Renal Denervation

Indication, Evidences, & Future

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Disclosure Statement of Financial Interest

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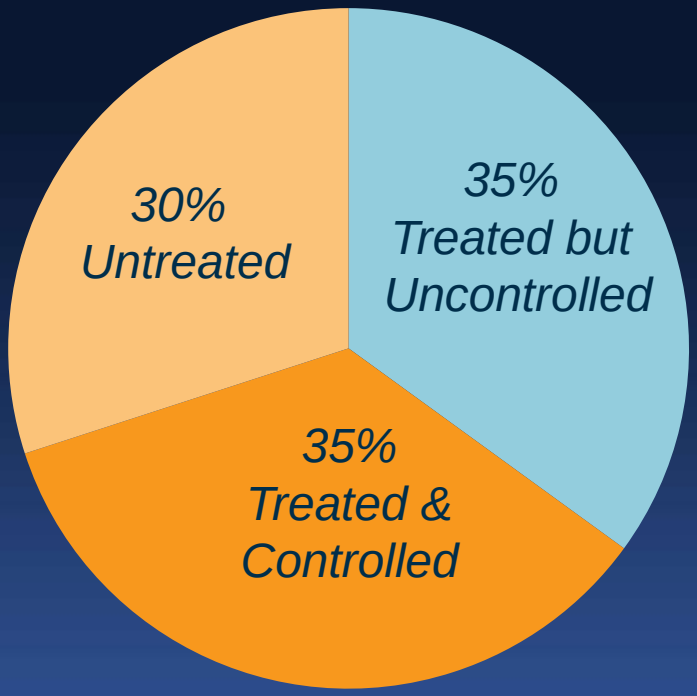
- No industry sponsorship

Hypertension Epidemiology



- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensive patients are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025
- **Resistant HTN : 5-30%**

Chobanian et al. Hypertension. 2003;42(6):1206–1252.

Effects of Increased Sympathetic Activity

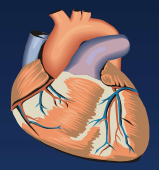
Causes of increased afferent signaling from the kidney to central integrative structures

Consequences of increased efferent sympathetic outflow to the kidney and other organs

Factors that might contribute to increased renal afferent signaling:

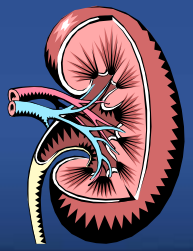
- Adenosine
- Acidosis
- Oxidative stress
- Inflammation
- Endothelial factors
- Angiotensin II
- ischemia

Renal denervation



- Remodeling
- Hypertrophy
- Arrhythmias
- Ischemia
- Apoptosis

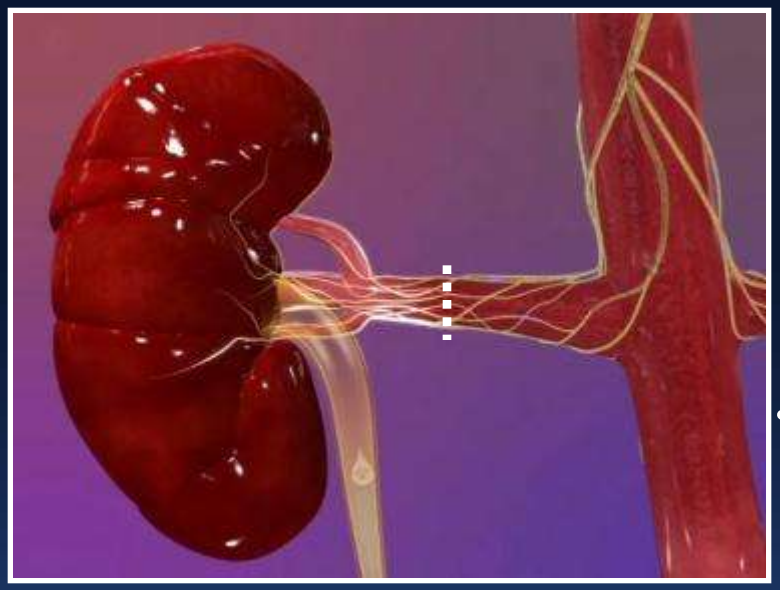
- Medial hyperplasia
- Arterial compliance ↓
- Endothelial dysfunction

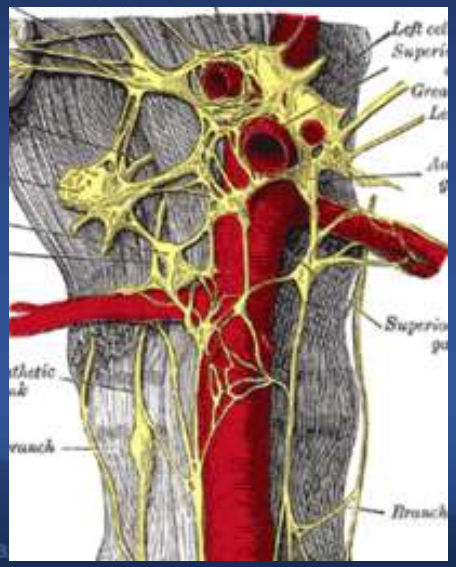


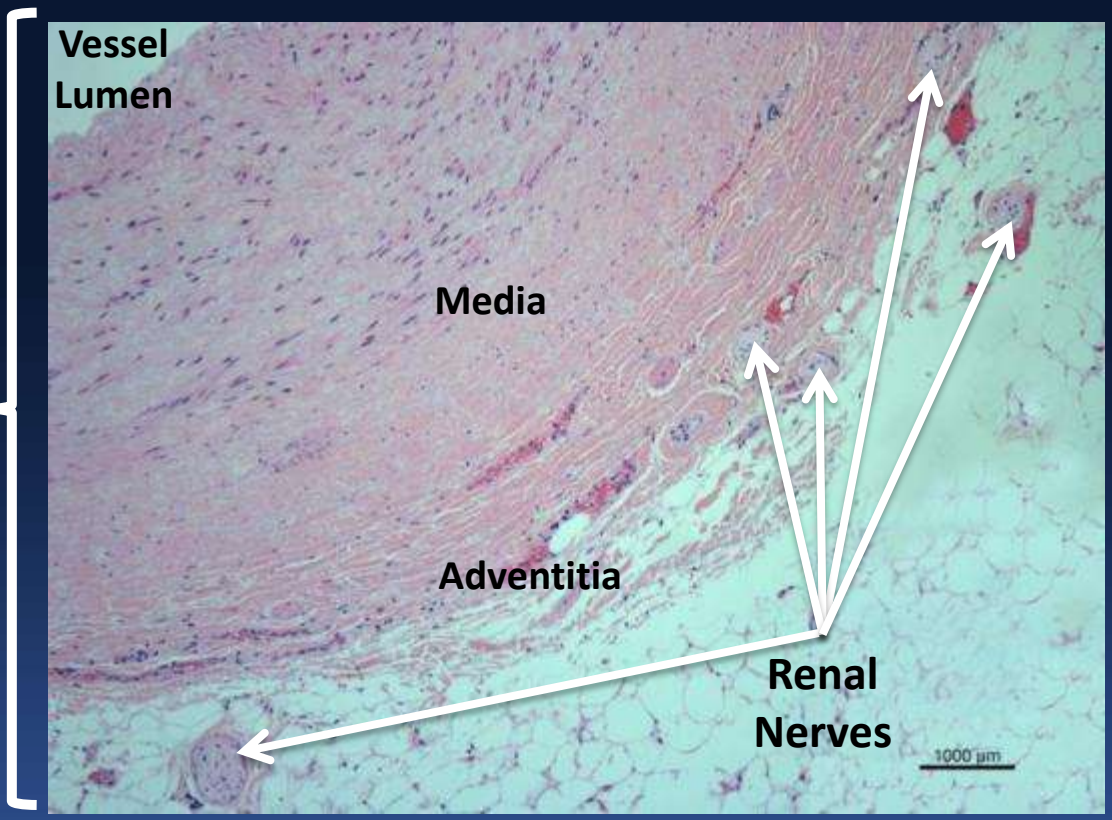
Renal injury / Renal ischemia

- Na^+ / H_2O retention
- Reduced renal blood flow
- Activation of the RAAS
- Proteinuria
- Glomerulosclerosis

Renal Nerves as a Therapeutic Target







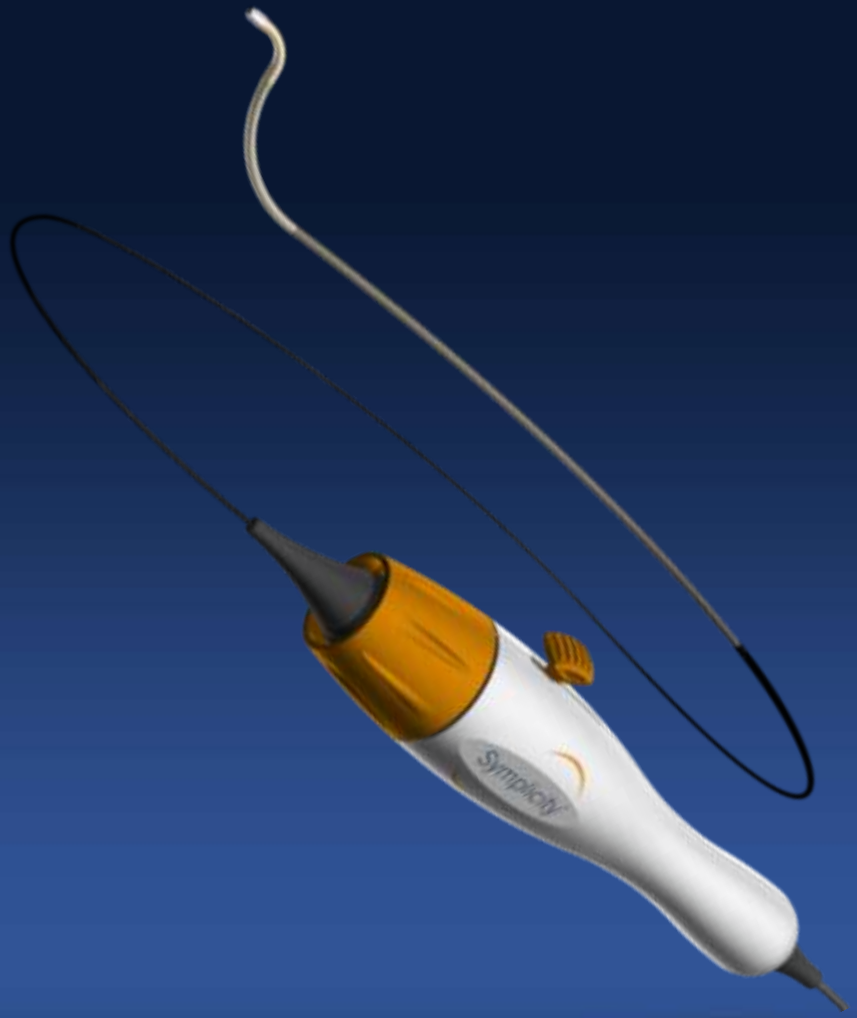
- Arise from ~ T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

