Renal Sympathetic Denervation for Resistant Hypertension

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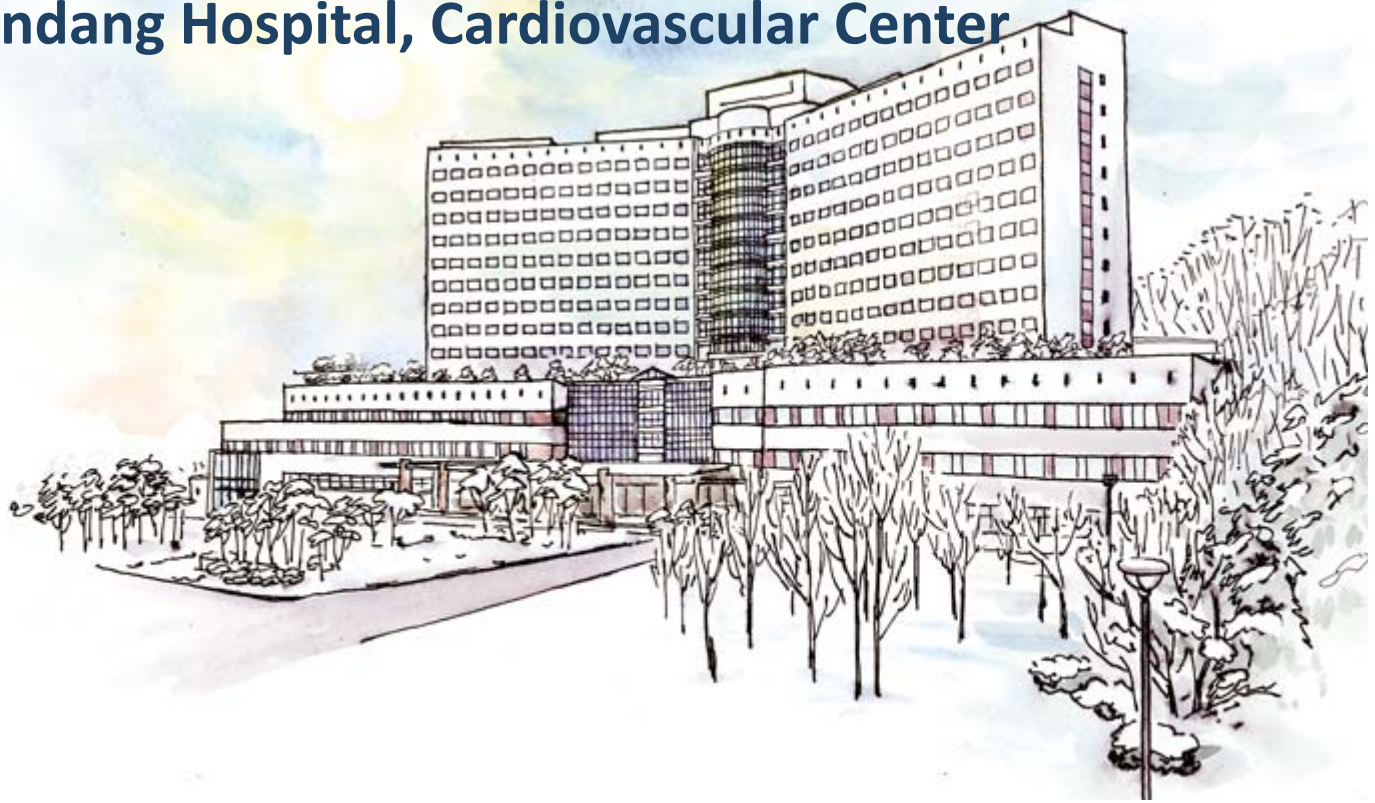
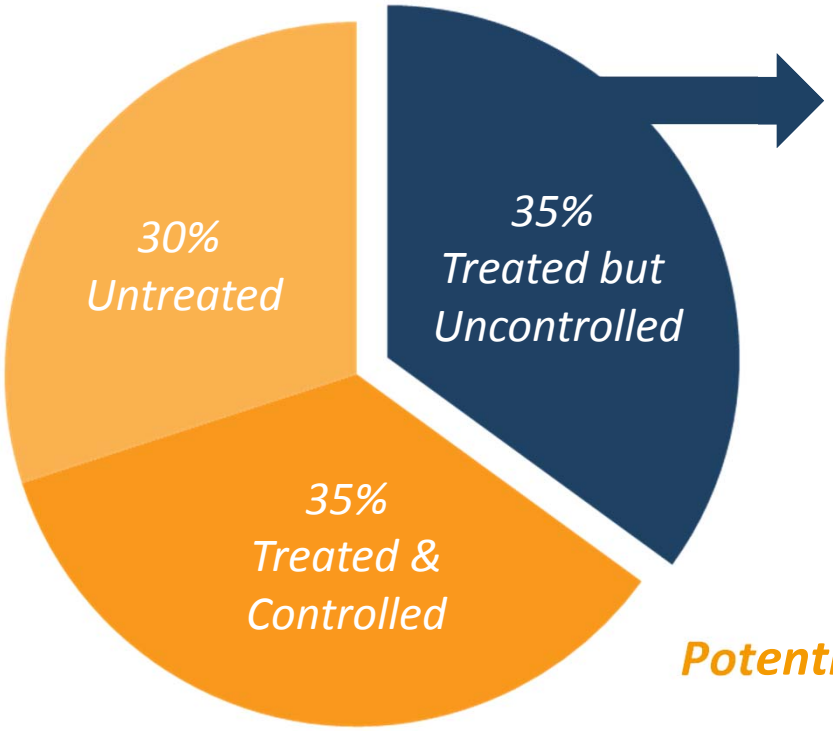


Drugs Work, But Not as Well as You May Think



Current approach failing

- Physician inertia
- Patient compliance
- Resistant HTN

Renal Denervation (RDN) =
Potentially a compliance-independent therapy

WELL ESTABLISHED SCIENTIFIC FOUNDATION : Why renal denervation?

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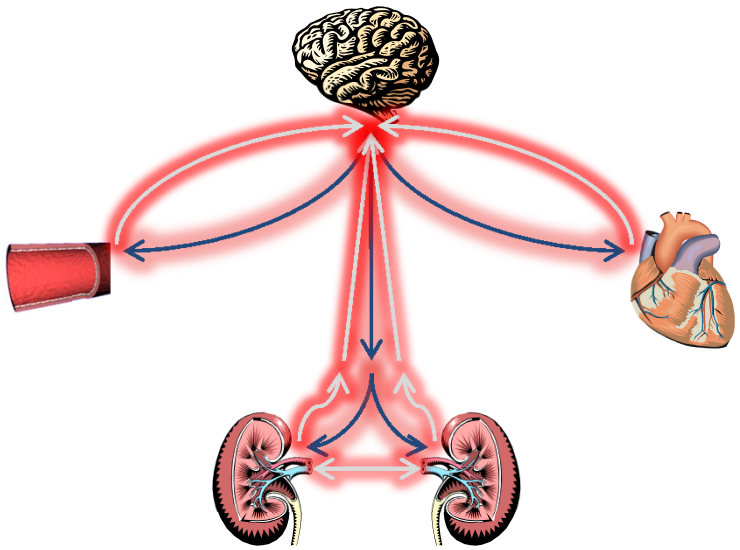
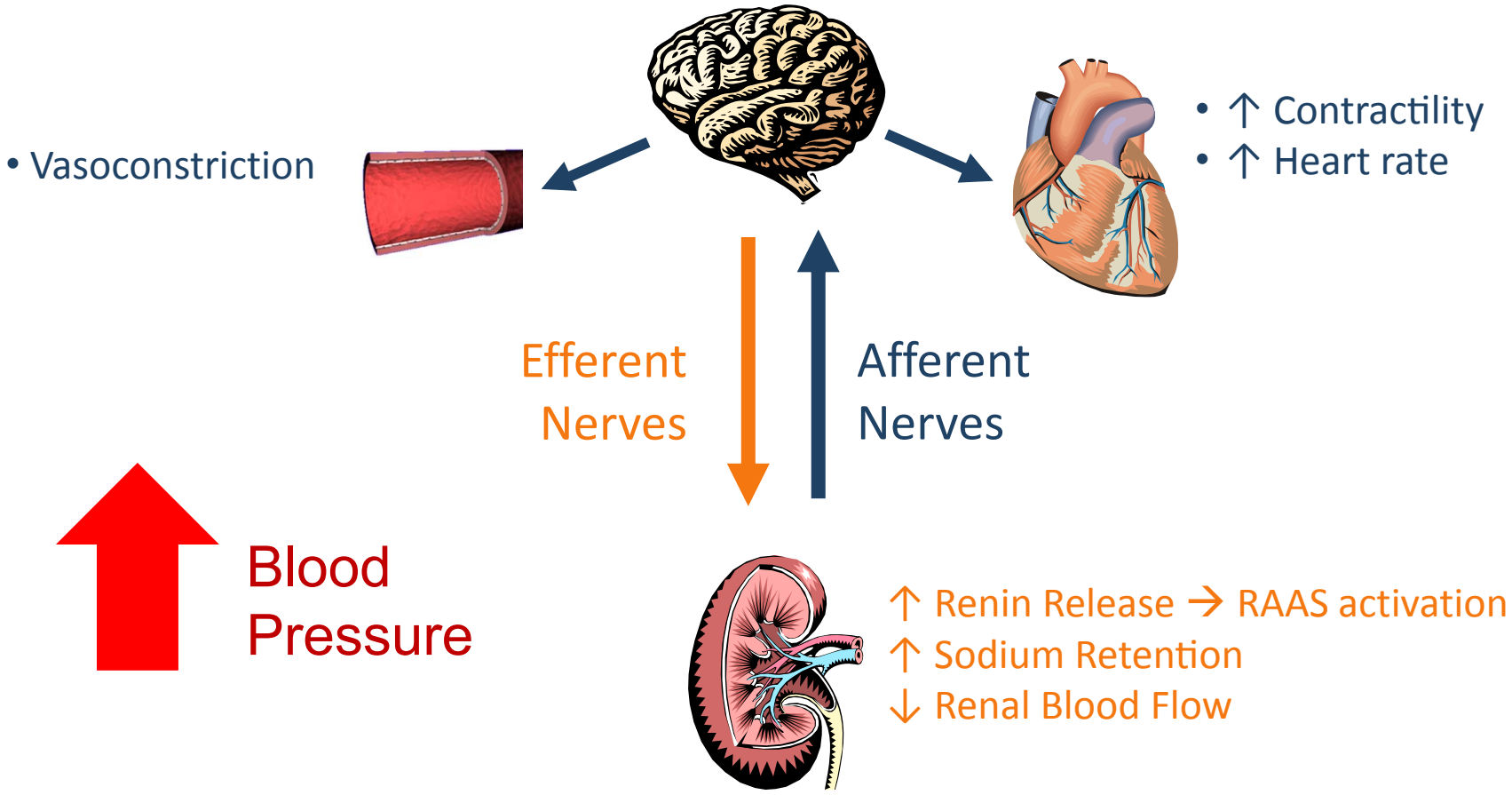
Renal Sympathetic Connection



- Role of kidneys & sympathetic nervous system in development & progression of HTN is well established
- Pharmaceuticals modify physiology at intermediate steps in pathway
- RDN attempts to break the cycle at its source

Renal Sympathetic Nerve Activity:

