# Resistant Hypertension

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# Disclosures

- **Drs. Valentine and Mazzaferri are site-PI's for Symplicity HTN-3 and Symplicity HTN-4 trials at the The Ohio State University's Wexner Medical Center**
- **Identified slides from Dr. Mazzaferri's talk adapted from Symplicity HTN slide deck (permission from Medtronic, Inc.)**

# Objectives

- **Define Resistant Hypertension**
- **Review JNC 8 thresholds for treatment**
- **Discuss lifestyle modification**
- **Review common secondary causes of hypertension**
- **Discuss pharmacotherapy of resistant hypertension**
- **Introduction to Catheter based renal denervation**
  - **Evidence, trial, data**
  - **Late Breaking news on Renal Denervation**

# Resistant Hypertension (RH)

- **BP above goal in spite of concurrent use of 3 antihypertensive agents of different classes.**
- **One should be a diuretic.**
- **All should be at optimal doses.**
- **Includes patients who are controlled on 4 or more meds.**

## Uncontrolled HTN

- Less specific term than RH
- Also includes those who are not compliant or who are on an inadequate regimen

## JNC 8

- Recommendation 1
- In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

## JNC 8

- Recommendation 2
- In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90 mm Hg and treat to a goal DBP <90 mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

## JNC 8

- Recommendation 3
- In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)

## JNC 8

- Recommendation 4
- In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

## Prevalence of RH

- Truly not known
- ALLHAT was ethnically diverse and included 33,000 people
  - 27% required 3 or more meds
  - 49% controlled on 1 or 2 meds

## SBP vs DBP

- SBP is harder to control, and this gets worse with age.
- Framingham:
  - 90% achieved DBP goal of < 90mmHg
  - 49% achieved SBP <140mmHg
  - Strongest predictor of lack of BP control was age
  - LVH and obesity also associated with poor control

## Patient Characteristics Associated With RH

- Older age
- High baseline BP
- Excessive dietary Na intake
- CKD – Cr > 1.5 (Strongest predictor in ALLHAT)
- Obesity
- DM
- LVH
- Black race
- Female sex
- Residence in Southeast US

# Adherence

- 40% of patients with a new Dx of HTN will stop their medications within a year
- At 5-10 yr follow up, less than 40% take their prescribed meds

# Lifestyle

- Healthy diet, weight control, and exercise should be emphasized.
- Typical American sodium intake is much higher than 2 g a day
- Cessation of heavy ETOH intake reduced 24h SBP by 7 mmHg and DBP by 7mmHG, and reduced prevalence of HTN from 42% to 12%.

# Treatment: Lifestyle

- 10 kg wt loss associated with 6/4.6 mmHg decrease in BP
- Salt restriction can reduce BP by 5-10/2-6 mmHg
- Limit ETOH to 1-2 drinks/day
- DASH diet led to improvement in BP by 11/5.5 mmHg.
  - High fiber low fat diet. Rich in fruits, vegetables, low fat dairy products.

# Medications That May Elevate Blood Pressure

- NSAIDS
- ASA
- COX 2 inhibitors
- Alcohol
- Oral Contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Ephedra, ma huang
- Sympathomimetics - Decongestants, cocaine, diet pills
- Stimulants – Amphetamines, methylphenidate

# Evaluation

- Medication adherence?
- White Coat HTN? Need home or ambulatory BP.
- Lifestyle: obesity, inactivity, alcohol > 1-2 drinks/day, sodium.
- Adverse effect of other meds?
- If none of above are true, look for secondary causes.

# 24 hr ambulatory BP monitoring

- Mean ambulatory daytime BP >135/85 is considered elevated.
- If white coat effect is confirmed, treatment should be adjusted based on out-of-office BP.

# Secondary Causes of RH

- 12.7% of patients over age 50 referred to a HTN clinic had a secondary cause.
- Common
  - Renal artery stenosis
  - Primary Aldosteronism
  - Chronic kidney disease
  - Obstructive sleep apnea

# Renal Artery Stenosis

- CORAL Study NEJM Nov 18, 2013.
- 947 patients
- Medical therapy plus renal artery stenting vs. medical therapy
- 43 month follow up

## RAS - CORAL STUDY

- Medical Therapy:
  - ARB
  - With or without thiazide type diuretic
  - Add amlodipine if needed
  - Antiplatelet therapy
  - Statin

## RAS - CORAL Study

- Rate of primary composite endpoint did not differ (35.1% in stent group vs 35.8%).
- No significant difference in individual components of the endpoint – e.g. death from CV or renal cause, stroke, MI, CHF, progressive renal insufficiency, ESRD.