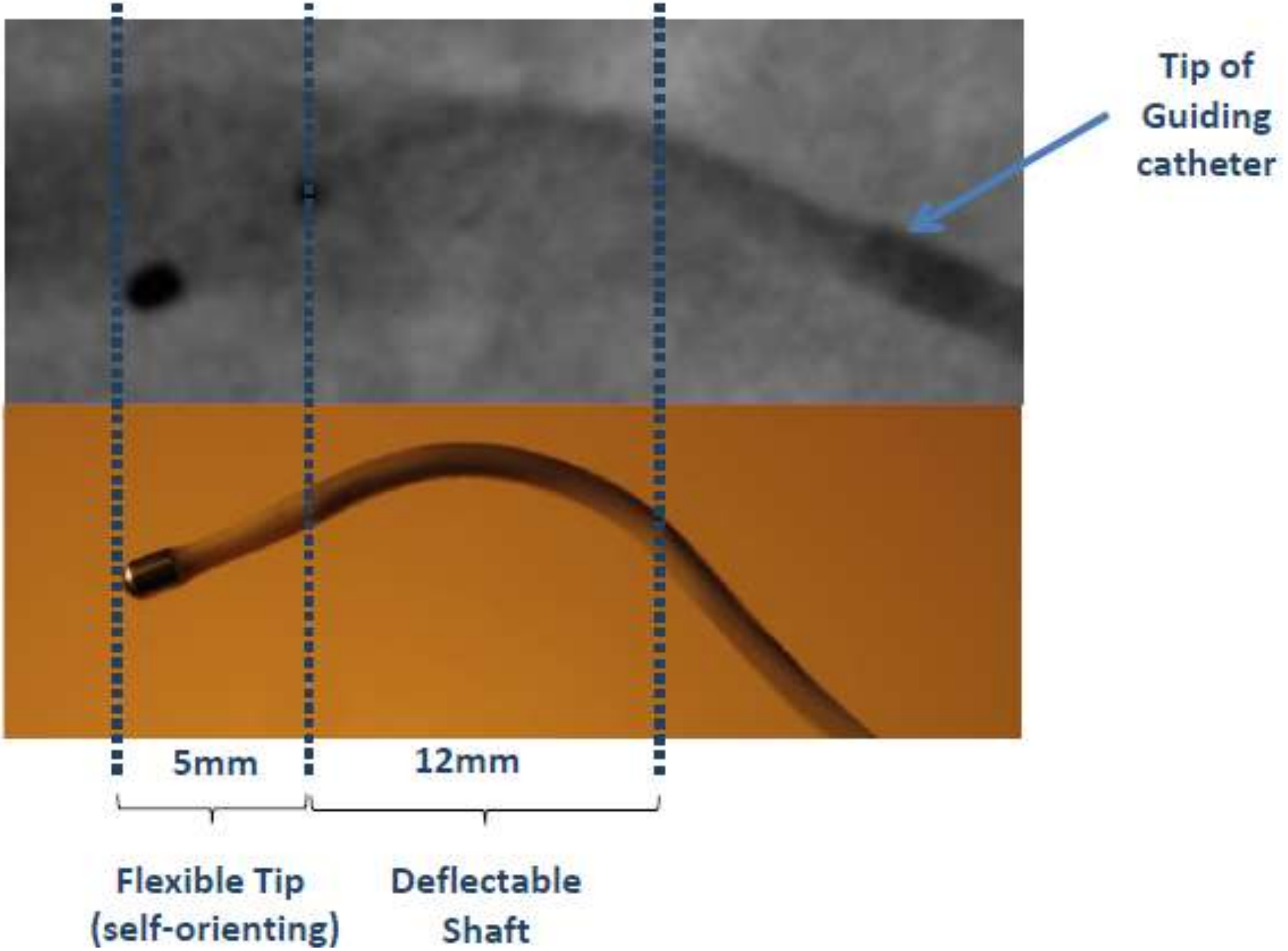
Generator

- Energy maximum 8 Watt
- It automatically switches off if
  - temperature increases too fast or too slowly
  - temperature is higher than 75 ˚C
  - Impedance does not decrease sufficiently

Simplicity™ Catheter

- Radiofrequency electrode tip
- Handle allows bending of the tip and rotation
- Compatible with a 6 F guiding catheter




Tip of Guiding catheter
5mm
12mm
Flexible Tip (self-orienting)
Deflectable Shaft

Procedural details

- Premedication
  - Aspirin 100 mg/day (to be continued for 1 week)
  - 10-20 mg morphin + sedatives
  - 5,000 U heparin
  - Nitro i.a.
- 6 F femoral sheath
- 6 F renal guiding catheter
- Angiography of all renal arteries
- Introduce radiofrequency catheter
- 4-8 ablations, 2 min each

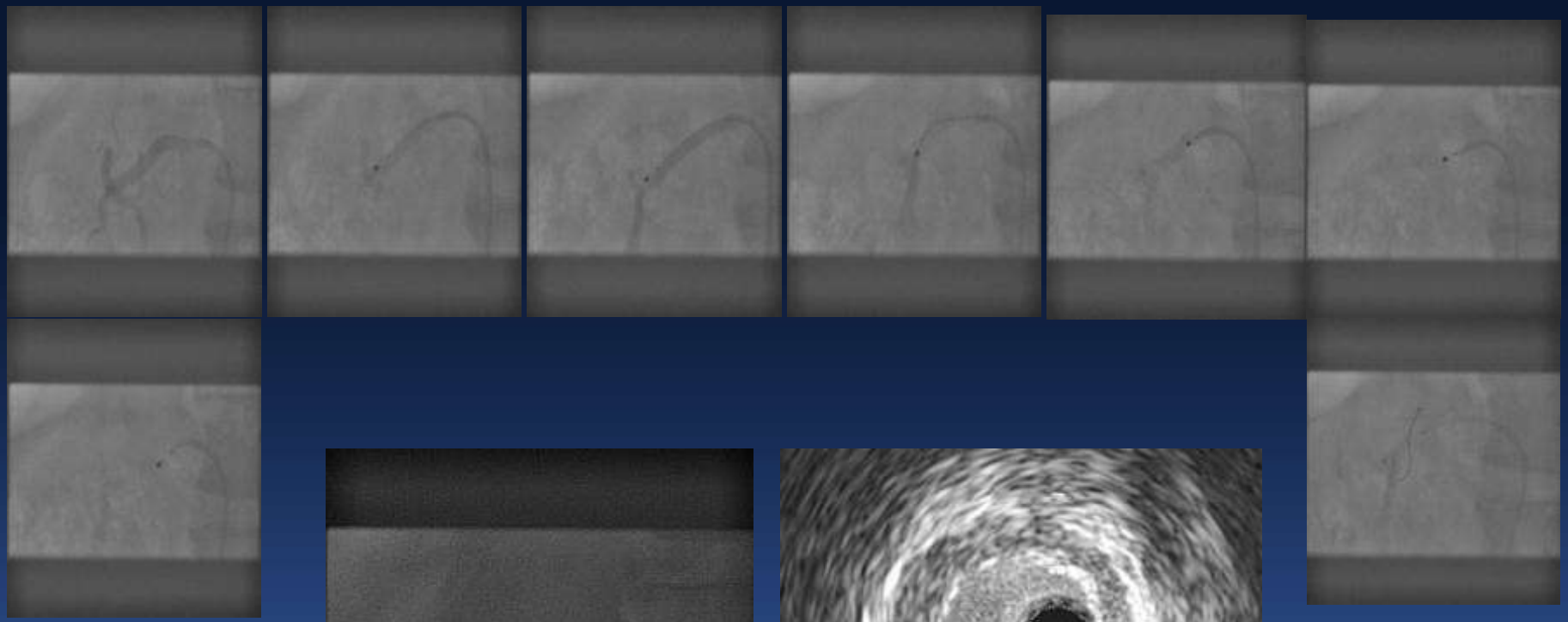
AMC Cases

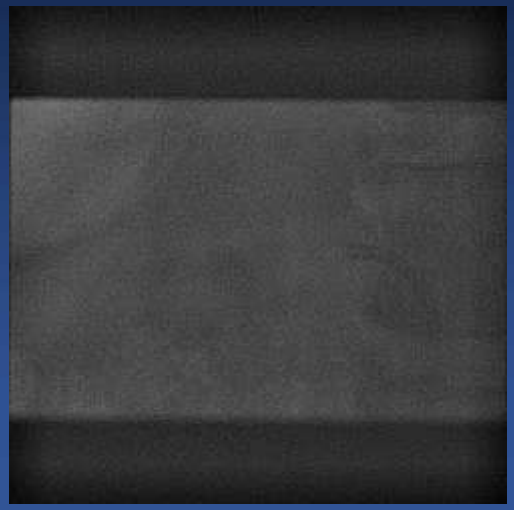
- 53/ M, 171cm, 78kg
- HTN, DM
- Caduet 5/20mg, cadura XL 1T, dichlozid 25mg, exforge 5/160mg, tenormin 50mg qd
- Initial BP: **167/88** mmHg
- Cr 0.97
- Procedure time; 80min
- Contrast medium ; Visipaque, 70 cc

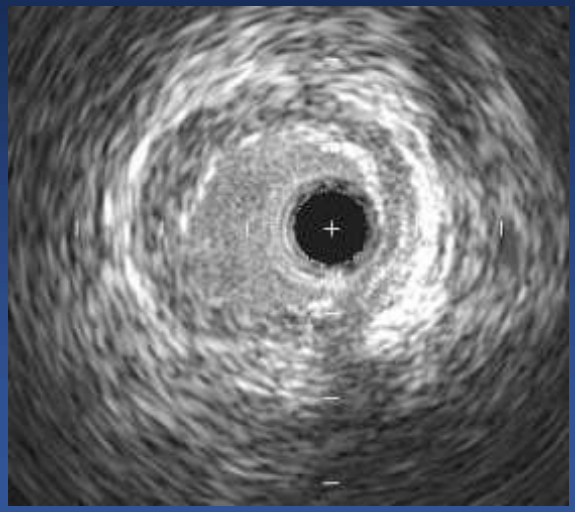
Successful Ablation in Left Renal Aretery

Totally, 8 ablations were done in Left Renal Artery

And Then, Right Renal Artery….