Kidney as Origin & Recipient of Central Sympathetic Drive



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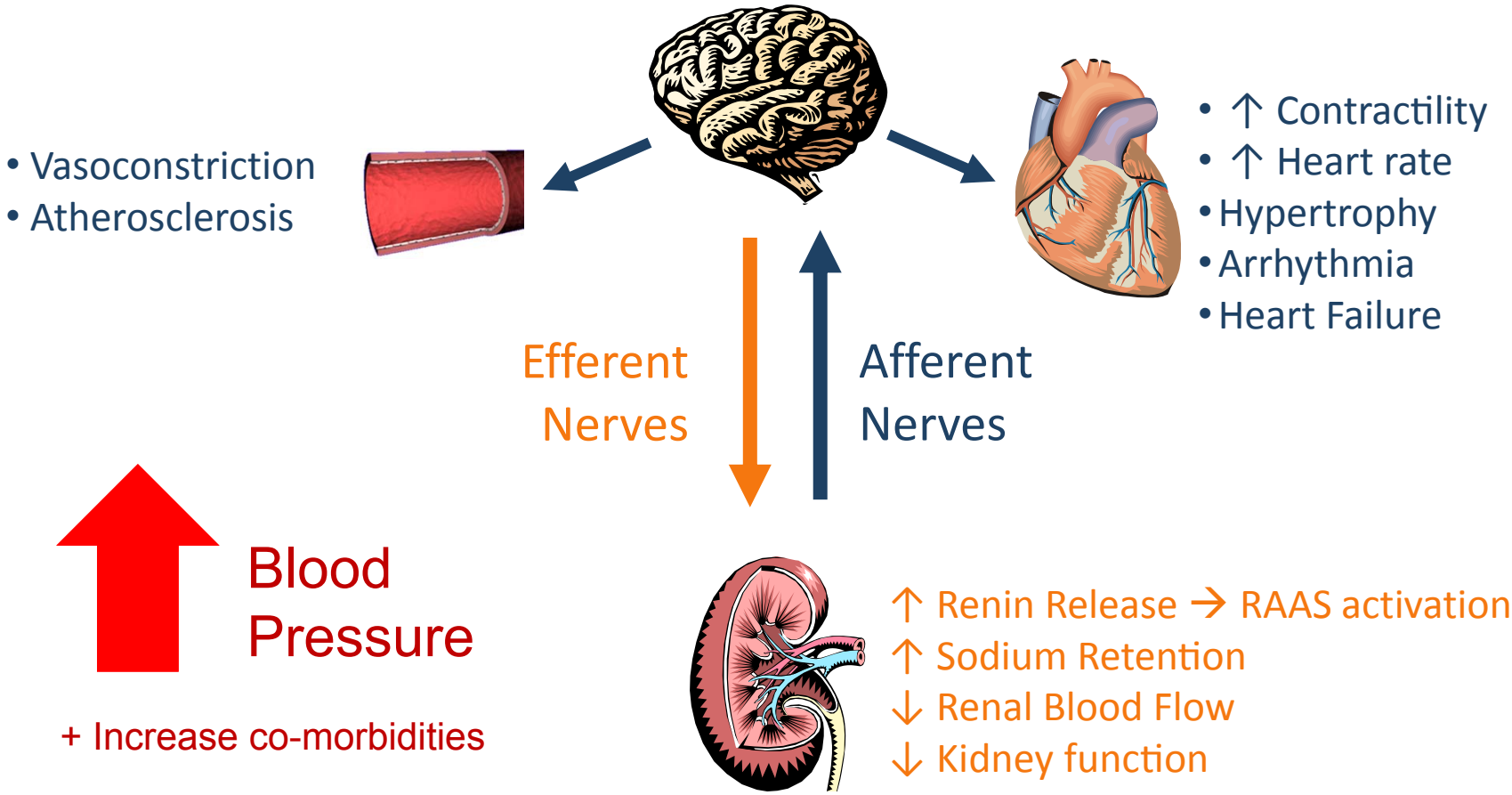

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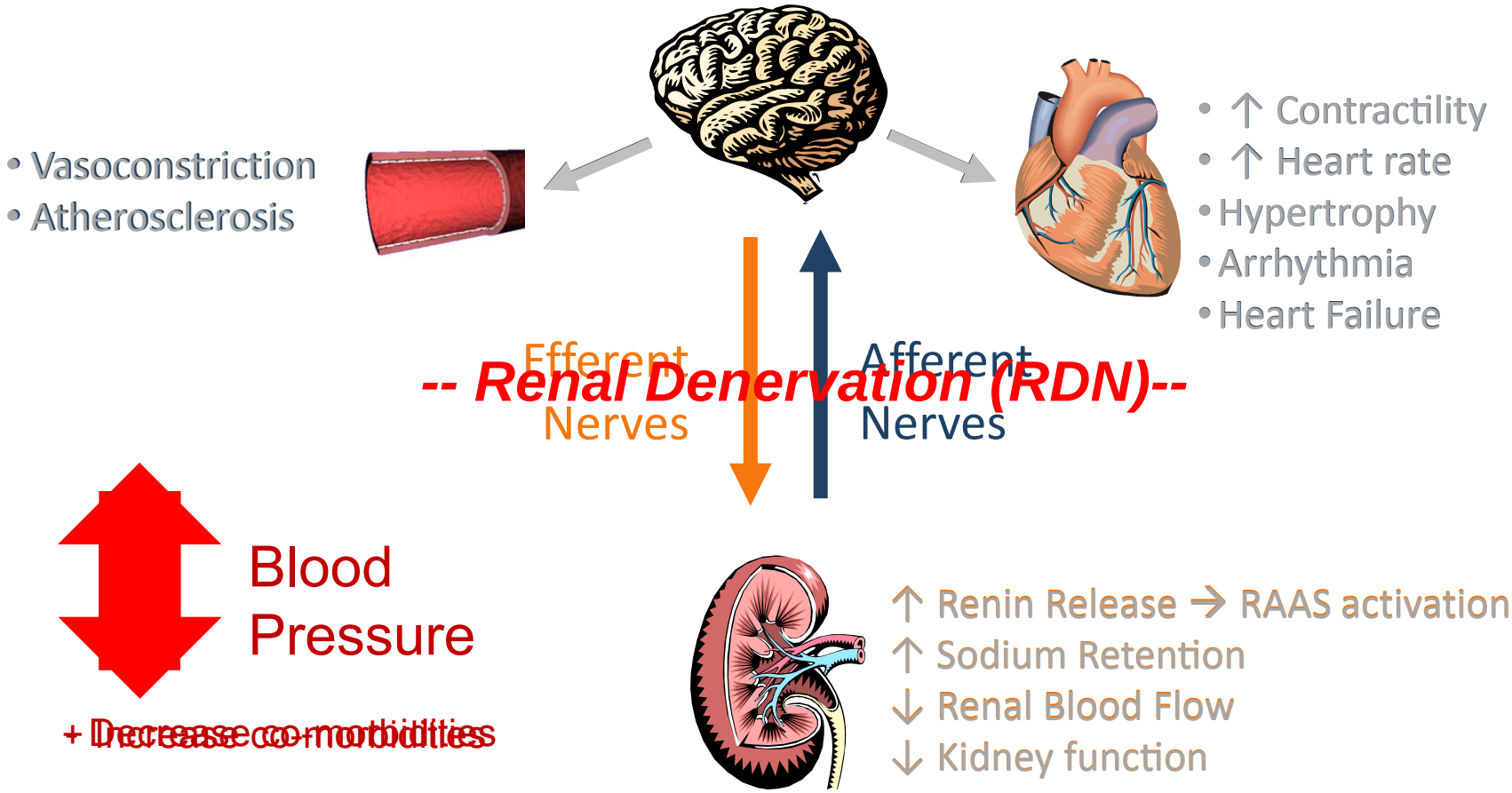


Concept Validated by Surgical History

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

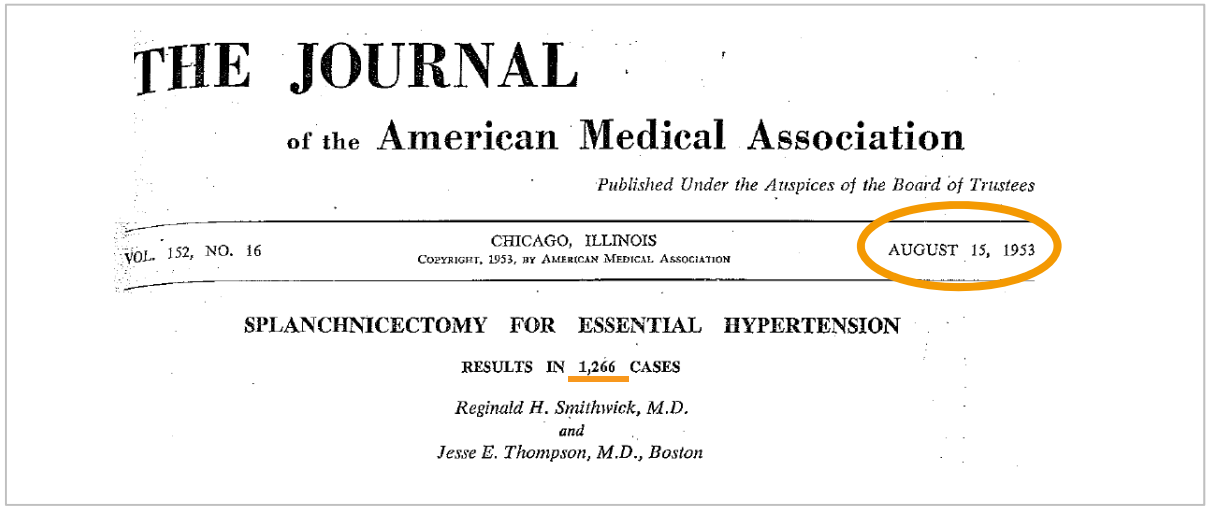
THE BRITISH JOURNAL OF SURGERY

1952

SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION*

A REVIEW OF 76 PATIENTS

By C. J. LONGLAND and W. E. GIBB



THE JOURNAL

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SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

Effective, but significant morbidity

- The concept is to remove the sympathetic chain from at least T 8 to L 2-3
- Effective in reducing blood pressure
- Today it is only performed for the treatment of Hyperhidrosis and Raynaud-Syndrome

A common question …

How will the kidney function without sympathetic control?

PHYSIOLOGIC RESPONSES OF THE TRANSPLANTED HUMAN KIDNEY*

Sodium Regulation and Renin Secretion

M. DONALD BLAUFOX, M.D., EDMUND J. LEWIS, M.D., PAUL JAGGER, M.D., DAVID LAULER, M.D., ROGER HICKLER, M.D. AND JOHN P. MERRILL, M.D.

- Transplanted kidneys lack innervation
- Yet effectively maintain fluid and electrolyte balance
- Establishes that sympathetic component of control represents "overdrive" system, rather than foundation of basic renal function

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A SIMPLER, MORE ELEGANT SOLUTION

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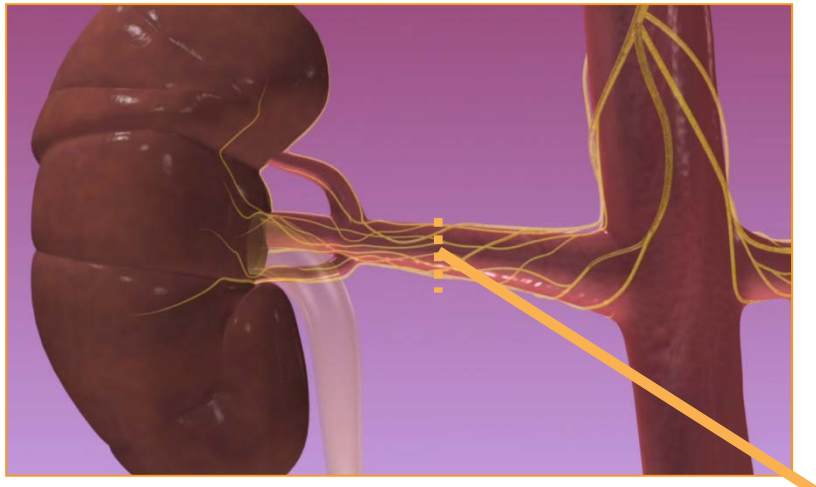
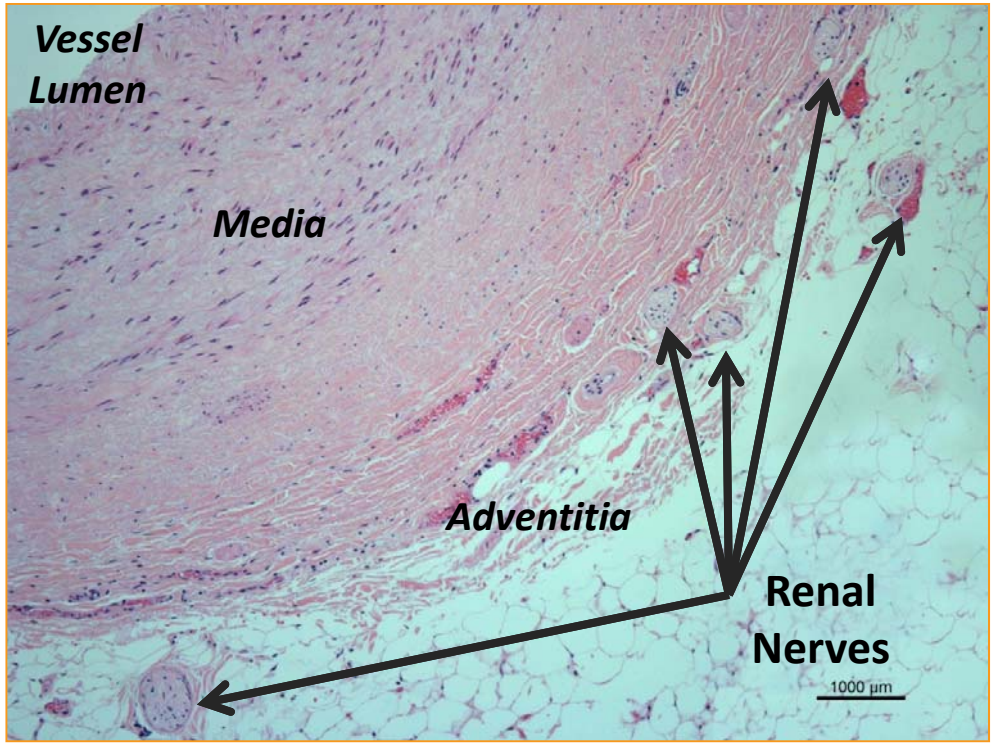
Renal Anatomy Allows a Catheter-Based Approach