## RAS – CORAL Study

- In atherosclerotic RAS with HTN or CKD, renal artery stenting did not confer significant benefit when added to comprehensive medical therapy.

## Obstructive Sleep Apnea

- In studies of RH, 80 - 90 % have obstructive sleep apnea.
- More common and severe in men.
- Intermittent hypoxemia and/or increased upper airway resistance cause increased sympathetic nervous system activity.

# Treatment: CPAP for obstructive sleep apnea

- Mixed results, but some studies show 9-14 mmHg decrease in SBP and 7-9 mmHg decrease in DBP.
- Largest benefit in severe OSA.
- BP effect is greater in resistant HTN.

# Treatment - Pharmacologic

- Maximize diuretic.
- Use loop diuretic if GFR < 30 or using minoxidil.
- Add mineralocorticoid receptor antagonist such as spironolactone.

Table 4. Evidence-Based Dosing for Antihypertensive Drugs

| Antihypertensive Medication | Initial Daily Dose, mg | Target Dose in RCTs Reviewed, mg | No. of Doses per Day |
|---|---|---|---|
| ACE inhibitors | | | |
| Captopril | 50 | 150-200 | 2 |
| Enalapril | 5 | 20 | 1-2 |
| Lisinopril | 10 | 40 | 1 |
| Angiotensin receptor blockers | | | |
| Eprosartan | 400 | 600-800 | 1-2 |
| Candesartan | 4 | 12-32 | 1 |
| Losartan | 50 | 100 | 1-2 |
| Valsartan | 40-80 | 160-320 | 1 |
| Irbesartan | 75 | 300 | 1 |
| β-Blockers | | | |
| Atenolol | 25-50 | 100 | 1 |
| Metoprolol | 50 | 100-200 | 1-2 |
| Calcium channel blockers | | | |
| Amlodipine | 2.5 | 10 | 1 |
| Diltiazem extended release | 120-180 | 360 | 1 |
| Nitrendipine | 10 | 20 | 1-2 |
| Thiazide-type diuretics | | | |
| Bendroflumethiazide | 5 | 10 | 1 |
| Chlorthalidone | 12.5 | 12.5-25 | 1 |
| Hydrochlorothiazide | 12.5-25 | 25-100[a] | 1-2 |
| Indapamide | 1.25 | 1.25-2.5 | 1 |

# MC Receptor Antagonists

- RH patients have a high prevalence (20%) of primary aldosteronism.
- Spironolactone 12.5 – 50 mg daily lowered BP by 25/12 mmHg in referral patients already on 4 medications.
- BP response was not associated with baseline aldo/renin ratio or 24hr urine aldosterone.

# Resistant Hypertension

**Ernest Mazzaferri Jr., MD**
**Medical Director, Richard M. Ross Heart Hospital**
**Associate Professor - Clinical**
**Department of Cardiovascular Medicine**
**The Ohio State University Wexner Medical Center**

# Introduction to Catheter based renal denervation

## Resistant Hypertension

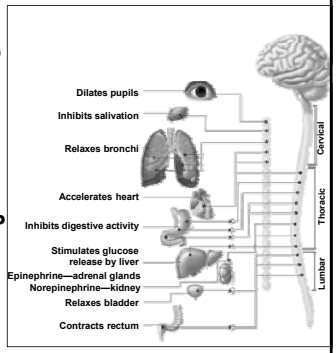
| Causes of Pseudoresistant Hypertension[1,2] | Secondary Causes of Hypertension[1,2] |
|---|---|
| Suboptimal dosing of antihypertensive agents | Obstructive sleep apnea |
| White coat effect | Primary aldosteronism |
| Suboptimal BP measurement technique | Renal artery stenosis |
| Physician inertia | |
| Lifestyle factors | |
| Medications that interfere with BP control | |
| Pseudoresistance caused by poor adherence to prescribed medication | |

**However, a majority of patients with resistant hypertension and no identifiable secondary causes have an activated sympathetic nervous system and increased sympathetic outflow[3]**

1. Calhoun DA, et al. *Circulation.* 2008;117:e510-e526.
2. Makris A, et al. *Int J Hypertens.* 2011;doi: 10.4061/2011/598694.
3. Papademetriou V, et al. *Int J Hypertens.* 2011;doi:10.4061/2011/196518.

