Heart & Vascular Research Center

Novel Therapies for Treatment of Resistant Hypertension

Sanjay Gandhi, MD, FACC,FAHA
Director, Endovascular Cardiology

Case Western Reserve University

MetroHealth Heart and Vascular Center

Disclosures

- No financial conflicts of interest
- Co-PI at Metrohealth for Ardian Simplicity pilot trial and for Medtronic Simplicity HTN 3 trial
- I will be discussing investigational use of products

MC

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- 47 year old man HTN for > 10 years, obesity, sleep apnea
- Recurrent admissions with hypertensive urgency associated with chest pain and recurrent headaches.
- BP during these periods- 200-220/100-110 systolic. Resting BP 160-180/90-100
- No prior history of MI , stroke or PAD
- Strong family history of HTN

MC

- His medications include
  - Labetalol 300 mg bid,
  - Amlodipine 10 mg daily
  - Valsartan 320 mg daily
  - HCTZ 25 mg daily
  - ASA 81 mg
  - Simvastatin 20 mg qhs
- Compliant with medications. Works as security guard
- Exam significant for BP 160/100 HR of 60
- Cardiac exam regular S1/S2 with S4
- Normal distal pulses with no bruits

MC

- Mild proteinuria
- Normal chemistry including K , BUN of 12, Cr of 1.13
- Normal CBC

What would you do next?

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1. Evaluate for secondary HTN
2. Escalation of drug therapy
3. Titration of therapy for sleep apnea
4. All of the above

MC

- Previously checked normal urine catecholamines
- Normal TSH
- Renal ultrasound- normal renal size bilaterally, poor quality for vascular assessment
- CTA abdomen with single bilateral renal arteries without stenosis
- Echo with LVH
- Coronary angiography with normal coronary
- Sleep study with adequate control of OSA with CPAP

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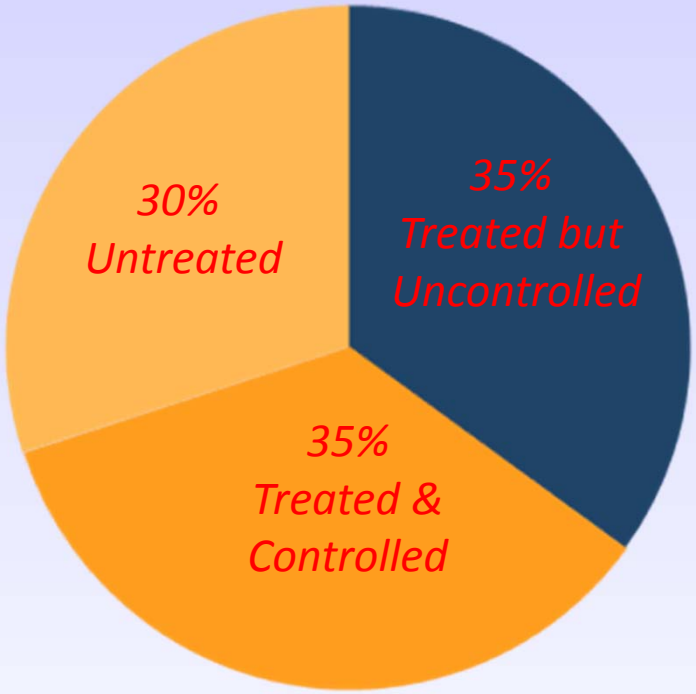
So what now?

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
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025

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

Reasons for uncontrolled HTN

- About 1/3 are untreated
- Of those that are treated only half achieve control
  - Therapeutic inertia due to under-treatment- 72%
  - Treatment resistant hypertension
    - BP uncontrolled on a rational regimen including >/= 3 or controlled on >/= 4 anti-hypertensive medications
    - Increased from 15.9% in 1998-2004 to 28% in 2005-2008 in NHANES survey
    - Related to obesity, chronic kidney disease and high Framingham 10 year coronary risk score

Egan et al. Circulation. 2011;124:1046-1058

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Mechanical therapies for Resistant HTN

Autonomic Modulation

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Approach	Disease States	Companies	Sympathetic Modulation	Parasympathetic Modulation
Baroreflex Activation	Hypertension Heart Failure	CVRx	Yes	Yes
Vagal Stimulation	Heart Failure	Biocontrol	No	Yes
Spinal Cord Stimulation	Heart Failure	MDT	No	Yes
Renal Nerve Ablation	Hypertension	MDT, BSX, St Jude, Kona, Cryomedix, Cryomend, Mercator, Northwind	Yes	No

Carotid Baroreflex Physiology

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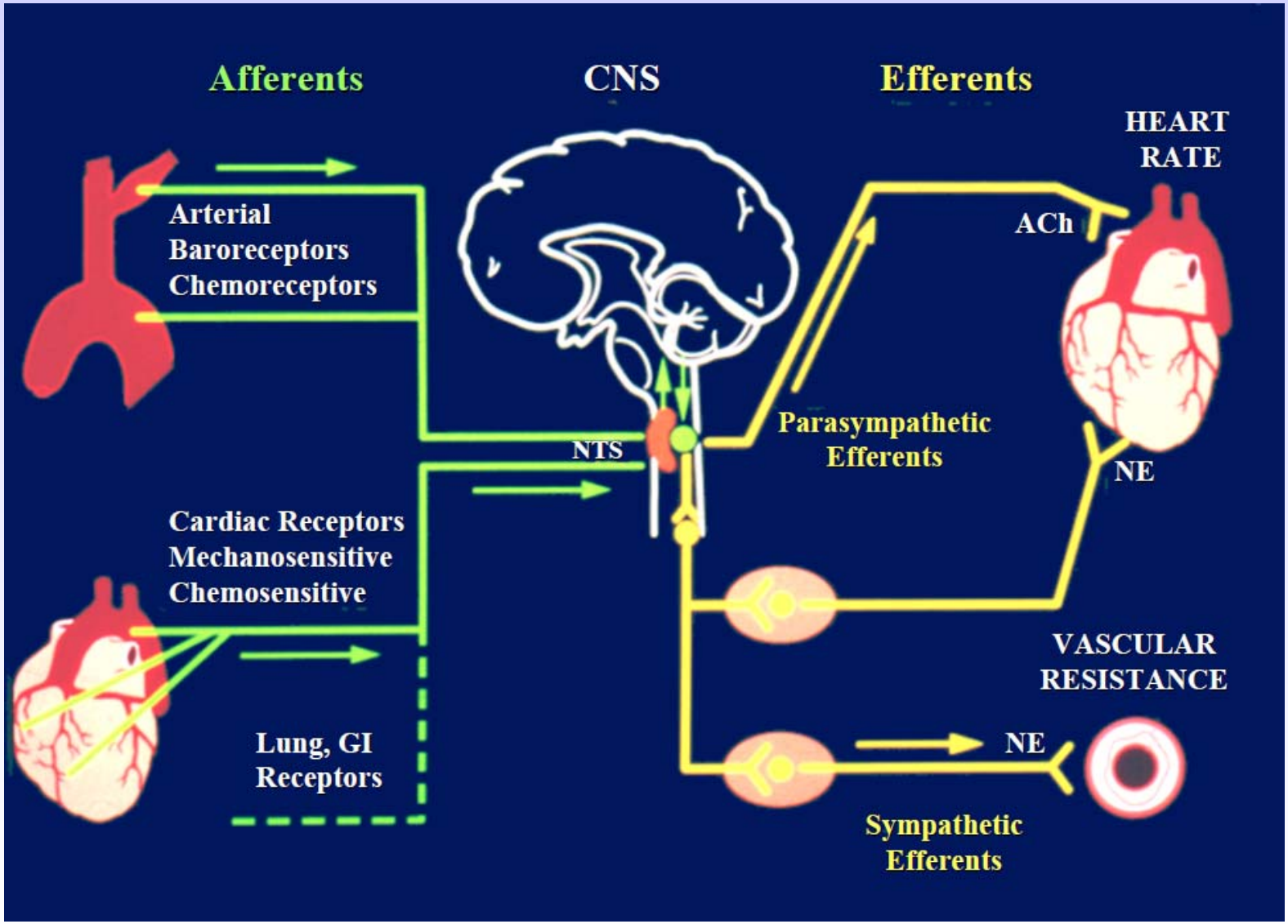
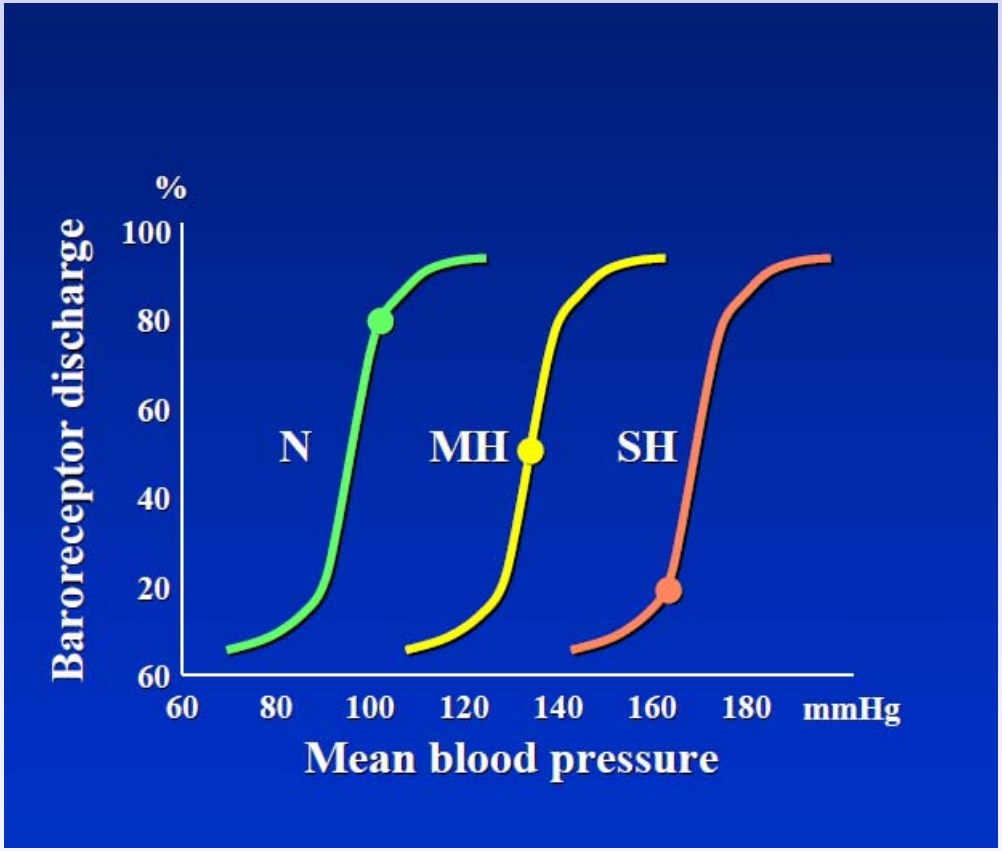


Carotid Baroreflex Physiology



N= normal
MH= Moderate HTN
SH= Severe HTN

Become less sensitive with chronic hypertension
Goal to restore sensitivity via exogenous stimulation

Initial Experience

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The New England Journal of Medicine

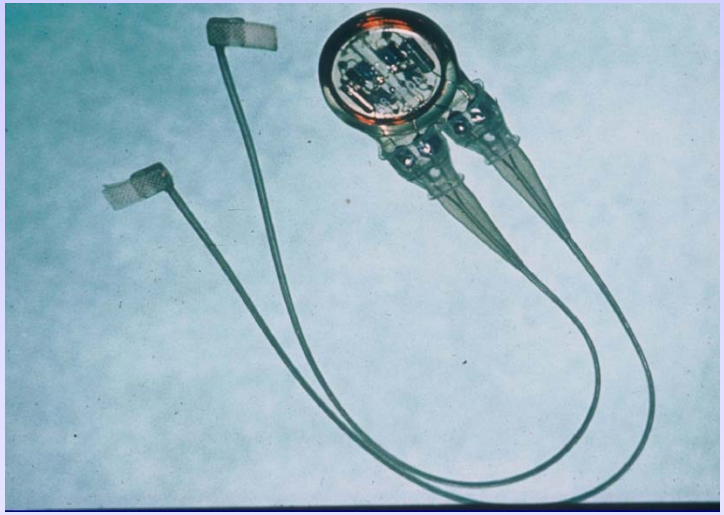
Volume 277 DECEMBER 14, 1967 Number 24

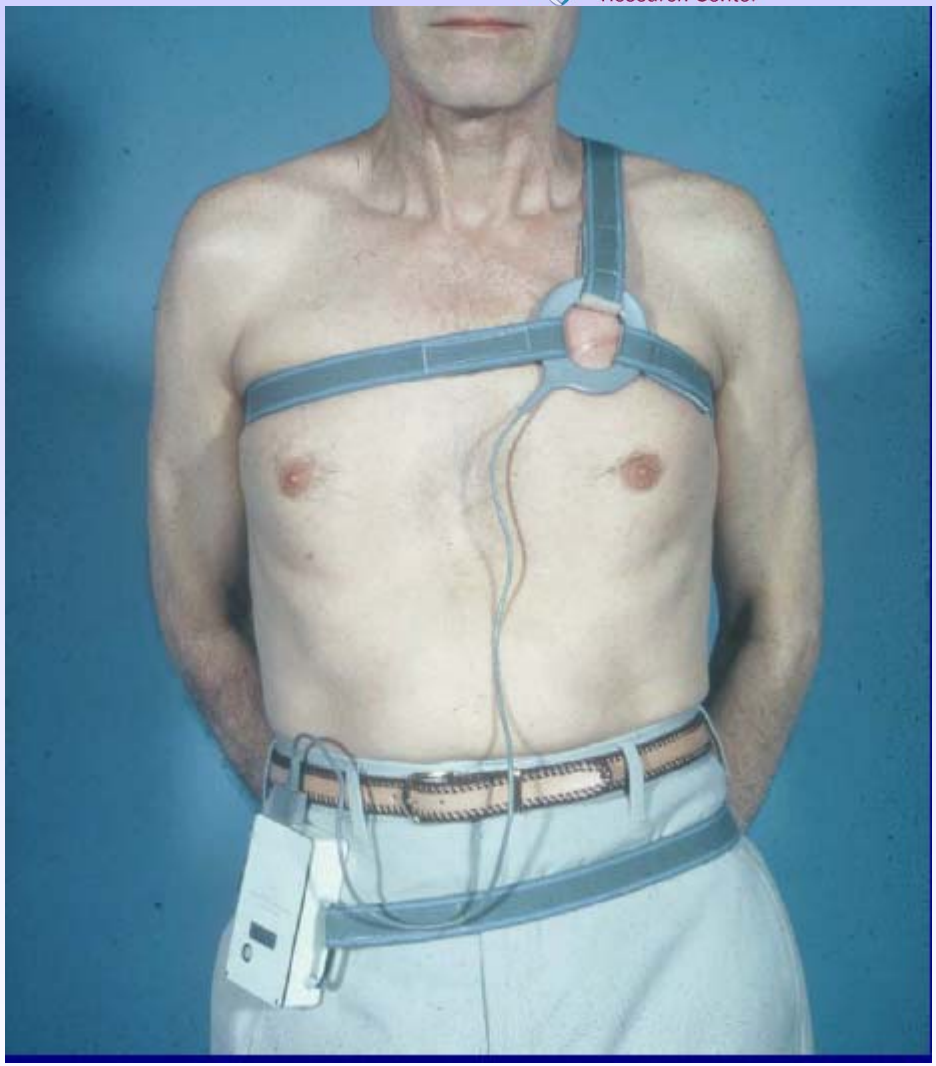
RELIEF OF ANGINA PECTORIS BY ELECTRICAL STIMULATION OF THE CAROTID-SINUS NERVES*