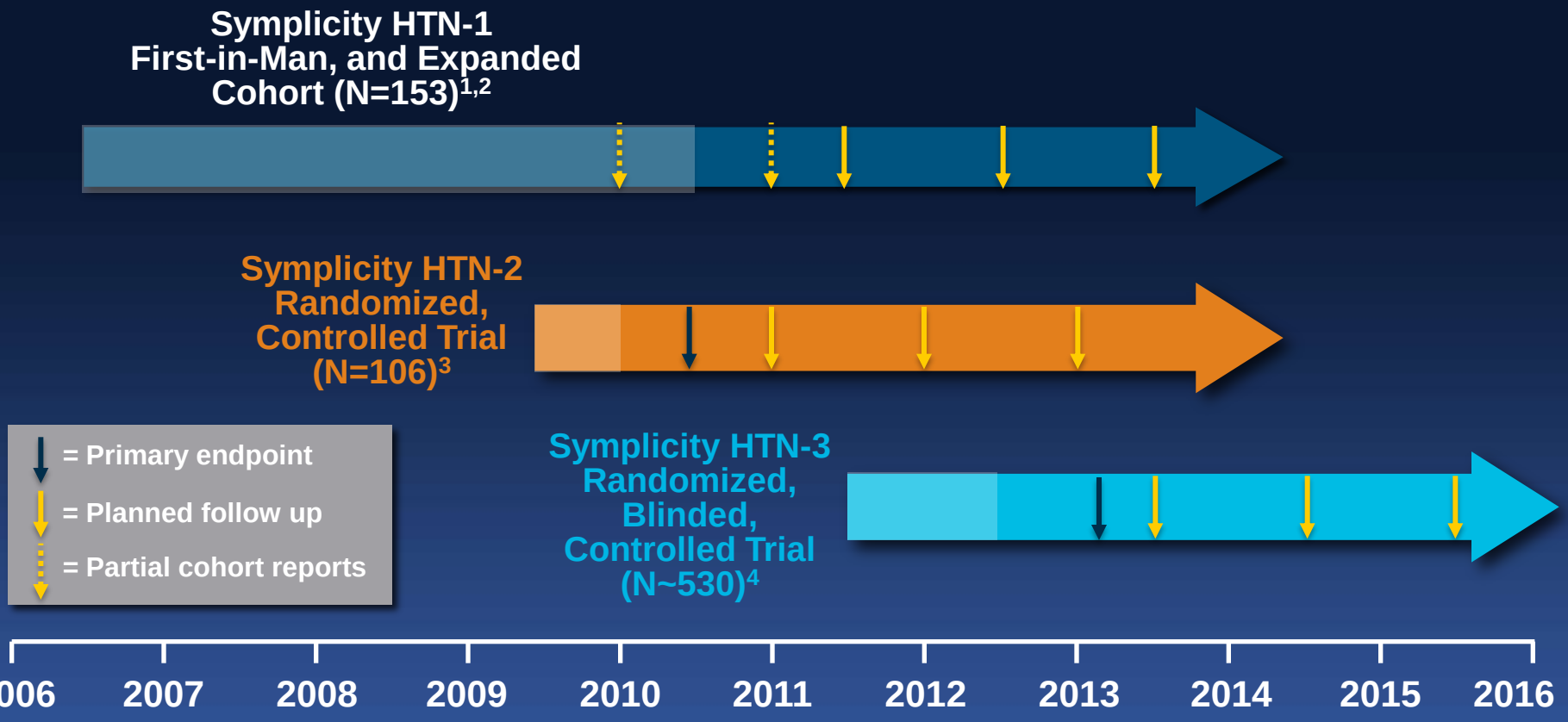
Additionally, 8 ablations were done in Right Renal Artery

Follow Up

- No procedure related complication
- Discharge 1 day later
- 1 month follow up : 155/85 mmHg, HR 78
- 3 months : 145/85 mmHg, HR 77
- 6 months : **135/78** mmHb, HR 65

Clinical studies

The Symplicity HTN Clinical Trial Program



Shading on bars indicates clinical trial enrollment periods.
Enrollment period for HTN-3 is estimated.

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

Symplicity HTN-1


THE LANCET

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Bogusław Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281


Hypertension

Celebrating 30 Years: 1979 to 2009

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Catheter-based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Hypertension. 2011;57:911-917.

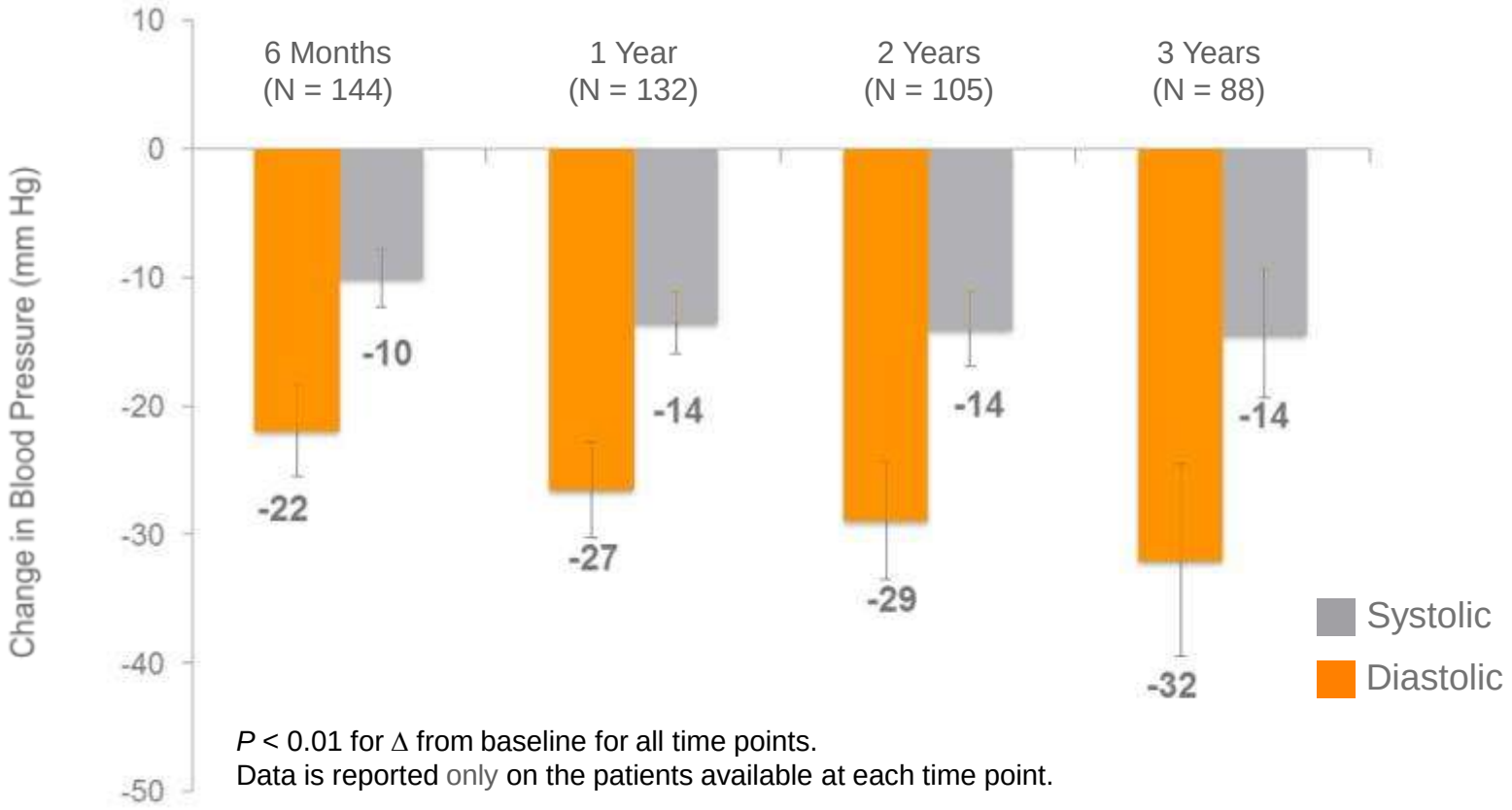
Initial Cohort – Reported in the *Lancet*, 2009:

- 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**

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: Significant, Sustained BP Reduction to 3 Years



P < 0.01 for Δ from baseline for all time points.
Data is reported only on the patients available at each time point.

Expanded results presented at the European Society of Cardiology Annual Meeting, 2013.

