Heart & Vascular Research Center

Novel Therapies for Treatment of Resistant Hypertension

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Disclosures

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

MC

- 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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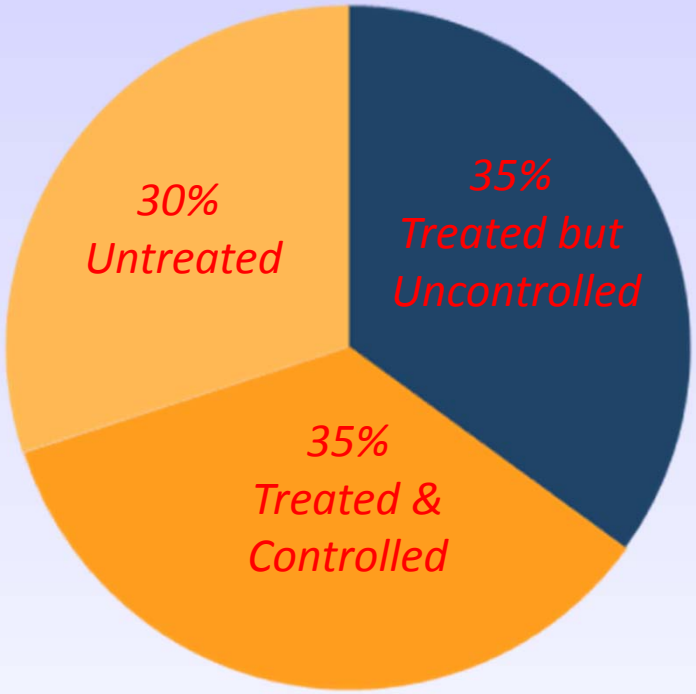
So what now?

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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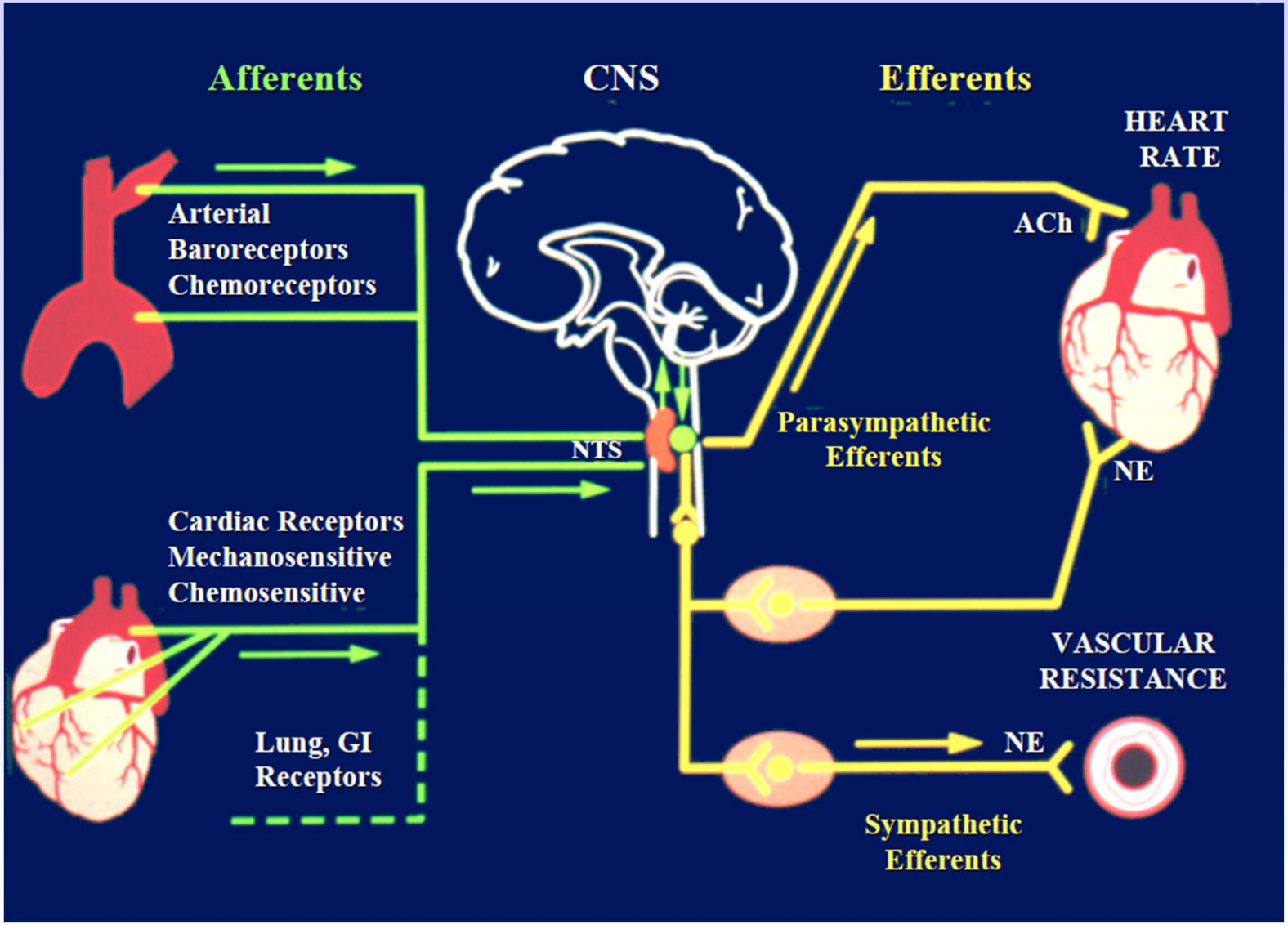
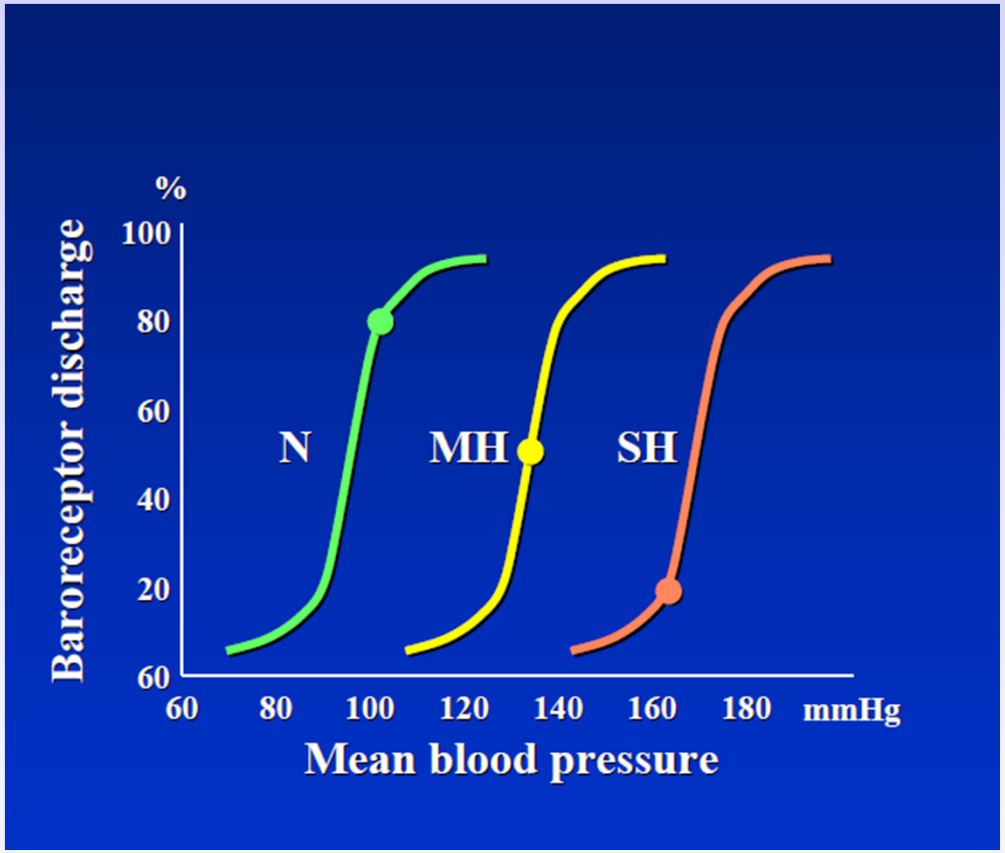


Carotid Baroreflex Physiology



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

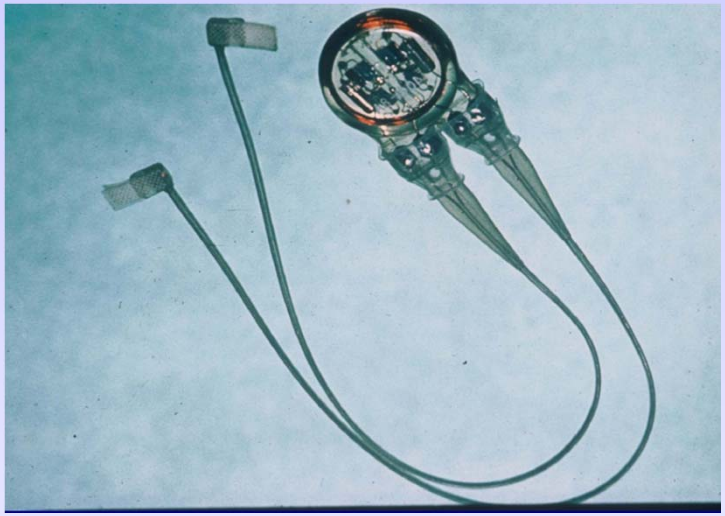
Volume 277 DECEMBER 14, 1967 Number 24

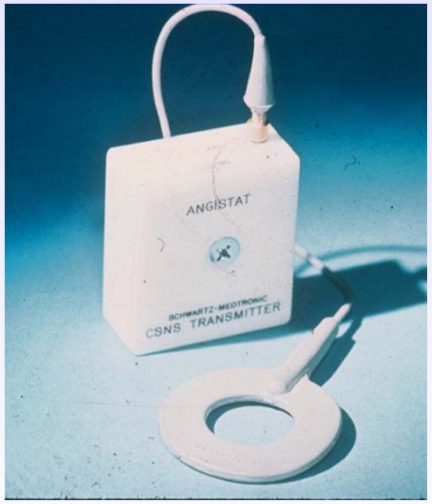
RELIEF OF ANGINA PECTORIS BY ELECTRICAL STIMULATION OF THE CAROTID-SINUS NERVES*

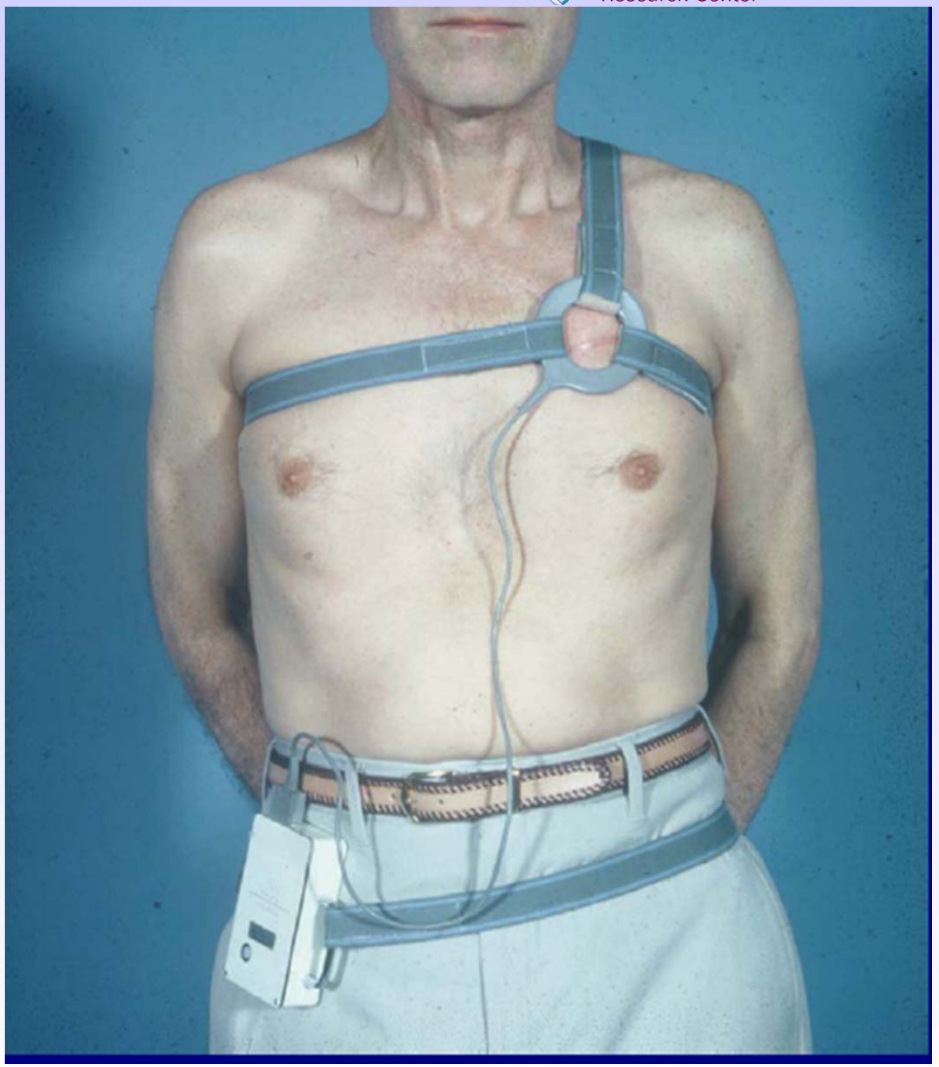
EUGENE BRAUNWALD, M.D.,† STEPHEN E. EPSTEIN, M.D.,‡ GERALD GLICK, M.D.,‡ ANDREW S. WECHSLER, M.D.,§ AND NINA S. BRAUNWALD, M.D.¶