EUGENE BRAUNWALD, M.D.,† STEPHEN E. EPSTEIN, M.D.,‡ GERALD GLICK, M.D.,‡ ANDREW S. WECHSLER, M.D.,§ AND NINA S. BRAUNWALD, M.D.¶

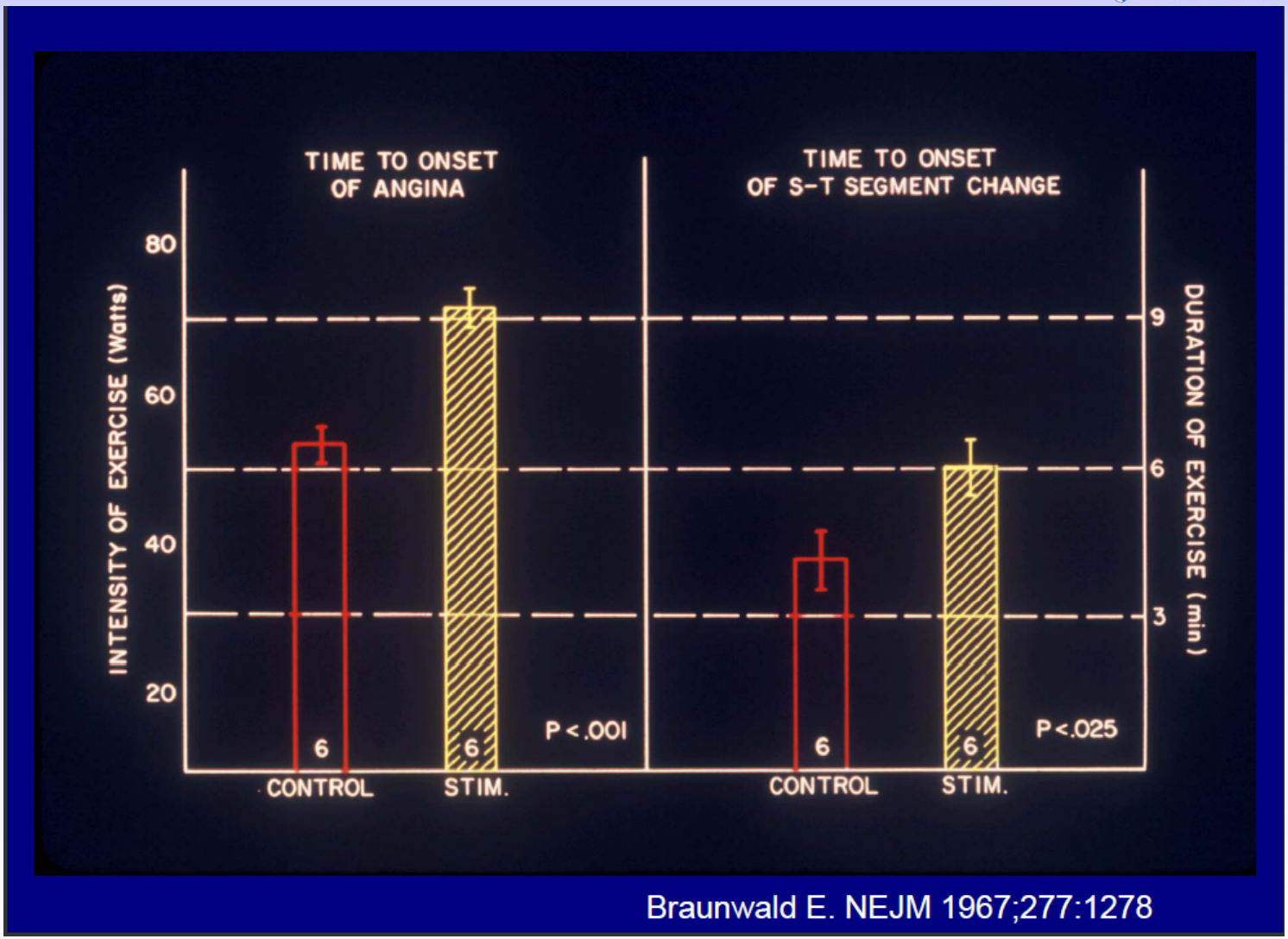
BETHESDA, MARYLAND

Initial Experience



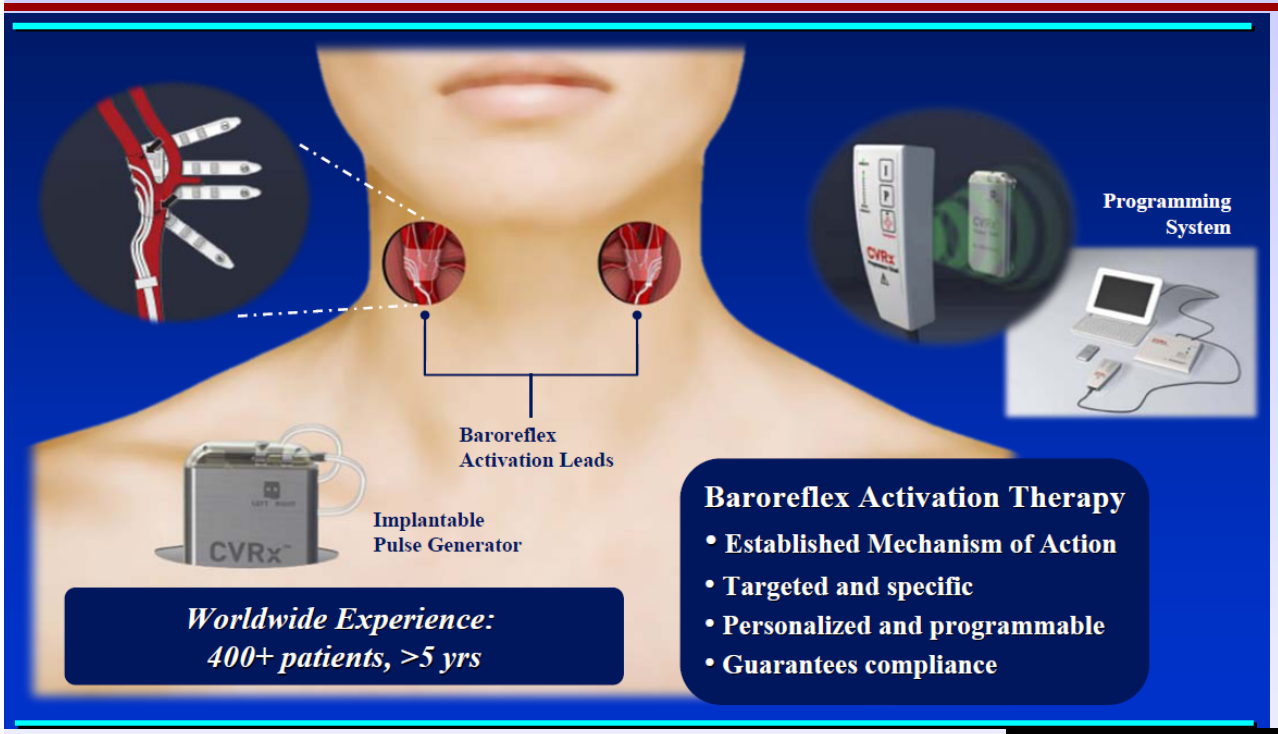


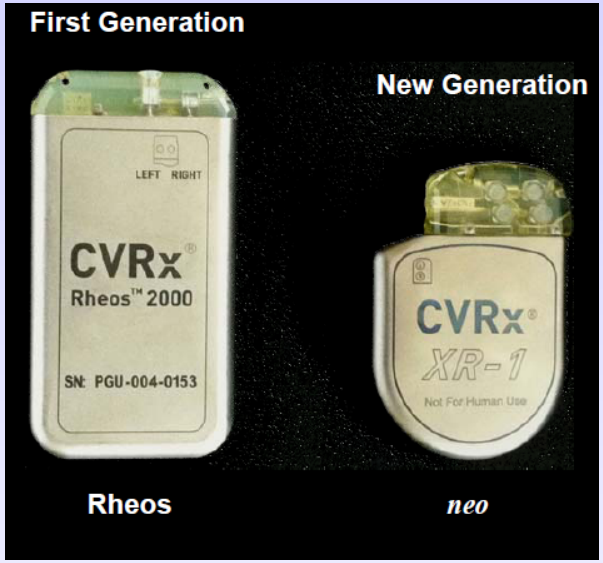
Effect of Barostim

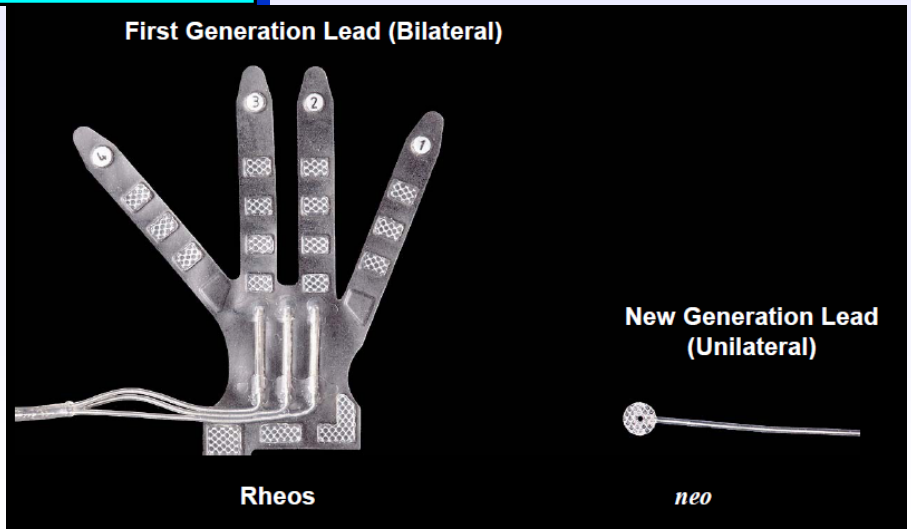


Braunwald E. NEJM 1967;277:1278

Rheos And Barostim neo System (CVRx Inc.)







Rheos Pivotal Trial

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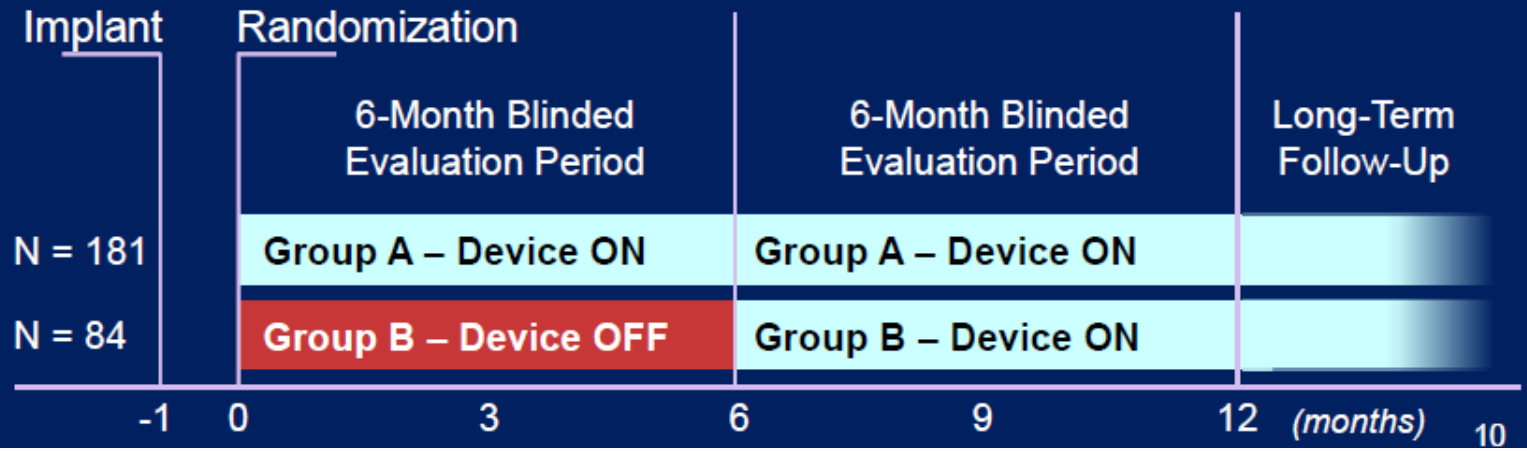
Baroreflex Activation Therapy Lowers Blood Pressure in Patients With Resistant Hypertension: Results From the Double-Blind, Randomized, Placebo-Controlled Rheos Pivotal Trial

John D. Bisognano, George Bakris, Mitra K. Nadim, Luis Sanchez, Abraham A. Kroon, Jill Schafer, Peter W. de Leeuw, and Domenic A. Sica