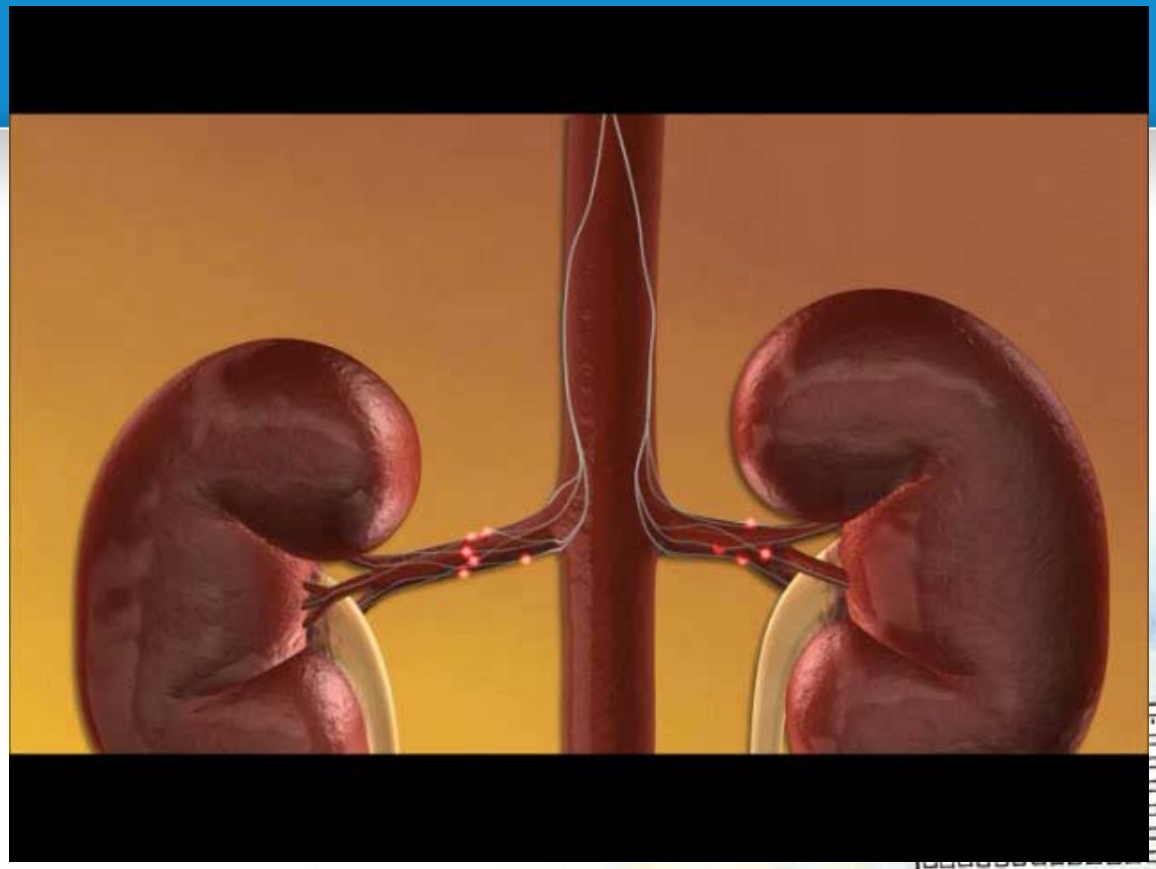




- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent & afferent nerves travel together

Symplicity® Catheter System™

- Low profile, electrode tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Standard interventional technique
- 40-minutes from first to last RF delivery



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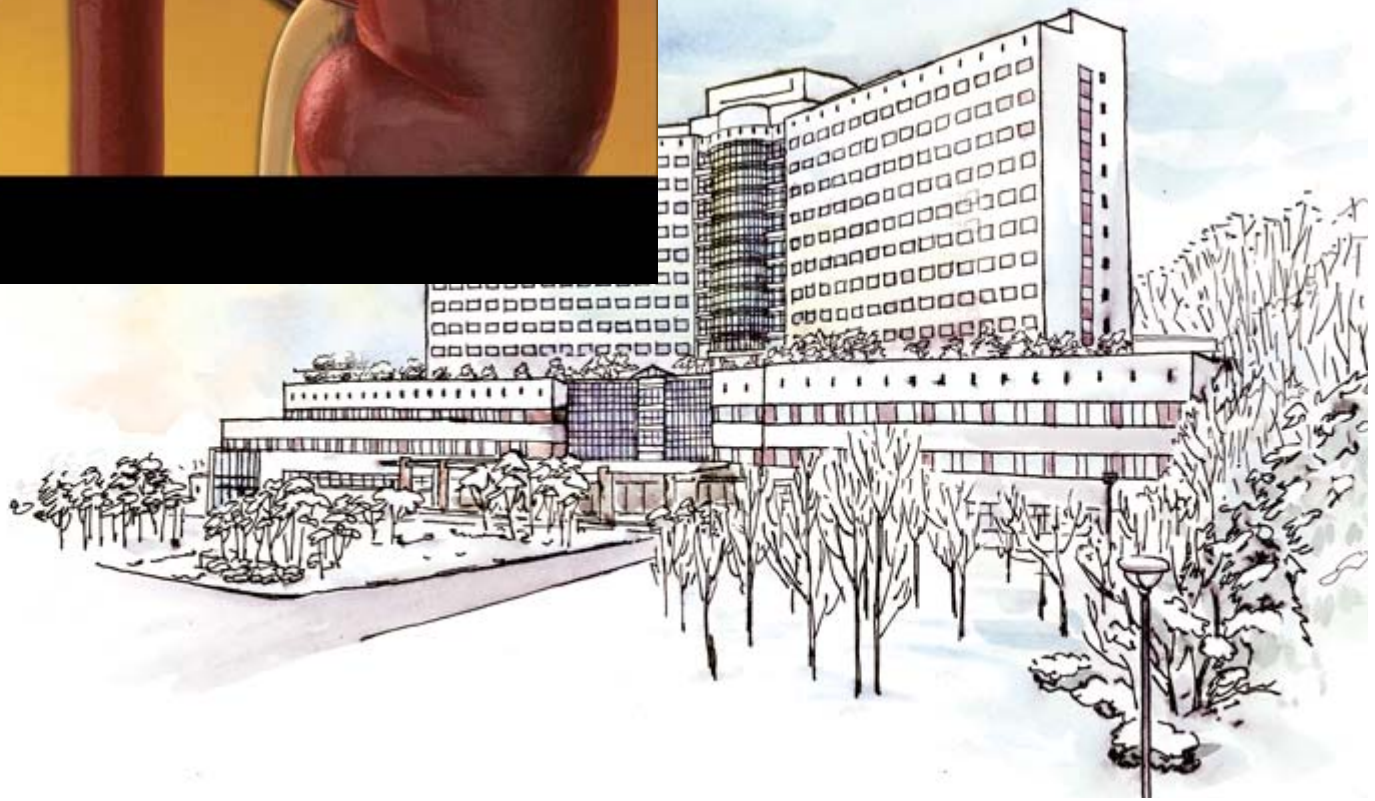
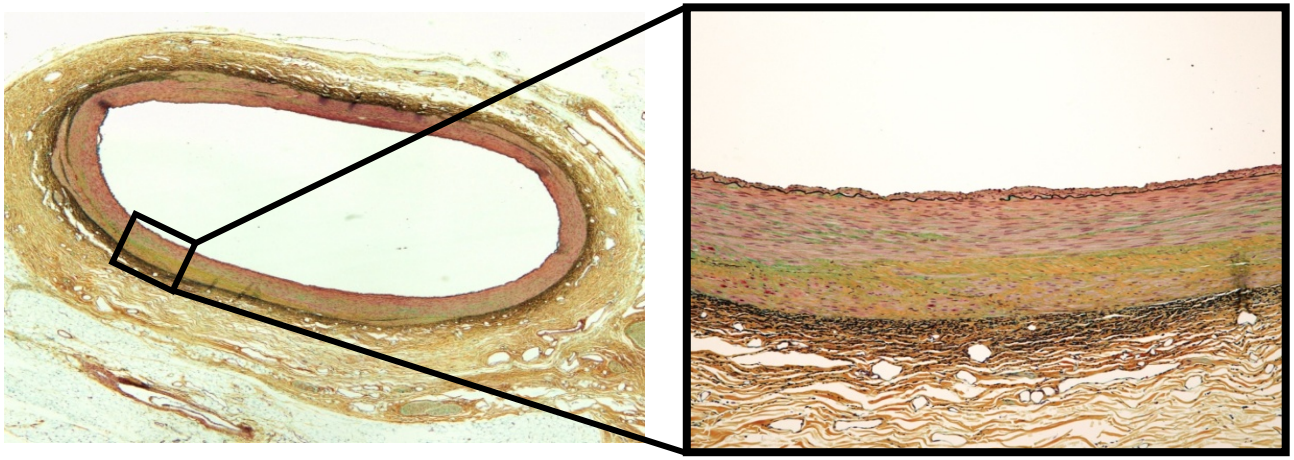


Vascular Safety Predicted by Preclinical Studies

- Extensive research in >300 swine
- Angiography and pathology at 7, 30, 60 & 180 days
- No stenosis or luminal reduction seen in treated arteries
- RF Generator algorithm optimized to minimize vascular injury



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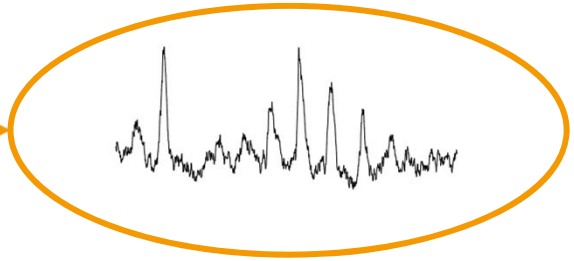
SCIENTIFIC PROOF OF CONCEPT

Cardiovascular Center, Seoul National University Bundang Hospital

Quantifying Human SNS Activity

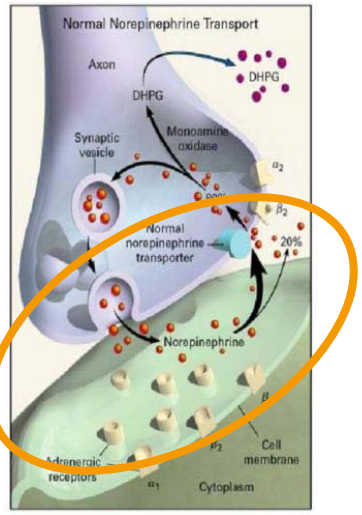
Central Sympathetic Nerve Activity



Muscle Sympathetic Nerve Activity (MSNA)

recording postganglionic nerve traffic

Renal Sympathetic Nerve Activity



Norepinephrine Spillover

measuring transmitter release from sympathetic nerves to plasma

Proof of Principle: Direct Measurement of Reduced Central Sympathetic Nerve Activity

Denervation of Patient w/Essential HTN:

	* 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)

Proof of Principle:
Related Changes in Underlying Physiology

		Baseline	1 mo	Δ
Office BP	*(mmHg)*	161/107	141/90	
Renal NE spillover	*(ng/min)*			
- left kidney		72	37	-48%
- right kidney		79	20	-75%
Total body NE spillover	*(ng/min)*	600	348	-42%
Plasma Renin	*(μg/l/hr)*	0.3	0.15	-50%
Renal Plasma flow	*(ml/min)*	719	1126	57%

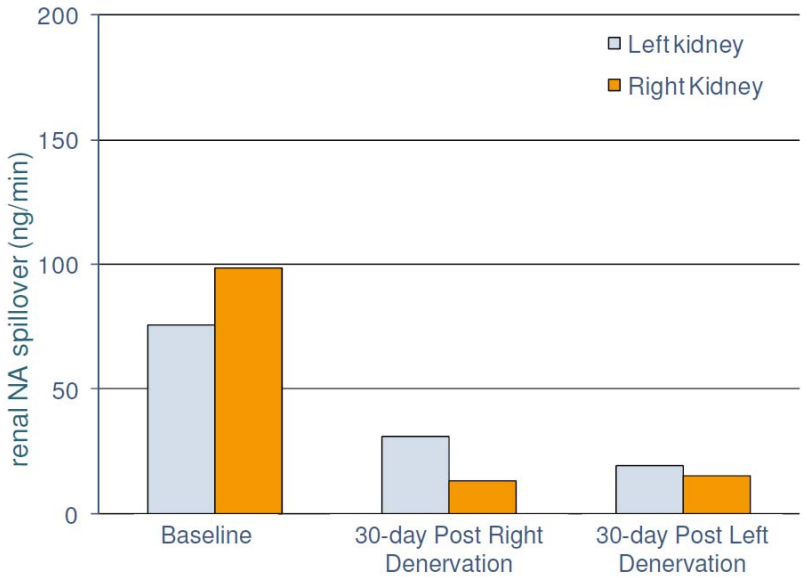
LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m^2) from baseline to 12 months

Consistent with Expected Effects of Denervation

Renal Norepinephrine Spillover: 10 cases

- Mean total renal norepinephrine spillover ↓ 47%, p=0.023 (95% CI: 28–65%)
- Mean total body NE spillover ↓ 28%, p=0.043 (95% CI: 4–52%)