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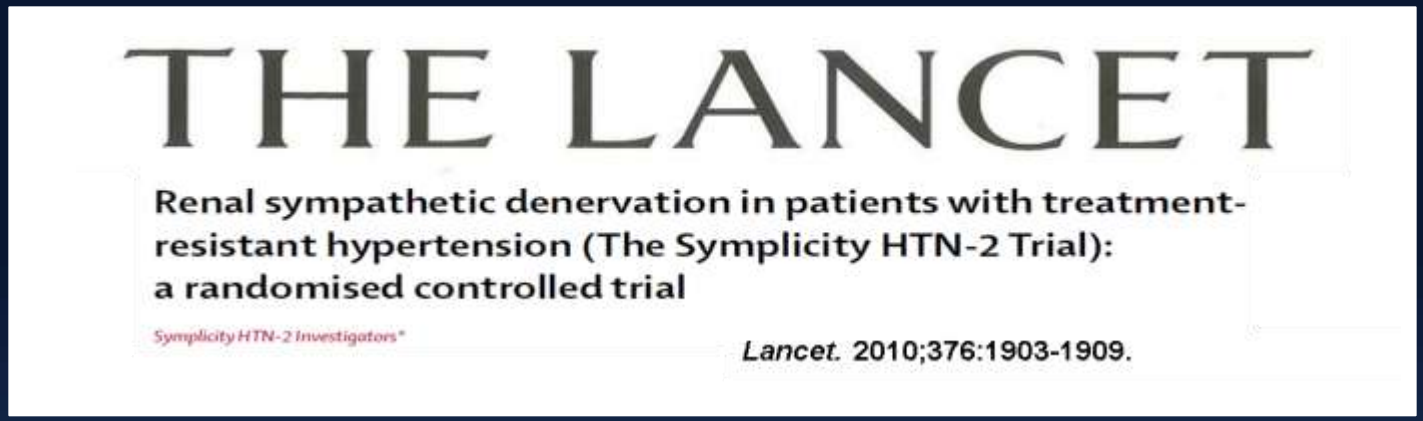
Symplicity HTN-2


THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

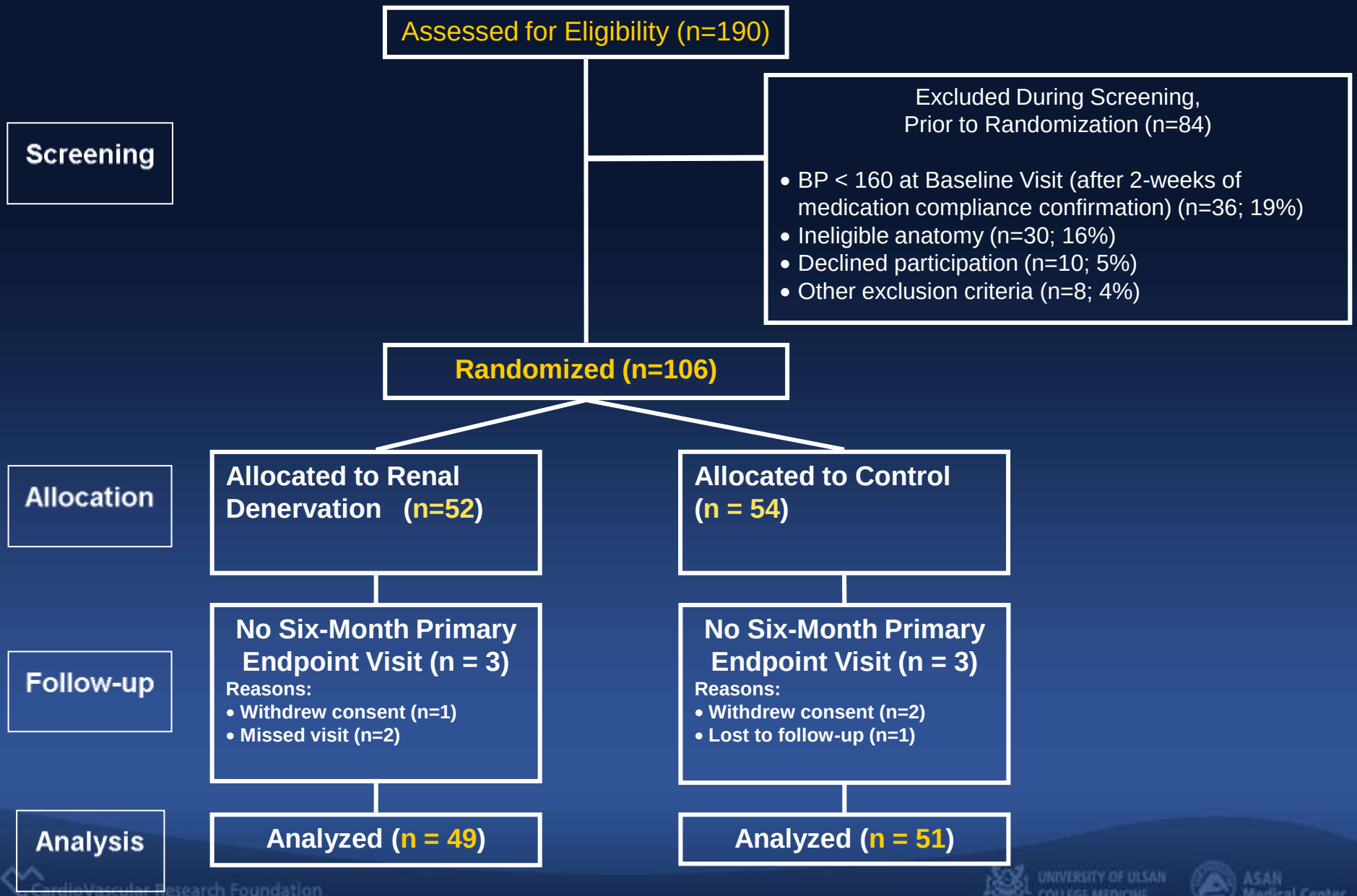
Symplicity HTN-2 Investigators*

Lancet. 2010;376:1903-1909.

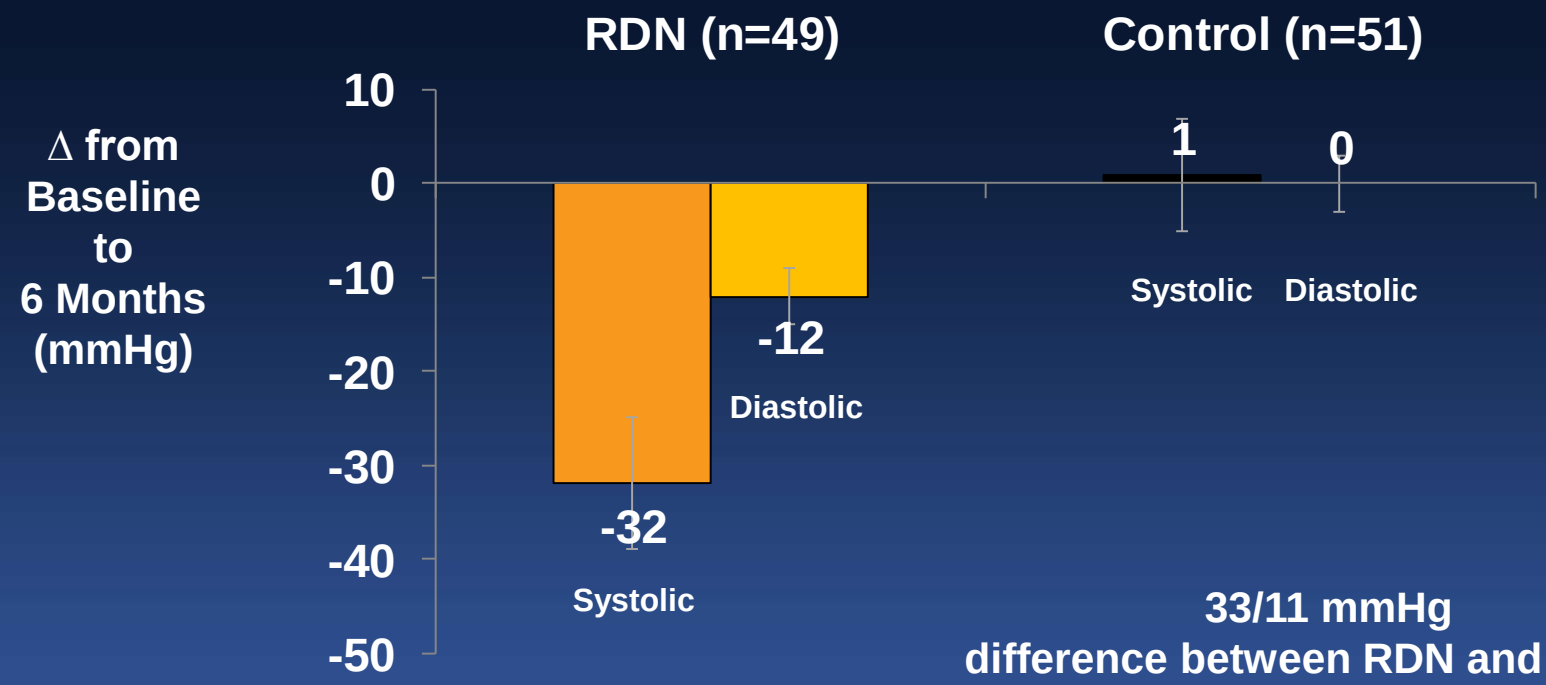
- Purpose: To demonstrate the effectiveness of catheter-based renal denervation (RDN) for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- Patients: 106 patients with drug-resistant hypertension randomized 1:1 to treatment with RDN vs. control
- Clinical Sites: 24 centers in Europe, Australia, & New Zealand
  - 67% were designated hypertension centers of excellence
- Primary Endpoint: Office systolic BP change from baseline at 6 months

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-9.

Patient Disposition



Primary Endpoint: 6-Month Office BP



33/11 mmHg difference between RDN and Control (p<0.0001)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-9.

SYMPLICITY HTN-2: BP Reductions Sustained to 3 Years

Sustained Reductions in the Pooled (RDN and Crossover) Group*

*Crossover patients only had 30 months post-procedure data.

Whitbourn, TCT 2013

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Medtronic RDN SYMPLICITY HTN-3

Trial Objectives

- SYMPLICITY HTN-3 is the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.
- The trial included 535 patients enrolled by 88 participating US centers.