J. Am. Coll. Cardiol. published online Jul 28, 2011;
doi:10.1016/j.jacc.2011.06.008

Study Design

- Prospective randomized double-blind trial
  - 322 patients at 49 sites
  - 55 roll-in patients / 265 randomized (2:1)
- Co-primary endpoints
  1. Short Term Acute Response
  2. Long Term Sustained Response
  3. Short Term Procedural AEs
  4. Short Term Hypertension Therapy AEs
  5. Long Term Device AEs



Inclusion Criteria

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- SBP ≥ 160 mmHg
- DBP ≥ 80 mmHg
- 24 hour ABPM ≥ 135 mmHg
- At least one month of maximally tolerated therapy with at least three appropriate antihypertensive medications, including a diuretic

Baseline Data

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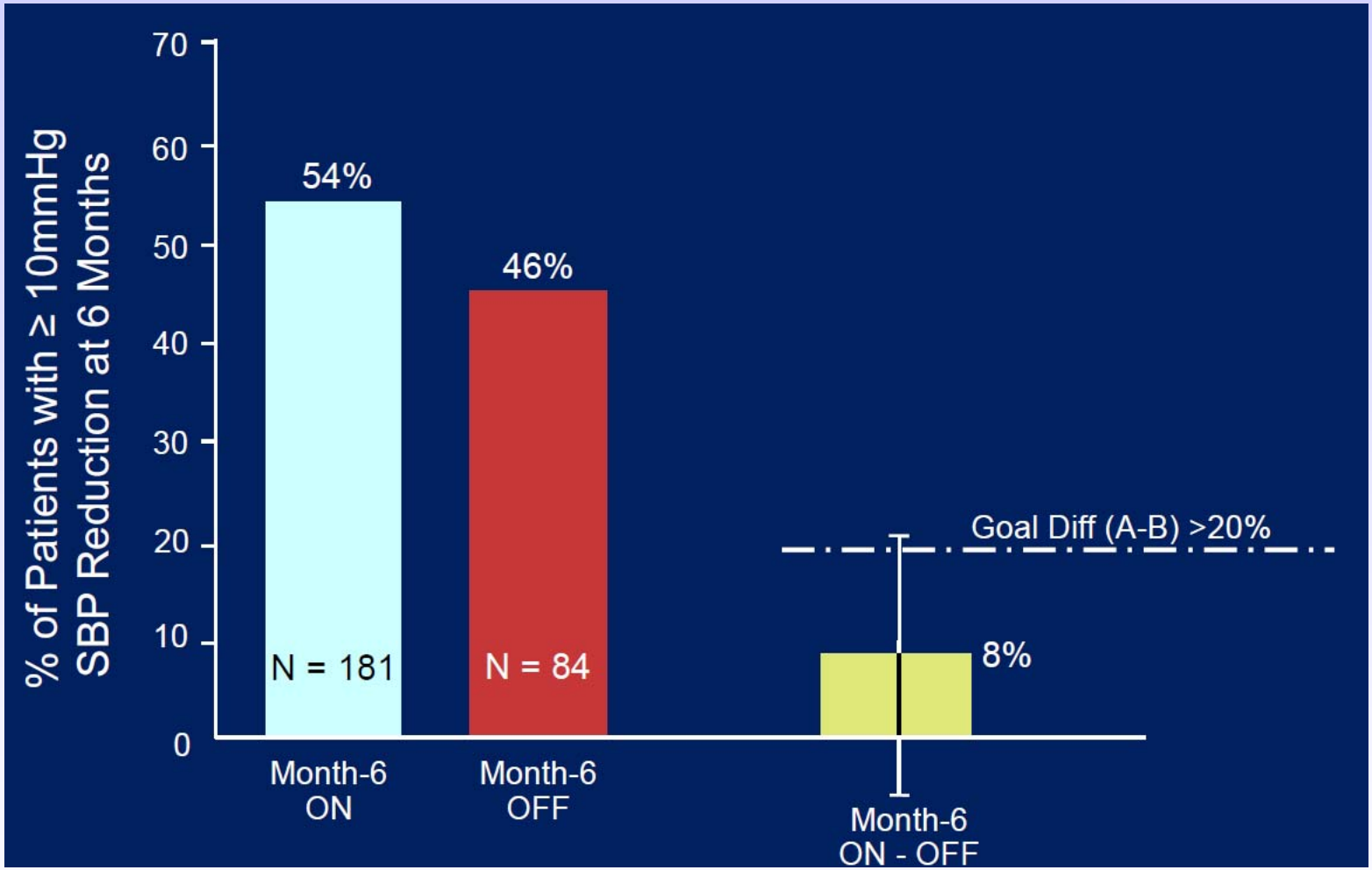
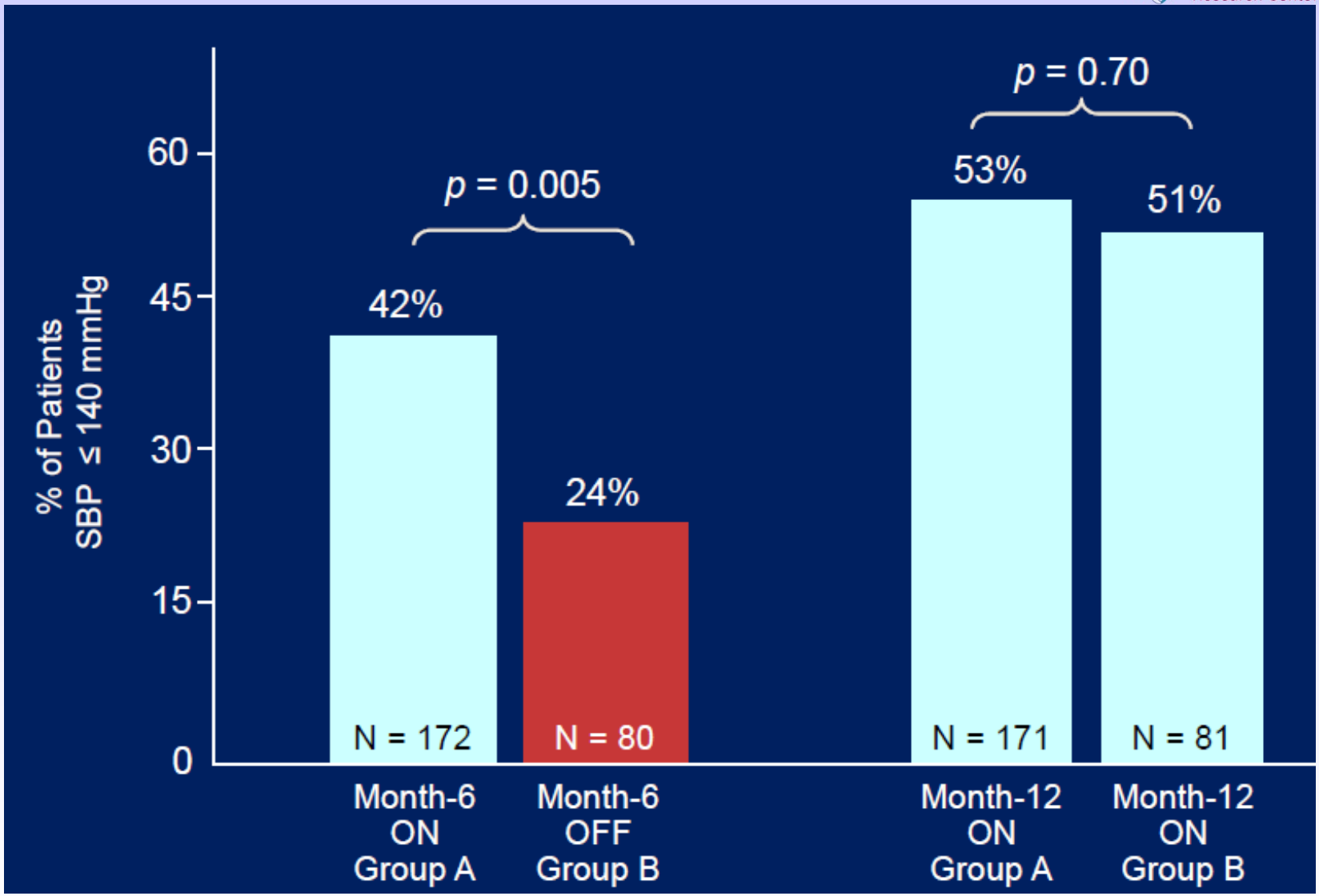
	Group A (N = 181)	Group B (N = 84)
Gender	64% Male	55% Male
Race	73% Caucasian	78% Caucasian
Age (mean years ± sd)	54 ± 11	53 ± 10
BMI (mean kg/m^2 ± sd)	33 ± 5	32 ± 6
Antihypertensive Meds (mean # ± sd)	5.2 ± 2	5.2 ± 2
Systolic BP (mean mmHg ± sd)	179 ± 22	176 ± 22
Diastolic BP (mean mmHg ± sd)	103 ± 16	103 ± 13
Heart Rate (mean bpm ± sd)	74 ± 14	75 ± 16

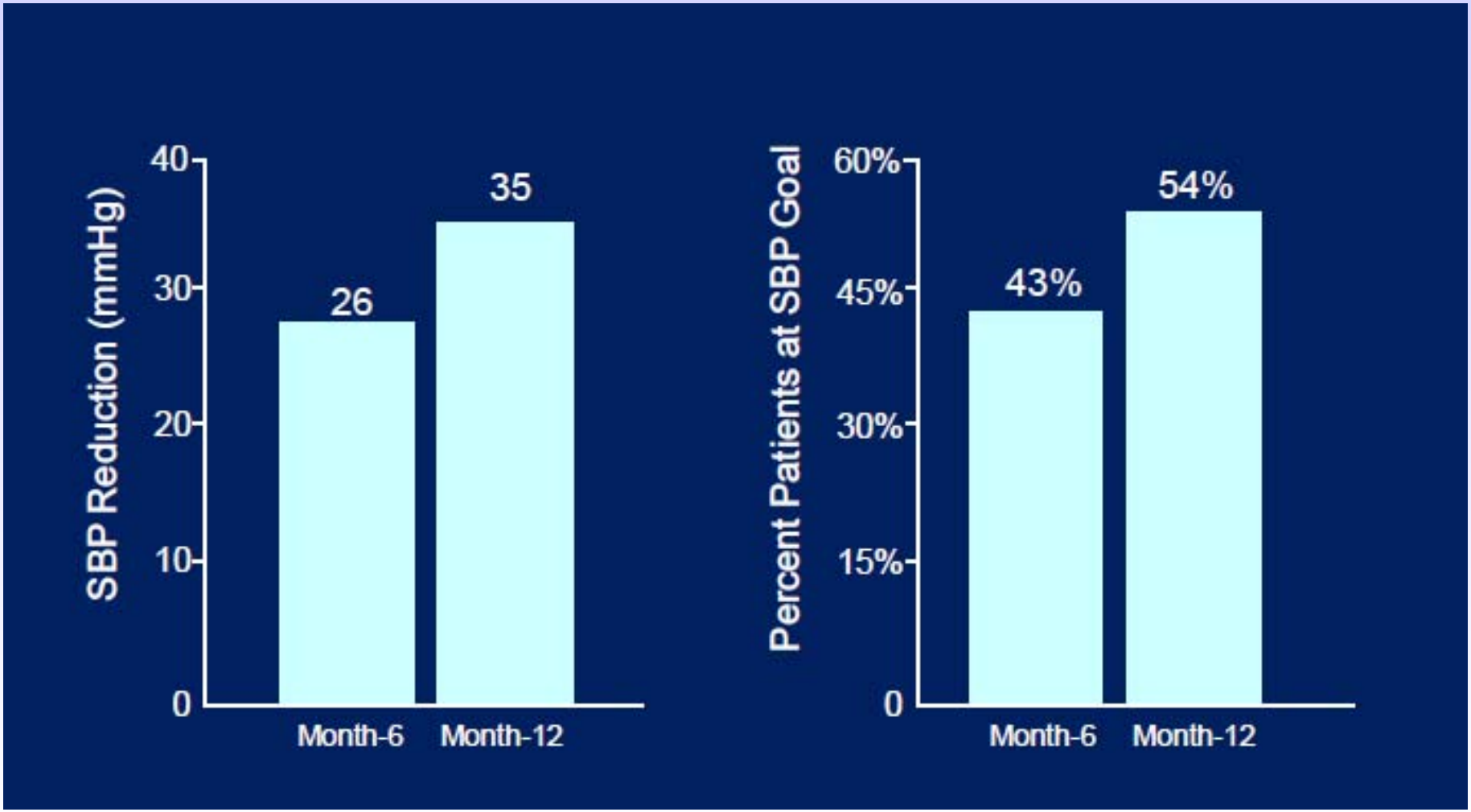
Procedural efficacy
% of patients >10 mm reduction



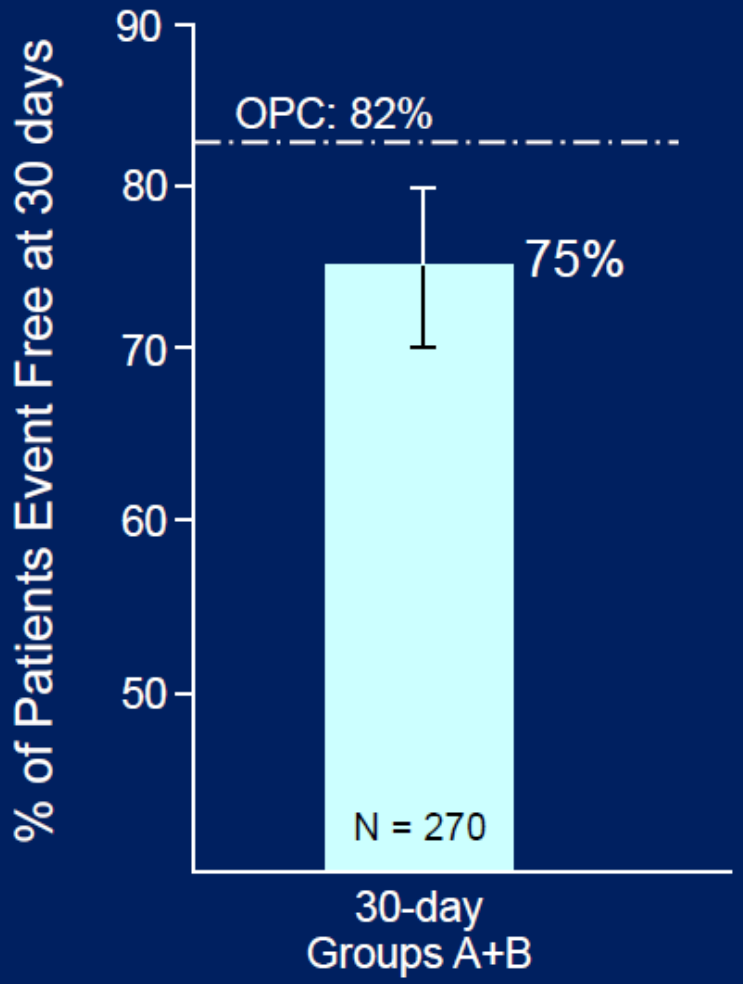
Procedural efficacy
% of patients with SBP<140