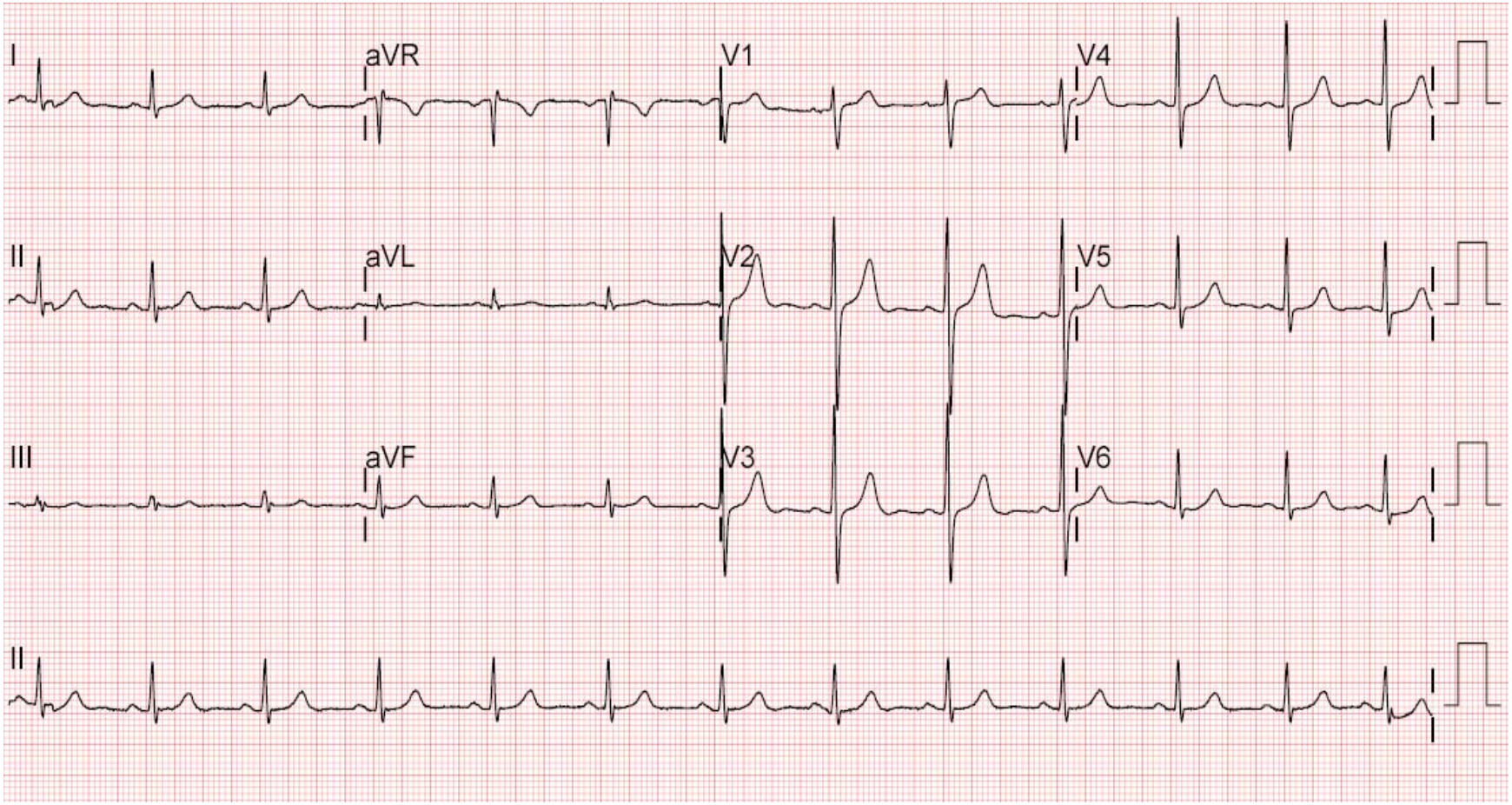
Example Case:
Left: 75 % reduction
Right: 85 % reduction



YU ET M/71 15845438

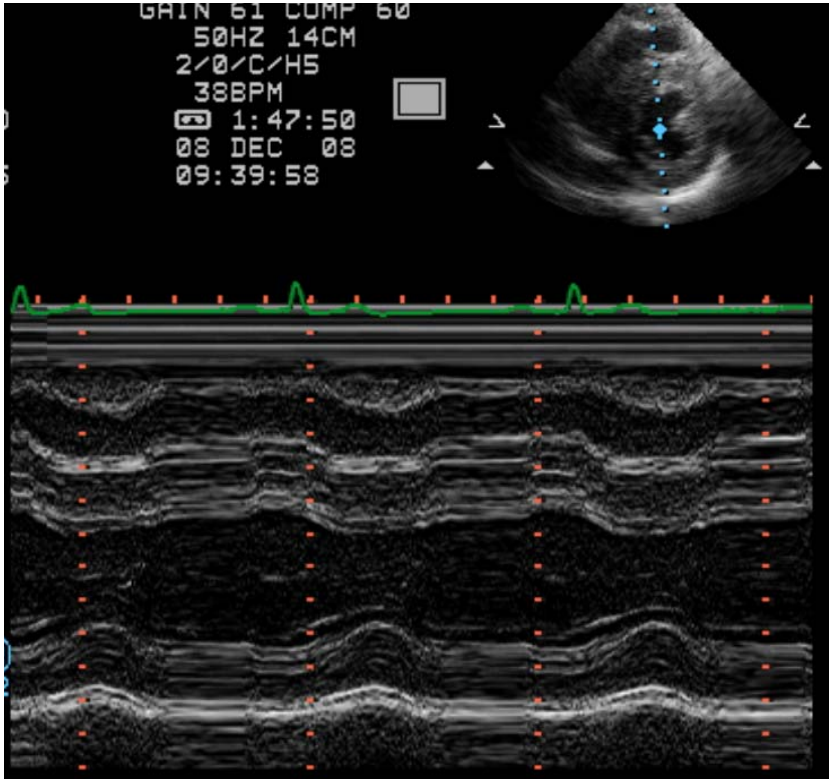
- 2007, HTN
- 2010, DM
- 2010, CAOD 2VD -> PCI at mRCA
- Medications :
  - Astrix 100mg cap (Aspirin enteric coated)
  - Clopidogrel 72mg tab
  - Vaxar 2mg tab(Lacidipine)
  - Dichlozid 25mg tab (Hydrochlorothiazide)
  - Cozaar 50mg tab(Losartan)
  - Janumet 50/850mg (Sitagliptin/Meformin)

ECG (2012-04-16)



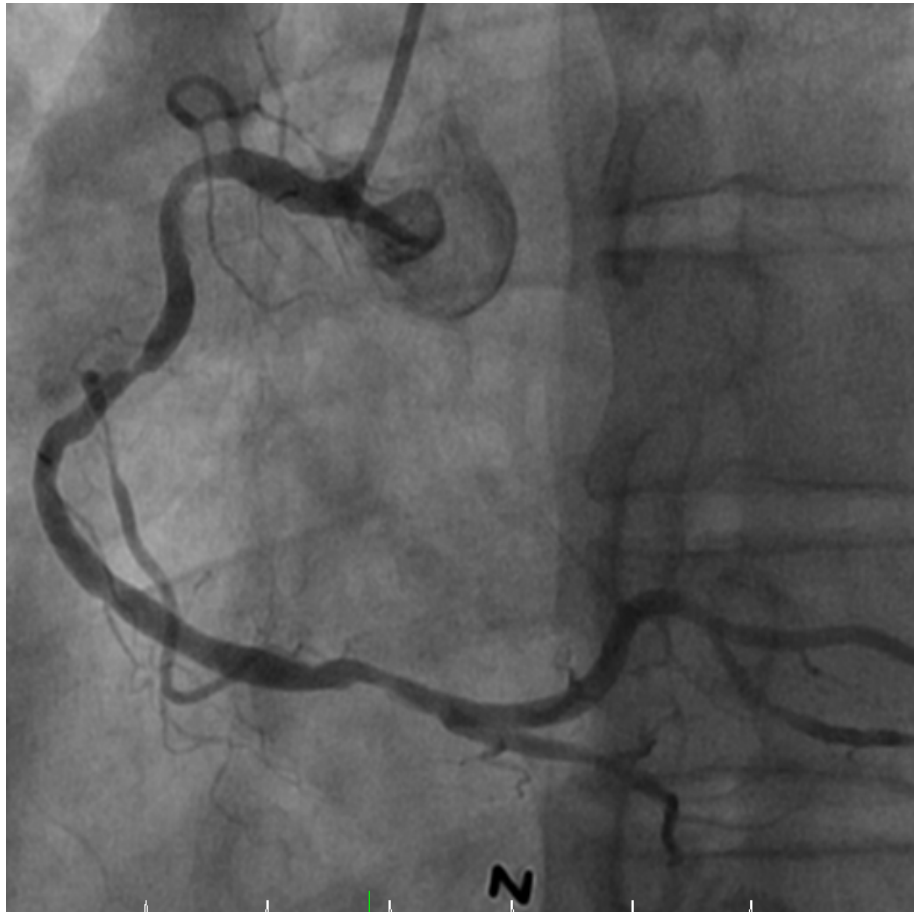
Non-Invasive Tests

- TTE (2010-07-09)
  1. Normal LV cavity size (EDD=51mm) and systolic function; EF=64%
  2. Normal valvular structure and function

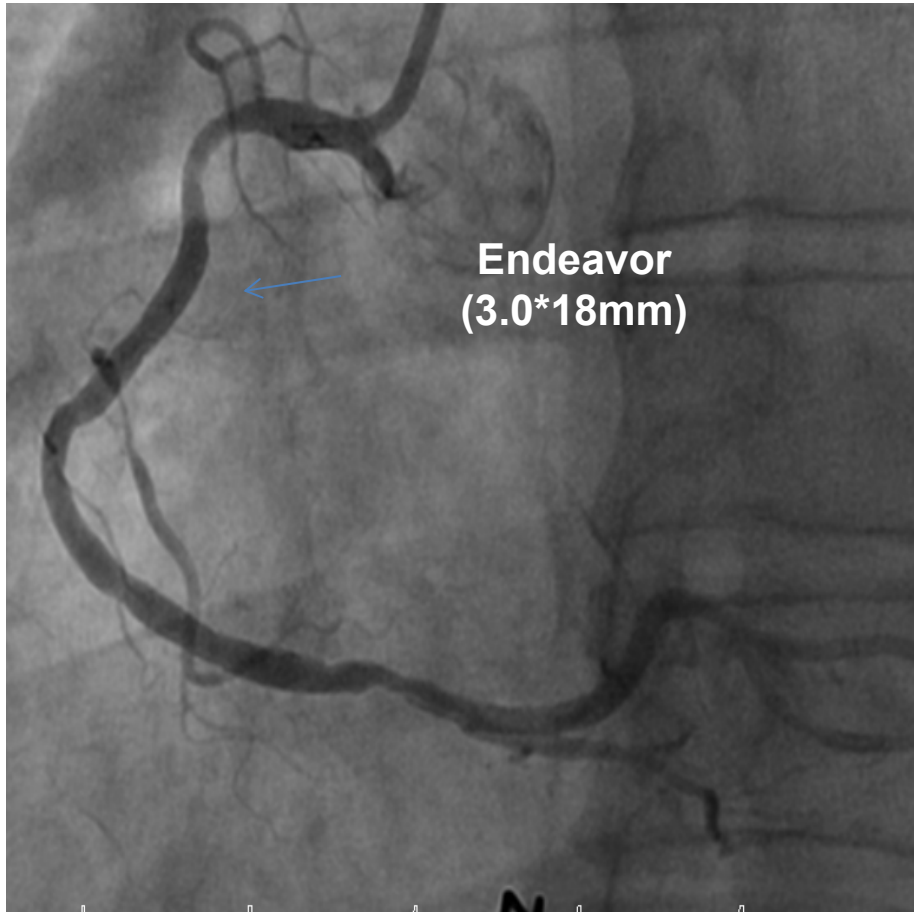


CAG & PCI (2008.12.08)

Pre stenting

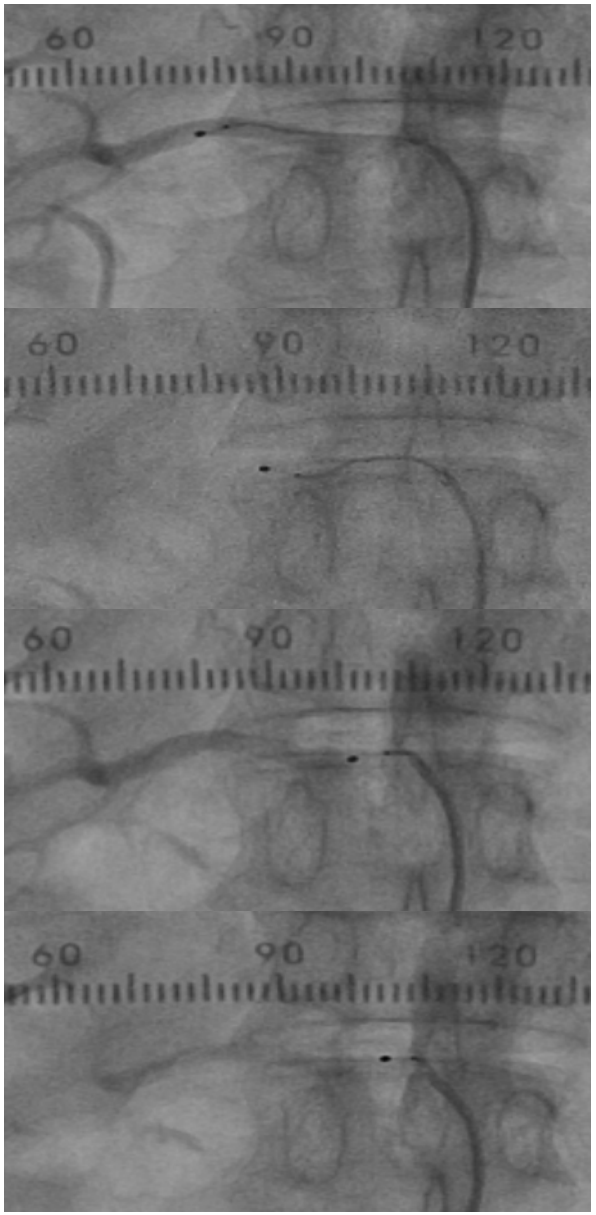


Post stenting



DSA of both renal arteries (2012.04)

Rt. renal a. ← Ablation → Lt. renal a.