## The Sympathetic Nervous System

- **The SNS supplies catabolic signals to the body, acting whenever rapid response to the environment is needed**
- **Functions include:**
  - **Accelerating the heart**
  - **Dilating coronary vessels**
  - **Increasing arterial BP**
  - **Emptying blood reservoirs**
  - **Dilating bronchi**
  - **Releasing glucose**
  - **Inhibiting GI activity**

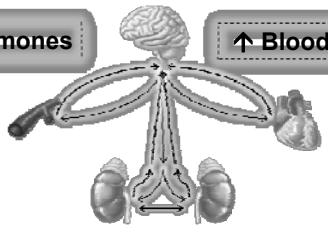



Adapted from Campbell WW. *DeJong's The Neurologic Examination: Incorporating the Fundamentals of Neuroanatomy and Neurophysiology.* 6th ed. 2005.

## Chronic Effect of Increased Sympathetic Nerve Activity

↑ Neurohormones

↑ Blood Pressure



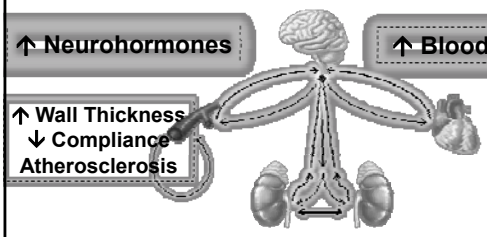
Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

## Chronic Effect of Increased Sympathetic Nerve Activity

↑ Neurohormones

↑ Blood Pressure

↑ Wall Thickness
↓ Compliance
Atherosclerosis



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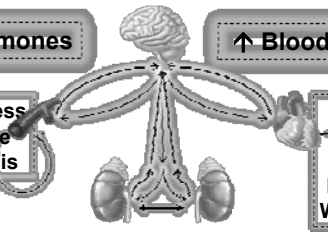

Hypertrophy
Ischemia
Arrhythmia
Heart Failure
Worsening HF

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

## Chronic Effect of Increased Sympathetic Nerve Activity

↑ Neurohormones

↑ Blood Pressure

↑ Wall Thickness
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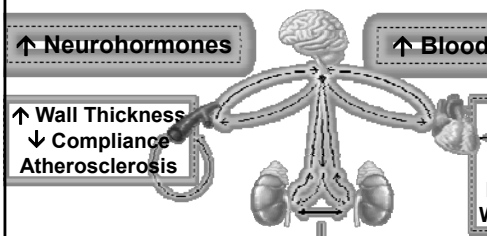
Atherosclerosis

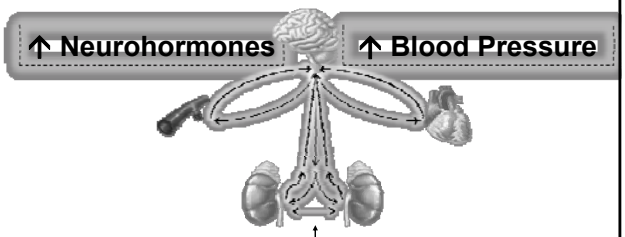


Hypertrophy
Ischemia
Arrhythmia
Heart Failure
Worsening HF

↓ GFR
Ischemia
Kidney Failure
Worsening Kidney Failure

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

# Renal Denervation

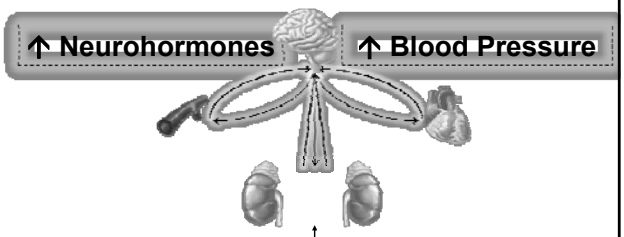



Disrupt the renal nerves, break the cycle

Simultaneously reduce both efferent & afferent effects

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.