Procedural efficacy



Safety endpoints



Types of Adverse Events

- 4.4% permanent nerve injury (numbness, dysphagia, dysphonia)
- 4.8% transient nerve injury
- 4.4% general surgical complications (86% resolved)
- 2.6% respiratory complaints (100% resolved)
- 76% of all adverse events fully resolved

OPC: Objective Performance Criteria

Summary

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- Trial did not meet two of five co-primary end points
- However, overall about 35 mm HG reduction in blood pressure at 12 months
- Over 50% achieved BP <140/90
- Procedural complications need to be addressed

Renal Sympathetic Denervation

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- Role of renal arteries in sympathetic control
- Anatomy of renal nerves
- Mechanism of denervation
- Physiological response to denervation
- Clinical data to support efficacy

ROLE OF KIDNEY IN SYMPATHETIC REGULATION

Renal Sympathetic Afferent Nerves:

Kidney as Origin of Central Sympathetic Drive

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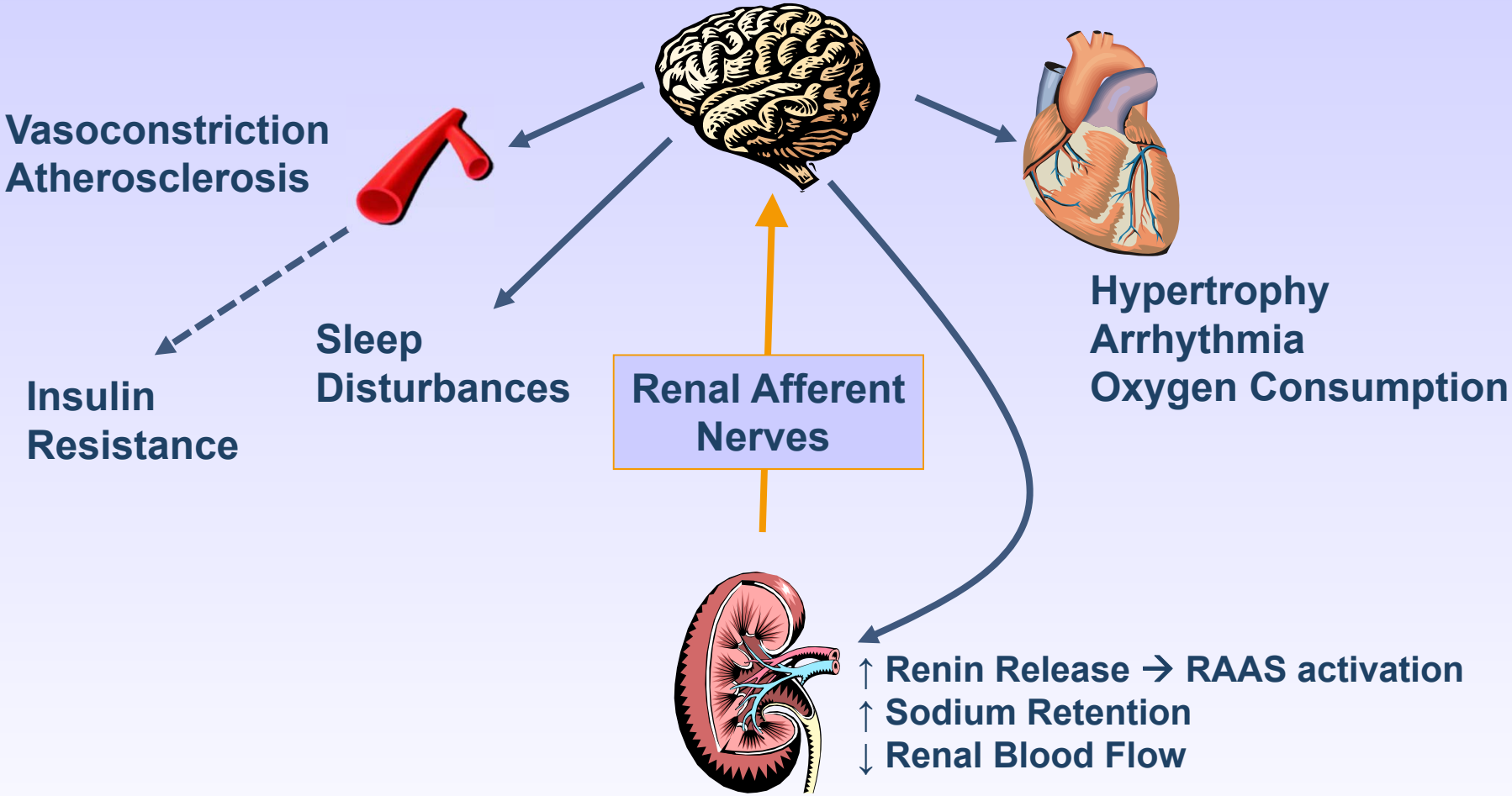
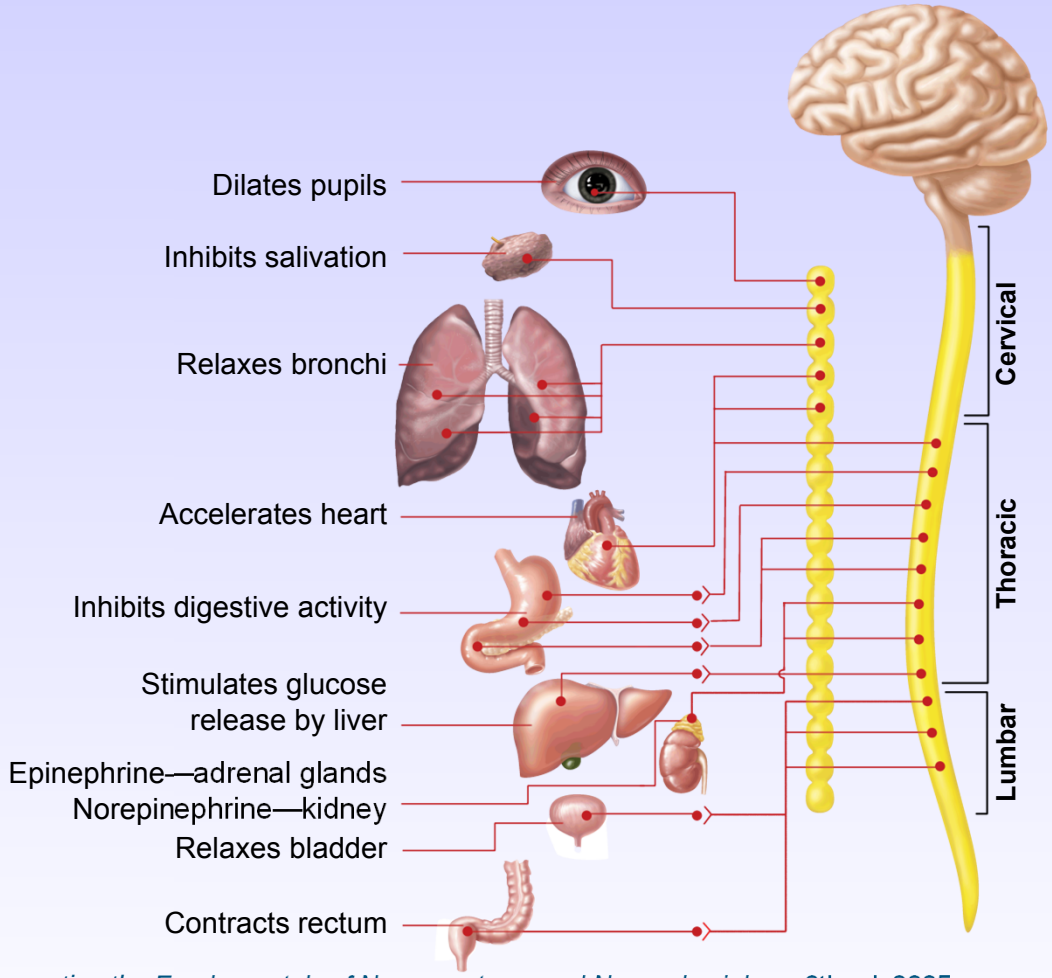


The Sympathetic Nervous System

- 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



GI=gastrointestinal.

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

Central Sympathetic Drive in Hypertension

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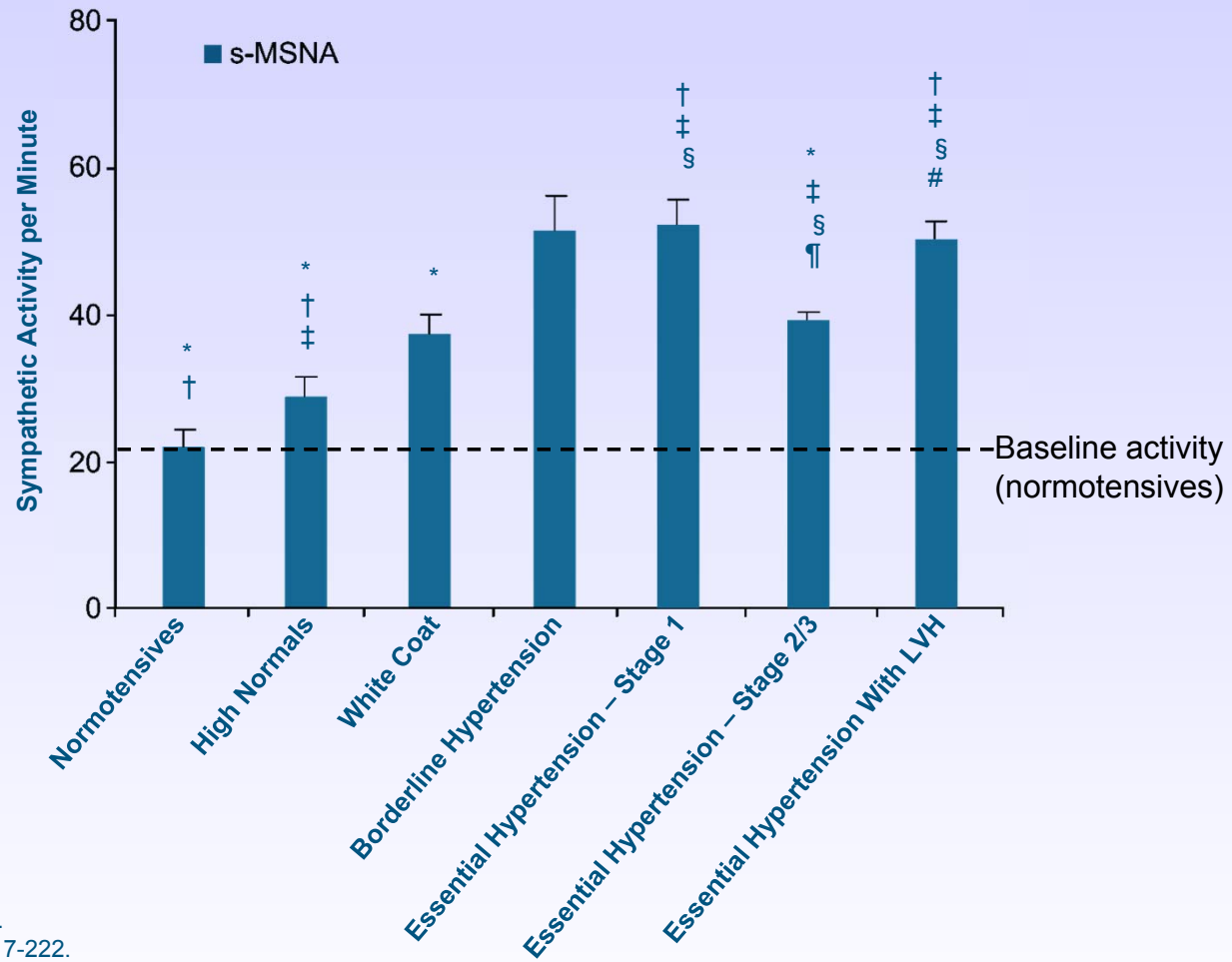
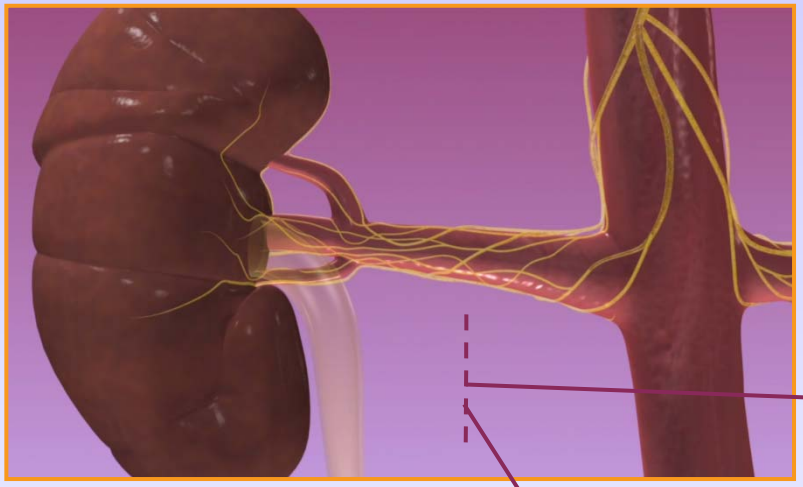
Sympathetic drive is elevated in multiple types of hypertension