BETHESDA, MARYLAND

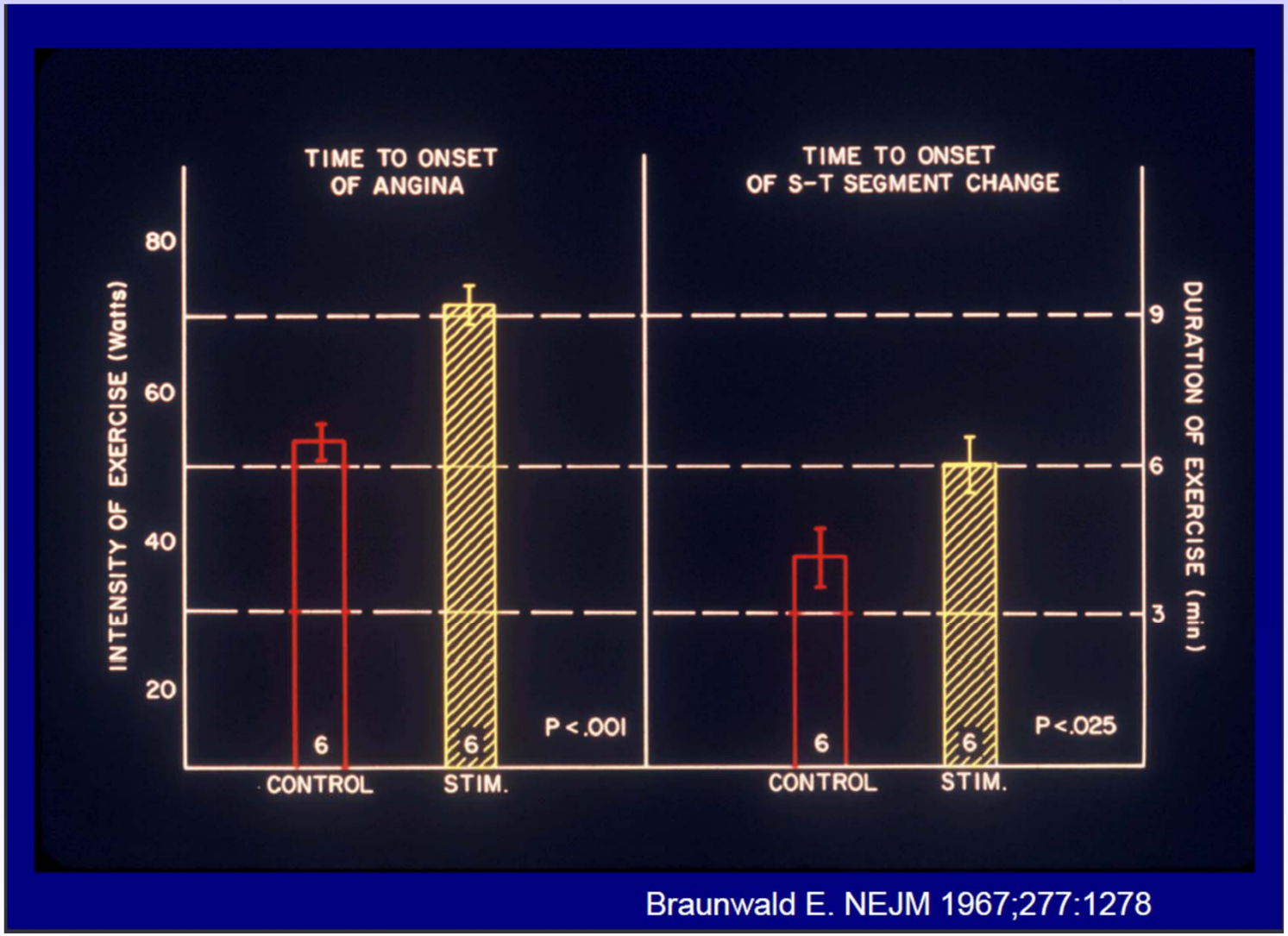
Initial Experience







Effect of Barostim



Reasons for early failure

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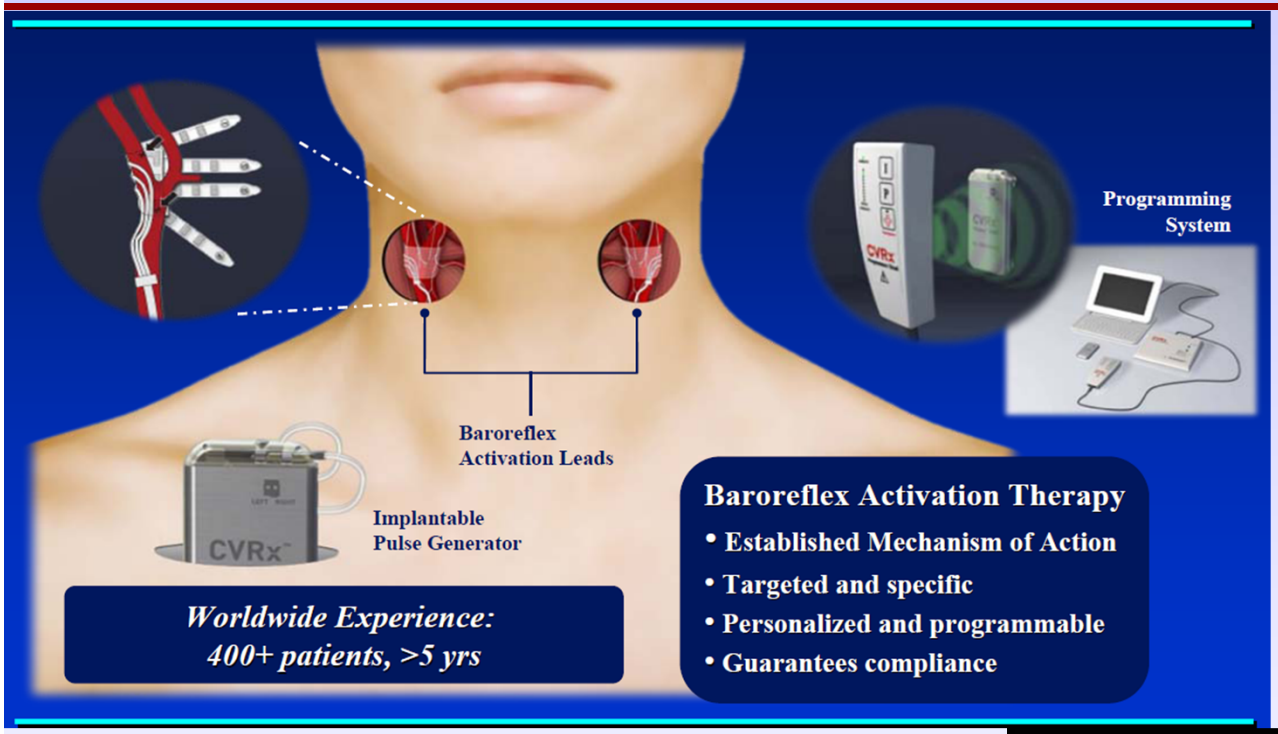
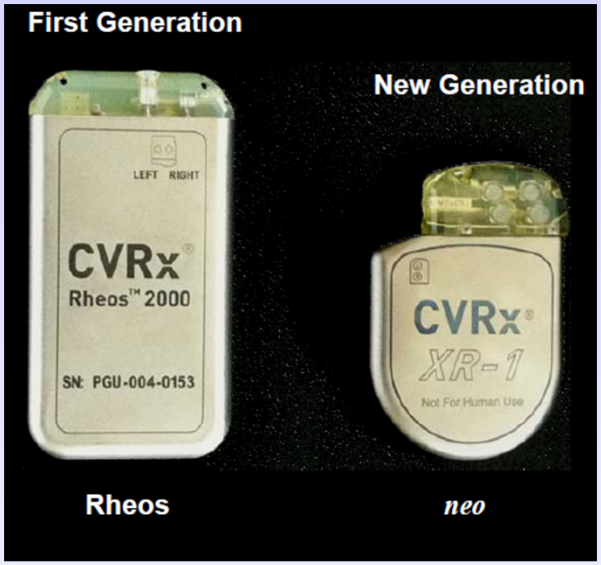
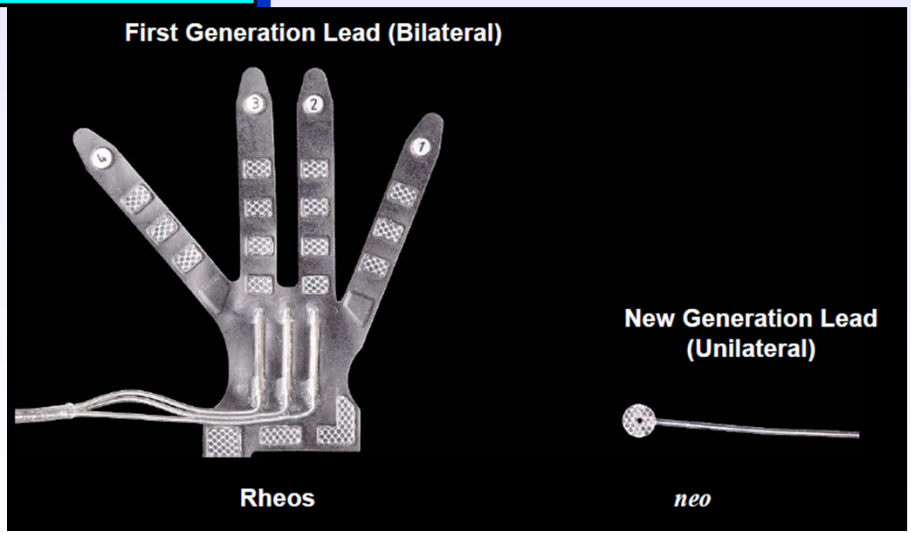
- Effects typically short lasting
- Opposition by aortic/cardiac mechano receptors
- Opposition by simultaneous chemoreceptor stimulation
- Technological limitation

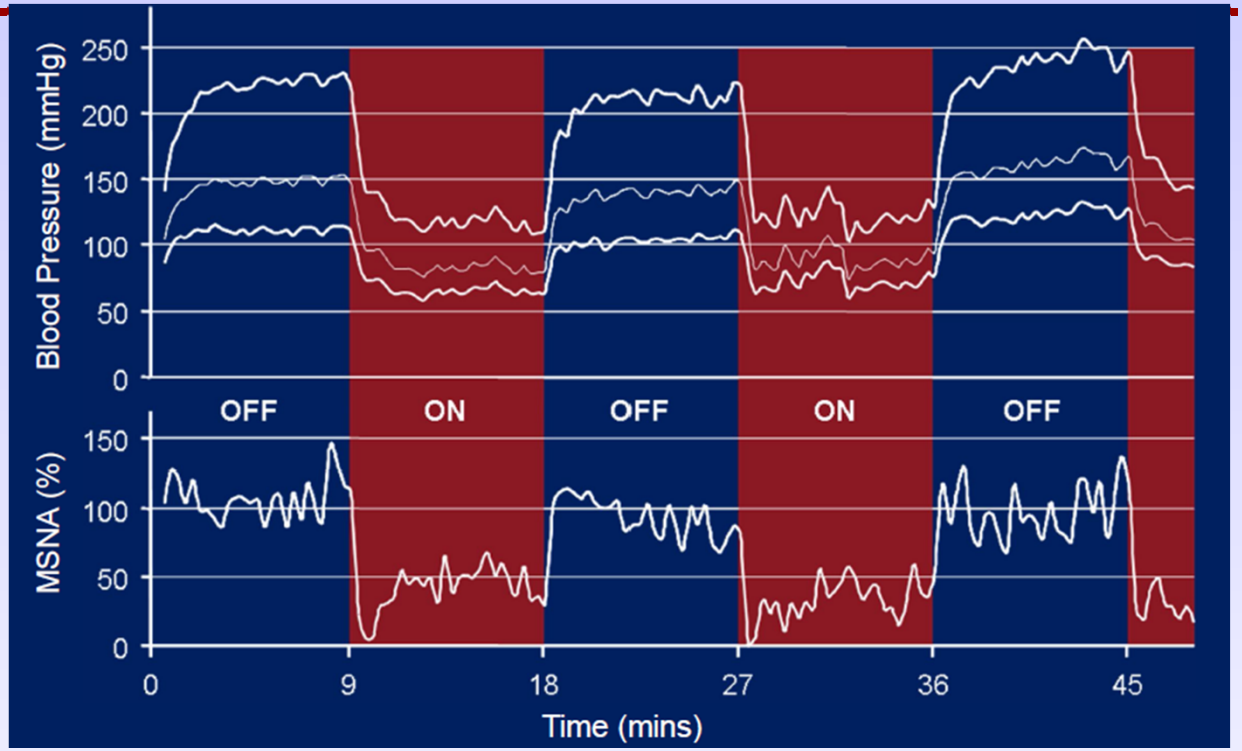
Rheos And Barostim neo System (CVRx Inc.)