# Renal Denervation

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Simultaneously reduce both efferent & afferent effects

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.


# Surgical Sympathectomy

**BENEFITS:** BP, Sx, LVH, Renal function, Stroke rate, Mortality improved

**RISKS:** Operative morbidity and mortality (abandoned in 1970's)


*1. Grimson KS. Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in the treatment of hypertension. Ann Surg 1941;114:753–75.*

*2. Peet M, Woods W, Braden S. The surgical treatment of hypertension: results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic gangliectomy. Clinical lecture at New York session. JAMA 1940;115:1875– 85.*

*3. Smithwick RH. Surgery in hypertension. Lancet 1948;2:65.*

*4. Grimson KS, Orgain ES, Anderson B, Broome RA, Longino FH. Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy. Ann Surg 1949;129:850 –71.*

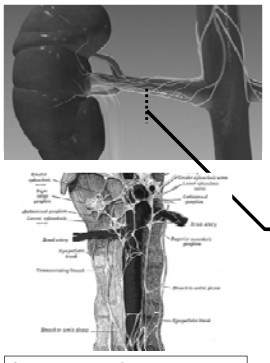
*5. Evelyn KA, Alexander F, Cooper SR. Effect of sympathectomy on blood pressure in hypertension: a review of 13 years' experience of the Massachusetts General Hospital. JAMA 1949;140:592– 602.*

*6. Hinton JW. End results of thoracolumbar sympathectomy for advanced essential hypertension. Bull N Y Acad Med 1948;24:239 –52.*

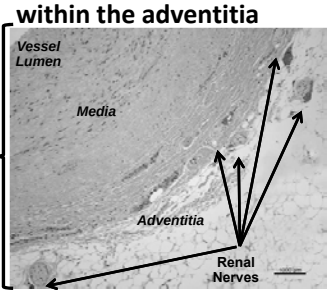
*7. Hammarstrom S, Bechgaard P. Prognosis in arterial hypertension: comparison between 251 patients after sympathectomy and selected series of 435 non-operated patients. Am J Med 1950;8:53– 6.*


# Targeting Renal Nerves

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

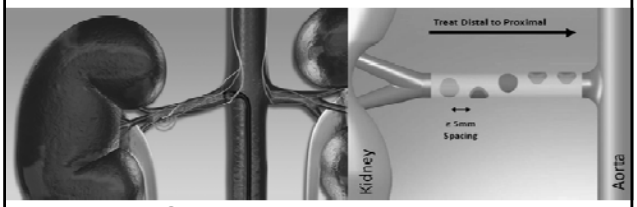







Slide courtesy of. Medtronic, Inc.,

## Renal Nerve Anatomy Allows a Catheter-Based Approach



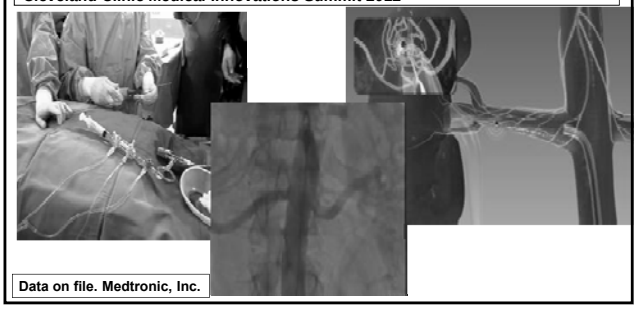

- Standard interventional technique
- 4-6 120-second treatments per artery
- RFA: heat generated from high frequency alternating current

Data on file. Medtronic, Inc.

## Catheter Based Renal Denervation

Catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension has seized the first place on a "Top 10 Medical Innovations List".

*~Cleveland Clinic Medical Innovations Summit 2012*



Data on file. Medtronic, Inc.

