat .......... YES
- Exclude ?
- Size relevance – Apparently Not
- CT Scans with competent (and caring) Core Lab
Overall Summary

- Find and Treat Accessories
- Diagnostics are still Pending MHI
- Variability of BP and Response
- Efficacy known by 2-weeks
- Correct Endpoint needed

Work in progress....
Analyses Pending

- Accessory Area, Mass/Area, Anatomy and effects
- Comparison with Transplant Donor and ASO patient Scans
- Ambulatory Blood pressure
- Proportional Threshold Analysis: Absolute vs Fractional
- Clinical Trial optimization/strategies
- Virmani/Anatomy

There is Nothing New Under the Sun.....
Case: 5 yo male

- Referral: Troubles in Kindergarten
- Severe HTN: BP 190/130
- Uncontrolled with Medical Rx
- Referral to Univ of OK
- Renal Biopsy Normal
- Non-Stim Renal V Renin 2:1
After consideration between the physicians and the parents, a decision was made to perform a partial nephrectomy to eliminate the source of the apparent renin-dependent hyper-tension of the aberrant artery was observed. Postoperatively he did well and was discharged 7 days later. His blood pressure was 130/90 at the time of discharge while off of all medications.
Renal Denervation – Fact or Fancy?
1/19/2015
MHI Grand Rounds

Robert S. Schwartz, MD, FACC