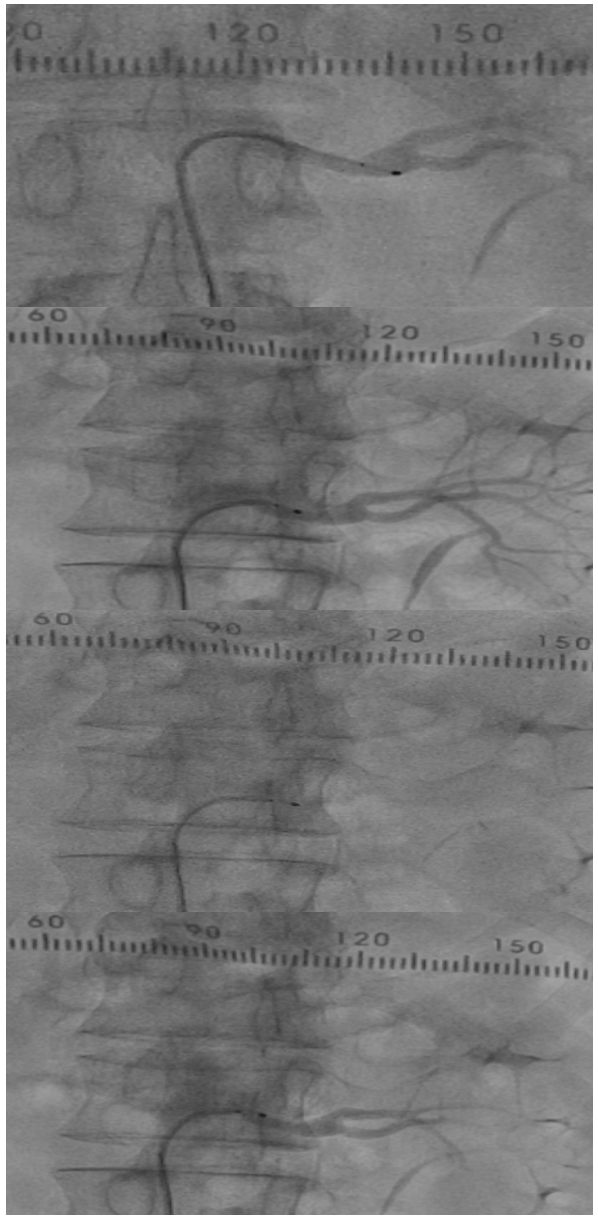


#1 Inferior

#2 Lateral

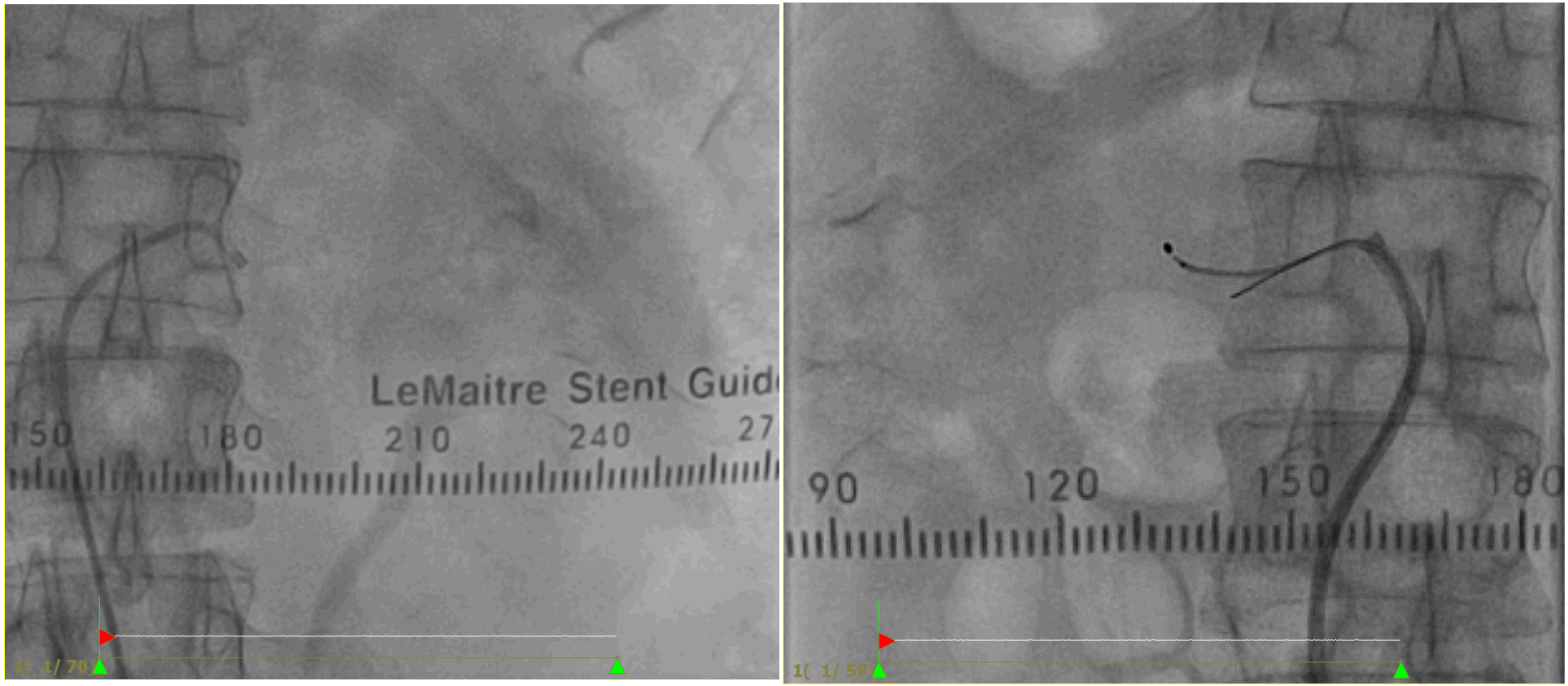
#3 Superior

#4 Superior - Anterior

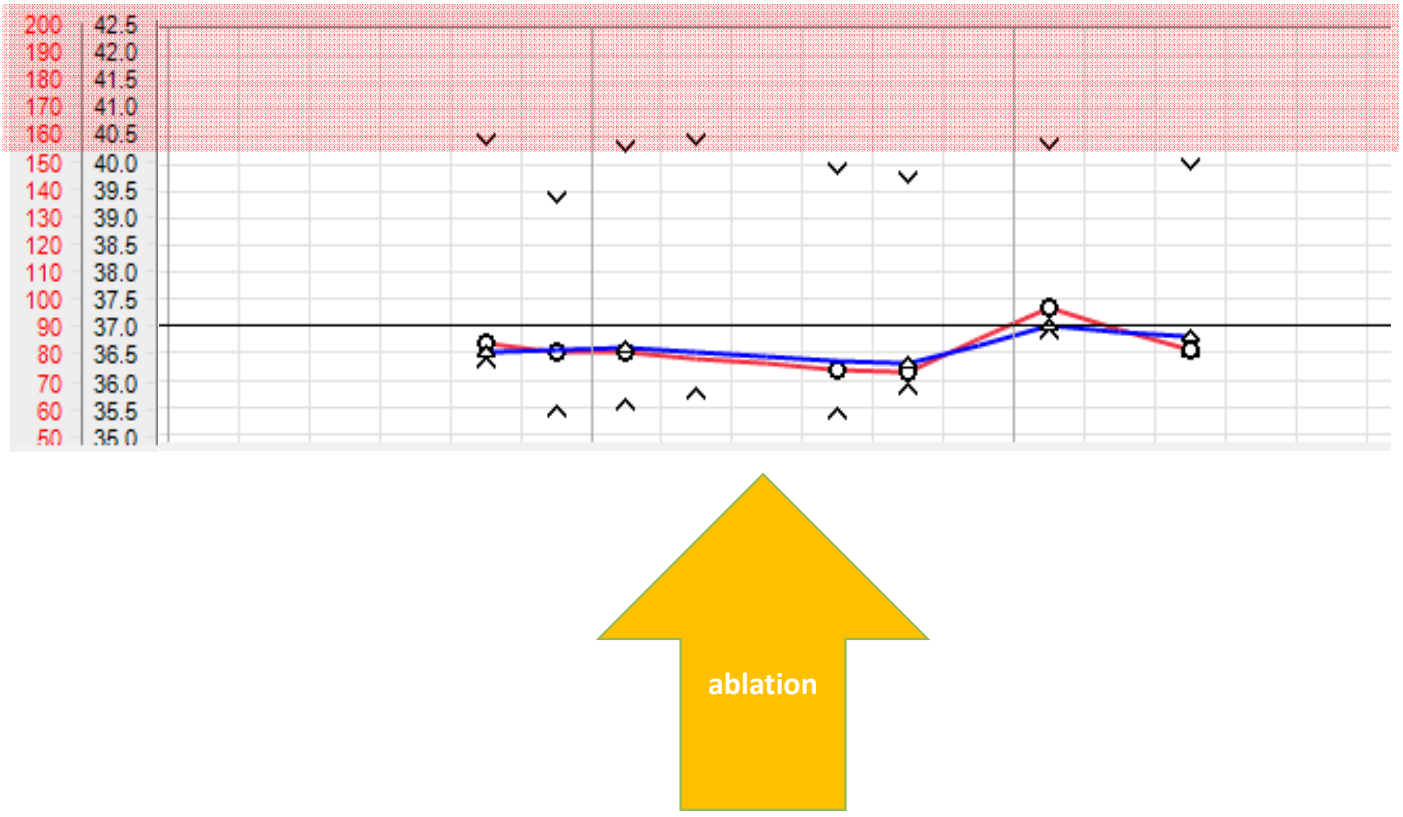


Renal Angiogram after Denervation

Renal Angiogram after Denervation
: Edematous lesions



BP during admission



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CLINICAL DATA

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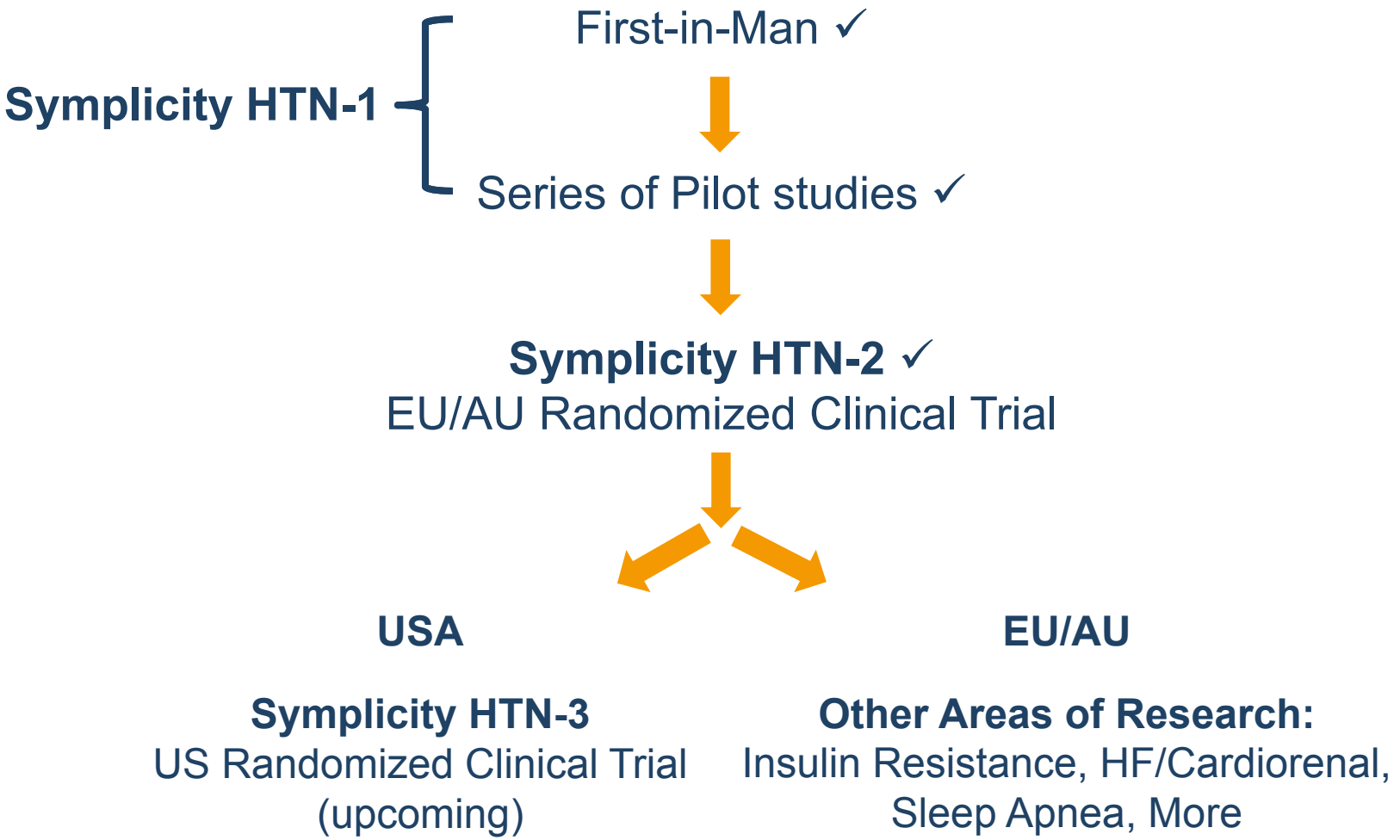
Staged Clinical Evaluation



Symplicity HTN-1

Lancet. 2009;373:1275-1281

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