Acute Effects of Electrical Stimulation



MSNA- Muscle sympathetic nerve activity

- 12 subjects
- Reduced systolic blood pressure by 32 mm HG
- Response correlated with reduced muscle sympathetic nerve activity
- Heart rate decreased by 4.5 beats/min
- Plasma renin concentration decreased by 20 %

(*Hypertension*. 2010;55:619-626.)

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

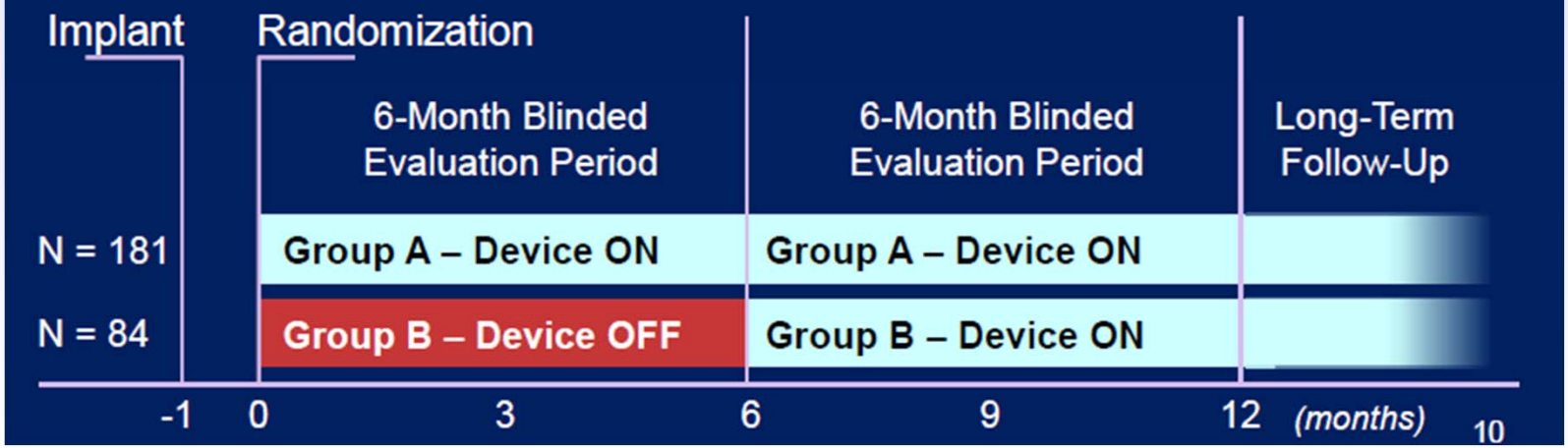
J. Am. Coll. Cardiol. published online Jul 28, 2011;
doi:10.1016/j.jacc.2011.06.008

JACC

JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY

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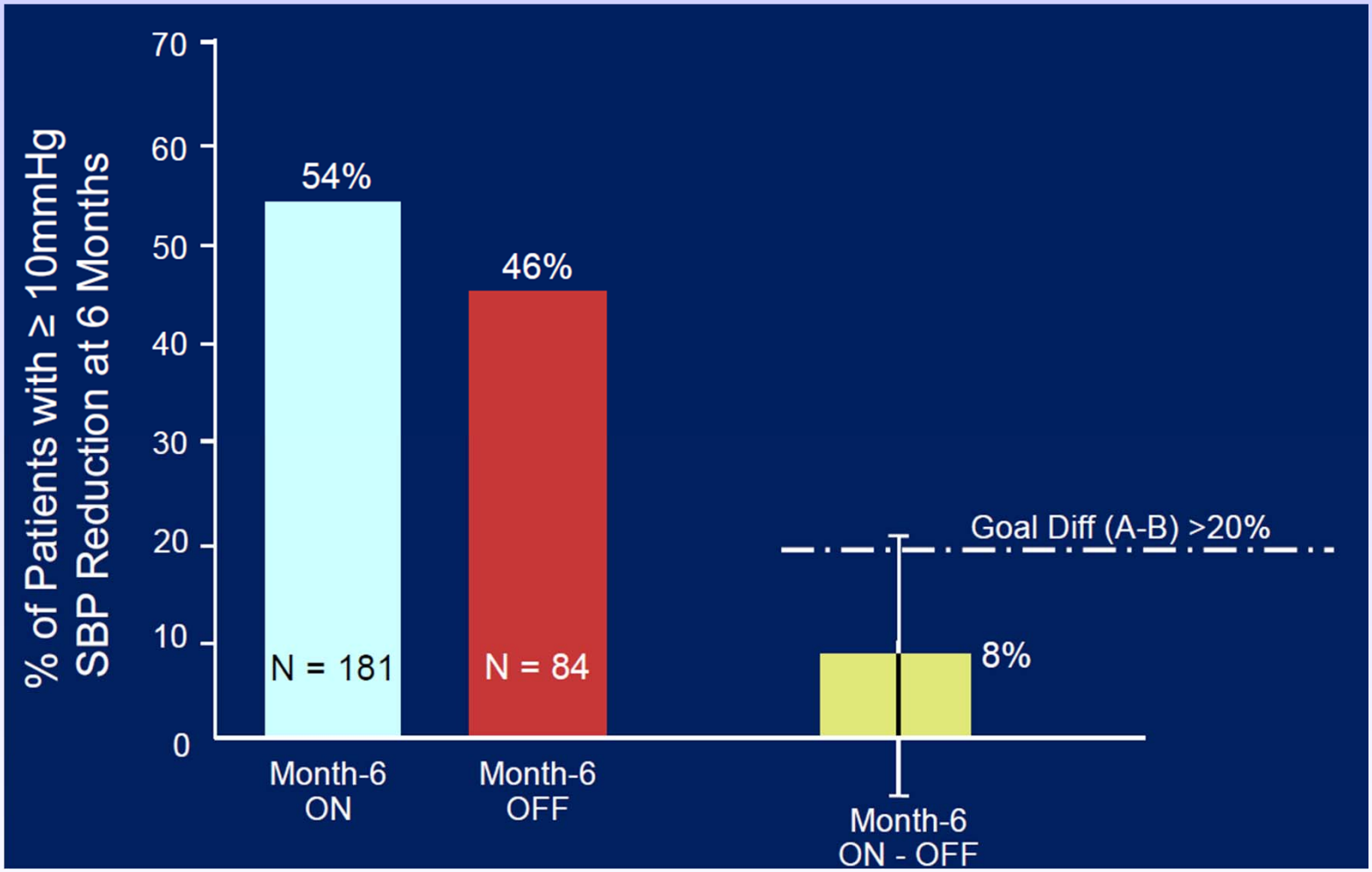
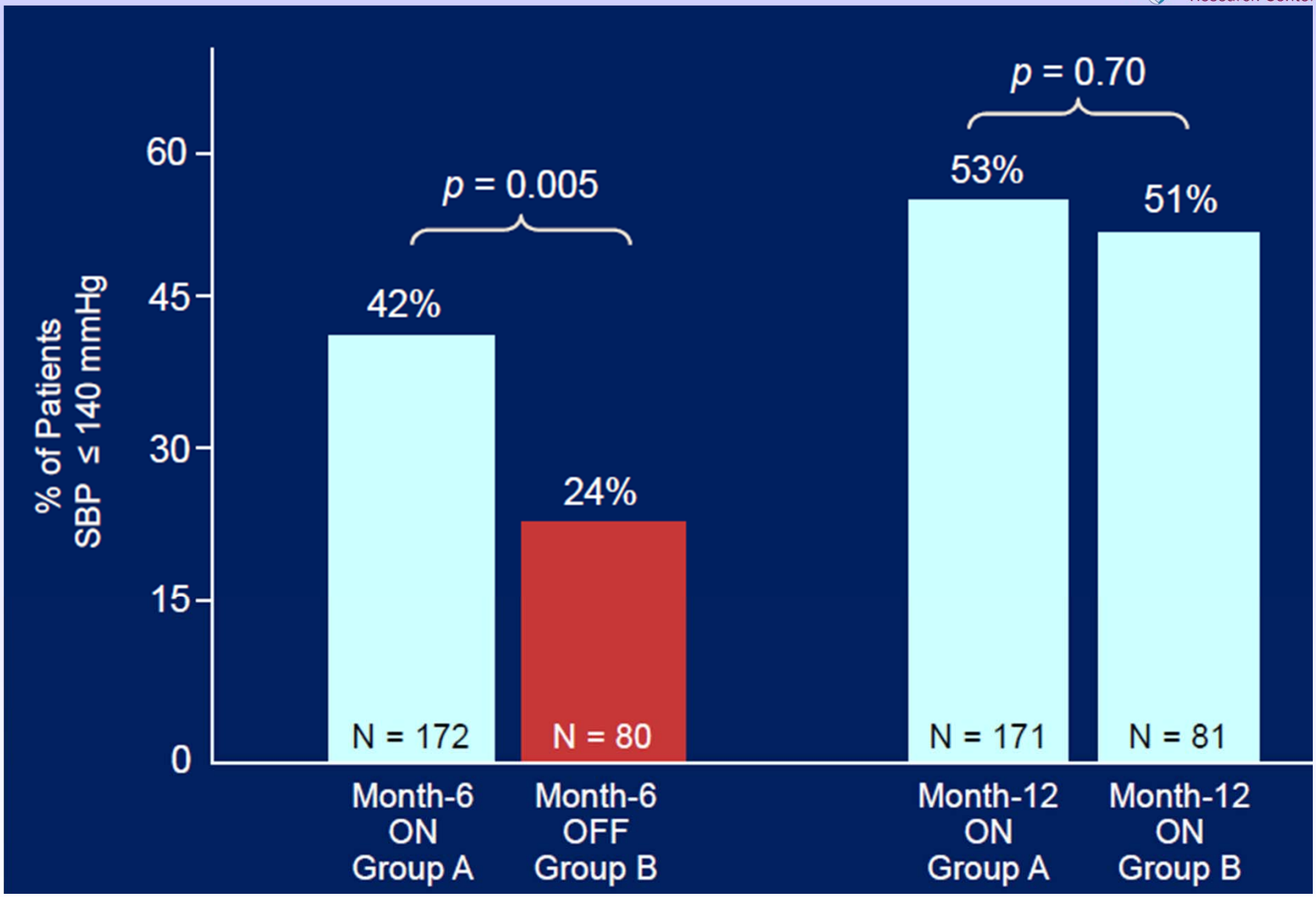
	Group A (N = 181)	Group B (N = 84)
Gender	64% Male	55% Male
Race	73% Caucasian	78% Caucasian
Age (mean years ± sd)	54 ± 11	53 ± 10
BMI (mean kg/m^2 ± sd)	33 ± 5	32 ± 6
Antihypertensive Meds (mean # ± sd)	5.2 ± 2	5.2 ± 2
Systolic BP (mean mmHg ± sd)	179 ± 22	176 ± 22
Diastolic BP (mean mmHg ± sd)	103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