## Radio Frequency-Based Renal Denervation Systems

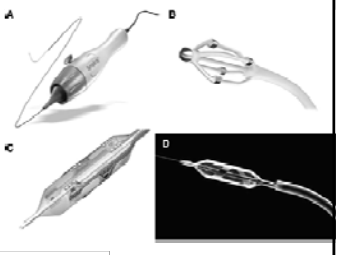
- Standard interventional technique
- Tissue Temp > 50° C, irreversible damage to adjacent nerve fibers
- RF Energy: heat generated from high frequency alternating current

A. Symplicity™
   - Medtronic, Santa Rosa CA

B. EnligHTN
   - St. Jude Medical, St Paul, MN

C. V2 (Vessix)
   - Boston Scientific Co, Natick, MA

D. OneShot
   - Maya Medical, Campbell, CA




Cardiovascular Revascularization Medicine 14 (2013) 229–235

## Ultrasound Energy-Based Renal Denervation

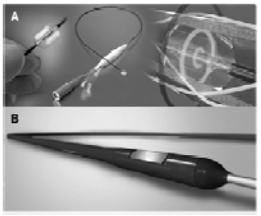
- Standard catheter based interventional technique
- High-frequency sound waves cause frictional heating in tissue
- Temperature ↑sufficient to cause injury to the renal nerves

A. PARADISE™ (Percutaneous Renal Denervation System)
   - ReCor Medical, Ronkonkoma NY

B. TIVUS system
   - Cardiosonic, Tel Aviv, Israel

In development:

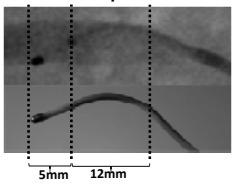
- Beta radiation/Beta-Cath
- Drug-based Renal Denervation
  - Local delivery



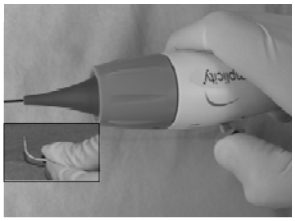

Cardiovascular Revascularization Medicine 14 (2013) 229–235

## First to Trial: 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 120 seconds or when either impedance or temperature exceed program limits




Flexible Tip (self-orienting) Deflectable Shaft



Data on file. Medtronic, Inc.

## Symplicity Trials

Symplicity HTN-1[2]
- First-in-Man[1]
- ⇩
- Series of Pilot Studies

⇩

Symplicity HTN-2[3]
EU/AU Randomized Clinical Trial

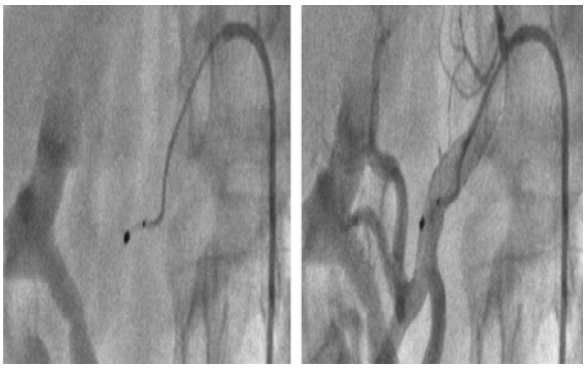
⇩

USA
Symplicity HTN-3[4]
US Randomized Clinical Trial
(enrolling)

Approved Geographies
Other Areas of Research:[4]
Global SYMPLICITY Registry,
Insulin Resistance, HF, Sleep Apnea, More

1. Krum H, et al. *Lancet.* 2009;373:1275-1281.
2. Symplicity HTN-1 Investigators. *Hypertension.* 2011;57:911-917.
3. Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909.
4. Data on file, Medtronic.

## Symplicity Catheter, Medtronic Corp.



## Medtronic/Ardian Symplicity Catheter Ablation

## The Symplicity HTN-1 Trial: Safety & Feasibility

- **Non-randomized, open-label, proof-of-concept study**
- **153 patients with treatment-resistant hypertension**
- **Endovascular catheter-based RDN using the Symplicity Renal Denervation System**
- **36 months (assessments at 1, 3, 6, 12, 18, 24, and 36 months)**
- **Primary efficacy measure: change in office BP**
- **Primary safety measures: based on physical examination, basic blood chemistries, and anatomic assessment of renal vasculature**