Baseline Patient Characteristics

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)	**5.0 ± 1.4**
	ACE/ARB (%)	90%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Vasodilator (%)	19%
	Diuretic (%)	95%
	Spironolactone (%)	21%

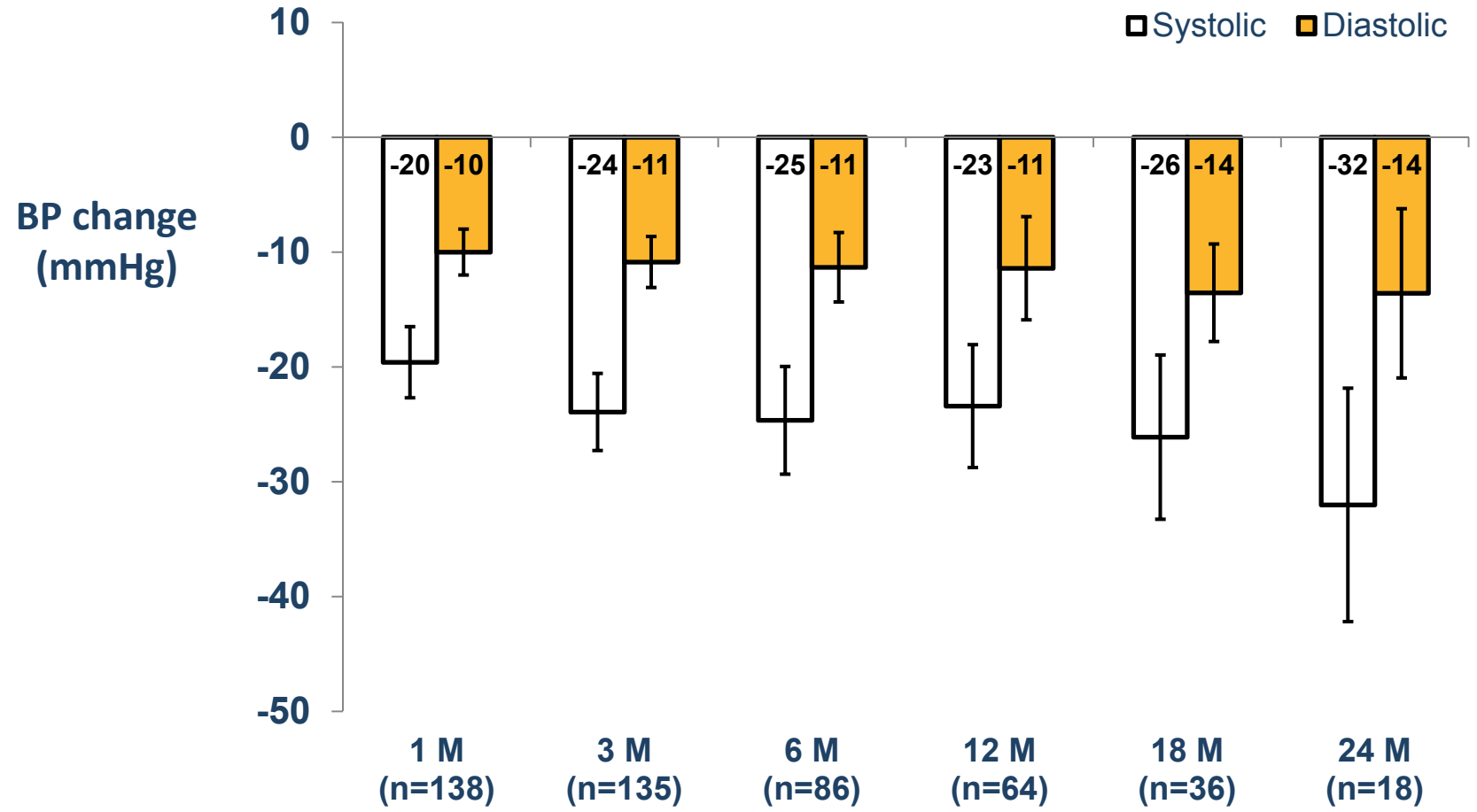
Procedure Detail & Safety

- 38 minute median time from first to last ablation
  - 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

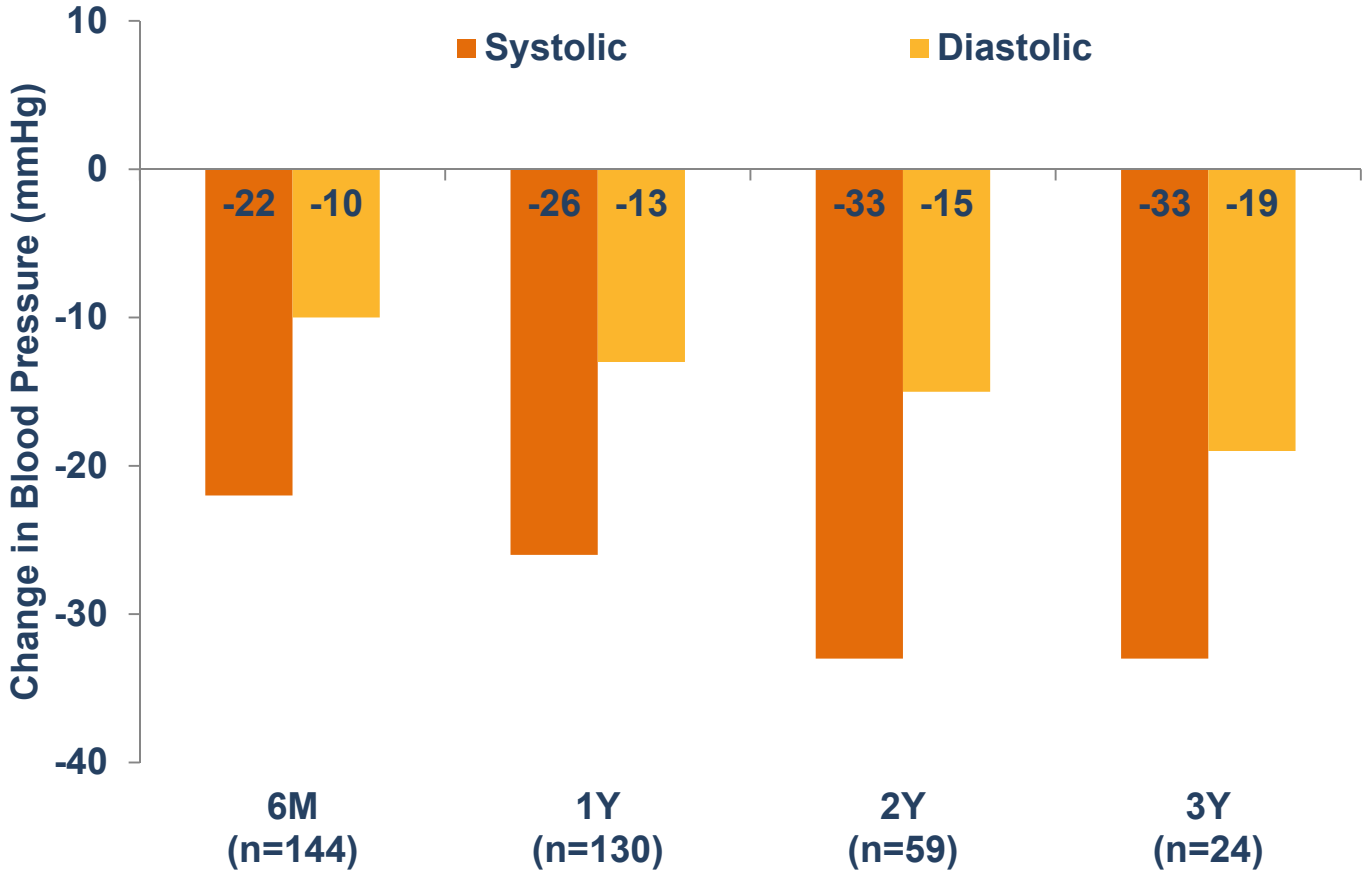
Chronic Safety

- 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 (Δ eGFR)
  - 12 Months: -2.9 mL/min/1.73m^2 (n.s.)

