Renal Sympathetic Denervation Beyond Hypertension: Therapy for Arrhythmias and for Autonomic Nervous System Dysfunction?

Vivek Y. Reddy, MD
Helmsley Trust Professor of Medicine
Director, Cardiac Arrhythmia Service
The Mount Sinai Hospital

vivek.reddy@moun tsinai.org
Disclosures

• Ablative Solutions: grant support
• Biosense-Webster: grant support, consultant
• Boston Scientific: grant support, consultant
• Cibiem: consultant, equity*
• Medtronic: grant support, consultant
• Perseus: consultant, equity*
• St Jude Medical: grant support, consultant

• I will be discussing off-label use of catheter ablation devices, as well as non-FDA approved devices.

[* I will not be discussing products from these companies]
Renal denervation: saving lives in Europe first

22/04/13 - Today you met Florence. While it’s true that Florence is an actress—her story is very real. Florence represents the many Europeans suffering from treatment-resistant hypertension. Hypertension, or simply “high blood pressure”, can usually be treated by pharmaceuticals. But in many cases, drugs alone will not stop the problem from getting worse or having significant side effects—especially as patients get older. The only option that these patients have is receiving an innovative medical device procedure called renal denervation.

The renal denervation procedure removes overactive nerves deep in the kidney that fuel rising blood pressure. Within 6 months of receiving the procedure, patients’ blood pressure begins to drop and often returns to a manageable level and saves the patient.

European patients have had access to the procedure and the device needed to perform it since 2010. As of today, an estimated 7 million patients in the US with treatment-resistant hypertension are still waiting.

Click here to hear the story of Merle, who was an athletic working mother and wife until her struggle with hypertension began to take its toll. Doctor after doctor prescribed a regiment of tablets that proved to be temporary fixes for her constant malaise. It was a renal denervation procedure that would be her saving grace.

For more about the technology responsible for Merle’s new lease on life, click here.
**The Excitement Abruptly Ends**

MEETING NEWS COVERAGE

**TCT 2014 Scientific Symposium**

**Simplicity Flex: Renal denervation misses primary endpoint in patients with mild hypertension**

September 25, 2014

WASHINGTON — In the Simplicity Flex trial of patients with mild refractory hypertension, renal denervation failed to significantly lower BP compared with a sham procedure.

Steffen Desch, MD, reported at TCT 2014 that the mean change in 24-hour systolic BP at 6 months in an intention-to-treat cohort was −7 ± 10.6 mm Hg for patients treated with renal denervation using the Simplicity Flex catheter (Medtronic) compared with −3.5 ± 9.4 mm Hg for patients treated with a sham procedure (P=.15).

“If you look at the per-protocol group, however, it is a completely different story,” Desch, from University of Schleswig-Holstein, Campus Lübeck, Germany, said at a press conference.

In the per-protocol cohort, the mean change in 24-hour systolic BP at 6 months was −8.3 ± 8.9 mm Hg for patients treated with renal denervation compared with −3.5 ± 9.5 mm Hg for patients treated with the sham procedure (P=.042). The per-protocol cohort also had a significant decrease in daytime systolic BP after renal denervation compared with the sham...
Can HTN be treated by an intervention?

Role of Sympathetic Nerves in HTN

Thoracolumbar Surgical Sympathectomy

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

Smithwick et al. *JAMA* 1953;152(16);1501-1504

Schlaich, W. Presented at ESH 2010
Placebo Controlled Trial of RSDN Symplicity HTN-3: No Significant Effect over Placebo

Bhatt et al. *NEJM* 2014; DOI: 10.1056/NEJMo1402670
Symplicity HTN-3
Why was it a negative study?