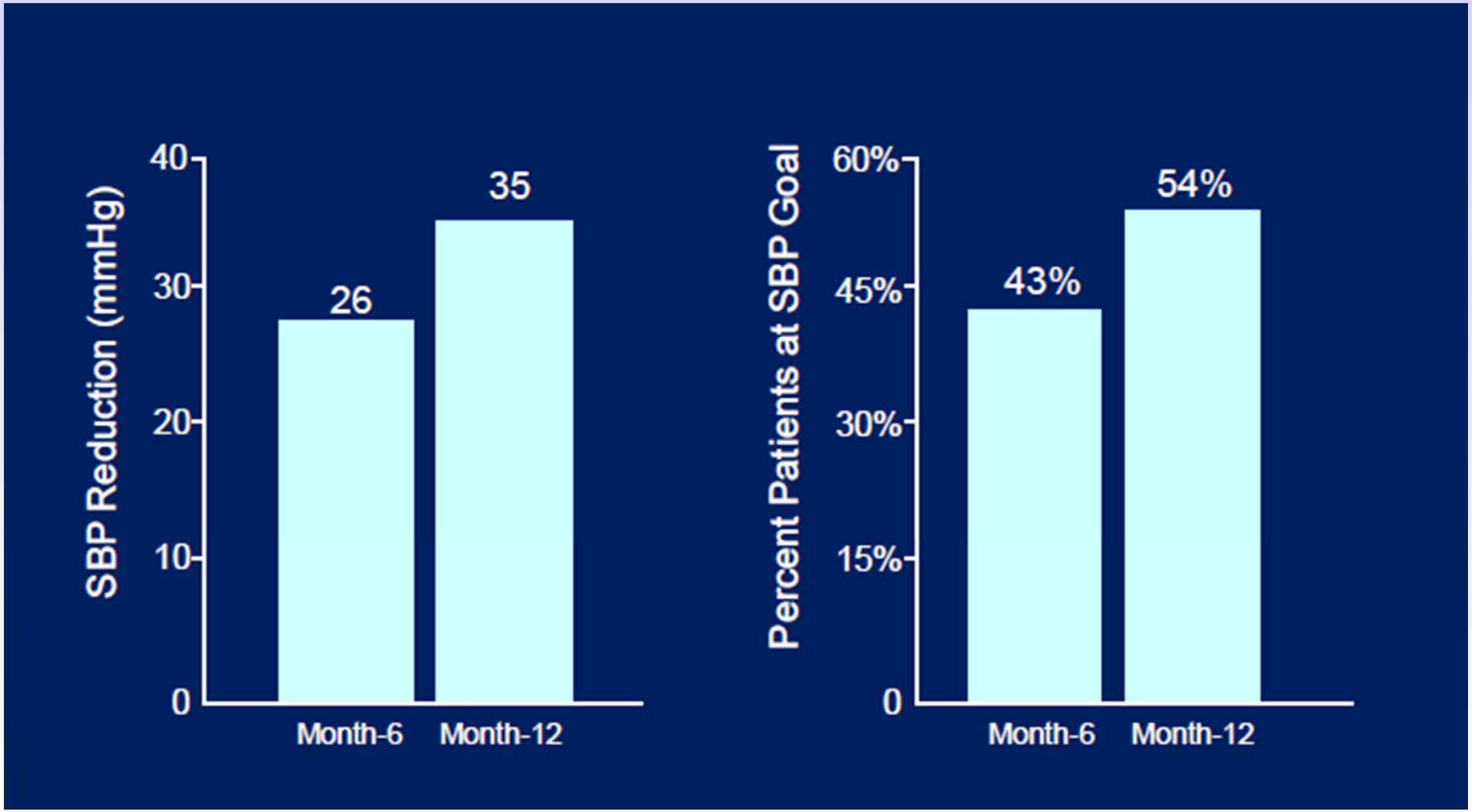
Procedural efficacy
% of patients >10 mm reduction



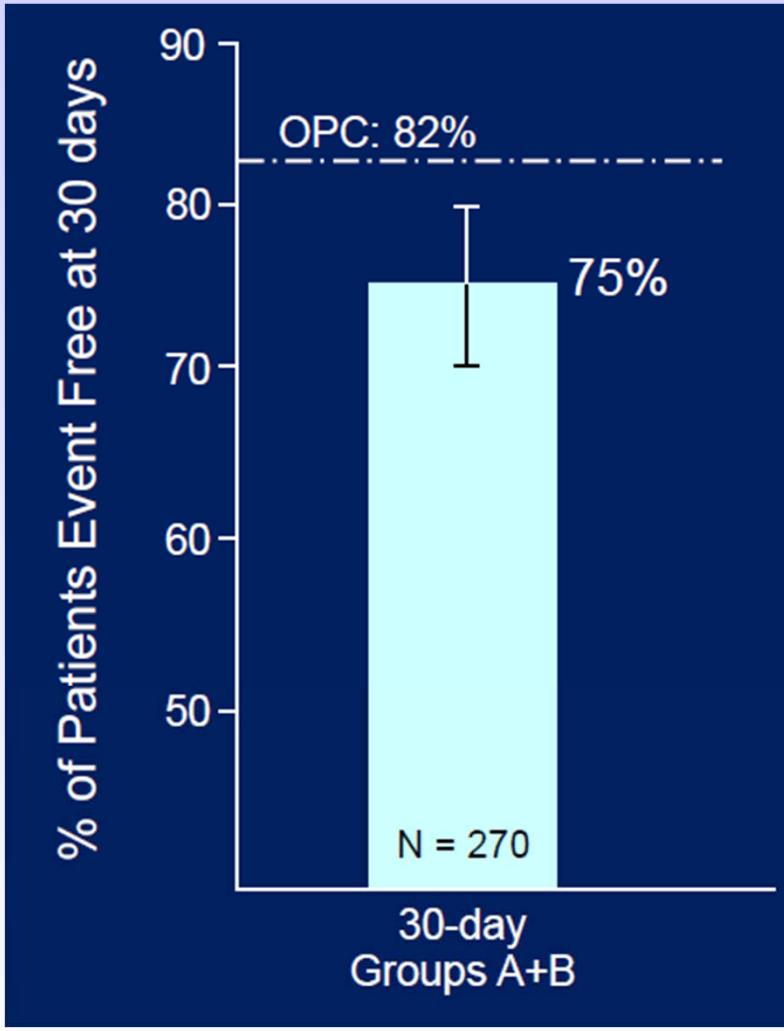
Procedural efficacy
% of patients with SBP<140



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

- 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

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Renal Sympathetic Denervation

Renal Sympathetic Afferent Nerves:

Kidney as Origin of Central Sympathetic Drive

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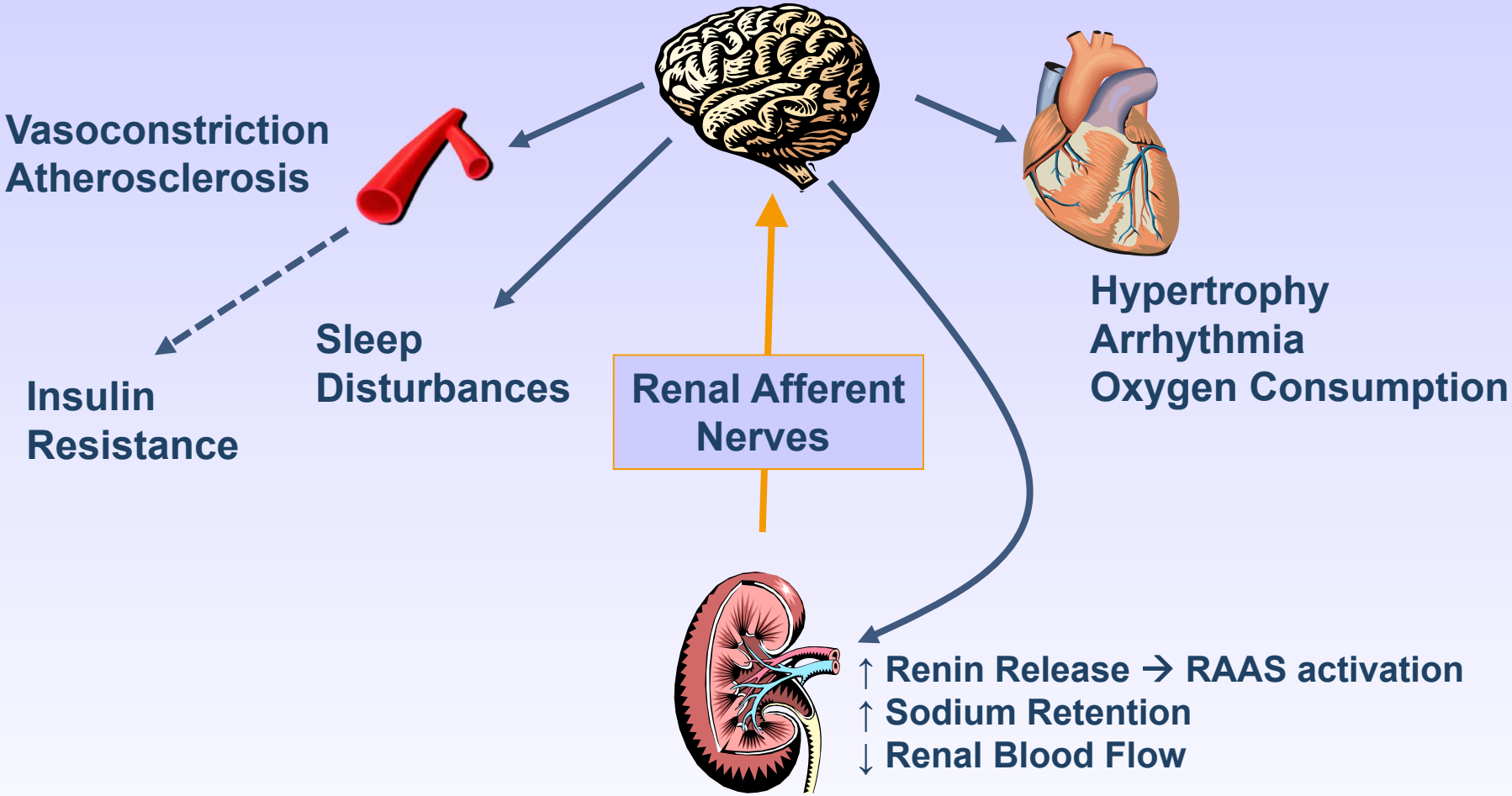
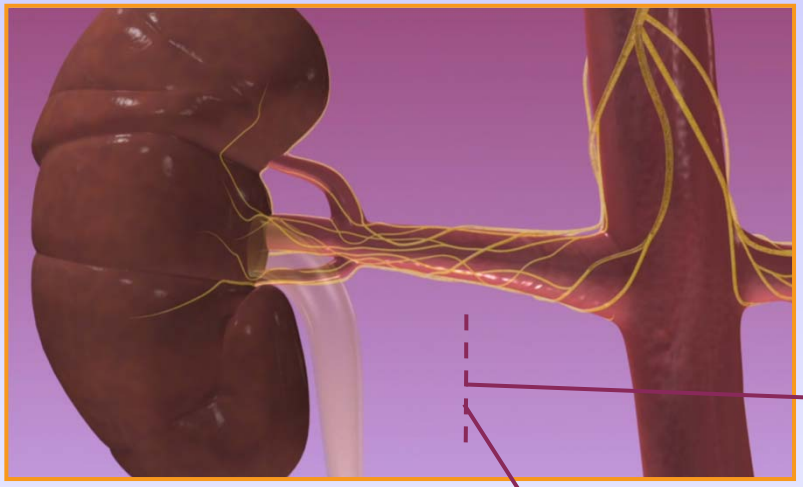
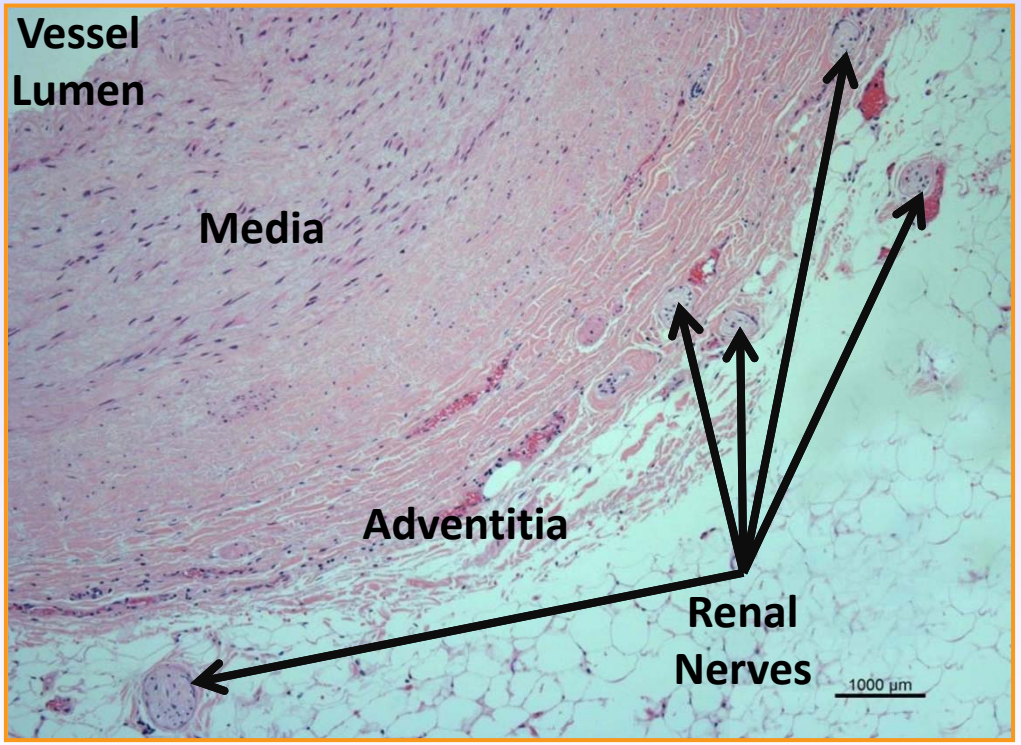