Key Inclusion/Exclusion Criteria

Key Inclusion:

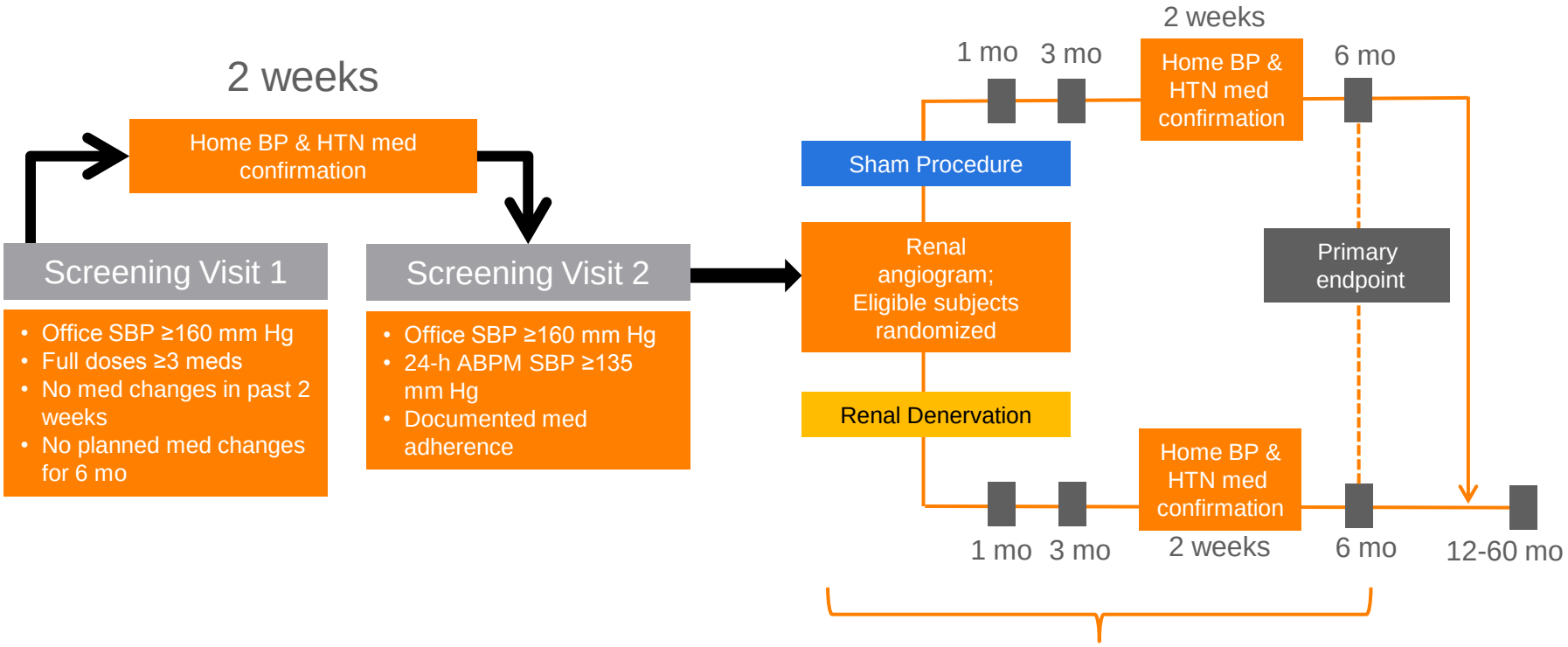
- Stable medication regimen including full tolerated doses of 3+ anti hypertensive medications of different classes, including a diuretic
- Office SBP ≥160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit

Key Exclusion:

- ABPM 24 hour average SBP <135 mm Hg
- eGFR of <45 mL/min/1.73 m^2
- Main renal arteries <4 mm diameter or <20 mm treatable length

SYMPLICITY HTN-3: Severe Drug-Resistant HTN Office SBP ≥160 mm Hg

- 2:1 randomization, blinded and controlled
- Sham procedure in control patients that included renal angiogram
- 535 subjects randomized out of 1441 enrolled (63% screen failure rate)
- 2-week screening process, including maximum tolerated doses of antihypertensives



- Patients, BP assessors, and study personnel all blinded to treatment status
- No changes in medications for 6 M

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Key Safety Endpoint

Safety analysis

- Composite endpoint of death, renal injury, vascular complications, and embolic tissue injury to 1 month and renal artery stenosis to 6 months. <7% MAE rate required to meet the primary safety endpoint.

Primary safety analysis

- A performance goal established from renal artery stenting required the major adverse event rate for safety be <9.8%. This requires the observed MAE rate to be <7%, given the expected confidence interval for this endpoint.

Key Efficacy Endpoints

Efficacy analysis

- Comparison of SBP change from baseline to 6 mo in RDN arm compared with change from baseline to 6 mo in control arm
  - **Endpoint = $(SBP_{RDN\ 6\ mo} - SBP_{RDN\ baseline}) - (SBP_{CTL:\ 6\ mo} - SBP_{CTL\ baseline})$**

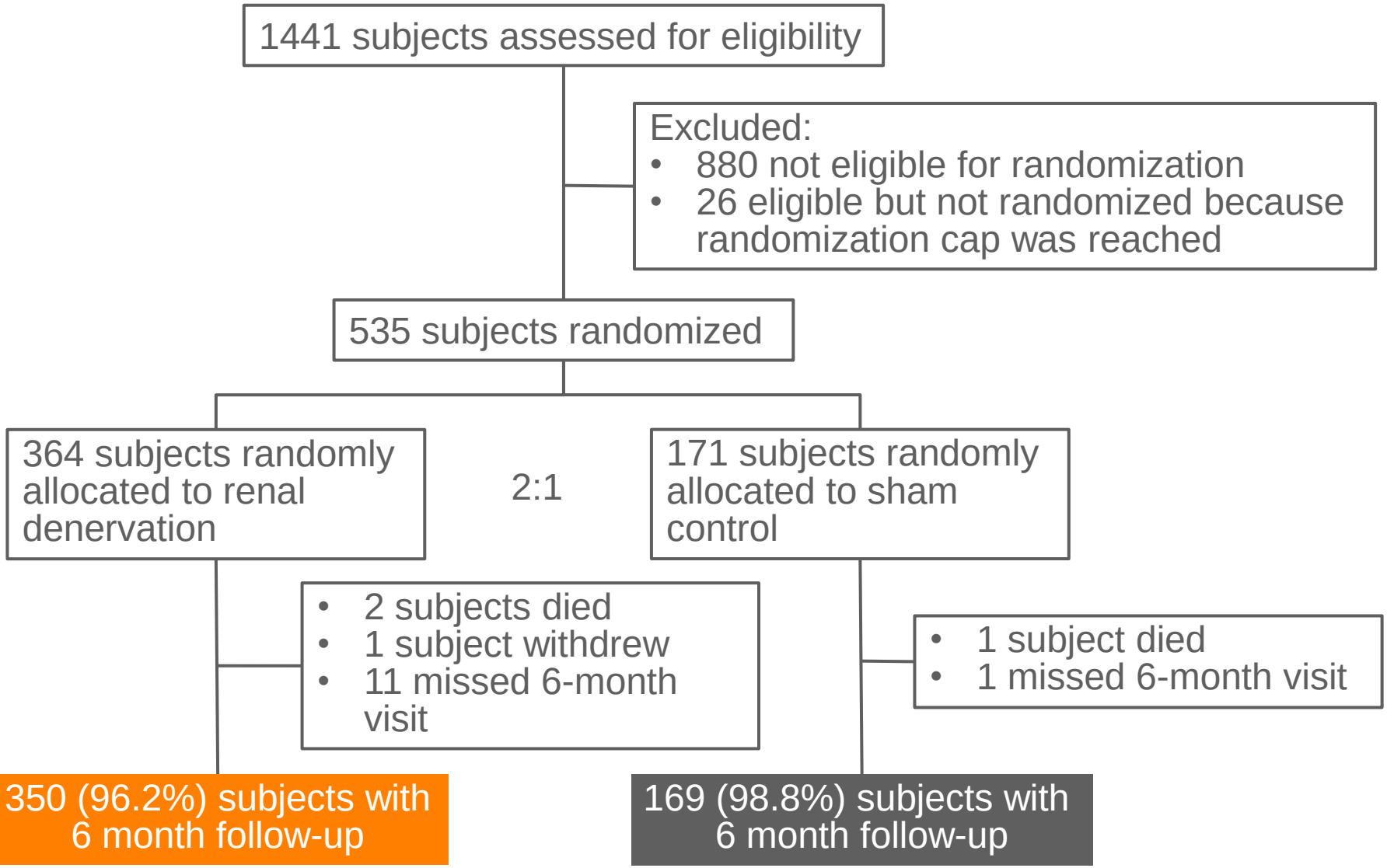
Primary efficacy (OBP) endpoint assumptions

- Superiority analysis
  - **Superiority margin of 5 mm Hg, per FDA recommendation**
- Assuming a standard deviation of 25 mm Hg for both arms, 10 mm Hg is the minimum treatment difference required to meet the efficacy endpoint (95% CI)

Secondary efficacy (ABPM) endpoint assumptions

- Superiority analysis
  - **Superiority margin of 2 mm Hg, per FDA recommendation**
- Assuming a standard deviation of 18 for both arms, 5.5 mm Hg is the minimum difference required to meet the efficacy endpoint (95% CI)

Patient Disposition



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Results: Population Demographics

Characteristic (Mean ± SD or %)	Renal Denervation (N = 364)	Sham Procedure (N = 171)	*P*
Age (years)	57.9 ± 10.4	56.2 ± 11.2	0.09
Male sex (%)	59.1	64.3	0.26
Office systolic blood pressure (mm Hg)	180 ± 16	180 ± 17	0.77
24-h mean systolic ABPM (mm Hg)	159 ± 13	160 ± 15	0.83
BMI (kg/m^2)	34.2 ± 6.5	33.9 ± 6.4	0.56
Race* (%)			0.57
African American	24.8	29.2	
White	73.0	69.6	
Medical history (%)			
Renal insufficiency (eGFR<60 mL/min/1.73 m^2)	9.3	9.9	0.88
Renal artery stenosis	1.4	2.3	0.48
Obstructive sleep apnea	25.8	31.6	0.18
Stroke	8.0	11.1	0.26
Type 2 diabetes	47.0	40.9	0.19
Hospitalization for hypertensive crisis	22.8	22.2	0.91
Hyperlipidemia	69.2	64.9	0.32
Current smoking	9.9	12.3	0.45

*Race also includes Asian, Native American, or other

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Results: Baseline Hypertensive Therapy

Characteristic mean ± SD or %	Renal Denervation (N = 364)	Sham Procedure (N = 171)
No. of antihypertensive medications	5.1 ± 1.4	5.2 ± 1.4
Angiotensin-converting enzyme inhibitor (%) At maximum tolerated dose	49.2 45.9	41.5 37.4
Angiotensin receptor blocker (%) At maximum tolerated dose	50.0 49.5	53.2 51.5
Aldosterone antagonist (%)	22.5	28.7
Alpha-adrenergic blocker (%)	11.0	13.5
Beta blocker (%)	85.2	86.0
Calcium channel blocker (%) At maximum tolerated dose	69.8 57.1	73.1 63.7
Centrally acting sympatholytic (%)	49.2	43.9
Diuretics (%) At maximum tolerated dose	99.7 96.4	100 97.7
Direct renin inhibitor	7.1	7.0
Direct-acting vasodilator	36.8	45.0