Significant, Sustained BP Reduction



Significant, Sustained Blood Pressure Reductions to at Least 3 Years

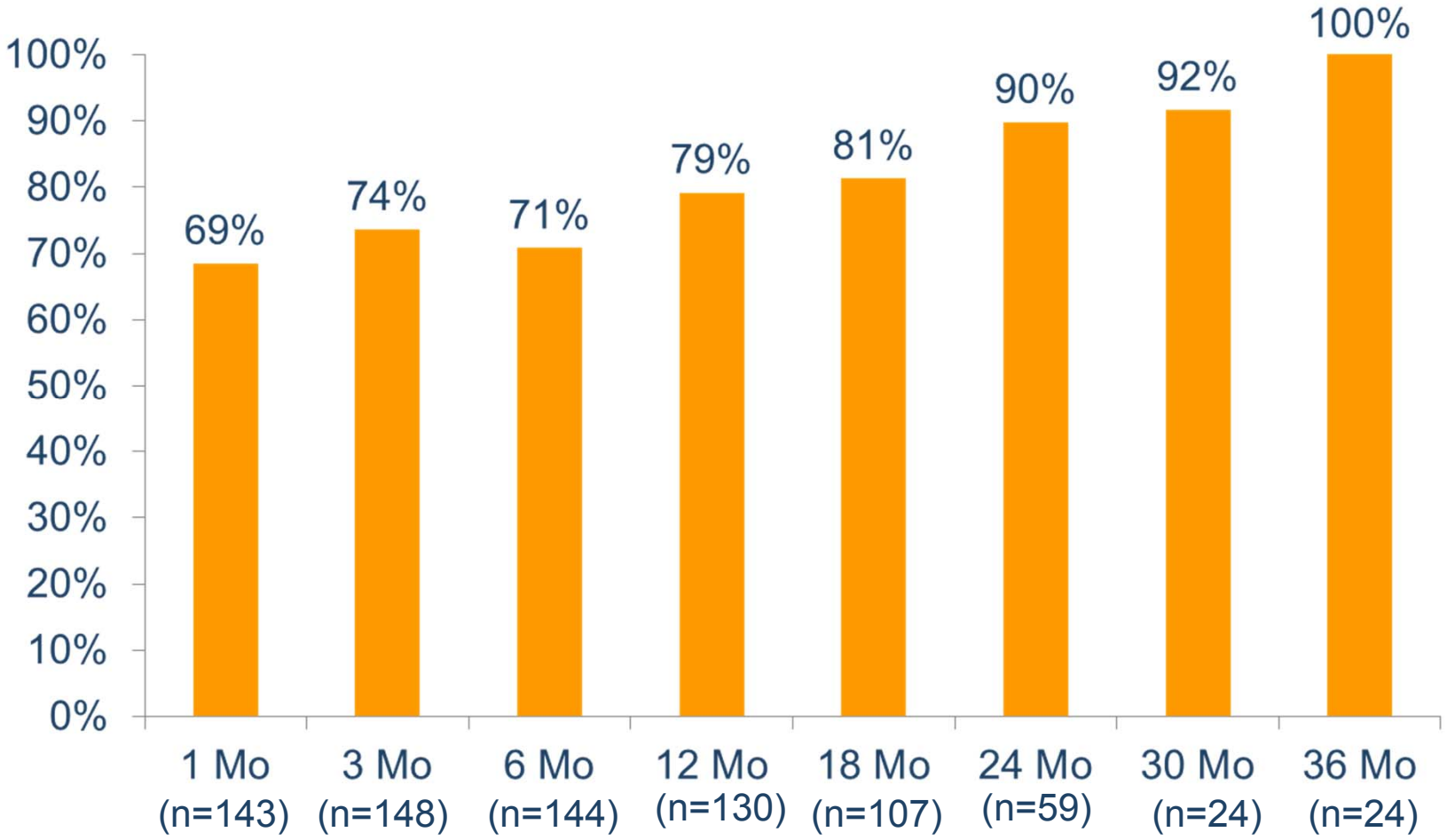


p <0.01 for Δ from baseline for all time points

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

Percentage Responders Increases Over Time

Responder was defined as an office SBP reduction ≥10 mmHg



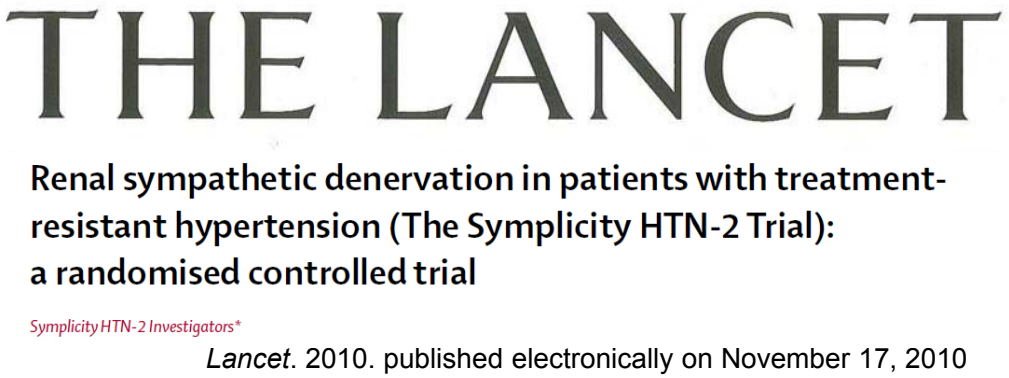
Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

Symplicity HTN-1: Response Rate Among 1-Month Non-responders (n=45)*

*Non-responder defined as a SBP reduction of <10 mmHg

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

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*

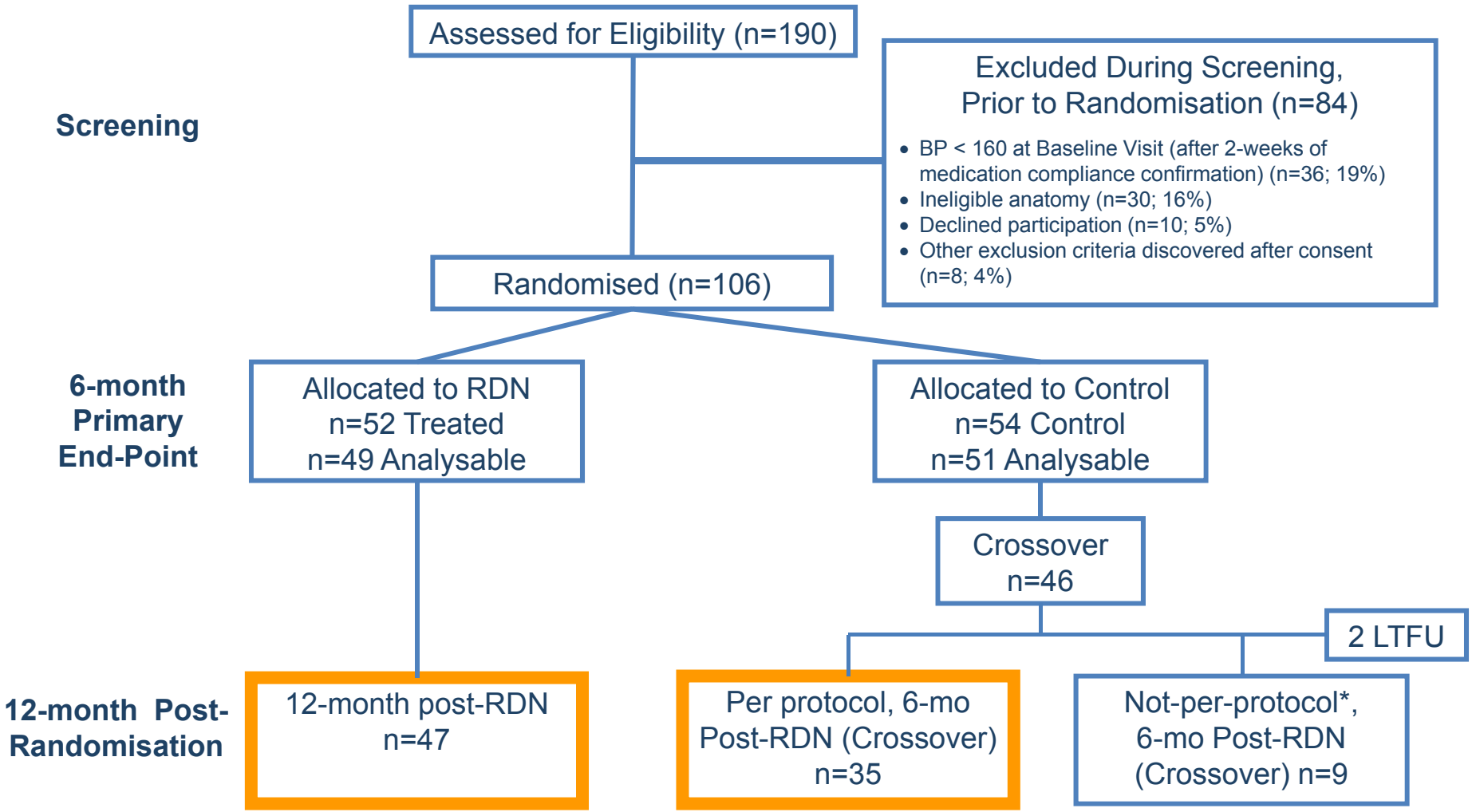
Lancet. 2010. published electronically on November 17, 2010

- **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 Trial

Key Inclusion/Exclusion Criteria
•Inclusion: – Office SBP ≥160 mmHg (≥150 mmHg with type 2 diabetes mellitus) – Stable drug regimen of 3+ more anti-HTN medications – Age 18–85 years •Exclusion: – 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 past 6 months

Patient Disposition



* Crossed-over with ineligible BP (<160 mmHg)

Baseline Characteristics

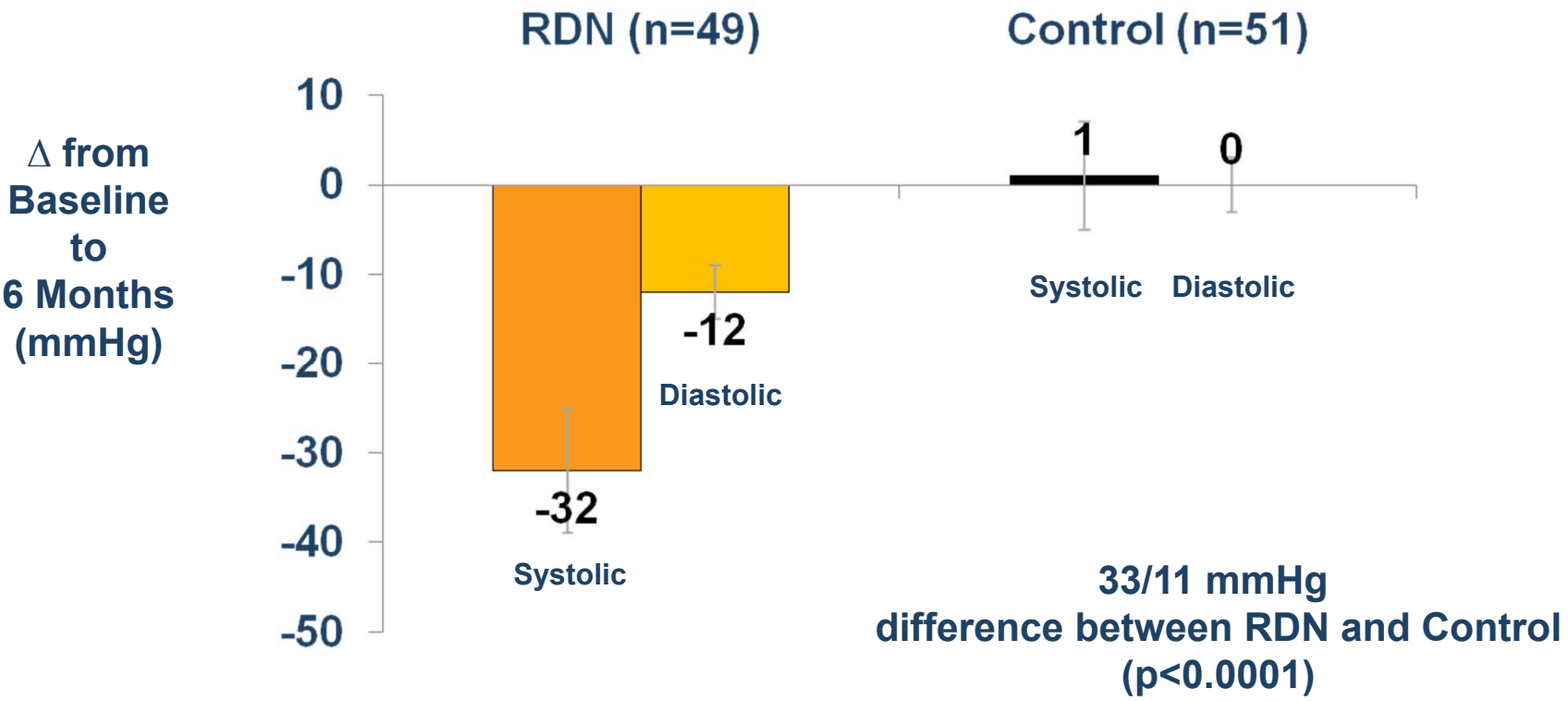
	RDN (n = 52)	Control (n = 54)	*p*-Value
Baseline systolic BP (mmHg)	178 ± 18	178 ± 16	0.97
Baseline diastolic BP (mmHg)	97 ± 16	98 ± 17	0.80
Number anti-HTN medications	5.2 ± 1.5	5.3 ± 1.8	0.75
Age	58 ± 12	58 ± 12	0.97
Gender (female) (%)	35%	50%	0.12
Race (Caucasian) (%)	98%	96%	>0.99
BMI (kg/m^2)	31 ± 5	31 ± 5	0.77
Type 2 diabetes	40%	28%	0.22
Coronary artery disease	19%	7%	0.09
Hypercholesterolemia	52%	52%	>0.99
eGFR (MDRD, $ml/min/1.73m^2$)	77 ± 19	86 ± 20	0.013
Serum creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.003
Urine alb/creat ratio (mg/g)*	128 ± 363	109 ± 254	0.64
Cystatin C (mg/L)†	0.9 ± 0.2	0.8 ± 0.2	0.16
Heart rate (bpm)	75 ± 15	71 ± 15	0.23

† n=42 for RDN and n=43 for Control, Wilcoxon rank-sum test for two independent samples used for between-group comparisons of UACR
†† n=39 for RDN and n=42 for Control

Baseline Medications

	RDN (n=52)	Control (n=54)	p-value
Number Anti-HTN medications	5.2 ± 1.5	5.3 ± 1.8	0.75
% patients on HTN meds >5 years	71%	78%	0.51
% percent patients on ≥5 medications	67%	57%	0.32
% patients on drug class:			
ACEi/ARB	96%	94%	>0.99
Direct renin inhibitor	15%	19%	0.80
Beta-adrenergic blocker	83%	69%	0.12
Calcium channel blocker	79%	83%	0.62
Diuretic	89%	91%	0.76
Aldosterone antagonist	17%	17%	>0.99
Vasodilator	15%	17%	>0.99
Alpha-1 adrenergic blocker	33%	19%	0.12
Centrally acting sympatholytic	52%	52%	>0.99