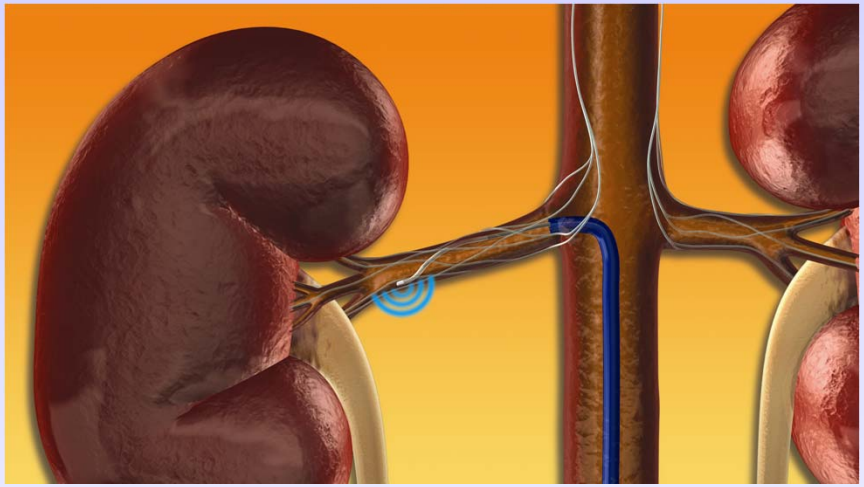
Renal Nerve Anatomy

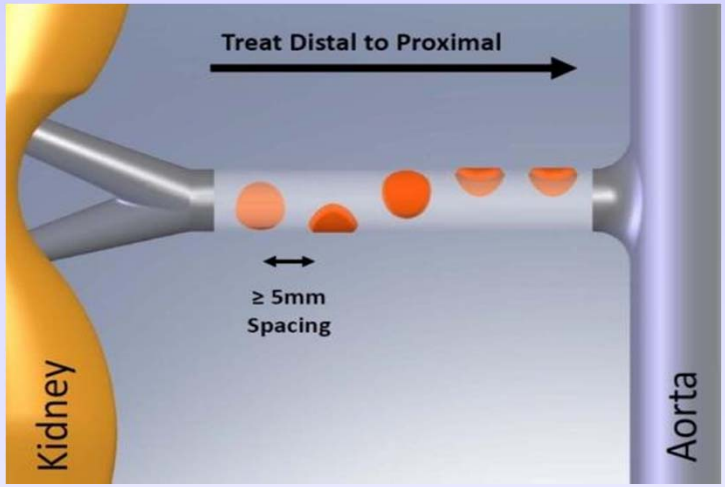


- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia



Renal Nerve Anatomy Allows a Catheter-Based Approach





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

Staged Clinical Evaluation

First-in-Man ✓

Symplicity HTN-1

- Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA

Symplicity HTN-3
US Randomized Clinical Trial
(upcoming)

EU/AU

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

Symplicity HTN-1


THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

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, Boguslaw 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

-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

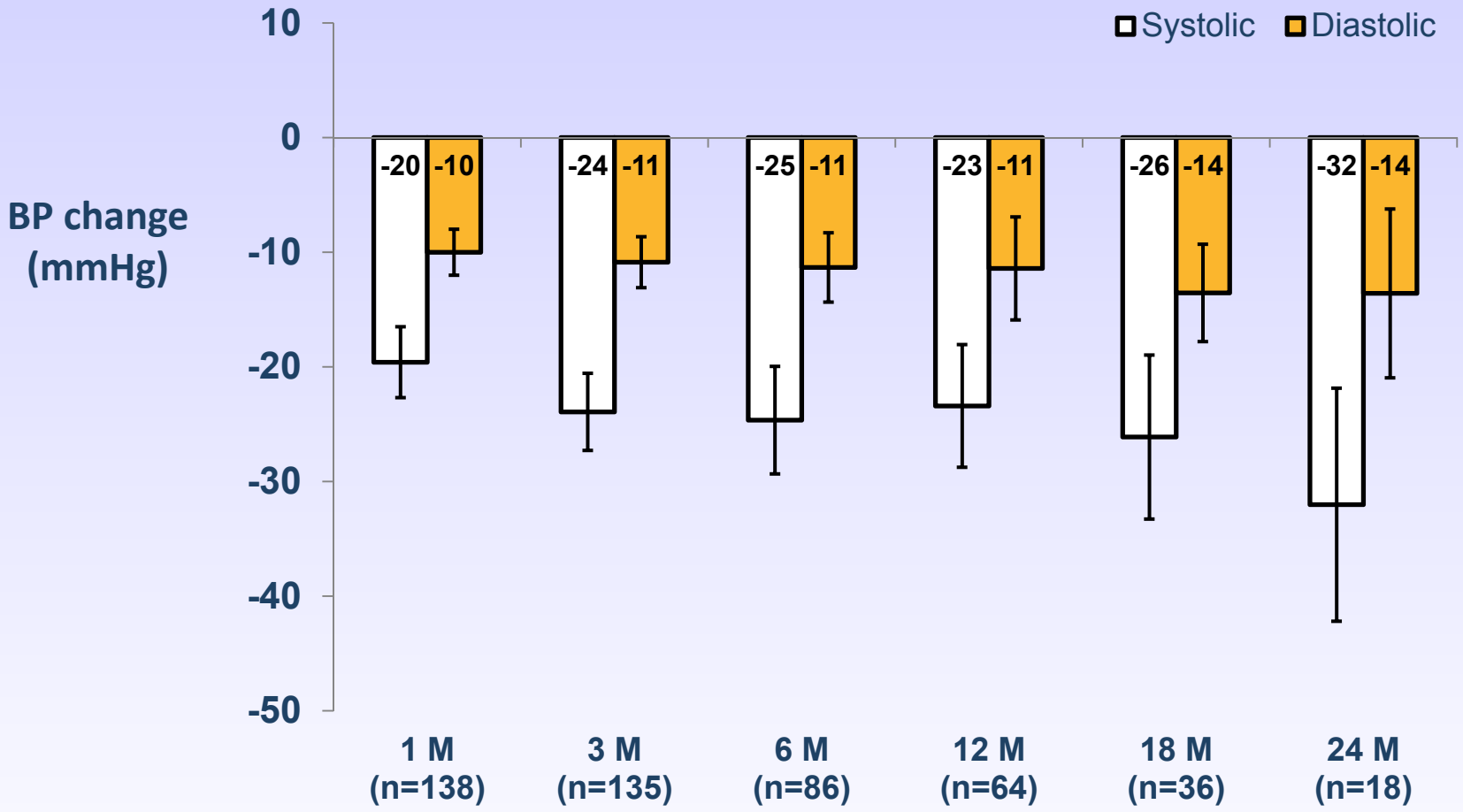
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Chronic Safety

- 81 patients with 6-month renal CTA, MRA, or Duplex
  - No vascular abnormalities at any site of RF delivery
  - One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- Two deaths within the follow-up period; both unrelated to the device or therapy
- No orthostatic or electrolyte disturbances
- No change in renal function at one year (Δ eGFR)
  - 12 Months: -2.9 mL/min/1.73m^2 (n.s.) (n=64)

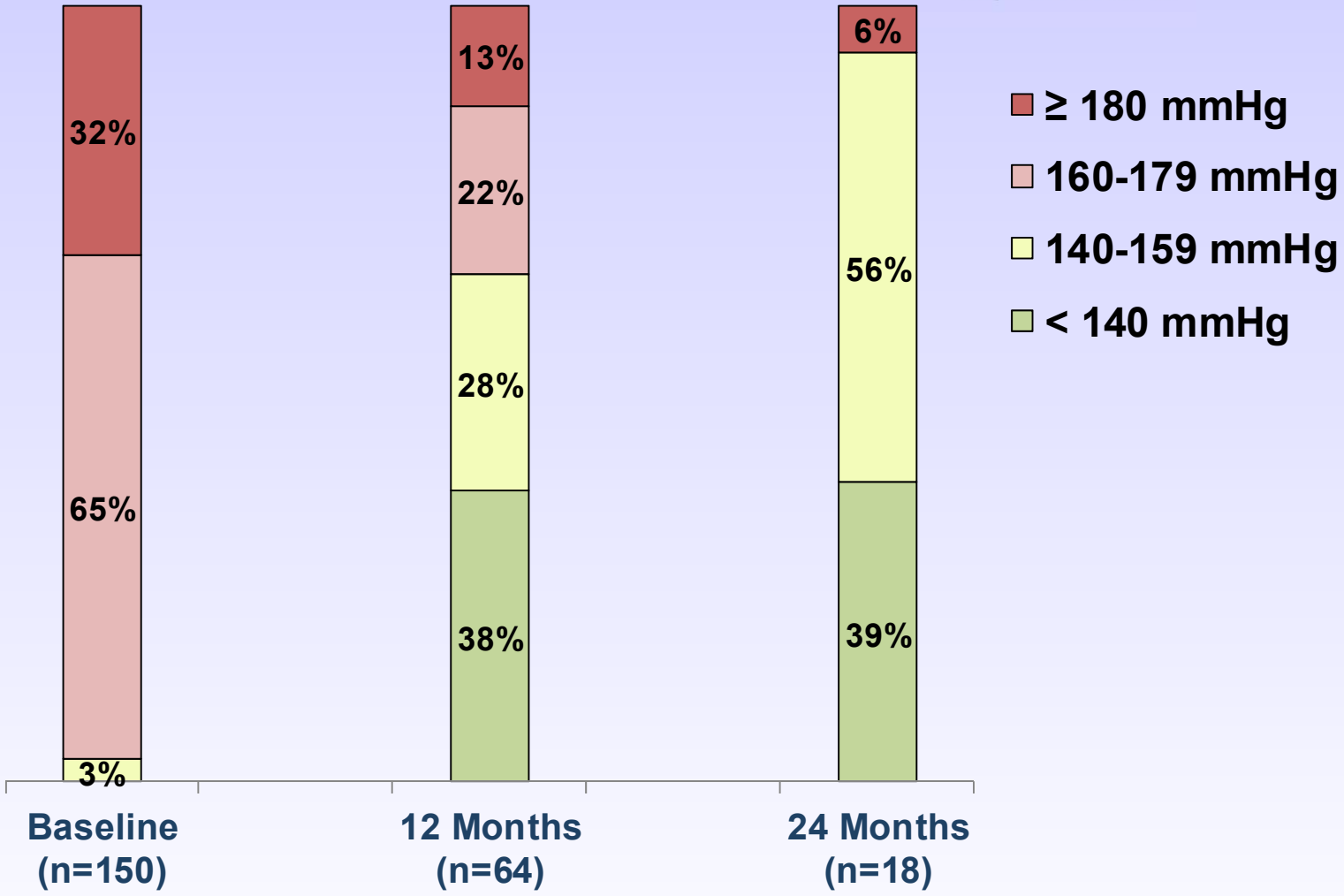
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

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.