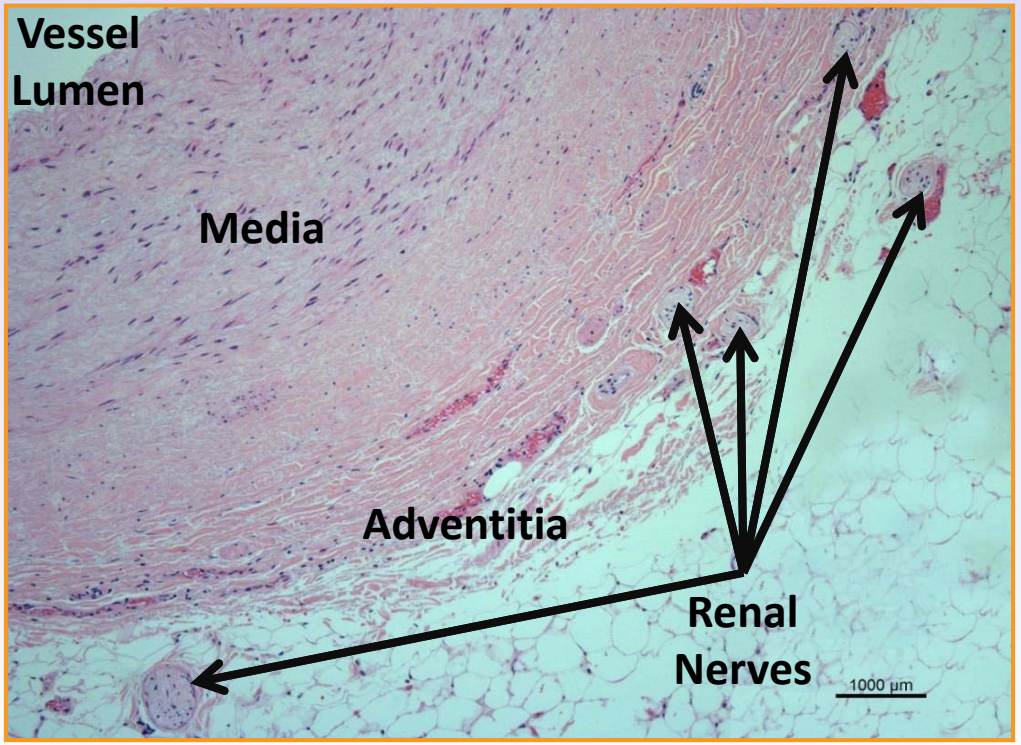
s-MSNA=single-unit efferent sympathetic nerve activity.
LVH=left ventricular hypertrophy.
*P<0.05 Compared with borderline hypertension.
†P<0.05 Compared with white coat hypertension.
‡P<0.05 Compared with normal pressure.
§ P<0.05 Compared with high-normal pressure.
¶P<0.05 Compared with essential hypertension–stage 1.
#P<0.05 Compared with essential hypertension–stage 2/3.
Adapted from Smith P, et al. *Am J Hypertens.* 2004; 17:217-222.

ANATOMY AND DENERVATION TECHNIQUE

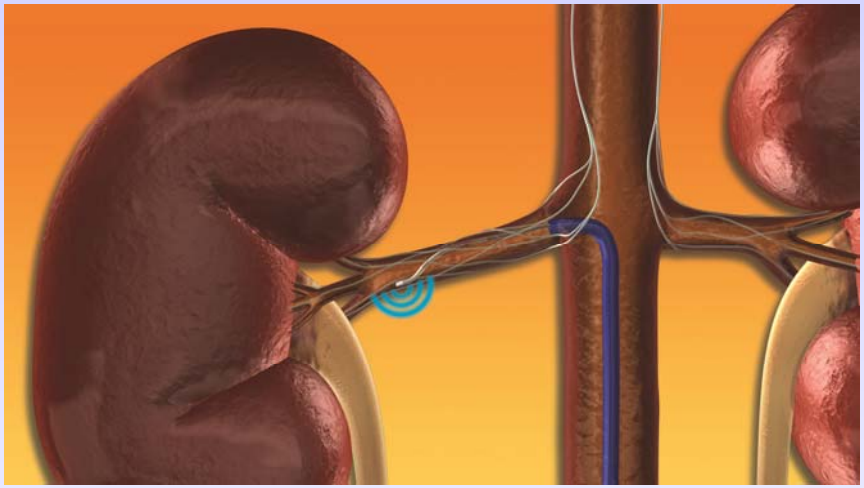
Renal Nerve Anatomy

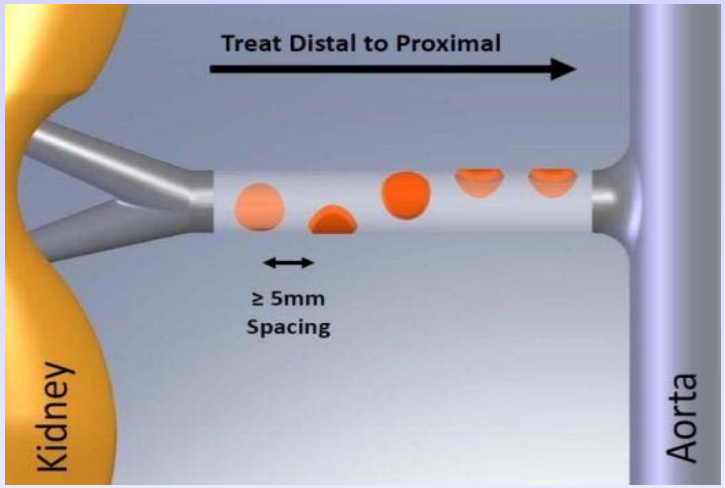


- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia



Renal Nerve Anatomy Allows a Catheter-Based Approach

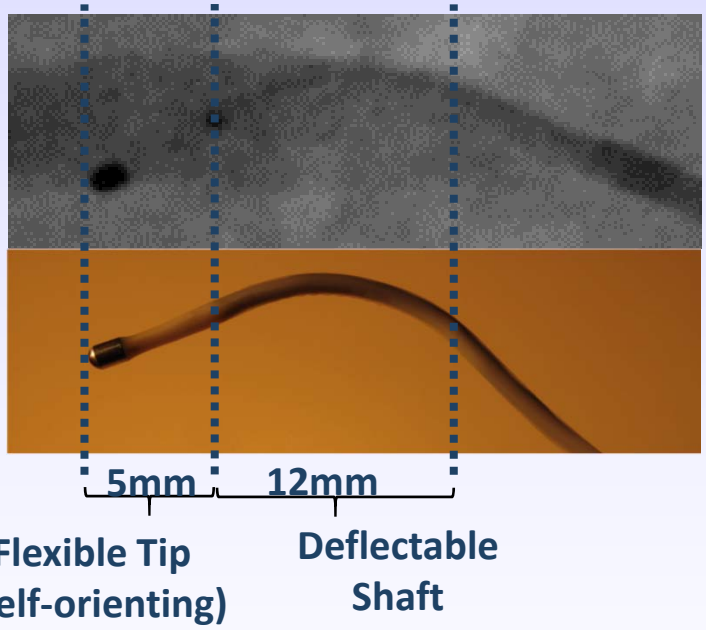




- Standard interventional technique
- 4-6 two-minute treatments per artery

Symplicity Investigational Catheter Device

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



RENAL NERVE INJURY

Six Month Post-Procedure Histology (Porcine Model) *Movat's Pentachrome Stain*

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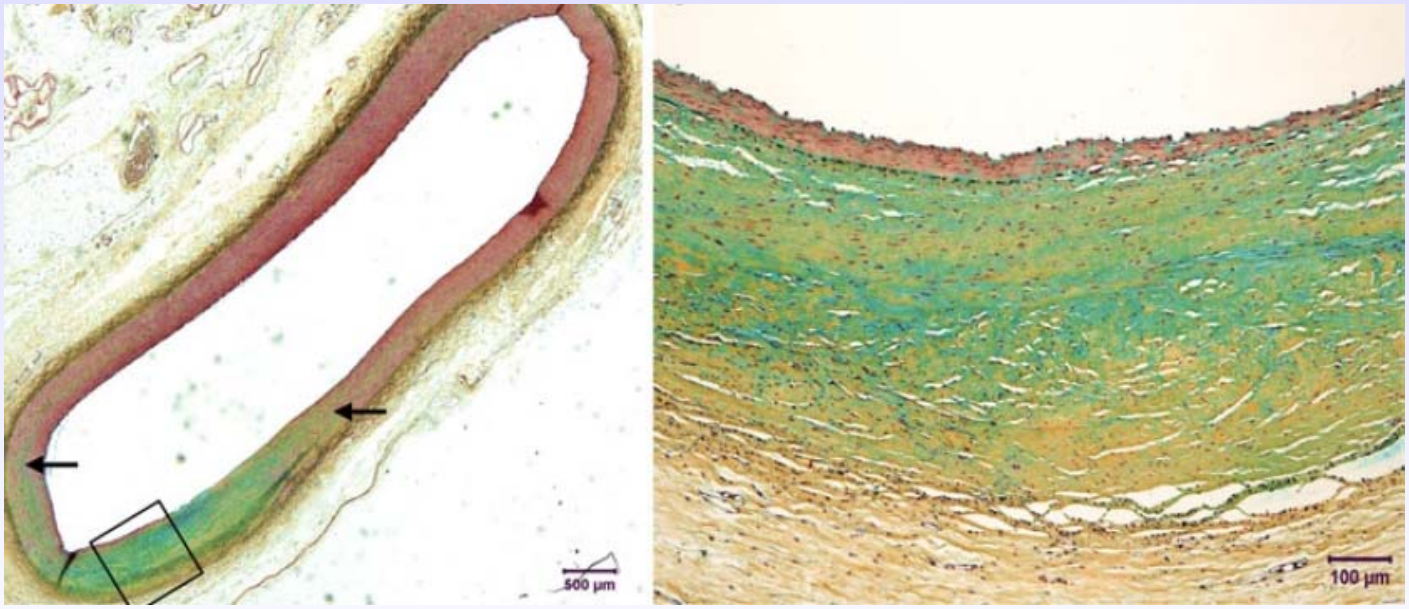
- An area of medial injury (yellow) is located between the arrows on the left. An enlargement of the boxed region is shown on the right
  - Findings: minimal intimal thickening and minimal internal elastic lamina injury overlying areas of mild full thickness medial fibrosis (yellow [fibrosis] with green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



Reproduced with permission from Rippy MK, et. al. *Clin Res Cardiol.* 2011;doi:101007s00392-011-0346-8.

Six Month Post-Procedure Nerve Histology (Porcine Model)

H&E

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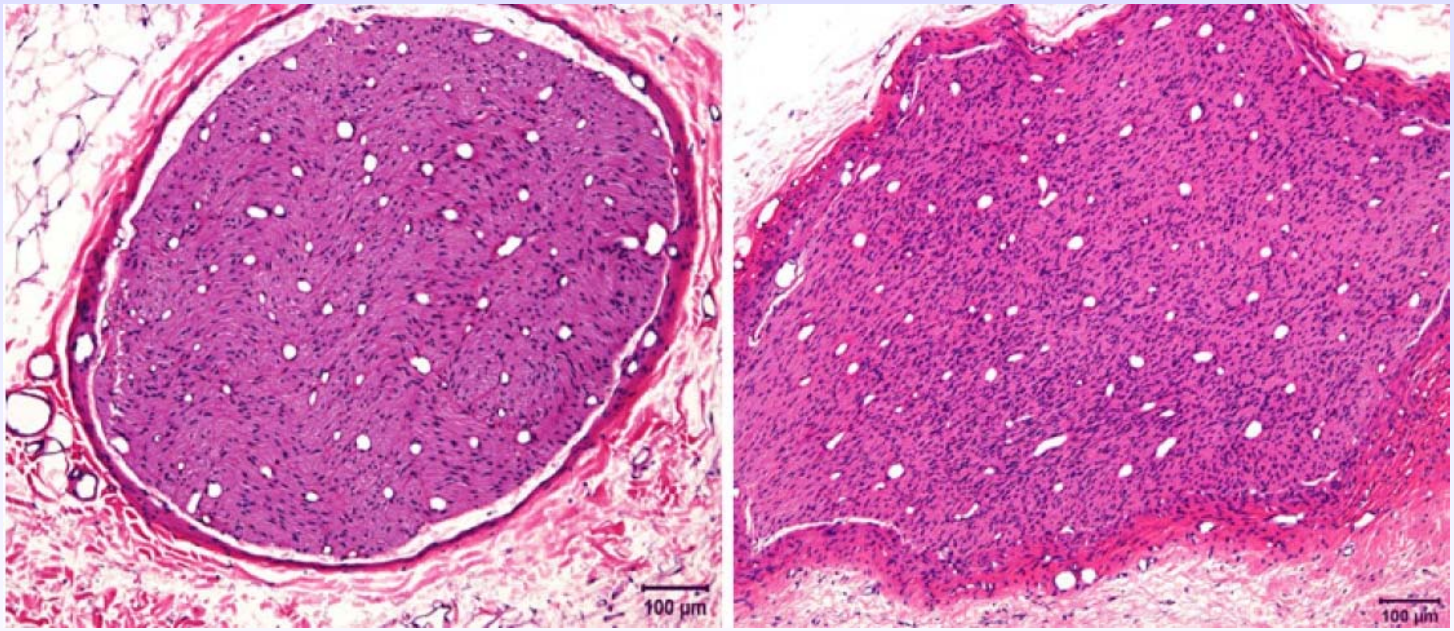
- **Nerve from untreated vessel:** Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- **Nerve from treated vessel:** Periarterial nerve bundle has a hypercellular appearance and the perineurium has a thickened and fibrotic appearance.

Nerve from Untreated Vessel Nerve from Treated Vessel



Reproduced with permission from Rippy MK, et. al. *Clin Res Cardiol.* 2011;doi:101007s00392-011-0346-8.