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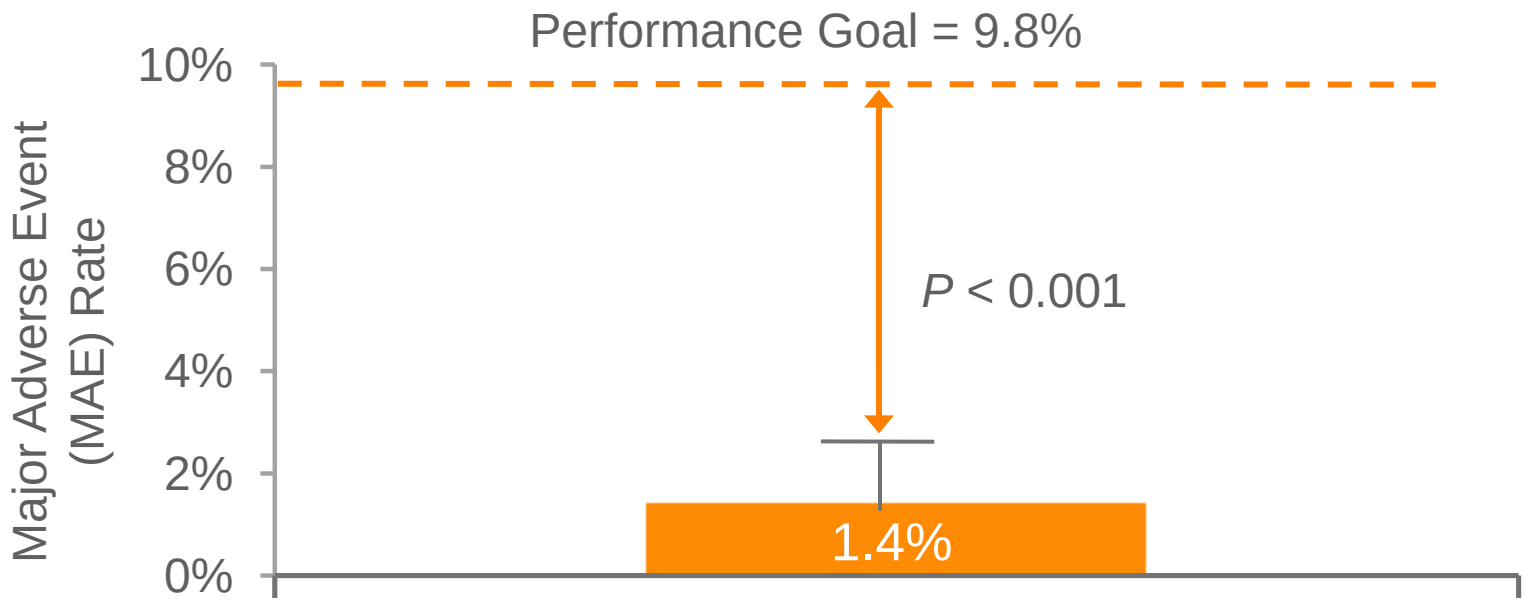
HTN-3 Results: Primary Safety Endpoint



Safety Measures	Renal Denervation (N = 364)	Sham Procedure (N = 171)	Difference (95% CI)	*P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% (-0.9%, 2.5%)	0.67

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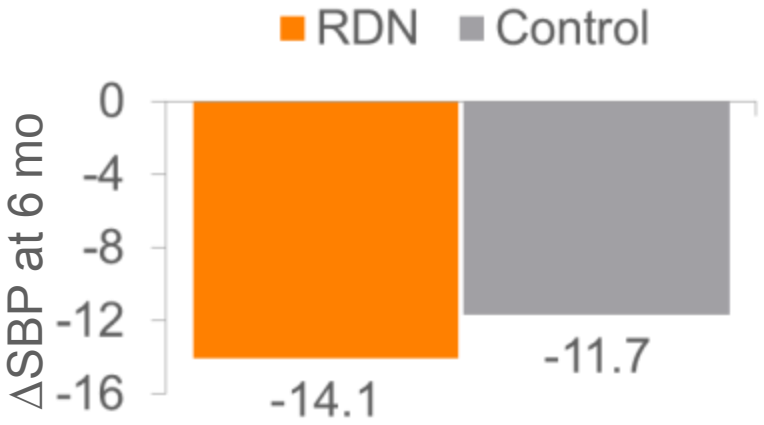
Primary Efficacy Endpoint

Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin



	RDN	Control	*P* value
Baseline SBP	179.7	180.2	0.765
6 mo SBP	165.6	168.4	0.260
Change	*-14.1* *P < 0.001*	*-11.7* *P < 0.001*	*0.255*[1]

-2.39 (-6.89, 2.12), *P* = 0.255 (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint

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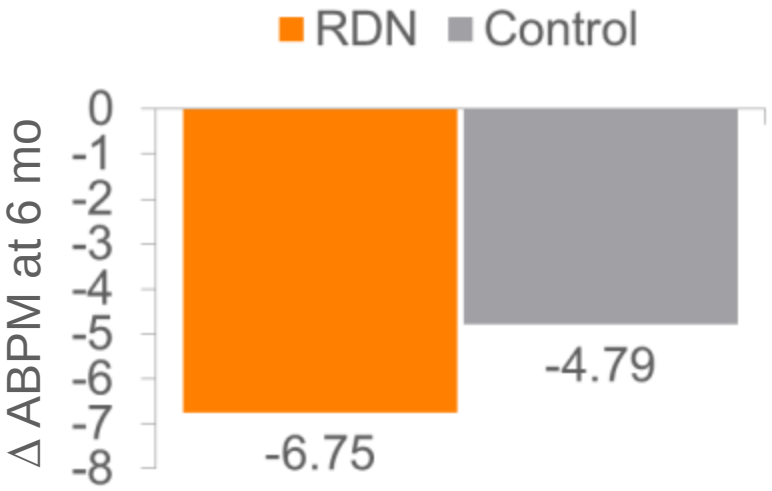
Secondary Efficacy Endpoint

Ambulatory Systolic Blood Pressure at 6 Months, 2 mm Superiority Margin



	RDN	Control	*P* value
Baseline SBP	158.55	158.85	0.828
6 mo SBP	151.80	154.05	0.201
Change	*-6.75* *P < 0.001*	*-4.79* *P < 0.001*	*0.979*

-1.96 (-4.97, 1.06), *P* = 0.979 (ITT analysis with 2 mm Hg superiority margin)

- Did not meet secondary efficacy endpoint

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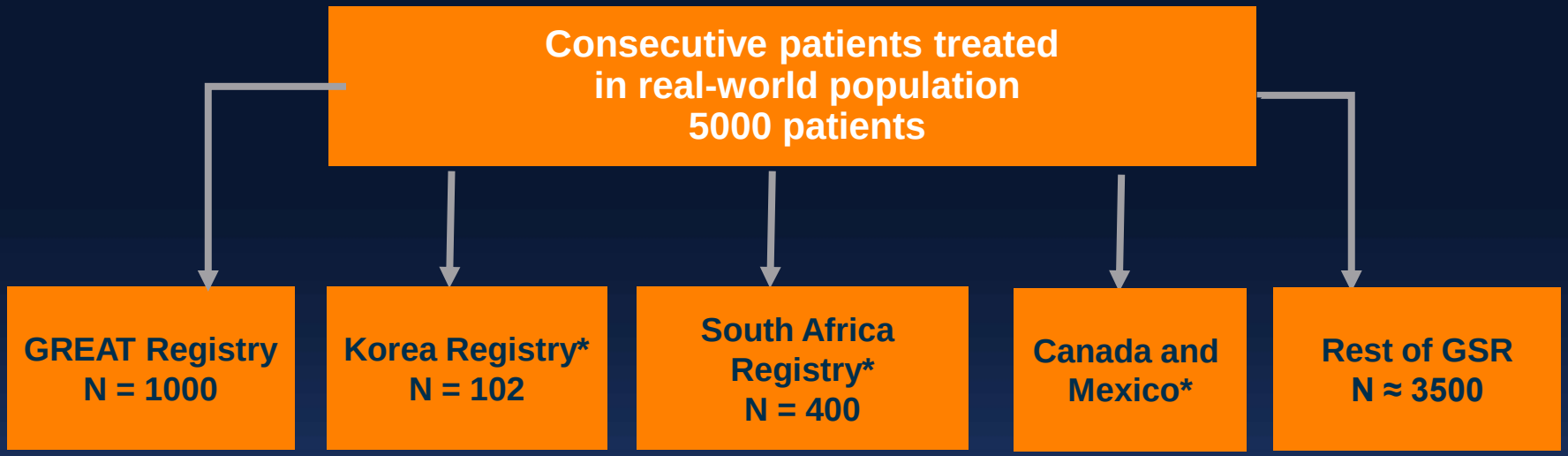
Global Symplicity Registry (GSR)