Source: Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

## The Symplicity HTN-1 Trial: Safety & Feasibility

**Inclusion Criteria**

**(SBP) ≥160 mm Hg**

**≥3 antihypertensive** medications (including 1 diuretic)

**Exclusion Criteria**

**eGFR <45** mL/min/1.73m$^2$

Type 1 diabetes mellitus

Known secondary cause of hypertension other than sleep apnea or chronic kidney disease

Significant renovascular abnormalities

Source: Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

## Symplicity HTN-1: Baseline Characteristics

| | | |
|---|---|---|
| Demographics | Mean age ± SD (years) | 57 ± 11 |
| | Gender (% female) | 39 |
| | Race (% non-Caucasian) | 5 |
| Comorbidities | Type 2 diabetes mellitus (%) | 31 |
| | Coronary artery disease (%) | 22 |
| | Hyperlipidemia (%) | 68 |
| | Mean eGFR ± SD (mL/min/1.73m$^2$) | 83 ± 20 |
| BP | Mean baseline BP ± SD (mm Hg) | 176/98 ± 17/15 |
| | Mean number of antihypertensive medications ± SD | 5.1 ± 1.4 |
| | Diuretic (%) | **95** |
| | Aldosterone blocker (%) | 22 |
| | Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) (%) | **91** |
| | Direct renin inhibitor (%) | 14 |
| | Beta-blocker (%) | **82** |
| | Calcium channel blocker (%) | **75** |
| | Centrally acting sympatholytic (%) | 33 |
| | Vasodilator (%) | 19 |
| | Alpha 1 blocker (%) | 19 |

Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

## Symplicity HTN-1: Procedure Characteristics

- **38-minute median procedure time**
  - **Average of 4 ablations per renal artery**
- **Intravenous narcotics and sedatives used to manage expected pain during delivery of radiofrequency (RF) energy**

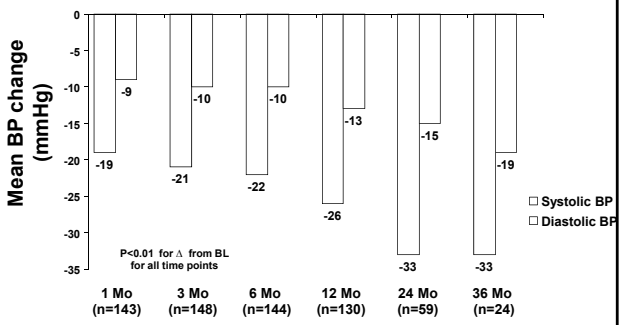
Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

## Symplicity HTN-1: Short Term Procedure Safety

- No catheter or generator malfunctions
- No major complications
- Minor complications in 4 of 153 patients:
  - 1 renal artery dissection during catheter delivery (prior to RF energy delivery); no sequelae
  - 3 access site-complications (pseudoaneurysm/hematoma); treated without further sequelae
- First 20 patients had short-term (14-30 days) follow-up angiography
  - No evidence of RAS or other abnormalities

Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

## Symplicity HTN-1: 36 Month Results




Sobotka P. Symplicity HTN-1: Long-term follow-up of catheter-based renal sympathetic denervation for resistant hypertension confirms durable blood pressure reduction. Presented at: ACC.12 61st Annual Scientific Session & Expo; March 25, 2012. Chicago, IL.

## SYMPLICITY HTN-1 Vascular Safety Out to 36-Months

*Possible Renal Artery Stenosis*

- Progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- New moderate stenosis which was not hemodynamically relevant, requiring no treatment
- Stenosis reported at 18 months via duplex – found non-significant at F/U angiography (20-30%)
- Stenosis at 24 months successfully stented