VALIDATION OF PHYSIOLOGY

Proof of Principle

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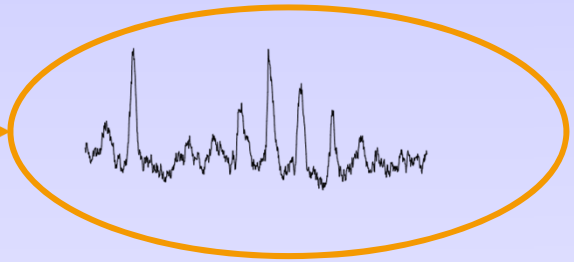
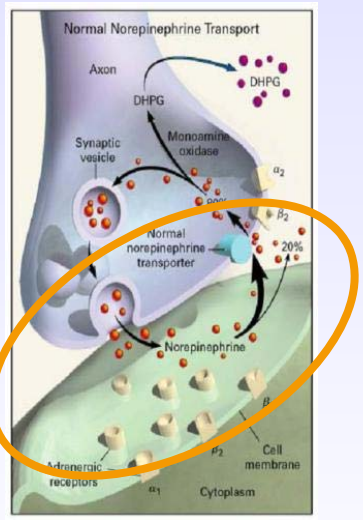
Central Sympathetic Nerve Activity



Muscle Sympathetic Nerve Activity (MSNA)

Renal Sympathetic Nerve Activity



Norepinephrine Spillover

Reduction of Renal Contribution to Central Sympathetic Drive: MSNA in Resistant Hypertension Patient

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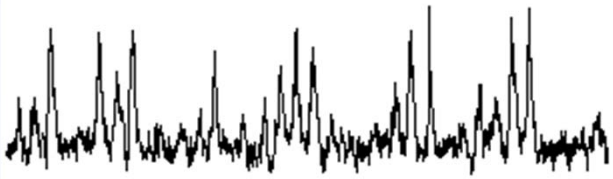
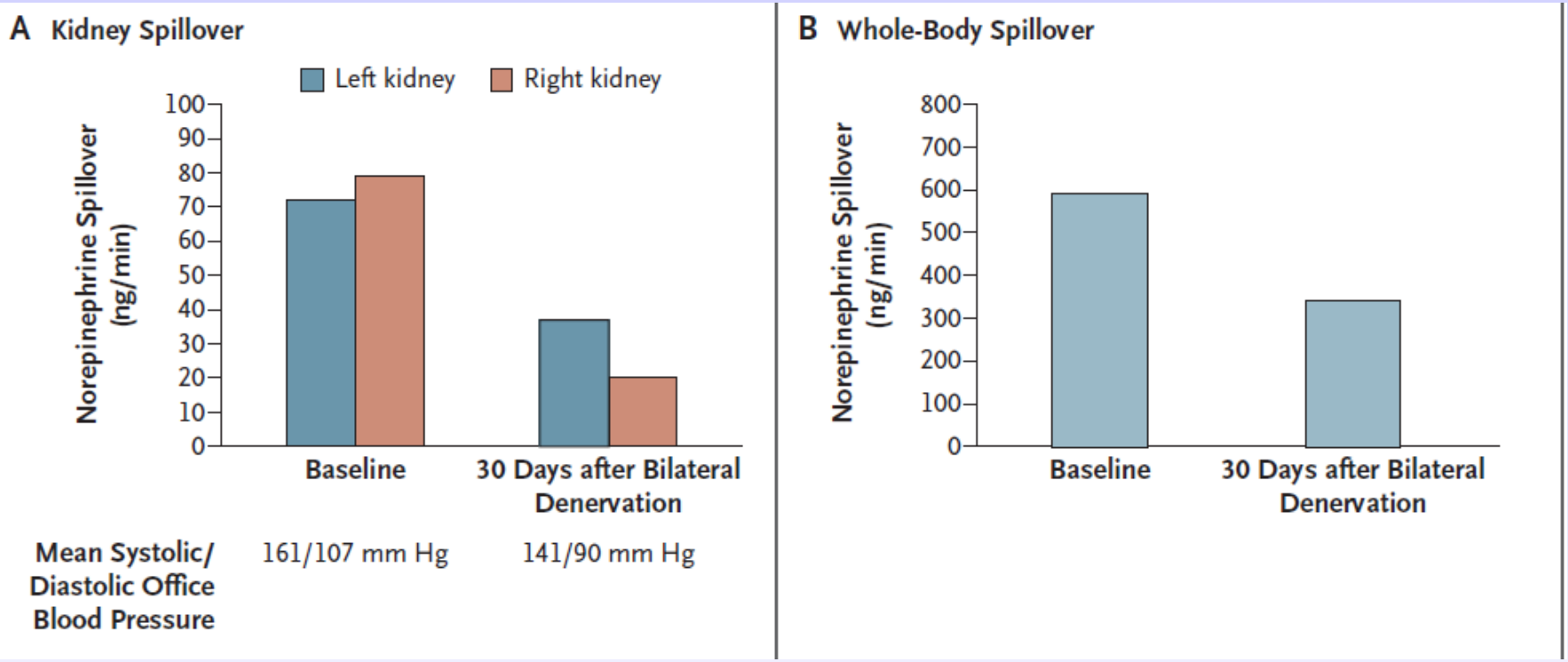
** 59 year old male on 7 HTN meds*

		MSNA (burst/min)		BP (mmHg)
Baseline		**56**	→	**161/107**
1 mo		**41** (-27%)	→	**141/90** (-20/-17)
12 mo		**19** (-66%)	→	**127/81** (-34/-26)

*** Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 →11.7 msec/mmHg)**

Schlaich et al. NEJM. 2009; 361(9): 932-934.

Related Changes in Underlying Physiology



LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m^2) from baseline to 12 months

Schlaich et al. NEJM. 2009; 361(9): 932-934.

DOES IT WORK- SHOW ME THE DATA

Symplicity Staged Evaluation in Hypertension and Beyond

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
(upcoming)

EU/AU

Other Areas of Research:[4]
Insulin Resistance, HF/Cardiorenal,
Sleep Apnea, More

Sources:
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 HTN-1

Lancet. 2009;373:1275-1281

Hypertension. 2011;57:911-917.

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

-First-in-man, non-randomized

-Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)

- 12-month data

Expanded Cohort – This Report (Symplicity HTN-1):

-Expanded cohort of patients (n=153)

-24-month follow-up

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

Baseline Patient Characteristics (n=153)

Demographics	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
Co-morbidities	Diabetes Mellitus II (%)	31%
	CAD (%)	22%
	Hyperlipidemia (%)	68%
	eGFR (mL/min/1.73m^2)	83 ± 20
Blood Pressure	**Baseline BP (mmHg)**	**176/98 ± 17/15**
	Number of anti-HTN meds (mean)	**5.1 ± 1.4**
	Diuretic (%)	95%
	Aldosterone blocker(%)	22%
	ACE/ARB (%)	91%
	Direct Renin Inhibitor	14%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Centrally acting sympatholytic (%)	33%
	Vasodilator (%)	19%
	Alpha-1 blocker	19%

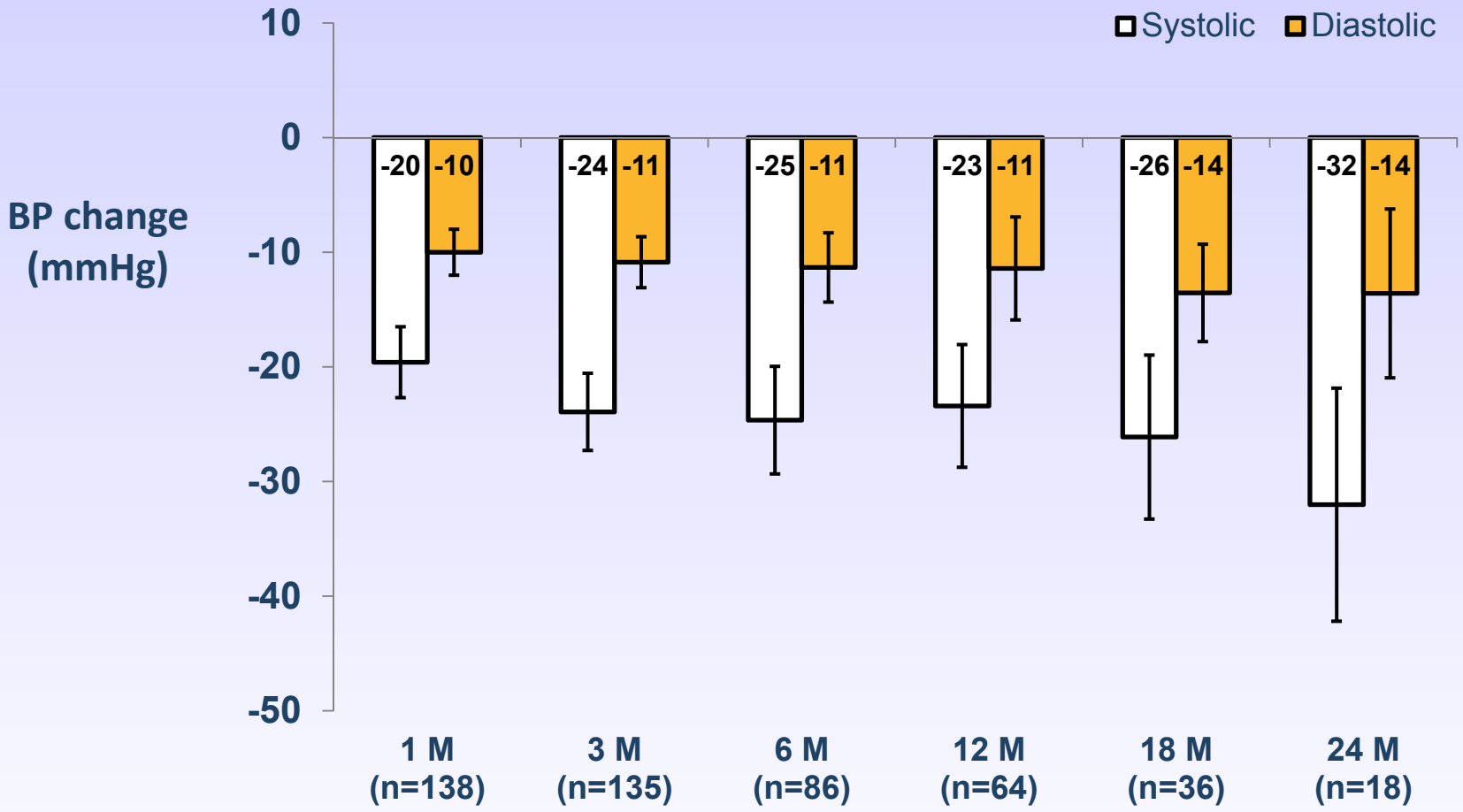
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Procedure Detail & Safety (n=153)

- 38 minute median procedure time
  - Average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- Minor complications 4/153:
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further sequelae

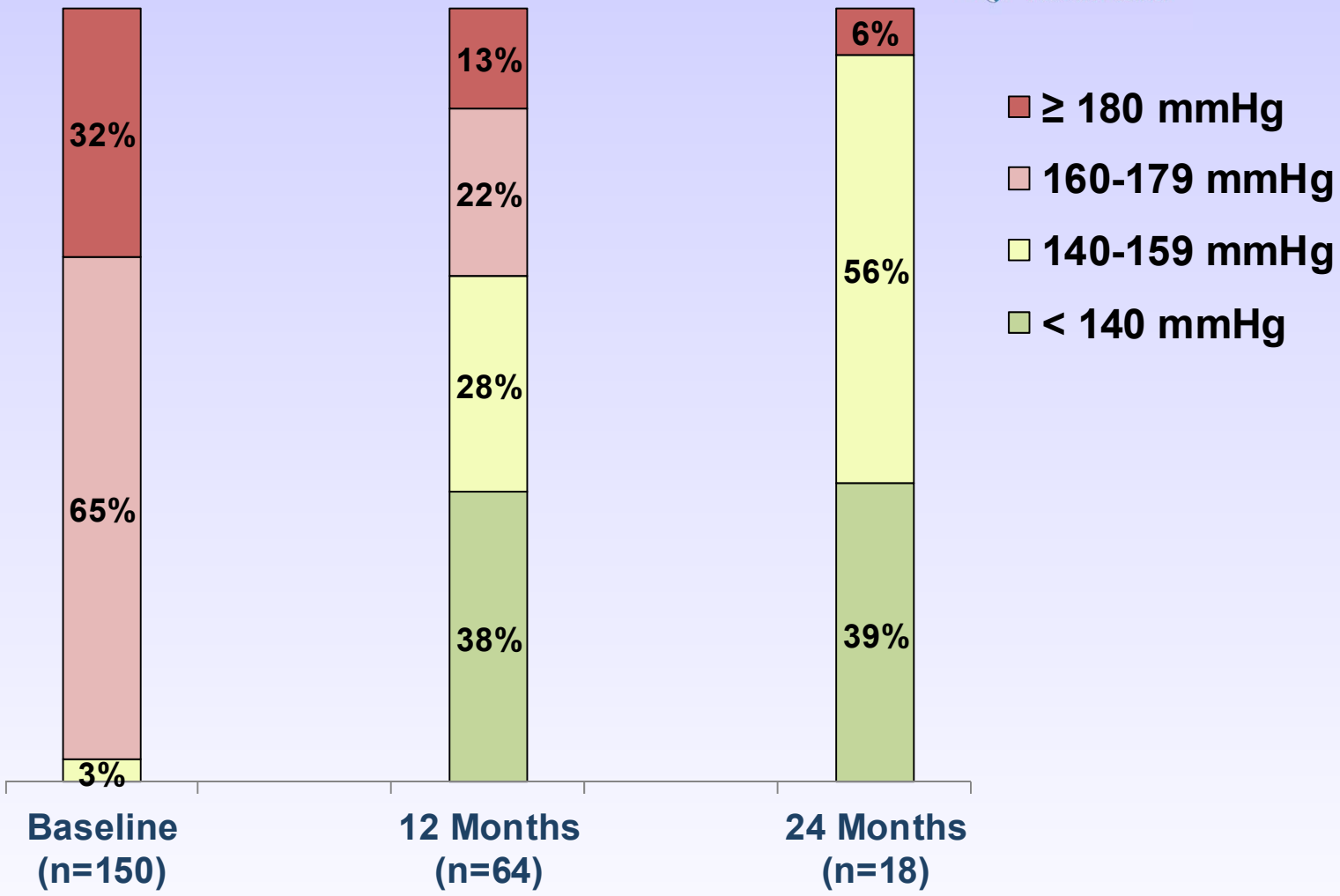
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Significant, Sustained BP Reduction



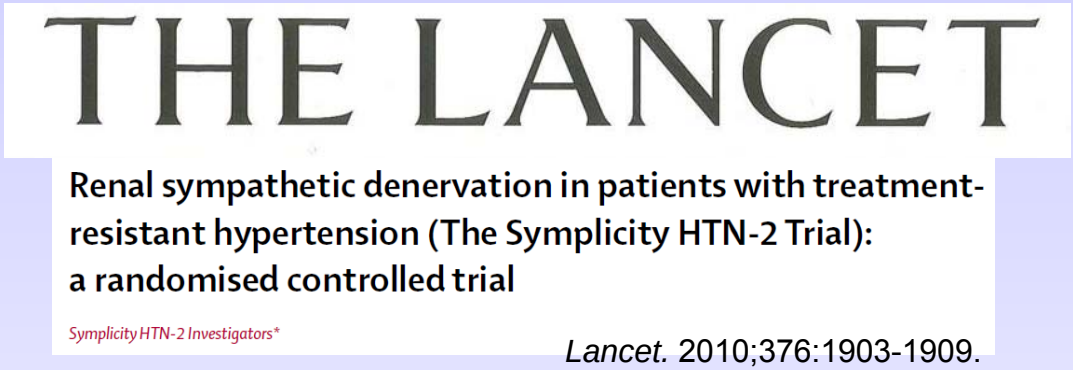
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Office Systolic BP Distribution at Baseline, 12 Months, and 24 Months



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

Symplicity HTN-2



Lancet. 2010;376:1903-1909.

- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)

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

Symplicity HTN-2 Trial

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Inclusion Criteria:

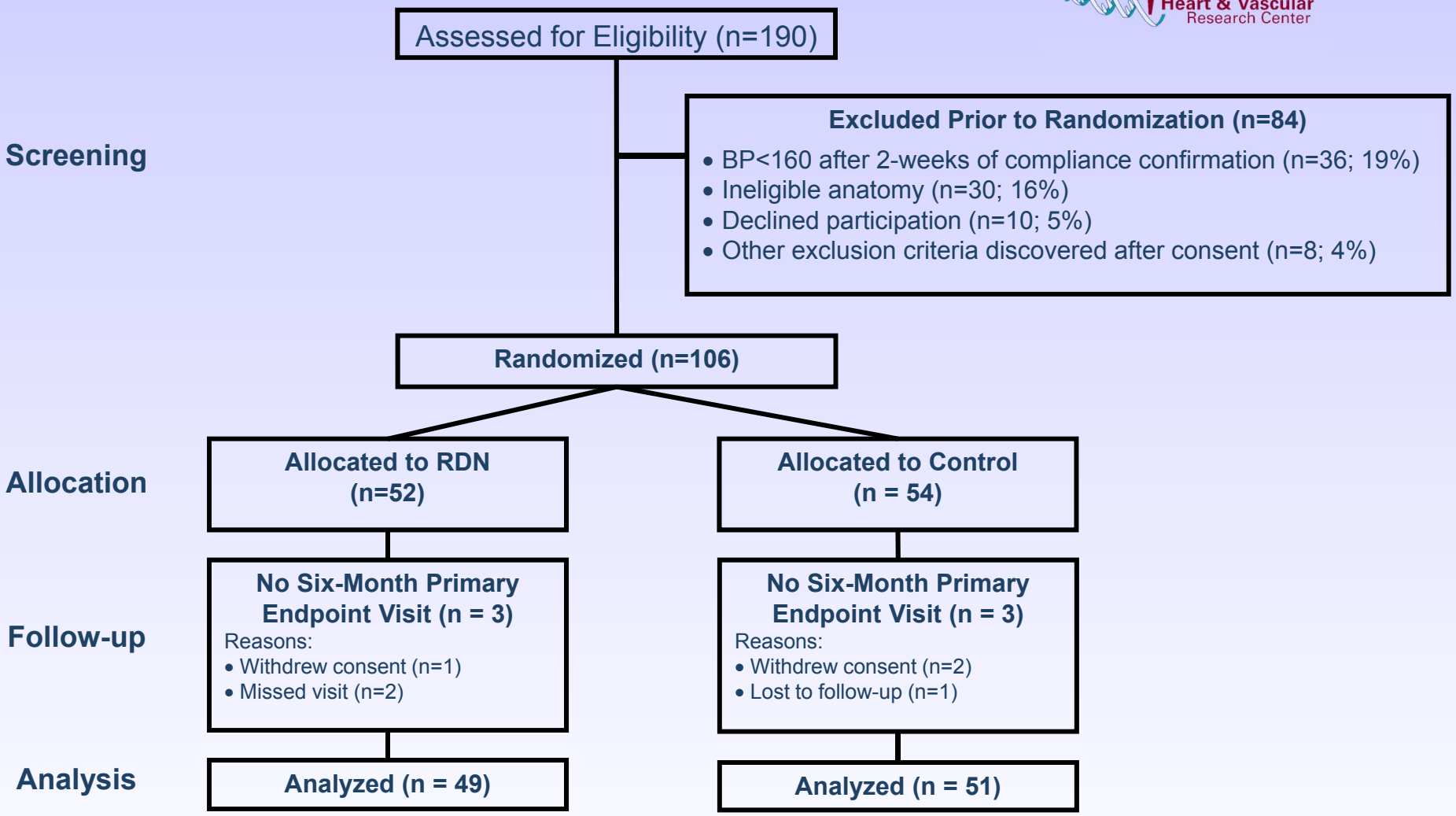
- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:

- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m^2 (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

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

Patient Disposition

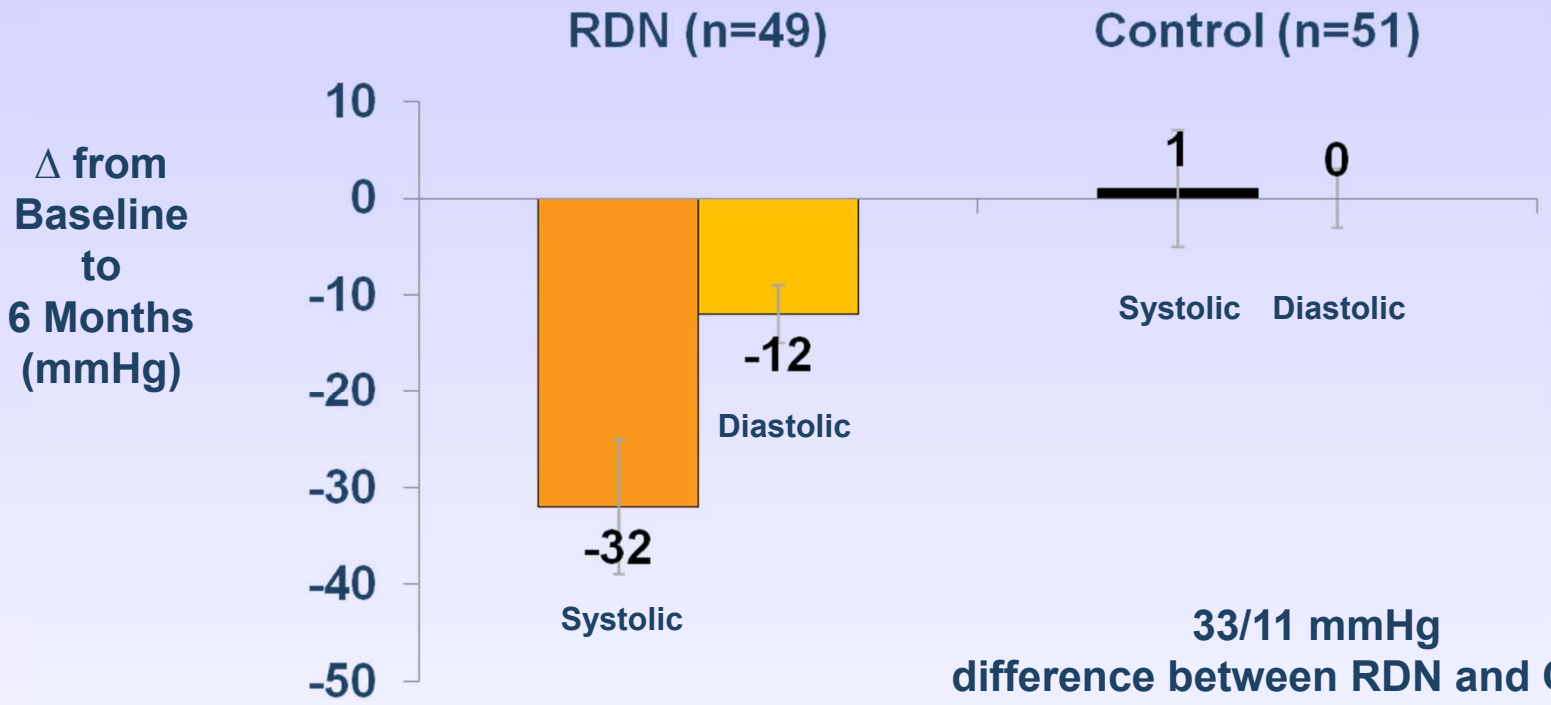


Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Baseline Characteristics

- BP 178+/- 18
- Antihypertensive drugs- 5.2
- Similar in both groups

Primary Endpoint: 6-Month Office BP



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

- **84% of RDN patients had ≥ 10 mmHg reduction in SBP**
- **10% of RDN patients had no reduction in SBP**

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

Medication Changes

Despite protocol guidance to maintain medications, some medication changes were required:

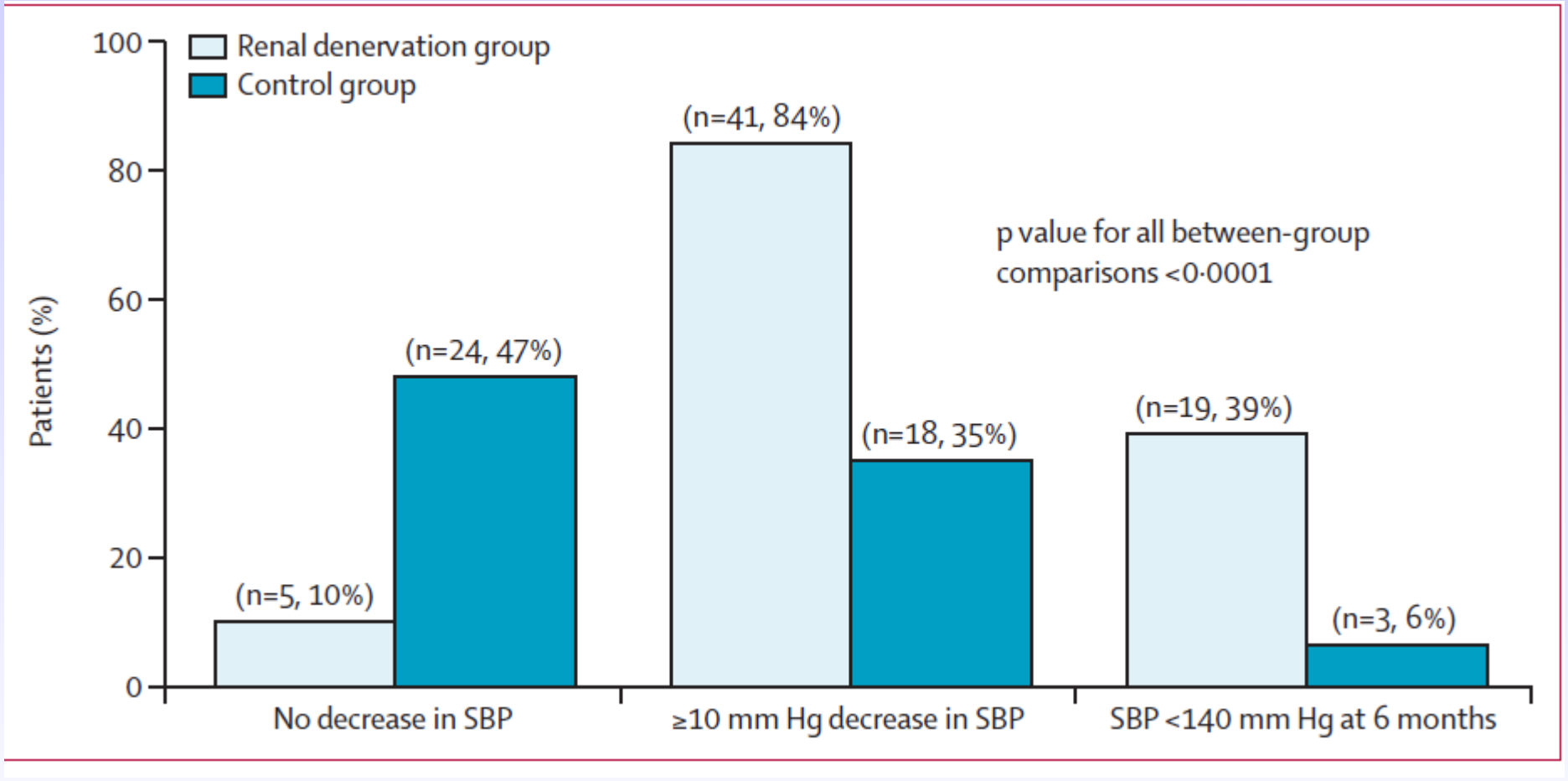
	RDN (n=49)	Control (n=51)	P-value
# Med Dose Decrease (%)	10 (20%)	3 (6%)	**0.04**
# Med Dose Increase (%)	4 (8%)	6 (12%)	0.74

Censoring BP after medication increases:

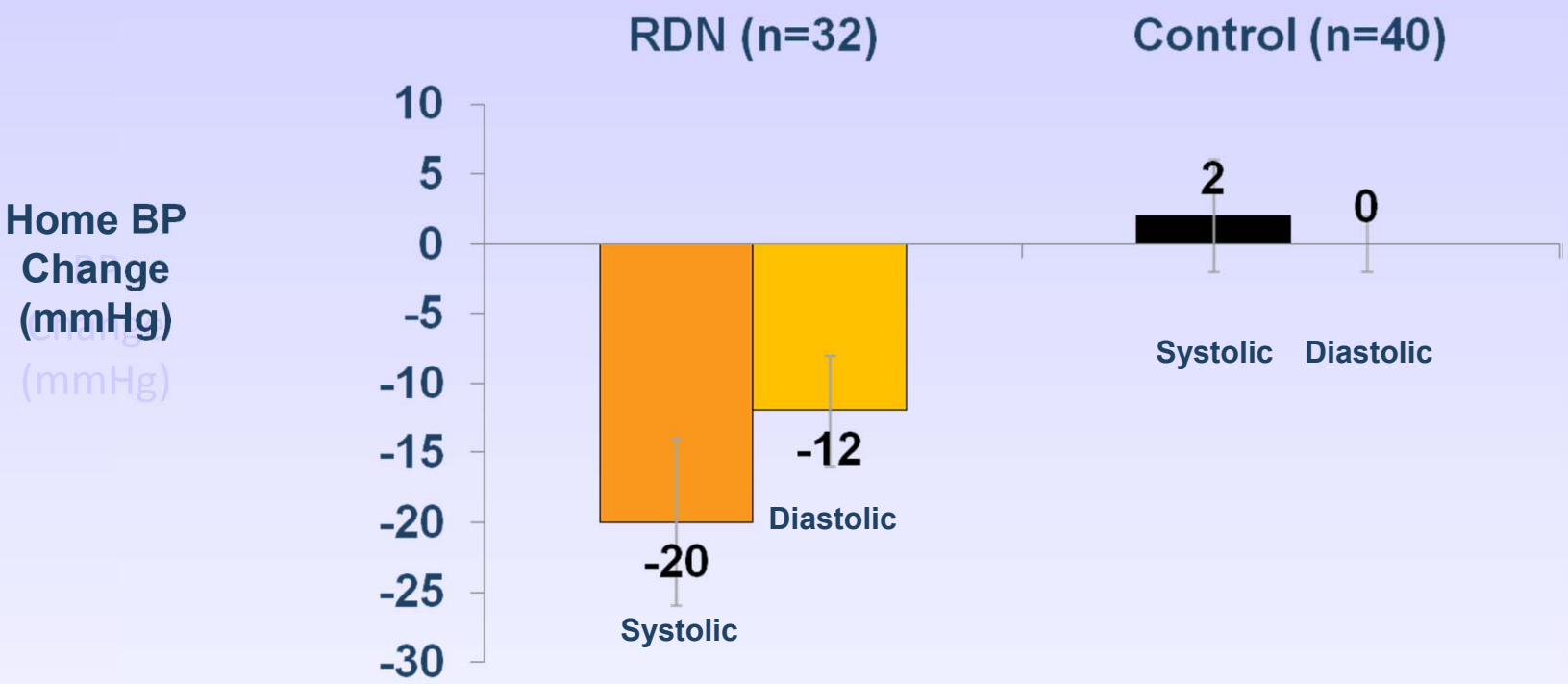
- Renal Denervation → Reduction of 31/12 ± 22/11 mmHg ($p<0.0001$ for SBP & DBP)
- Control → Change of 0/-1 ± 20/10 mmHg ($p=0.90$ & $p=0.61$ for SBP & DBP, respectively)

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

Proportion of patients with BP control



Home & 24 Hour Ambulatory BP



24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

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

Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 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.

Renal Function

Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0, 0.1)	0.31

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MC

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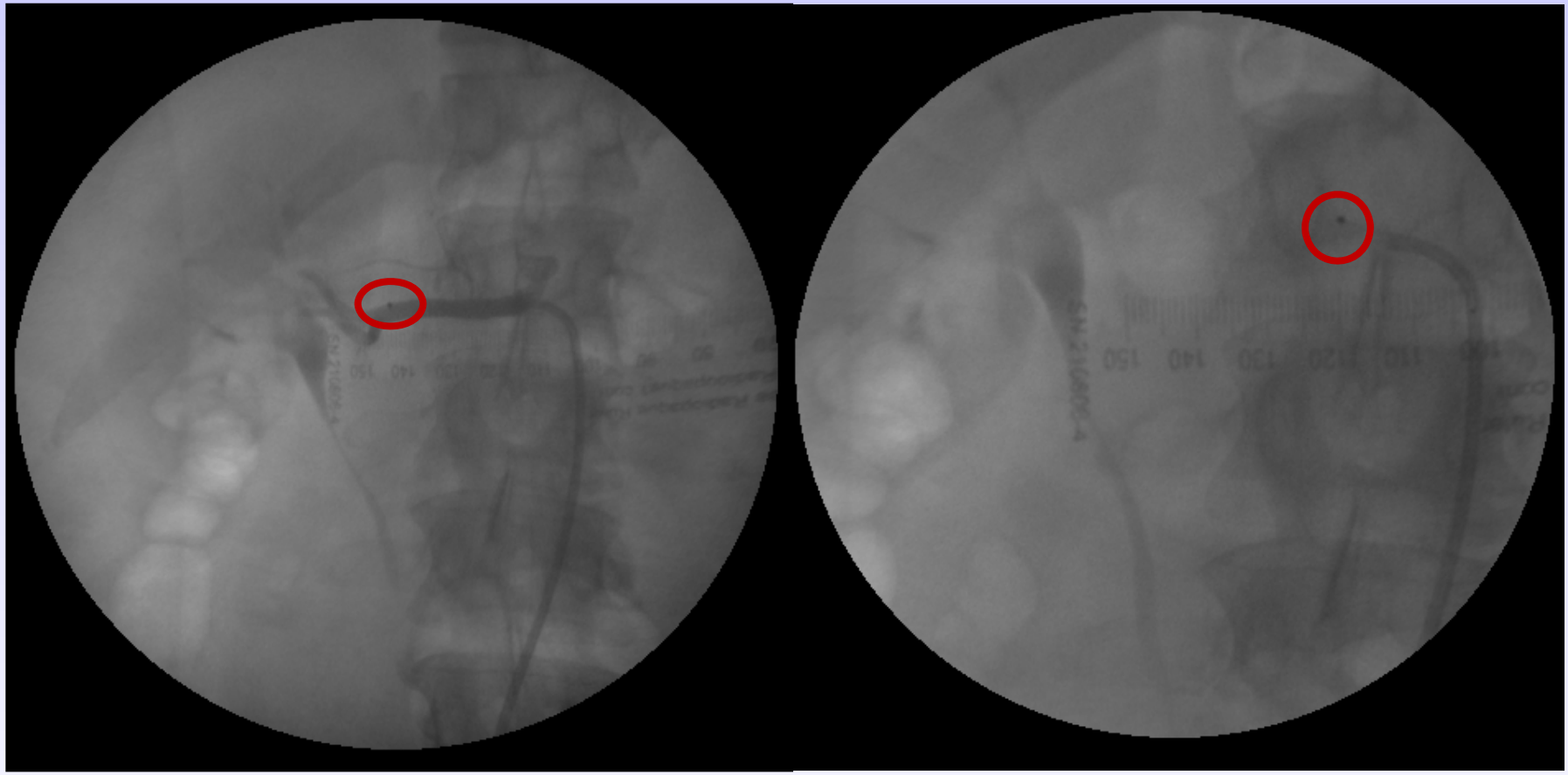
- 47 year old man HTN for > 10 years, obesity, sleep apnea
- Recurrent admissions with hypertensive urgency associated with chest pain and recurrent headaches.
- BP during these periods- 200-220/100-110 systolic. Resting BP 160-180/90-100
- No prior history of MI , stroke or PAD
- Strong family history of HTN

Clinical course for MC

- Enrolled in renal denervation study

Renal denervation – right renal



Renal denervation- left renal

Final Angiogram

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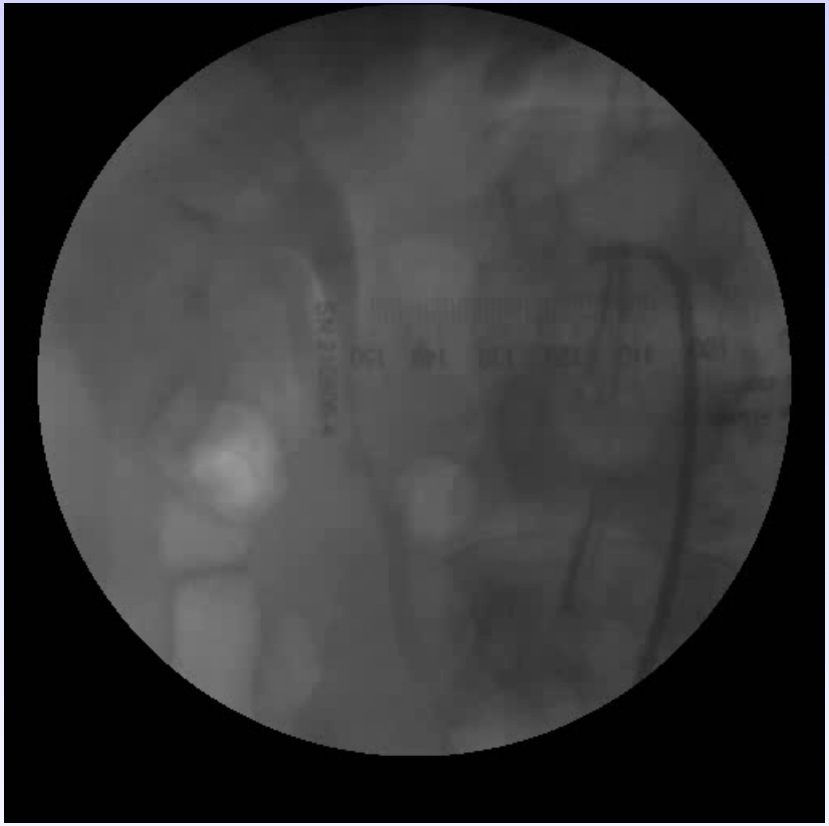
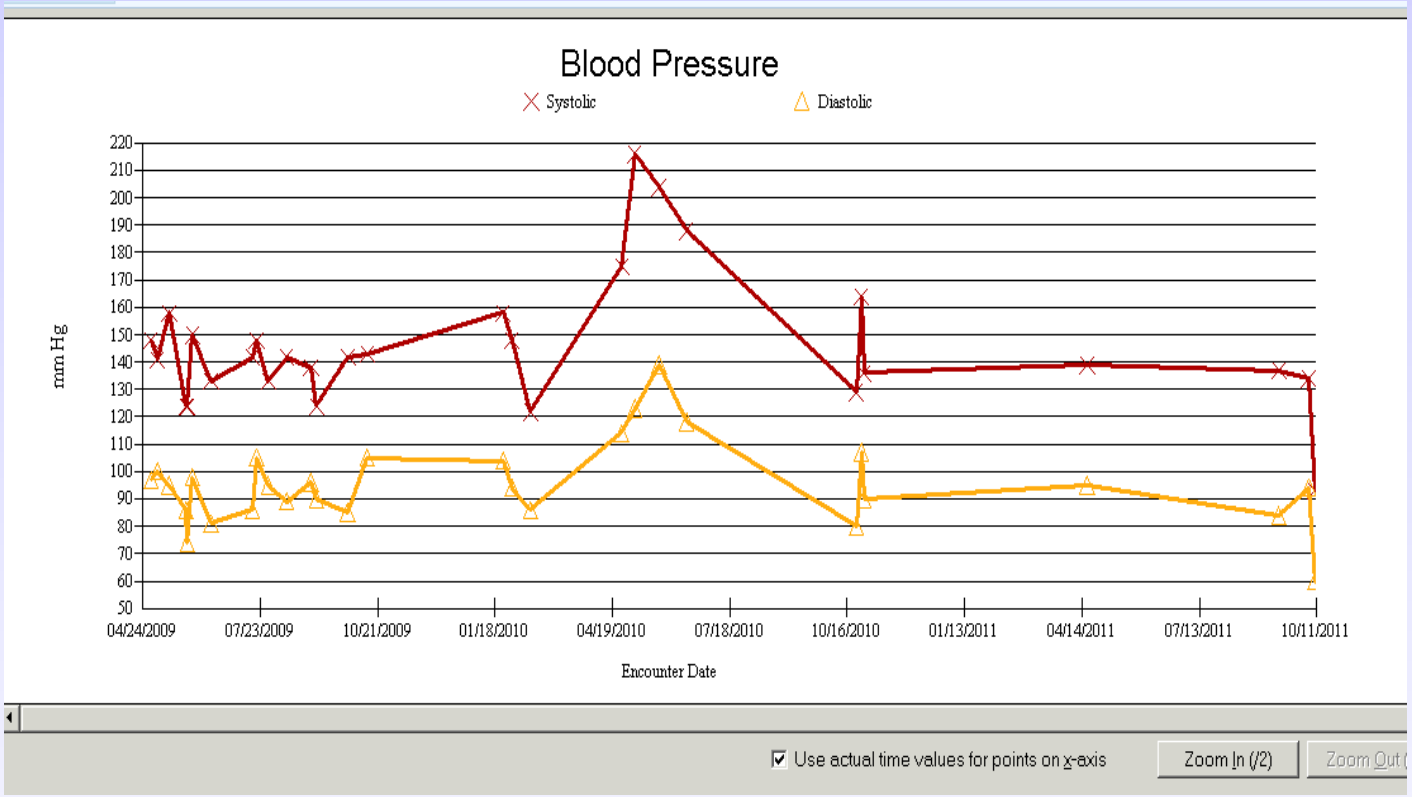


Clinical course



Remains on same medications
CTA at 4 months without evidence for RAS

Carotid Baroreflex Activation

- About 35 mm Hg reduction in SBP at one year
- 50% patients achieve goal of <140/90
- Involves surgery with learning curve
- Device implant
- Significant local complications

Renal Denervation

- Effective with about 30/12 mm reduction in BP
- About 39% reach target goal of <140/90
- Simple and relatively safe procedure
- Durable results up to 24 months

Symplicity HTN-3:Overview

- Design
  - Multicenter (90 sites in the United States), prospective, randomized, blinded, controlled study
- Population
  - 530 patients with treatment-resistant hypertension
- Treatment
  - Treatment group (endovascular catheter-based RDN with the Symplicity® Renal Denervation System™ plus baseline antihypertensive medications)
  - Control group (sham procedure* plus baseline antihypertensive medications)
- Primary Outcome Measures
  - Change in office SBP from baseline to 6 months
  - Safety

*The renal angiogram also acts as the sham procedure for patients in the control group.
Data on file, Medtronic.

Summary

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- Despite abundance of BP medications, optimal control of BP remains disappointingly low
- Both treatments appear to be promising though significant complications with carotid baroreflex activation
- Currently enrolling in Simplicity HTN 3 study

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Thank you