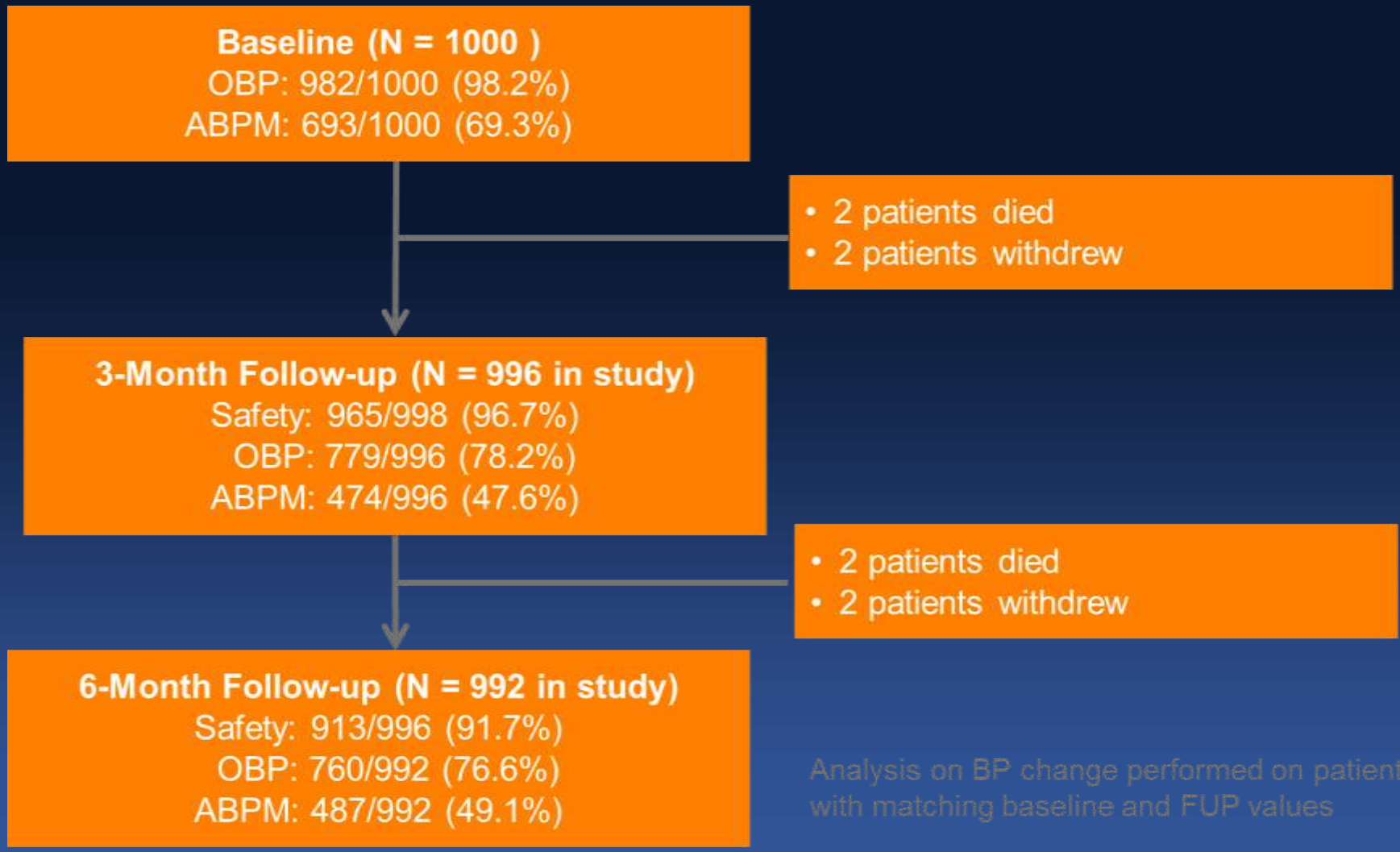


231 international sites in 37 countries
Min. 10% randomly assigned to 100% monitoring

Follow-up schedule

* Limited to resistant hypertension only

GSR Patient Disposition



Analysis on BP change performed on patients with matching baseline and FUP values

GSR Baseline Patient Characteristics

	All Patients (N = 1000)	SBP ≥160 mm Hg and Ambulatory SBP ≥135* mm Hg (N = 327)
Gender (% male)	61.2%	63.9%
Age (years)	60.7 ± 12.0	61.0 ± 10.9
BMI (kg/m^2)	30.5 ± 5.5	30.9 ± 5.5
Current smoking	10.0%	11.0%
History of cardiac disease	50.5%	52.9%
Renal impairment (eGFR <60 mL/min/1.73 m^2)	23.4%	27.9%
Sleep apnea (AHI≥5)	4.2%	5.9%
Diabetes, type 1	3.2%	2.5%
Diabetes, type 2	38.5%	42.6%
1 comorbidity	39.7%	36.7%
2 comorbidities	35.5%	34.6%
3+ comorbidities	24.6%	28.4%

* With ≥3 antihypertensive medication classes

GSR Antihypertensive Medication Use

	All Patients (N = 1000)	SBP ≥160 mm Hg and Ambulatory SBP ≥135 mm Hg* (N = 327)
Antihypertensive medication class	4.5 ± 1.3	4.7 ± 1.2
Beta-blockers	78.9%	81.0%
ACE inhibitors	33.8%	38.5%
Angiotensin receptor blockers	67.3%	67.9%
Calcium channel blockers	76.3%	78.9%
Diuretics	78.2%	79.8%
Aldosterone antagonists	21.1%	19.3%
Spironolactone	18.6%	15.9%
Alpha-adrenergic blockers	35.2%	40.1%
Direct-acting vasodilators	15.1%	19.0%
Centrally acting sympatholytics	33.2%	37.6%
Direct renin inhibitor	7.4%	7.7%

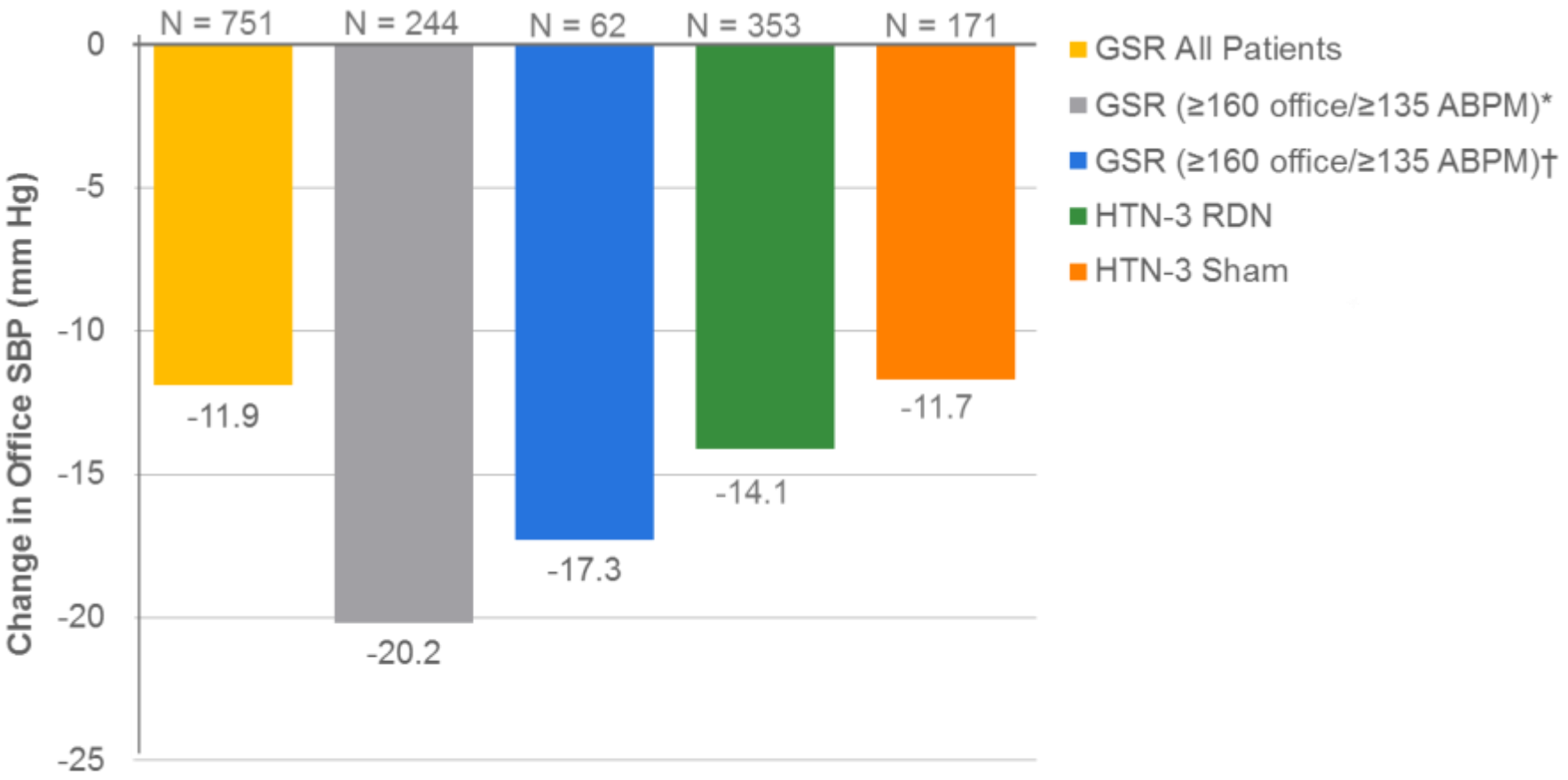
*With ≥3 antihypertensive medication classes.

Safety in HTN-3 and GSR

	HTN-3 RDN Arm (N = 364)	GSR All Patients (N = 1000)	GSR Office SBP ≥160 mm Hg and ABPM ≥ 135* mm Hg (N=327)
MAE	1.4%	0.8%	1.3%
At 6 months			
Death	0.6%	0.4%	0.3%
New-onset end-stage renal disease	0.0%	0.2%	0.3%
Significant embolic event resulting in end-organ damage	0.3%	0.0%	0.0%
Renal artery re-intervention	0.0%	0.2%	0.0%
Vascular complication	0.3%	0.4%	0.7%
Hypertensive crisis/emergency	2.6%	1.0%	1.7%
New renal artery stenosis >70%	0.3%	0.0%	0.0%

*With ≥3 antihypertensive medication classes.

Change in Office SBP at 6 Months for GSR and SYMPLICITY HTN-3 Patients



*With ≥3 antihypertensive medication classes.
†With ≥3 antihypertensive medications at maximum tolerated dose.