Krum H *Lancet 2013*

## SYMPLICITY HTN-1 Laboratory Results to 36-Months

| Mean ± SD | Na+ (mmol/L) | K+ (mmol/L) | SCr (µmol/L) | eGFR (mL/min/1.73m²) |
|---|---|---|---|---|
| **Baseline** | 140.4 ± 3.9 (143) | 4.1 ± 0.6 (145) | 83.8 ± 20.1 (143) | 85.2 ±19.0 (28) |
| **3 Months** | 140.4 ± 3.1 (125) | 4.1 ± 0.5 (125) | 85.8 ± 22.6 (132) | 84.1 ±25.7 (29) |
| **6 Months** | 140.5 ± 3.2 (136) | 4.1 ± 0.4 (136) | 85.2 ± 20.1 (142) | 81.6 ± 21.5 (29) |
| **12 Months** | 140.1 ± 3.3 (130) | 4.0 ± 0.4 (129) | 85.4 ± 19.8 (130) | 80.6 ± 18.0 (29) |
| **24 Months** | 139.9 ± 3.0 (43) | 4.1 ± 0.4 (43) | 92.9 ± 29.8 (43) | 79.3 ± 24.5 (28) |
| **36 Months** | 139.7 ± 243 (29) | 4.2 ± 0.9 (29) | 92.0± 32.5 (28) | 74.3 ± 28.0* (29) |

Krum H. ESC *2013*

* Denotes a significant change from baseline $p = 0.05$

## Symplicity HTN-2: Overview

- Multicenter - randomized, controlled study (no sham procedure)
- 106 patients with treatment-resistant hypertension
- Intervention group (endovascular catheter-based RDN with the Symplicity® Renal Denervation System™ plus baseline antihypertensive medications)
- Control group (baseline antihypertensive medications alone)
- 6 months (for the primary endpoint) with follow-up to 3 years
- Primary endpoint: between-group changes in average office SBP from baseline to 6 months

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

## Symplicity HTN-2: Overview

**Inclusion Criteria:**

- 18-85 years of age
- Elevated office SBP ≥160 mm Hg (or ≥150 mm Hg for type 2 diabetics)
- Documented compliance with ≥3 antihypertensive medications

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

## Symplicity HTN-2: Procedural Safety

**No serious device or procedure related adverse events (n=52)**

**Minor adverse events (5)**

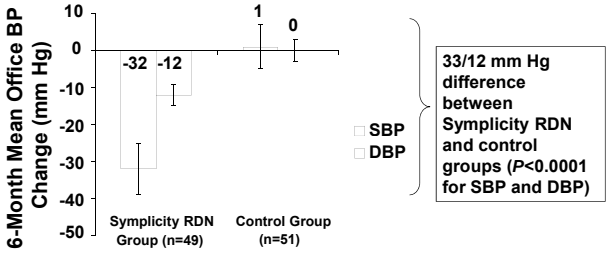
- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 post-procedural drop in BP resulting in a reduction in medication

**6-month renal imaging (n=43)**

- *No vascular abnormality* at any RF treatment site
- 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

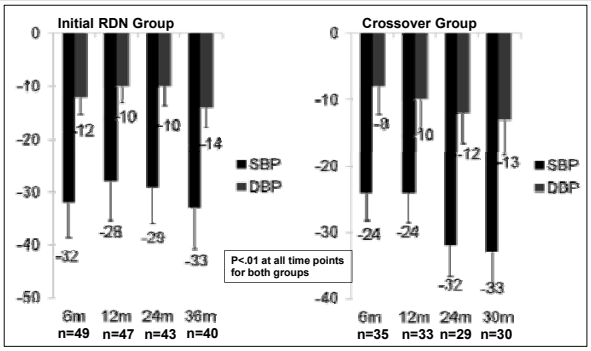
## Symplicity HTN-2: 6-Month Office BP* (Primary Endpoint)




- 84% of patients in the RDN group had ≥10 mm Hg reduction in SBP
- 10% of patients in the RDN group had no reduction in SBP

*Error bars represent 95% CIs.
Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

## SYMPLICITY HTN-2
## Change in Office Blood Pressure through 36-Months Post-Randomization*




Whitbourn R, TCT 2013

*only patients in the RDN group have reached their 36 month post procedure visit

## SYMPLICITY HTN-2
## Safety Through 36 Months of Follow up*

**Procedural** - haematoma, one dissection (unrelated to device), one hypotensive episode (resolved with decrease in medication)

### *0-12 Months Post-Procedure*

- 9 hypertensive events requiring hospitalization
- 2 hypotensive events which required hospitalization

- No clinically meaningful change in eGFR[Ŧ]

Whitbourn R, TCT 2013

*Only treatment group had post procedure data at 36 months;
[Ŧ]Measurements of eGFR were not obtained beyond 12 months