VALIDATION OF PHYSIOLOGY

Proof of Principle

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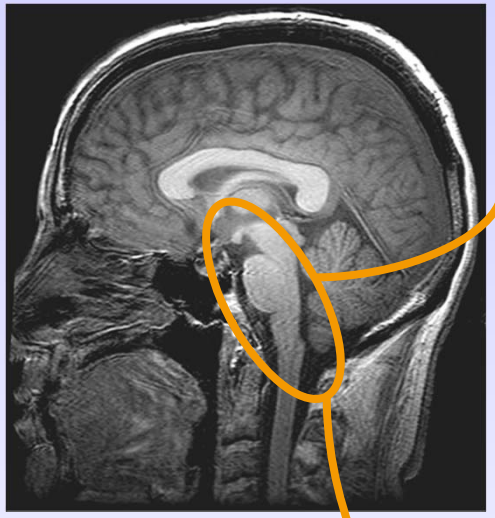
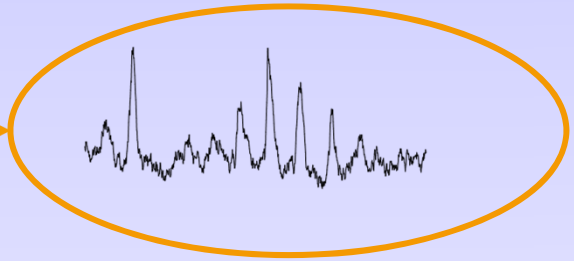
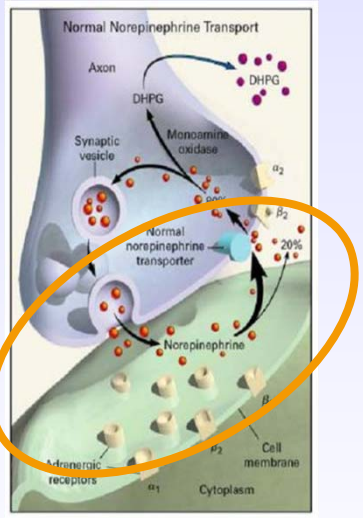


Central Sympathetic Nerve Activity



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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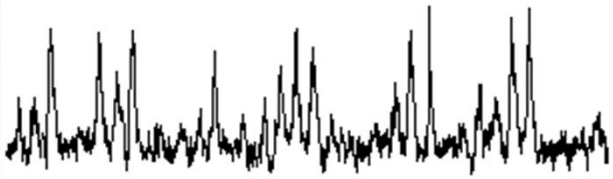
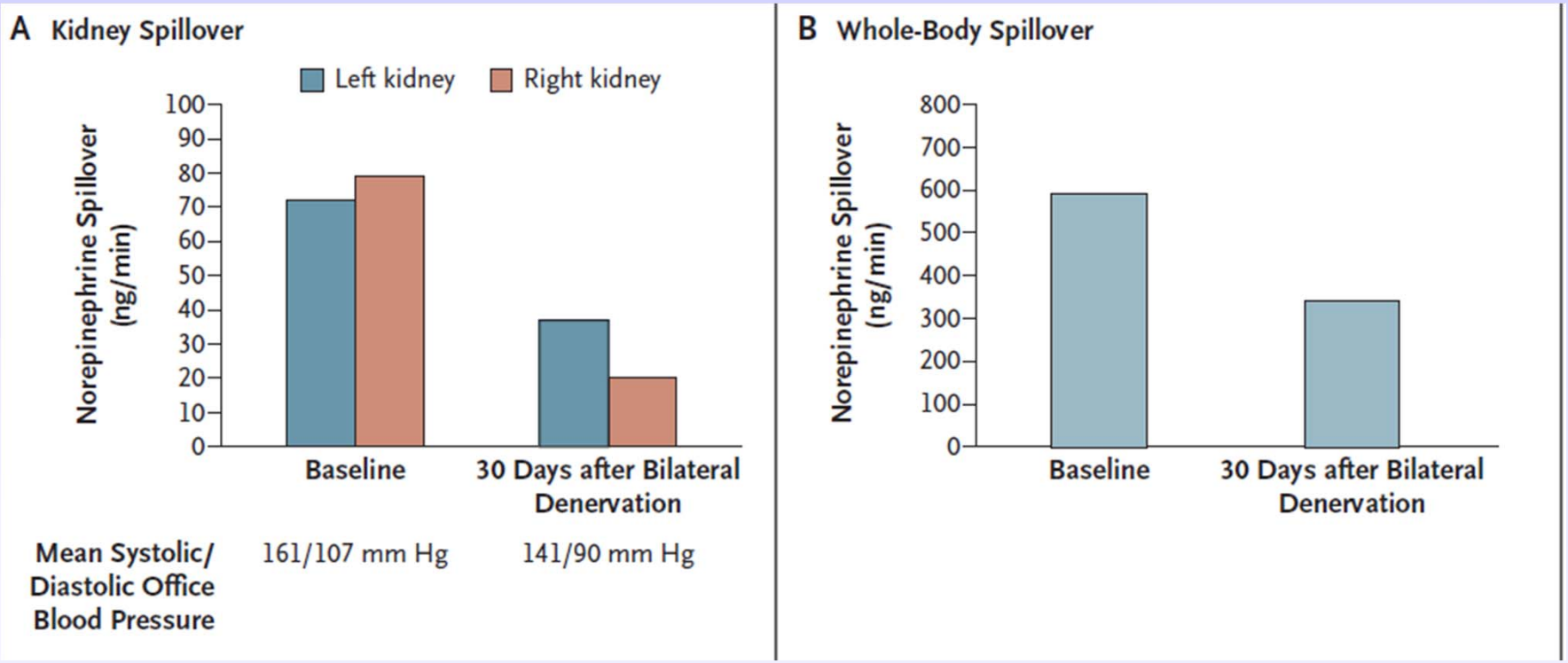
** 59 year old male on 7 HTN meds*

		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.

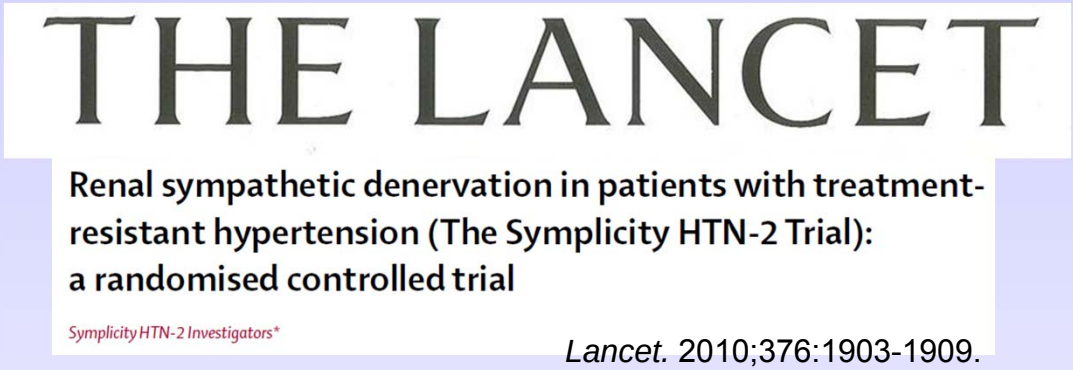
Proof of Principle: Related Changes in Underlying Physiology



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.

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 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

Inclusion Criteria:

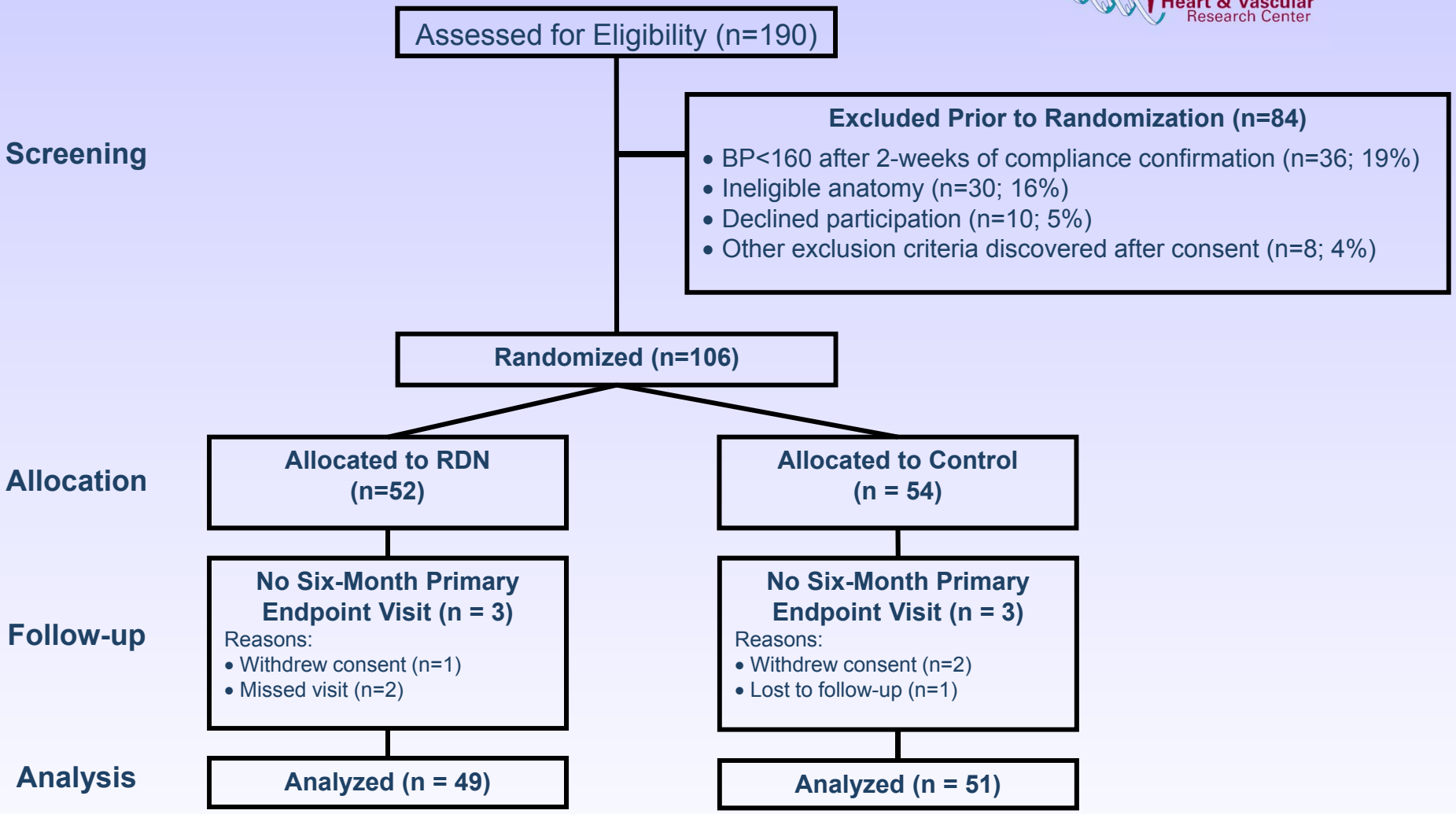
- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

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

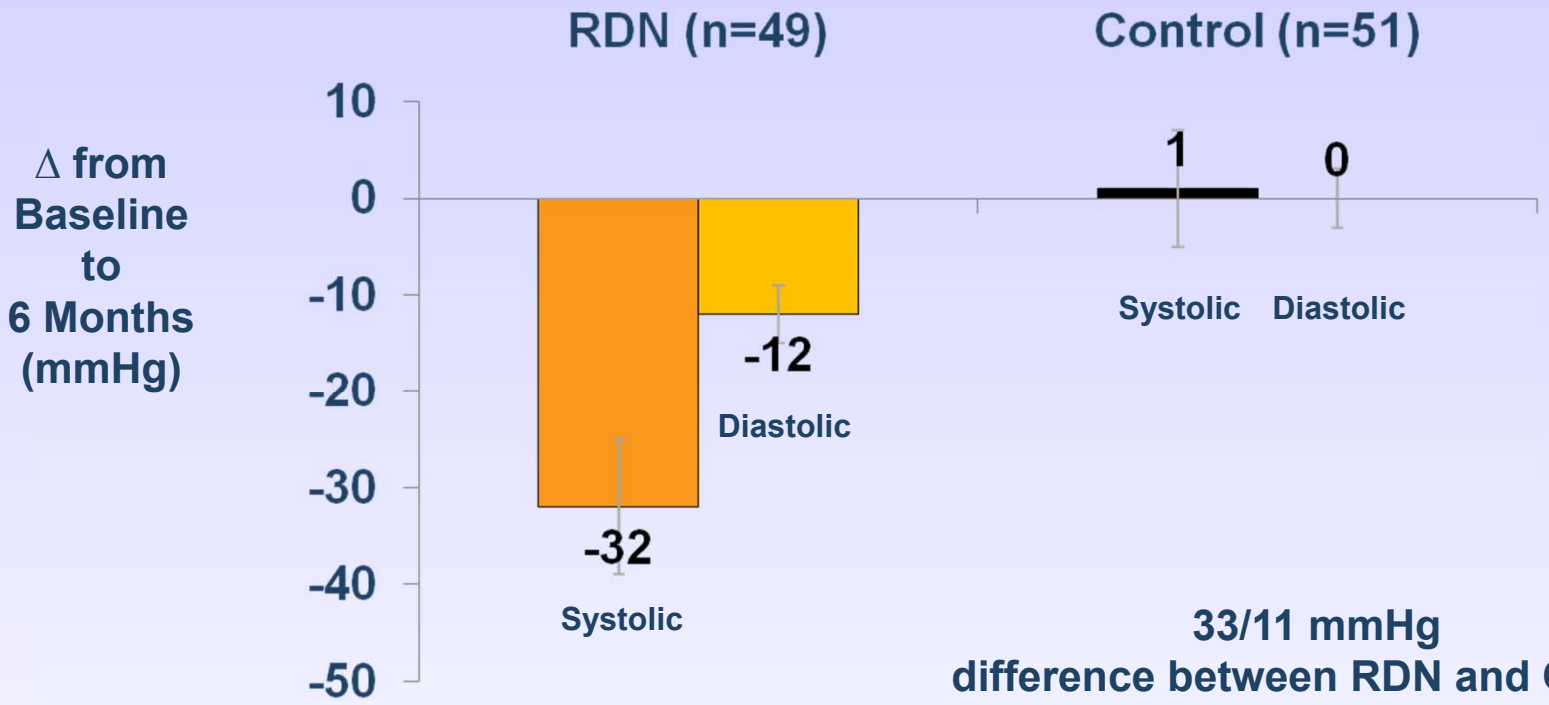


Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

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:

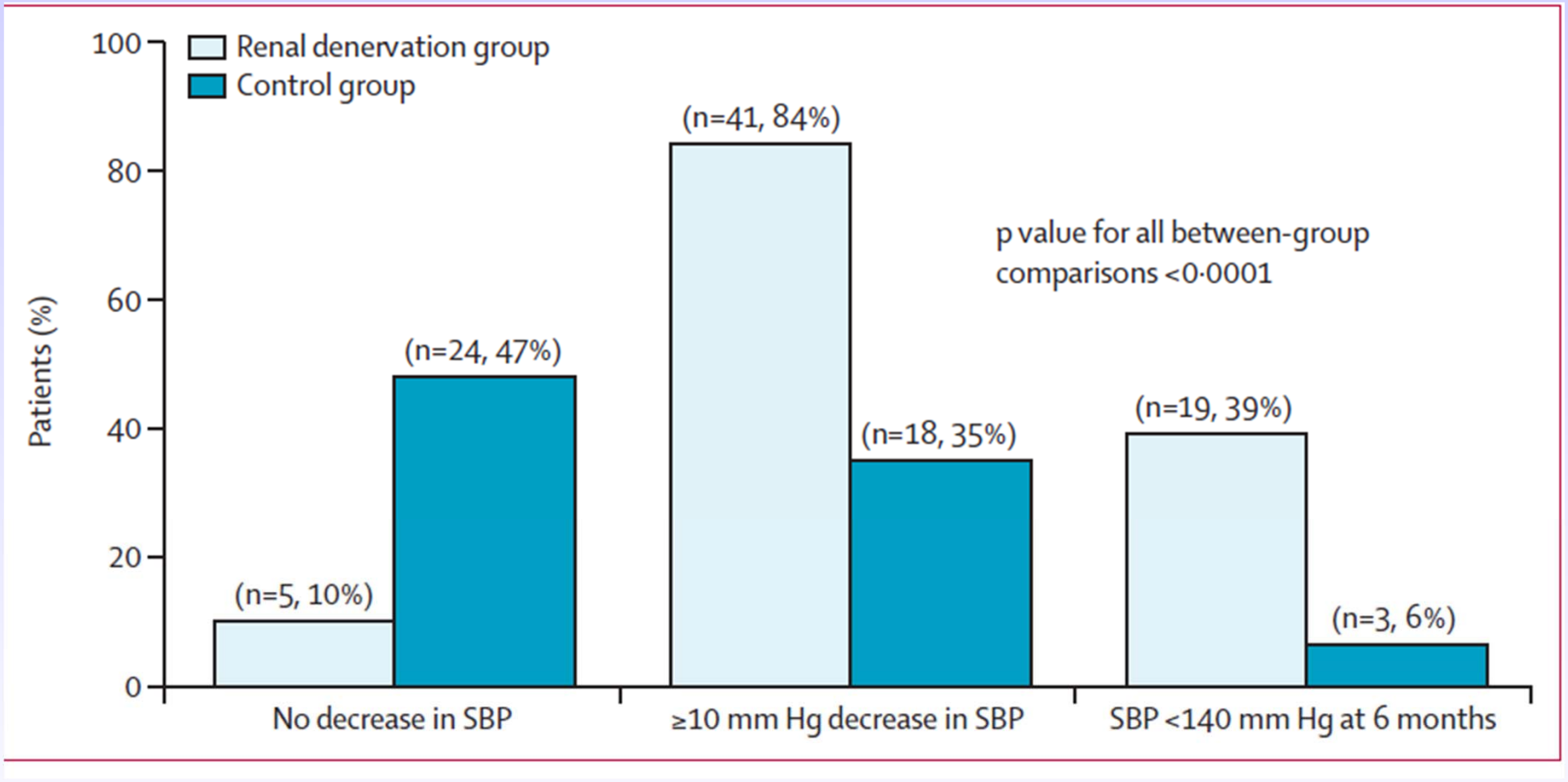
	RDN (n=49)	Control (n=51)	P-value
# Med Dose Decrease (%)	10 (20%)	3 (6%)	**0.04**
# Med Dose Increase (%)	4 (8%)	6 (12%)	0.74

Censoring BP after medication increases:

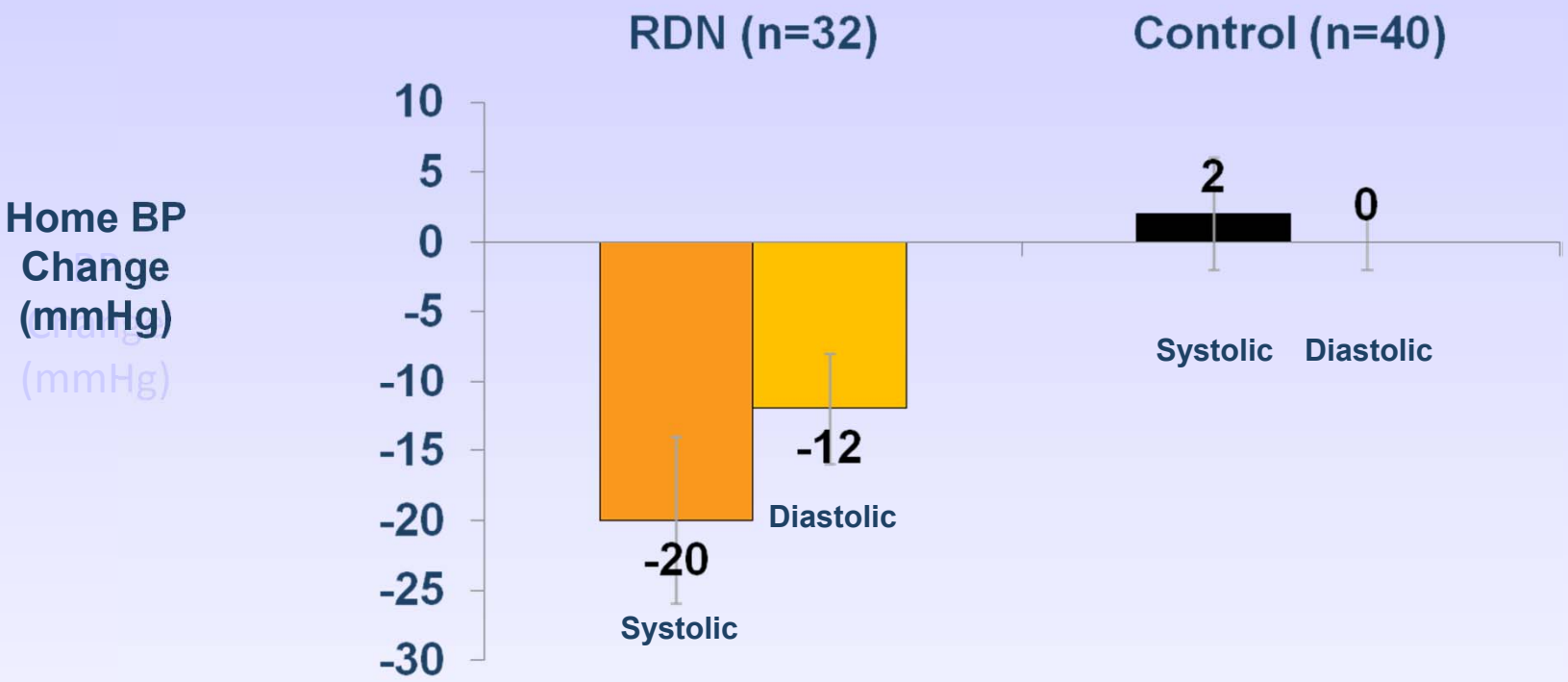
- Renal Denervation → Reduction of 31/12 ± 22/11 mmHg ($p<0.0001$ for SBP & DBP)
- Control → Change of 0/-1 ± 20/10 mmHg ($p=0.90$ & $p=0.61$ for SBP & DBP, respectively)

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

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

Other Safety

	RDN (n=49)	Control (n=51)
Composite CV Events		
Hypertensive event unrelated to non-adherence to medication	3	2
Other CV events	0	0
Other Serious AEs		
Transient ischemic attack	1	2
Hypertensive event after abruptly stopping clonidine	1	0
Hypotensive episode resulting in reduction of medications	1	0
Coronary stent for angina	1	1
Temporary nausea/edema	1	0