- **Clinical Trial Issues**: eg, not adequate roll-in period

- **Technical issues**: perhaps the catheter was not properly employed → Technical Expertise vs Design “Flaw”

- Refractory hypertension is not primarily “sympathetically-driven” (as modifiable by RSDN)
Symplicity HTN-3

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• **Clinical Trial Issues**: eg, not adequate roll-in period

• **Technical issues**: perhaps the catheter was not properly employed → Technical Expertise vs Design “Flaw”

• Refractory hypertension is not primarily “sympathetically-driven” (as modifiable by RSDN)
Does Technique Matter?
Pre-Clinical Data: Symplicity Flex & Spyral

Preclinical Data do Support a "Dose Response"

Medtronic Investor Briefing (March 2014)
Case: Autopsy in a RSDN Patient
Limited Destruction of the Nerves

Case: Autopsy in a RSDN Patient
Limited Destruction of the Nerves

Symplicity HTN-3

Procedural Variable: No. of Ablation Lesions

Denervation  Sham  $P$ value for trend = .01

<table>
<thead>
<tr>
<th>Baseline SBP</th>
<th>Denervation</th>
<th>Sham</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>178.2</td>
<td>-13.1</td>
<td>-11.5</td>
<td>.54</td>
</tr>
<tr>
<td>180.1</td>
<td>-14.1</td>
<td>-11.1</td>
<td>.27</td>
</tr>
<tr>
<td>178.6</td>
<td>-14.7</td>
<td>-9.4</td>
<td>.07</td>
</tr>
<tr>
<td>180.3</td>
<td>-14.7</td>
<td>-7.6</td>
<td>.04</td>
</tr>
<tr>
<td>178.2</td>
<td>-15.9</td>
<td>-7.6</td>
<td>.07</td>
</tr>
<tr>
<td>180.5</td>
<td>-18.6</td>
<td>-7.1</td>
<td>.03</td>
</tr>
<tr>
<td>179.0</td>
<td>-24.3</td>
<td>-10.2</td>
<td>.06</td>
</tr>
<tr>
<td>179.4</td>
<td>-25.4</td>
<td>-13.4</td>
<td>.18</td>
</tr>
<tr>
<td>179.1</td>
<td>-30.9</td>
<td>-18.5</td>
<td>.43</td>
</tr>
</tbody>
</table>

95% CI

| 178.2 | (-7.1 to 3.7) |
| 180.1 | (-8.6 to 2.4) |
| 178.6 | (-11.3 to 0.5) |
| 180.3 | (-13.9 to -0.3) |
| 178.2 | (-17.4 to 0.7) |
| 180.5 | (-21.8 to -1.2) |
| 179.0 | (-28.8 to 0.7) |
| 179.4 | (-30.0 to 5.9) |
| 179.1 | (-44.6 to 19.8) |

Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients.

* $P$ value change in SBP for RDN compared with sham.

Data presented are mean (SD).

Catheter/Energy Technologies for RSDN
RSDN: Chemical & Ultrasound
Minimal Effect on the Arterial Wall

RSDN Using External Ultrasound Energy

Minimal Effect on the Arterial Wall

Courtesy: P. Neuzil (Homolka/Prague)
Symplicity HTN-3

Why was it a negative study?

- **Clinical Trial Issues**: e.g., not adequate roll-in period

- **Technical issues**: perhaps the catheter was not properly employed → Technical Expertise vs Design “Flaw”

- Refractory hypertension is not primarily “sympathetically-driven” (as modifiable by RSDN)
Does Renal Denervation Do Anything?

Effect on Neurohormones

- **Schlaich et al. NEJM** 36:932-934 (2009)

**Mean office blood pressure**

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Δ</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renin</strong></td>
<td>0.8±0.3</td>
<td>0.6±.4</td>
<td>-0.2±0.6</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Aldosterone</strong></td>
<td>111±40</td>
<td>52±14</td>
<td>-60±33</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Metanephrine</strong></td>
<td>36±12</td>
<td>24±9</td>
<td>-12±4</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Normetanephrine</strong></td>
<td>67±22</td>
<td>49±21</td>
<td>-18±4</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

**BP**

- Baseline: 161/107 mmHg
- 12 M FU: 127/81 mmHg

**MSNA**

- Baseline: 56 bursts/min
- 12 M FU: 19 bursts/min
Blinded-Placebo Controlled Trial of RSDN
Single-Center RCT of “Mild-Resistant” HTN

- Design:
  - Sham vs RSDN (Symplicity Catheter)
    - 4-6 ablations / vessel
    - 1 Center / Experienced Operators
  - Inclusion:
    - Daytime ABPM: SBP=135-149 or DBP=90-94mmHg
    - Stable Drugs ≥ 3 including diuretic (No change for 4 wks pre-Random)
  - Primary Endpoint: ΔSBP at 6mo
  - Patient Demographics
    - Mean SBP (ABPM): 144 mmHg
    - No. anti-HTN Drugs: 4.3
  - Analysis: (71 pts Randomized)
    - ITT: 32 (RSDN) vs 35 (Placebo)
    - Per-P: 29 (RSDN) vs 34 (Placebo)

S, Desch et al. Presented at TCT 2014
Does Renal Denervation Do Anything?