## SYMPLICITY HTN-2
## Safety Through 36 Months of Follow up*

### *12-36 Months Post-Procedure*

- 5 hypertensive events requiring hospitalization
- 1 mild transient acute renal failure, resolved; deemed unrelated to treatment
- 1 acute renal failure due to acute interstitial nephritis; resolved; deemed unrelated to treatment
- 2 cases of Atrial Fibrillation
- 3 deaths considered unrelated to the device or therapy

1 suspected renal artery stenosis, found normal on angiogram

Whitbourn R, TCT 2013

*Only treatment group had post procedure data at 36 months;
[Ŧ]Measurements of eGFR were not obtained beyond 12 months

## SYMPLICITY HTN-3

- **Study Design**
  - **Multi-center, prospective, blinded, randomized controlled trial**
- **Study Objective**
  - **To demonstrate that catheter-based renal denervation is a safe and effective treatment for uncontrolled hypertension**
- **Study Population**
  - **Uncontrolled hypertension population**
    - **SBP ≥160 mmHg despite maximally tolerated doses of ≥3 antihypertensive medication classes**
    - **Without significant renal impairment (eGFR > 45mL/min)**
  - **530 randomized subjects at 90 sites**
    - **Randomization (2:1) – sham procedure**
    - **All patients maintained on baseline meds for 6 months**
- **Enrollment Completed May 2013**

## SYMPLICITY HTN-4

- Study Design
  - Multi-center, prospective, blinded, randomized controlled trial
- Study Objective
  - To demonstrate that catheter-based renal denervation is a safe and effective treatment for uncontrolled hypertension
- Study Population
  - Uncontrolled hypertension population
    - Office BP 140 ≤ SBP < 160 mmHg despite maximally tolerated doses of at least 3 antihypertensive medication classes
    - Without significant renal impairment (eGFR ≥ 30mL/min)
    - 24 ABPM average SBP ≥ 135 mmHg
  - 580 randomized subjects at up to 100 sites
    - Randomization (2:1)
    - All patients maintained on baseline meds for 6 months
- Enrollment closed January 9, 2014

Medtronic

NEWS RELEASE

FOR IMMEDIATE RELEASE

MEDTRONIC ANNOUNCES U.S. RENAL DENERVATION PIVOTAL TRIAL FAILS TO MEET PRIMARY EFFICACY ENDPOINT WHILE MEETING PRIMARY SAFETY ENDPOINT

**MINNEAPOLIS –** January 9, 2014 – Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLICITY 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.

## Is this the end of Renal Denervation?

- Data base locked at end of year, preliminary results released
- HTN 3 has met safety endpoint, but did not meet efficacy endpoint
- Independent panel of advisors to advise Medtronic on next steps
- Full Data Set will be released in peer reviewed journal and presented at upcoming national meeting

## Is this the end of Renal Denervation?

- Enrollment suspended in 3 countries where HTN trials are ongoing (US, HTN Japan, HTN India)
  - HTN 4 (study at OSU is suspended)
- FDA – access available in 86 countries where the device is approved – discussions with regulatory bodies ongoing
- Global registry, 5000 plus patients, post market surveillance ongoing.
- Next steps for HTN-3 – follow patients for 5 years; cross over patients procedures suspended
- Other devices may still come to trial to better understand this technology

## Conclusions

- A significant percentage of hypertensive patients are poorly controlled, but the exact prevalence of resistant hypertension is unknown
- In the general population aged ≥60 years, initiate pharmacologic therapy at SBP ≥150 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <150 mm Hg and DBP <90 mm Hg. (Strong Recommendation – Grade A)

## Conclusions (continued)

- In the general population <60 years, initiate pharmacologic therapy to at DBP ≥90 mm Hg and treat to a goal DBP <90 mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A)
- In the general population <60 years, initiate pharmacologic therapy at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)

## Conclusions (continued)

- A majority of patients with resistant hypertension (and no secondary cause) have an activated sympathetic nervous system and increased sympathetic outflow
- Until yesterday, preliminary efficacy data for renal denervation was promising

## Conclusions (continued)

- The Symplicity Trials reinforce the importance of blinded randomized clinical trials
- Symplicity HTN-3 was a very well designed trial that did not meet it's efficacy endpoint
  - Stay tuned, more to come!