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

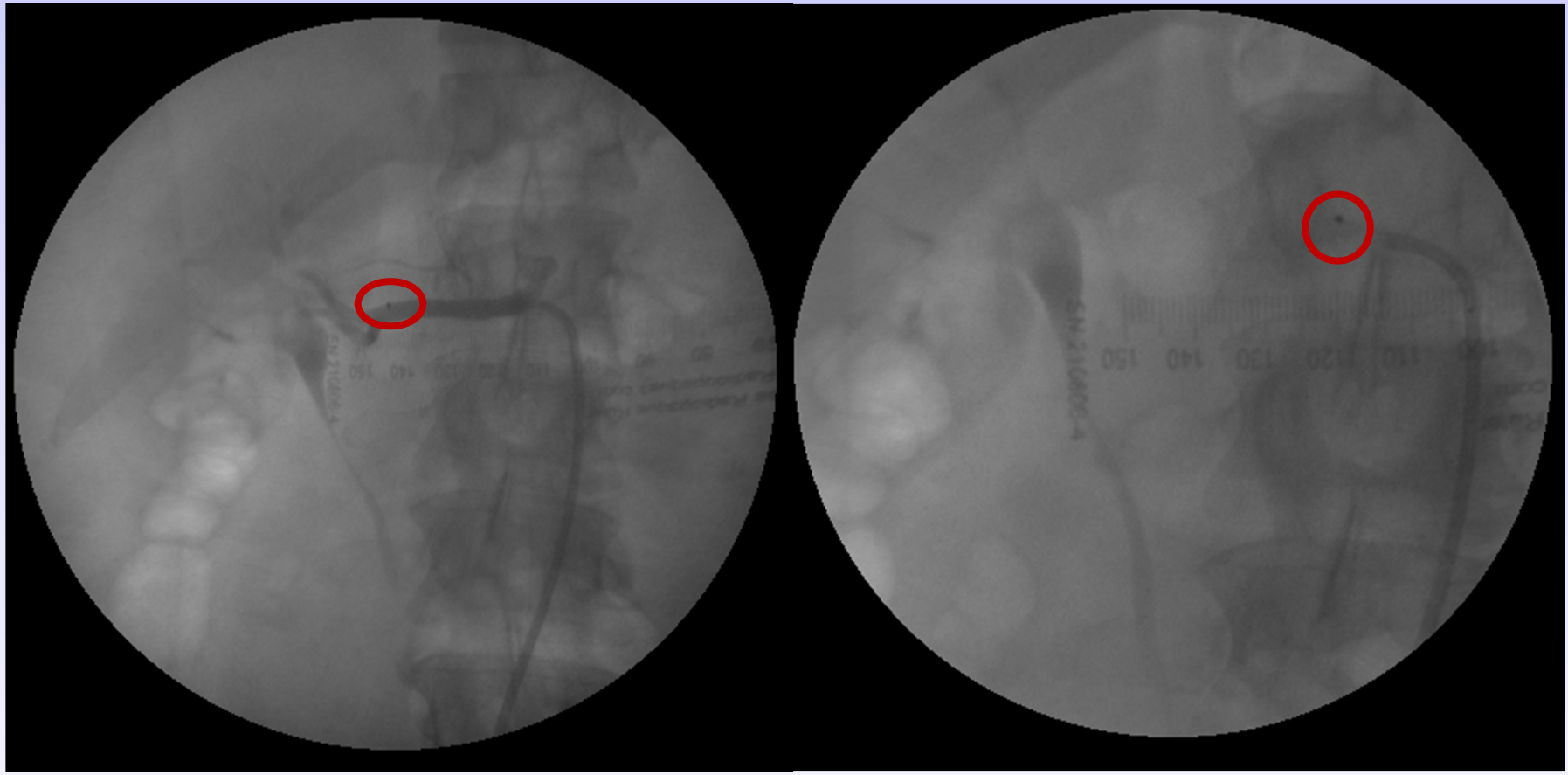
MC

- 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

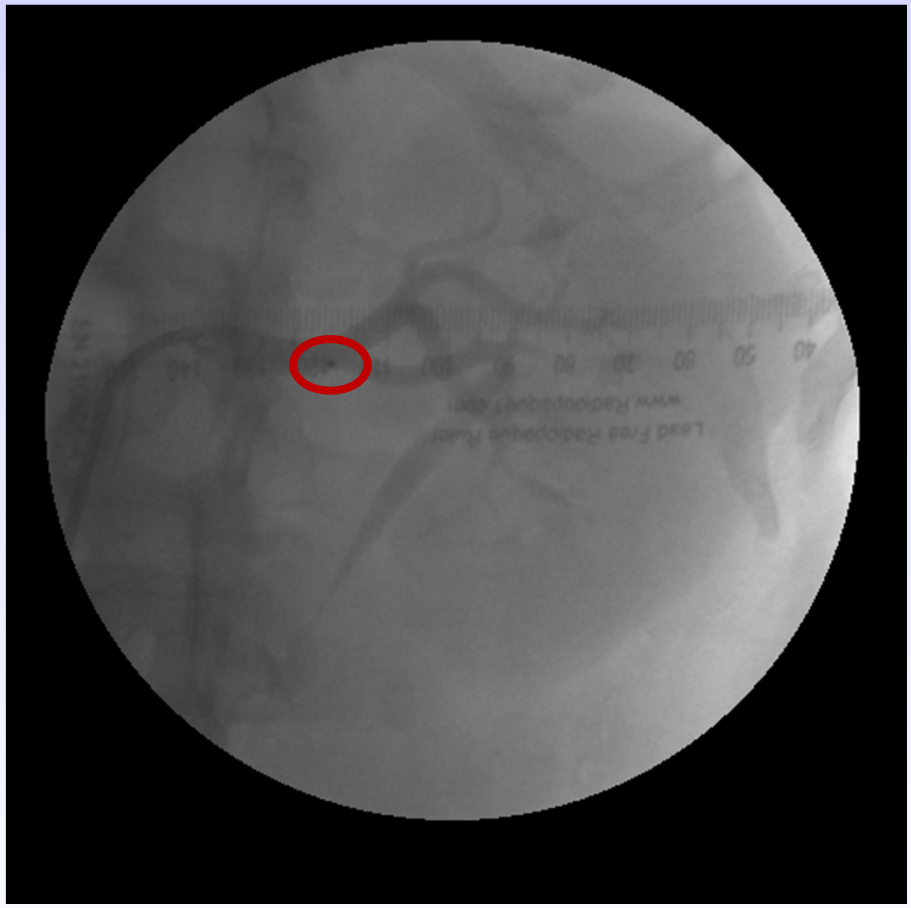
Clinical course for MC

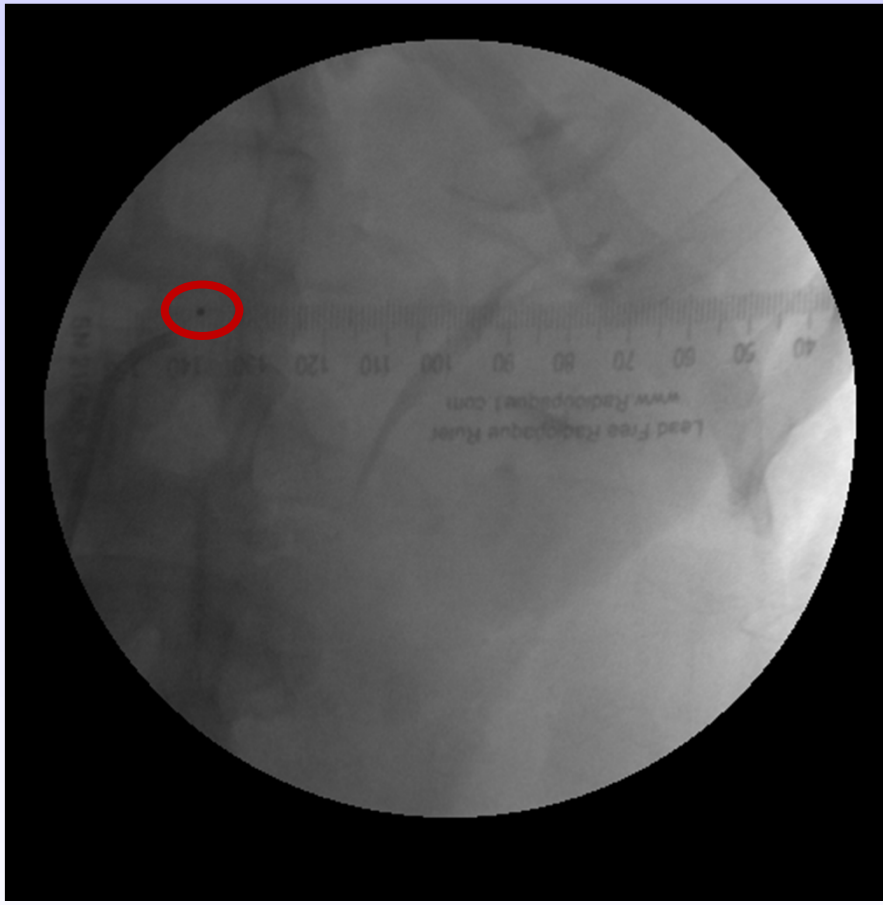
- Enrolled in renal denervation study

Renal denervation – right renal



Renal denervation- left renal





Final Angiogram

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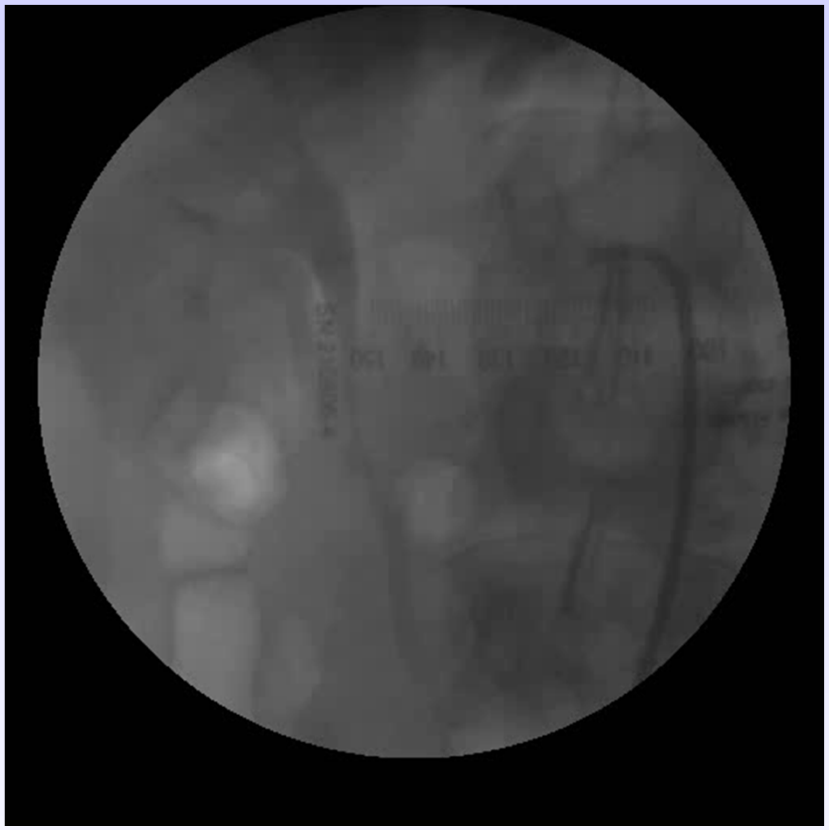
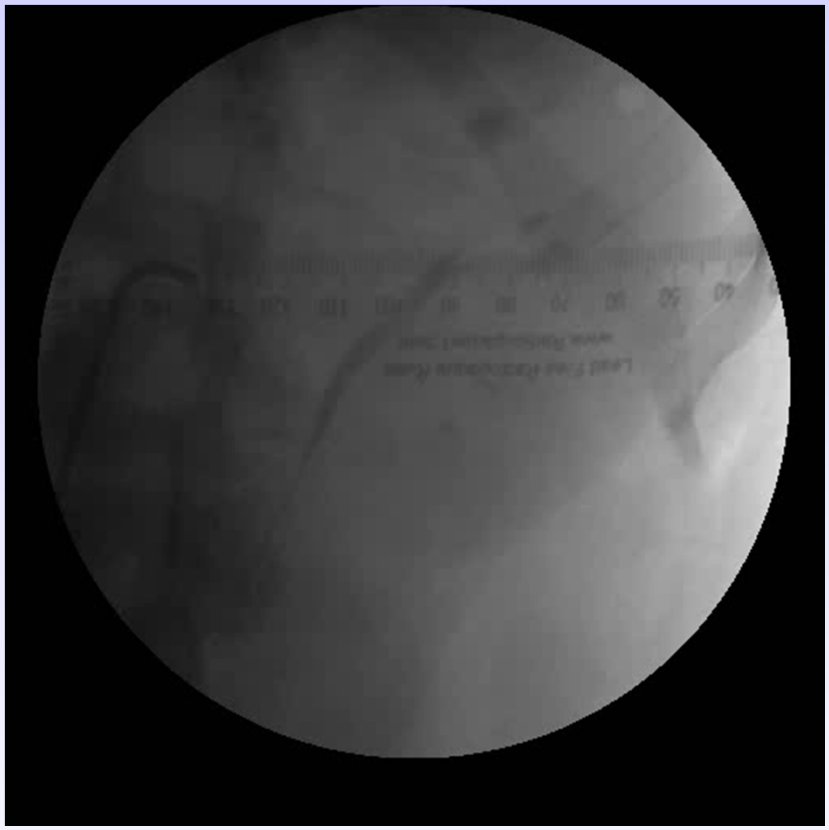
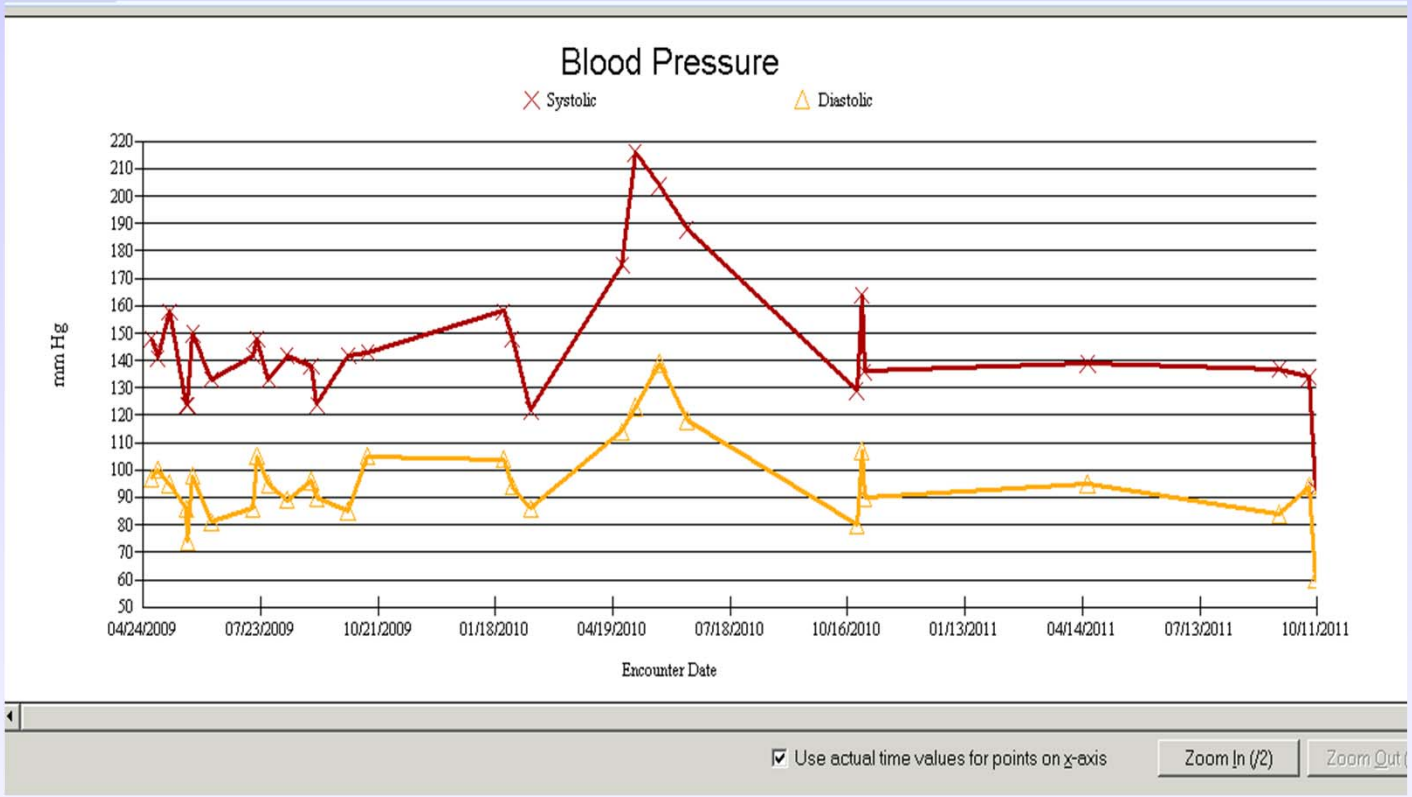




Clinical course



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
- Only 39% reach target goal of <140/90
- Simple and relatively safe procedure
- Durable results up to 24 months

Summary

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- Despite abundance of BP medications, optimal control of BP remains disappointingly low
- Both treatments appear to be promising but the jury is still out
- Need further long term data in larger patient population in randomized controlled trials

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Thank you