RSDN in ESRD/HD: Case Example

**Case:** 70 yo woman w/ CKD/HD x 7yrs, L-nephrectomy 20 yrs ago (cancer), Refractory HTN (Hydal / Nifed / Coreg / Aldac / ARB) → Office BP: 208/68
- Difficulty with HD b/c hypotension
- At 6 weeks, stopped 2 meds
- No need to stop HD b/c hypotension
- **Office BP:** 208/68 → 148/75
Is Hypertension the best “Target” for RSDN?
HTN and AF: Progressive Atrial Remodeling in an Ovine Model

*Heart Rhythm 2010;7:1282–1290*
Predictors of Recurrence After AF Ablation

- Retrospective Analysis of 292 patients undergoing PVI for AF
- Non-Dilated LA (<40mm) = 178 pts vs Dilated LA (>40mm) = 114 pts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis p value</th>
<th>Multivariate analysis p value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, years</td>
<td>0.10</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>0.16</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF, %</td>
<td>0.34</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.02</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of AF, years</td>
<td>0.003</td>
<td>0.03</td>
<td>1.11</td>
<td>1.01–1.21</td>
</tr>
<tr>
<td>Structural heart disease, %</td>
<td>0.12</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>0.91</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>0.33</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>0.49</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>0.83</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of failed AADs</td>
<td>0.38</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RASIs after EIPVsI, %</td>
<td>0.98</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.31</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>0.83</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.35</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>0.75</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LADs, mm</td>
<td>0.81</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.04</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Takigawa et al. JRAS, DOI: 10.1177/1470320312446212 (2012)
Patients undergoing PVI (n=88) underwent $^{123}$I-mIBG imaging (cardiac neuronal imaging) 5 days post-ablation.

The only multivariate predictor of AF recurrence was a high $^{123}$I-mIB washout rate (excessive SNS activation).

Arimoto et al. *JCE* (2011)
OSA-Related Atrial Arrhythmias
Effect of RSDN

- Porcine model of Obstructive Sleep Apnea
  - Tracheostomy and application of negative tracheal/thoracic pressure (NTP)
  - NTP (4 times per hour) x 4 hours

OSA-Related Atrial Arrhythmias
Effect of RSDN

- Porcine model of Obstructive Sleep Apnea
  - Tracheostomy and application of negative tracheal/thoracic pressure (NTP)
  - NTP (4 times per hour) x 4 hours

Pathogenesis of Atrial Fibrillation
Potential Modulation by RSDN

Refractory HTN Patients with AF
RSDN as Adjunctive Therapy to AF Ablation


Table 1
Baseline Characteristics of Patient Population

<table>
<thead>
<tr>
<th></th>
<th>PVI (n = 14)</th>
<th>PVI + Renal (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56 ± 9</td>
<td>57 ± 8</td>
<td>0.41</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/4</td>
<td>11/2</td>
<td>0.47</td>
</tr>
<tr>
<td>PAF/PersAF</td>
<td>5/9</td>
<td>4/9</td>
<td>0.72</td>
</tr>
<tr>
<td>AF History, yes</td>
<td>5.3 ± 3.2</td>
<td>5.7 ± 4.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>2 (14.2%)</td>
<td>1 (7.7%)</td>
<td>0.32</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66 ± 4</td>
<td>65 ± 5</td>
<td>0.39</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>50 ± 6</td>
<td>49 ± 7</td>
<td>0.62</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>80.2 ± 4.6</td>
<td>78 ± 6.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>178 ± 8</td>
<td>181 ± 7</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>96 ± 4</td>
<td>97 ± 6</td>
<td>0.58</td>
</tr>
<tr>
<td>CAD</td>
<td>2 (14.2%)</td>
<td>2 (15.3%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3 (21%)</td>
<td>3 (23%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28 ± 5</td>
<td>28 ± 6</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (21%)</td>
<td>4 (30%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>13 (92%)</td>
<td>13 (100%)</td>
<td>0.73</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>14 (100%)</td>
<td>12 (92%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>11 (78%)</td>
<td>10 (77%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>10 (71%)</td>
<td>10 (76%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>3.6 (2–5)</td>
<td>3.8 (2–5)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Mean BP changes from baseline, mm Hg