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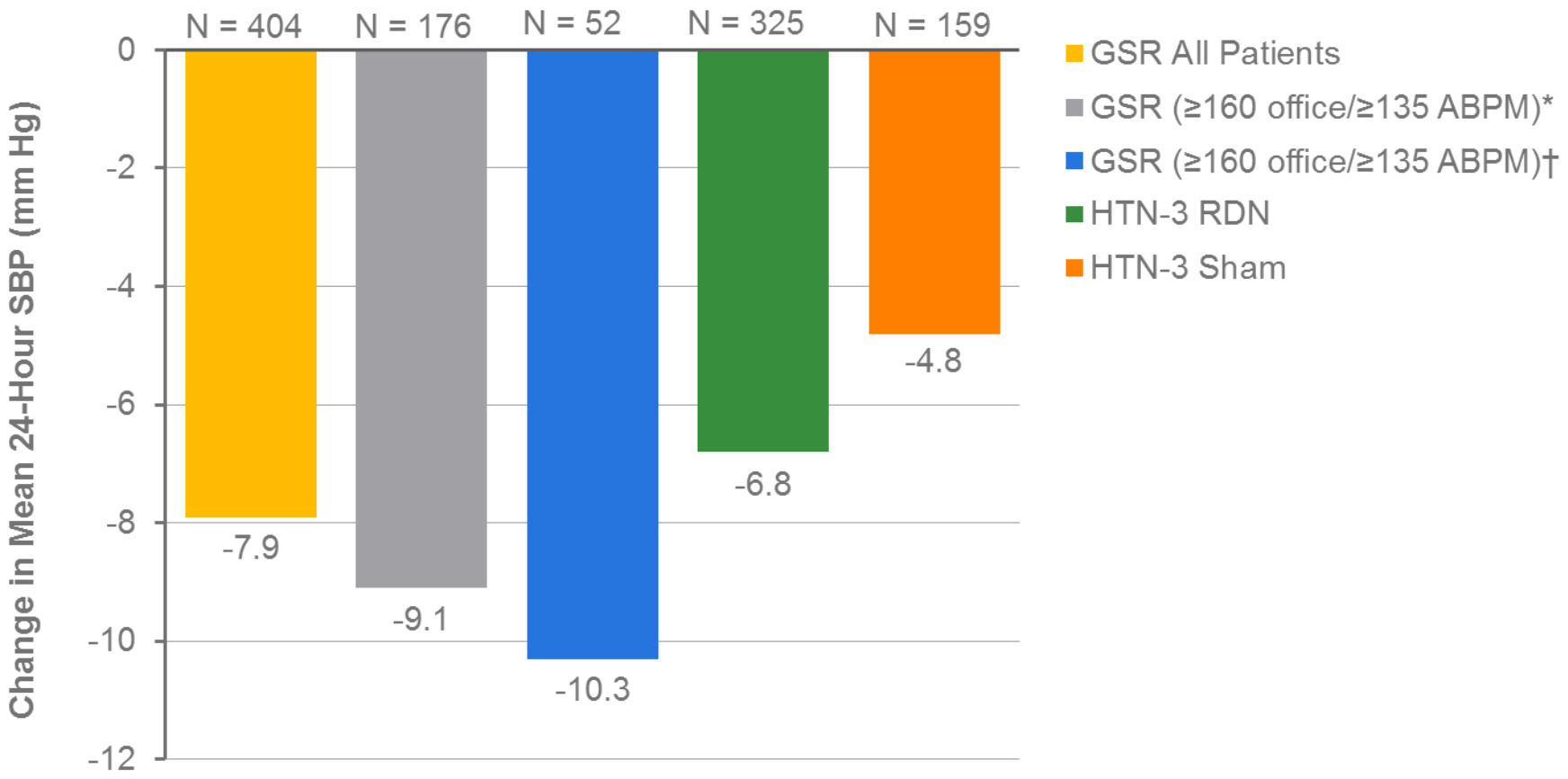
Change in Ambulatory SBP for GSR and SYMPLICITY HTN-3 Patients



*With ≥3 antihypertensive medication classes.
†With ≥3 antihypertensive medications at maximum tolerated dose.

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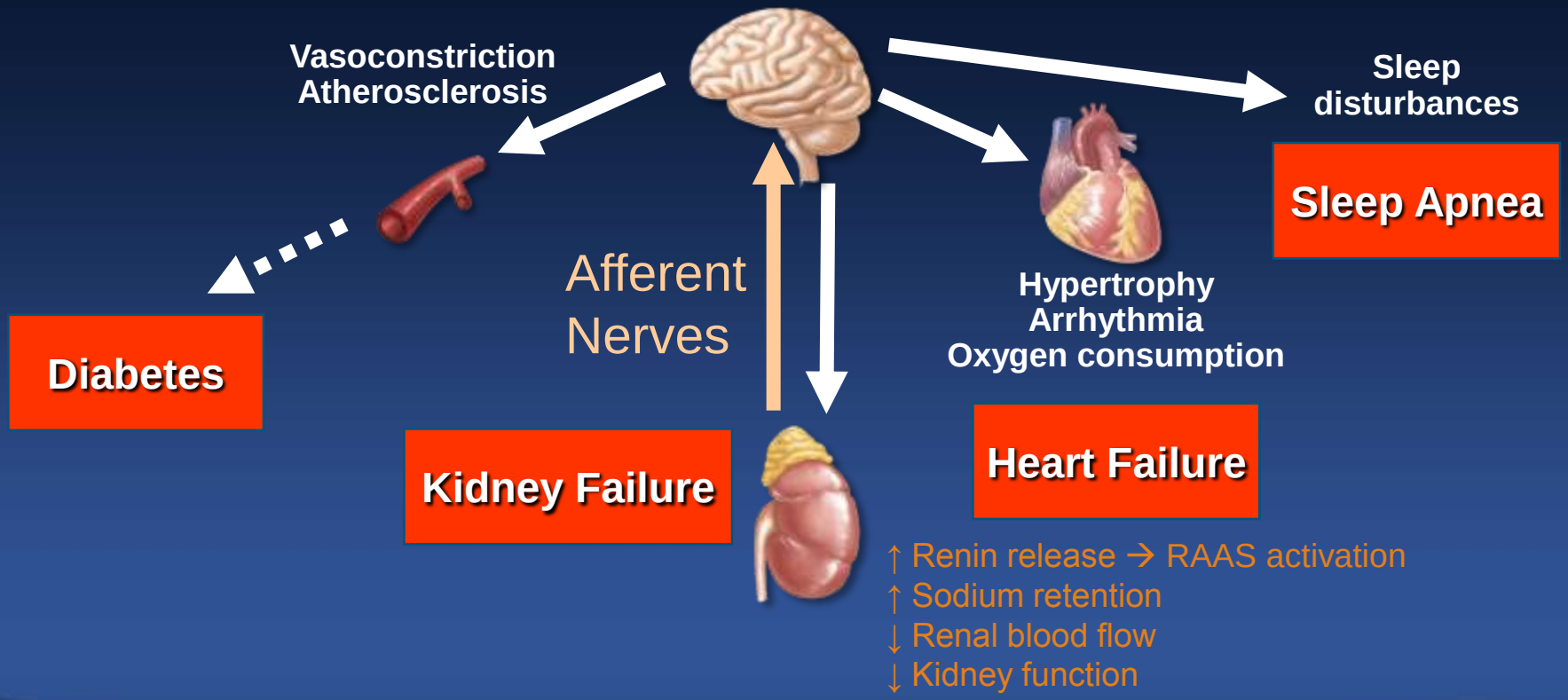
GSR Conclusions

- Excellent procedural and clinical safety profile in the largest data set of real-world RDN patients to date.
- Significant reductions in both office and ambulatory BP from baseline.
  - Differences from SYMPLICITY HTN-3 include randomization, blinding, sham control, BP inclusion criteria, antihypertensive-drug treatment intensity, and an African American cohort in HTN-3.
  - Despite the limitations of comparing a registry with a randomized, blinded, controlled study, the reduction in blood pressure is numerically larger in the GSR at 6 months after treatment.
  - Due to the nature of registry studies, it is difficult to account for the magnitude of a possible placebo effect in GSR.

Beyond the Hypertension

Future Directions for Research

- Chronic activation of renal nerves is common in multiple conditions/disease states[1,2]
- Future research may be warranted in disease states characterized by hyperactive afferent and efferent renal nerves



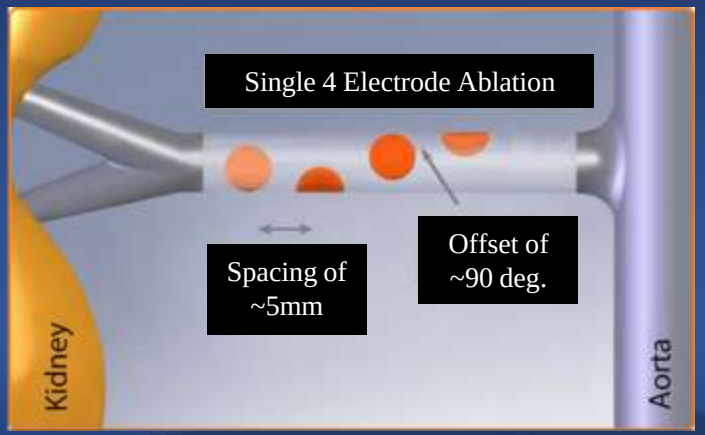
RAAS = renin-angiotensin-aldosterone system.

1. Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.
2. Blankestijn PJ, et al. *Nephrol Dial Transplant*. 2011;26:2732-2734.

New Devices

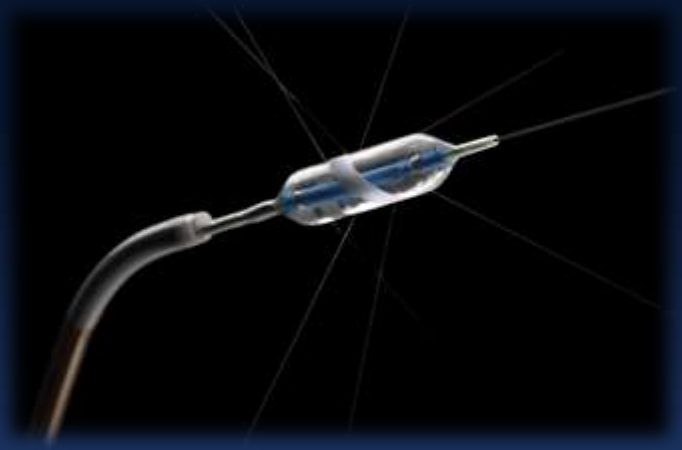
Medtronic's Multi-Electrode

- RF, multi-electrode, simultaneous firing
- 60 second ablation time per artery
- FIM completed, PI: Robert Whitbourn, M.D
- N=9 patients



Covidien OneShot™ Renal Denervation System

- Balloon with spiral electrode
  - 20 mm long
  - 5, 6 and 7mm diameter
  - Low pressure (<1atm)
  - 0.014" guidewire
  - 8F guide compatible
- Cooling by irrigation holes placed alongside spiral electrodes
  - Protects non-treated region of artery
  - Enhances control and consistency of the treatment effect
  - Prevents sticking of electrode to tissue
- 2 min. ablation per artery



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

Key Takeaways

- SYMPLICITY HTN-3 did not reach the primary or powered secondary efficacy endpoints in this trial. There may be many factors that contributed to the outcome, which we continue to investigate.
- SYMPLICITY HTN-3 did meet its safety endpoint, which is consistent with all other Symplicity trials, including the Global SYMPLICITY Registry.
- Based upon detailed analysis of HTN-3, further clinical investigation is warranted and Medtronic will, in consultation with FDA, pursue a new IDE trial.
- An unmet need in this uncontrolled hypertension population still exists. Medtronic will continue to provide access to the Symplicity system in countries where it has regulatory approval and will continue to support a global hypertension clinical program.