- Systolic BP
  - PVI
  - PVI + Renal ablation

- Diastolic BP
  - PVI
  - PVI + Renal ablation

Freedom from AF/AT

Log-rank test, p = 0.033
Refractory HTN Patients with AF
RSDN as Adjunctive Therapy to AF Ablation

- Of course, most AF pts don’t have refractory hypertension.
- Could RSDN might be beneficial in the majority of our AF ablation patients (who typically have milder/controlled hypertension)?

RSDN as Upstream Therapy in AF?

**HFIB Study**

- AF + HTN population:
  - AF ablation vs AF ablation+RSDN
- Single-Blind (Sham-RSDN), Randomized-Controlled Trial
- FDA Approval: IDE# G120025
- Primary Endpoint: AF Recurrence
- PI: V. Reddy / Mount Sinai

- Pilot (Enrollment of 50 pts):
  - Renal Artery Dissection → 3 pts
  - Renal Artery Stenosis → 3 pts

- Plan for Full Study:
  - Dedicated RSDN Catheter

---

**H-FIB**

AF + Hypertension → AF Ablation → Renal Angiogram → R

- Placebo
- RSDN

Follow-Up AF Recurrences

RSDN for Refractory VT Storm
Clinical Case Series

- 4 Patients / 3 Centers
  - 2-NICM / 2-Isch Dz
  - Prior Ablations in all
    - 2 – Endo Only
    - 2 – Endo/Epi
- RSDN Performed in all
  - EP catheter (Irrigated or non-irrigated)
- Follow-Up
  - 8.8 ± 2.6 months (range 5–11 mo)
  - No hemodynamic deterioration
  - No change in renal function
  - Decrease in VT Episodes
    - 11±4 episodes → 0.3 ±0.1 episodes

RSDN for Ventricular Arrhythmias: Preventing Shocks in High-Risk ICD Patients

- ICD recipients:
  - Scar-Related VT
  - Secondary Prevention or Inducible Primary Prevention Populations
- Primary Endpoint: ICD Therapy
- Single-Blind (Sham-RSDN), Randomized-Controlled Trial
- FDA Approval: IDE# G120147
- PI: V. Reddy / Mount Sinai
- Protocol Design:
  - Pilot Phase: 20 Patients (Done)
  - Full Study: ~450 Patients
- Trial Design Details:
  - Funding by Boston Scientific, Inc.
  - RSDN Catheter: Vessix System

**RESCUE-VT**

2° Prevention
1° Prevention + Inducible VT

ICD Implantation

Renal Angiogram

Placebo RSDN

Follow-Up ICD Therapy
Multiple Clinical Trials are Ongoing

### Table 1: Overview of design, sites and time schedule of ongoing trials

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Official title</th>
<th>Sites</th>
<th>Interventions</th>
<th>Status</th>
<th>Expected completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01635998</td>
<td>Adjunctive renal sympathetic denervation to modify hypertension as upstream therapy in the treatment of atrial fibrillation (H-FIB)</td>
<td>11 centers from US and Europe</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>07/2017</td>
</tr>
<tr>
<td>NCT01686542</td>
<td>Circumferential pulmonary vein isolation (CPVI) plus renal sympathetic modification versus cpvi alone for AF ablation: a pilot study</td>
<td>The Second Affiliated Hospital of Chongqing Medical University Chongqing, China</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>12/2016</td>
</tr>
<tr>
<td>NCT01713270</td>
<td>Safety and effectiveness study of percutaneous catheter-based renal sympathetic denervation in patients with drug-resistant hypertension and symptomatic atrial fibrillation</td>
<td>First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>06/2015</td>
</tr>
<tr>
<td>NCT01814111</td>
<td>Safety and effectiveness study of percutaneous catheter-based sympathetic denervation of the renal arteries in patients with hypertension and paroxysmal atrial fibrillation</td>
<td>The First Hospital of Nanjing Medical University, Nanjing, Jiangsu, China</td>
<td>RDN vs. best medical treatment (AF)</td>
<td>Recruiting</td>
<td>06/2015</td>
</tr>
<tr>
<td>NCT01873352</td>
<td>Evaluate renal artery denervation in addition to catheter ablation to eliminate atrial fibrillation (ERADICATE-AF) trial</td>
<td>The Valley Health System, New York, US; Meshalkin Research Institute of Pathology of Circulation, Novosibirsk, Russian Federation</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>06/2014</td>
</tr>
<tr>
<td>NCT01897545</td>
<td>The role of renal denervation in improving outcomes of catheter ablation in patients with atrial fibrillation and arterial hypertension</td>
<td>The Valley Health System, New York, US; Athens Euroclinic, Athens, Greece; State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation</td>
<td>PVI + RDN vs. PVI only</td>
<td>Completed</td>
<td>06/2014</td>
</tr>
<tr>
<td>NCT01898910</td>
<td>Ganglionated plexi ablation vs renal denervation in patients undergoing pulmonary vein isolation: A randomized comparison</td>
<td>Meshalkin Research Institute of Pathology of Circulation, Novosibirsk, Russian Federation</td>
<td>PVI + RDN vs. PVI + Ganglionated Plexi ablation</td>
<td>Completed</td>
<td>06/2013</td>
</tr>
<tr>
<td>NCT01907828</td>
<td>A feasibility study to evaluate the effect of concomitant renal denervation and cardiac ablation on AF recurrence</td>
<td>Recruiting</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>05/2016</td>
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<tr>
<td>NCT01952743</td>
<td>Concomitant renal denervation therapy in hypertensive patients undergoing atrial fibrillation ablation: A Feasibility Study</td>
<td>Mayo Clinic, Rochester, Minnesota, US</td>
<td>PVI + RDN vs. PVI only</td>
<td>Recruiting</td>
<td>09/2016</td>
</tr>
<tr>
<td>NCT01952925</td>
<td>Combined atrial fibrillation ablation and renal artery denervation for the maintenance of sinus rhythm and management of resistant hypertension</td>
<td>Oregon Health and Science University, Portland, Oregon, United States</td>
<td>PVI + RDN vs. PVI only</td>
<td>Not yet open</td>
<td>01/2019</td>
</tr>
<tr>
<td>NCT01959997</td>
<td>Randomized comparison of redo pulmonary vein isolation with vs. without renal denervation for recurrent atrial fibrillation after initial pulmonary vein isolation</td>
<td>The Valley Health System, New York, US; State Research Institute of Circulation Pathology, Novosibirsk, Russian Federation</td>
<td>Redo PVI vs. Redo PVI + RDN</td>
<td>Recruiting</td>
<td>09/2016</td>
</tr>
</tbody>
</table>

Is this a fool’s errand?
Upstream Therapy for AF?

RCT: Intensive Weight Reduction Plan vs General Lifestyle Advice

Improving the Success of AF Ablation
Role of Adjunctive Sympathetic Inhibition

G. Giannopoulos et al, Circulation (in press)

12-mo AF Recurrence
Moxonidine  20%
Placebo  37%
(p=0.007)
Final Thoughts

• What is the right technique?
  – Technology vs Physiology
  – Need Outcome data with new ablation approaches
  – Efficacy: Only Blinded RCTs matter

• Who is the right patient?
  – Hypertension:
    • Refractory HTN → What design?
    • Moderate HTN → RSDN as replacement for Drugs?
    • Endpoint: ABPM vs Office BP?
  – Arrhythmias?
    • Adjunctive to AF Ablation?
    • Reducing ICD shocks?
  – Congestive Heart Failure?
Final Thoughts

• Irrational Exuberance vs Irrational Nihilism

• The Autonomic Nervous System and Cardiovascular Disease
  – Need to explore means to modulate the sympathetic (& parasympathetic) nervous systems
  – RSDN is one of several novel approaches to modulate the autonomic nervous system
  – Other Approaches being tested:
    • Vagal Stimulation
    • Baroreceptor Stimulation
    • Spinal Cord Stimulation
    • Carotid Body Ablation
    • Celiac Ganglion Ablation