Primary Endpoint: 6-Month Office BP



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

Medication Changes

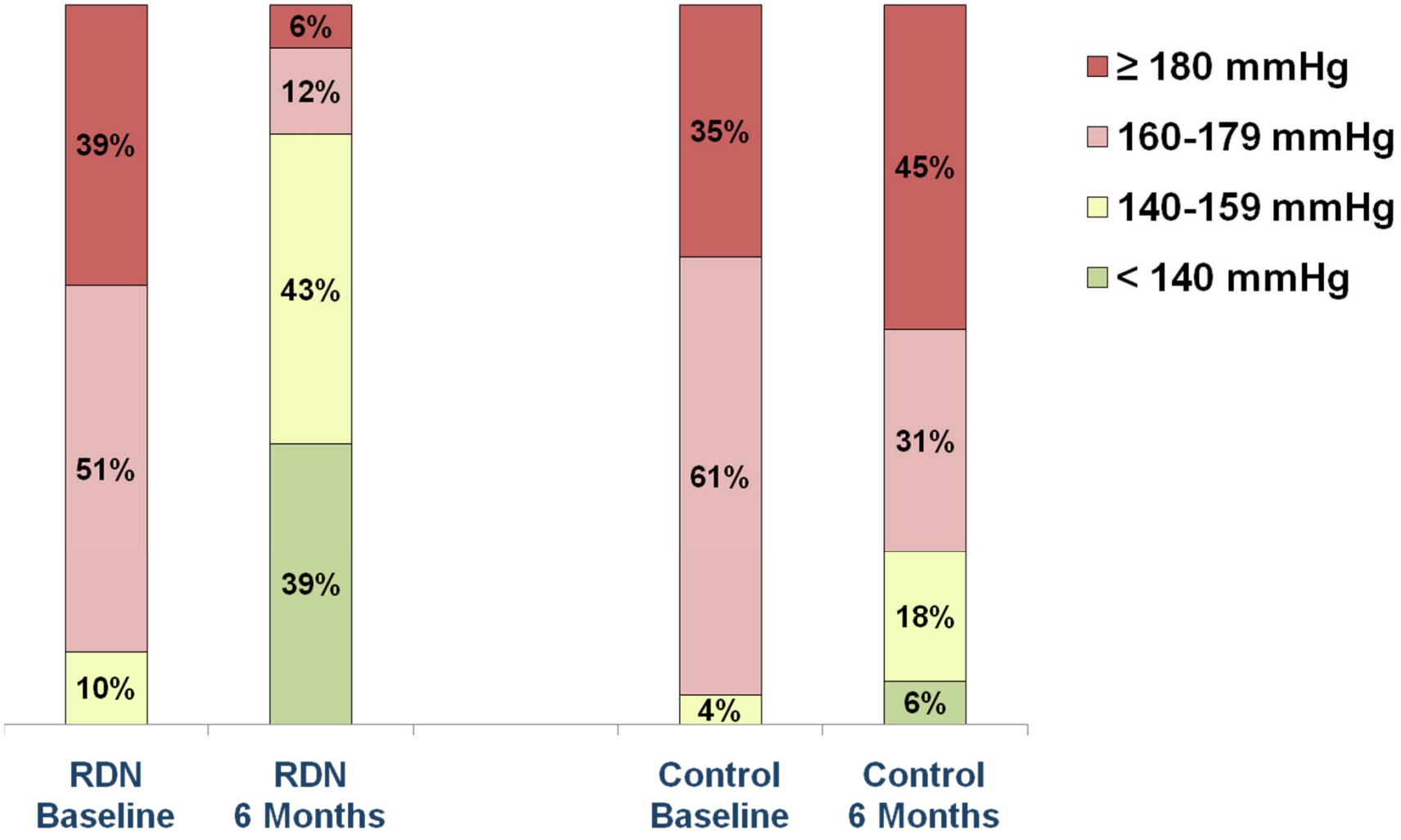
Despite protocol guidance to maintain medications, some medication changes were required:

	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

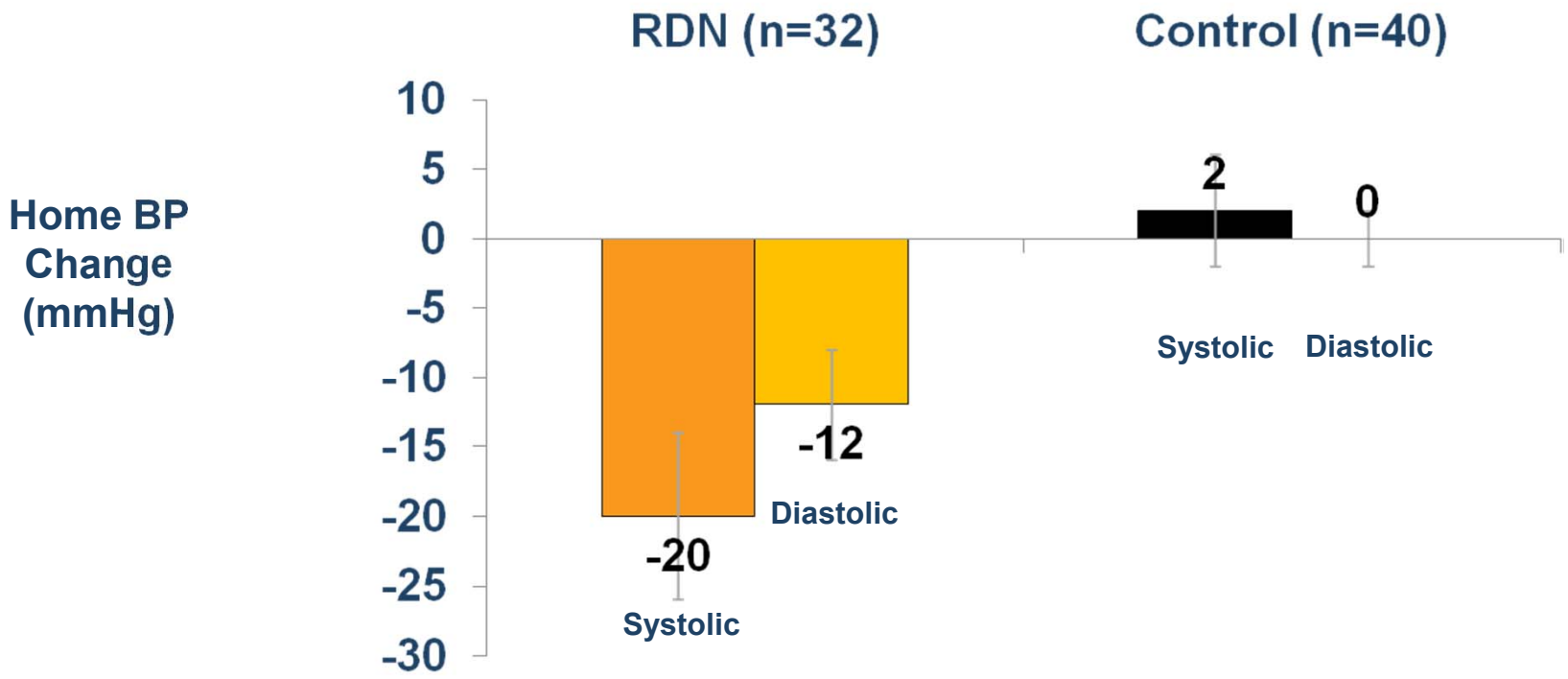
Censoring BP after medication increases:

- 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)

Office Systolic BP Distribution



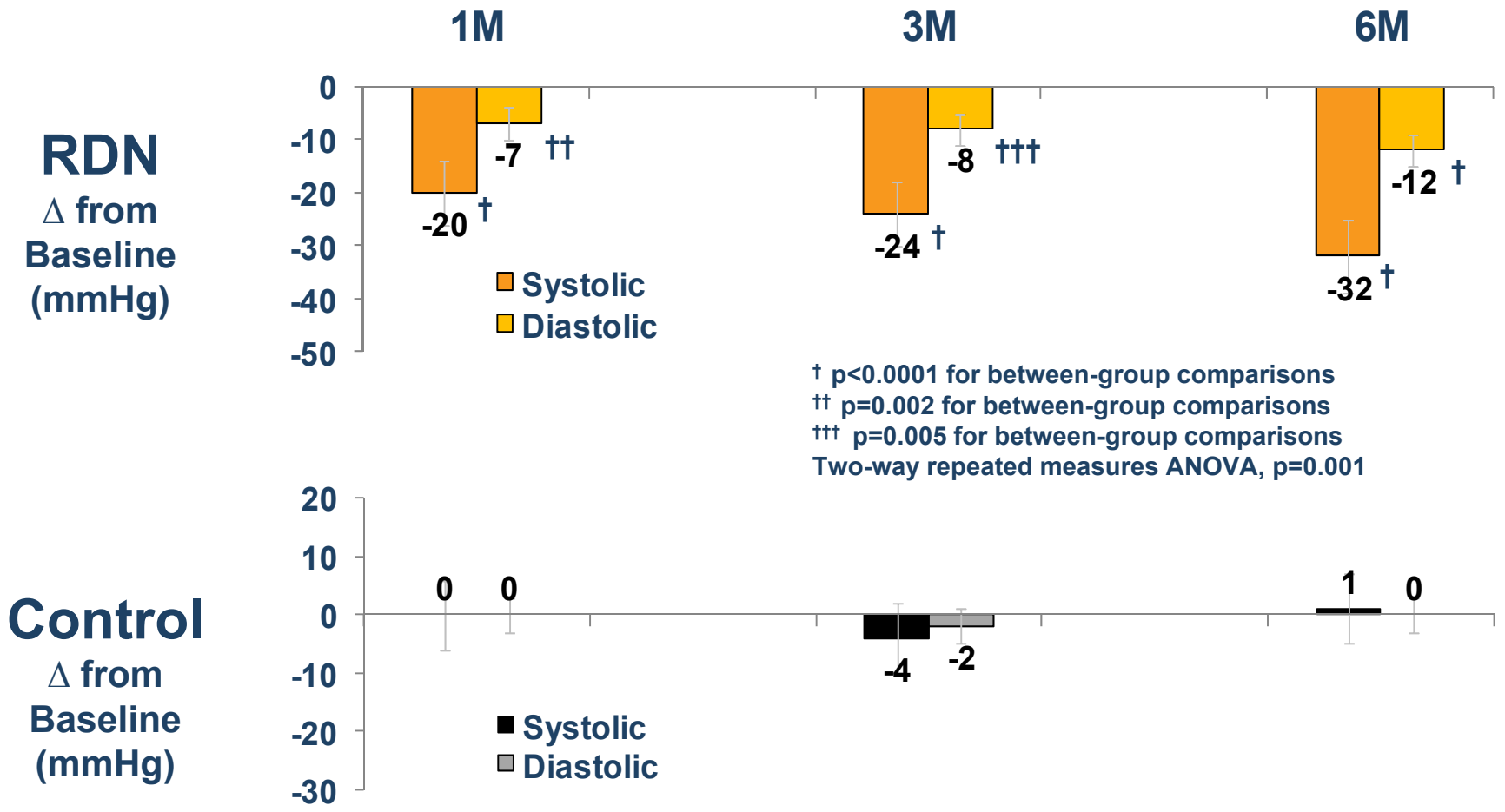
Home & 24 Hour Ambulatory BP



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)

Time Course of Office BP Change



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)

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

Other Safety

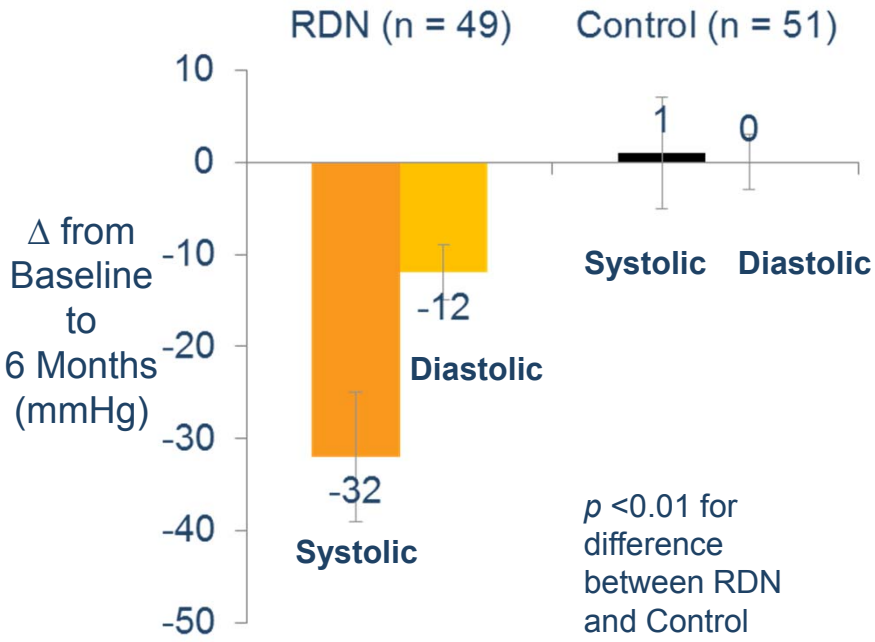
	RDN (n=49)	Control (n=51)
Composite CV Events		
Hypertensive event unrelated to non-adherence to medication	3	2
Other CV events	0	0
Other Serious AEs		
Transient ischemic attack	1	2
Hypertensive event after abruptly stopping clonidine	1	0
Hypotensive episode resulting in reduction of medications	1	0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

Simplicity HTN-2 : Conclusions at 2010

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.
- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality
- The technique was applied without major complications.
- This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.
- Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Symplicity HTN-2: RDN Superior to Medical Management, Reductions Sustained to 12M

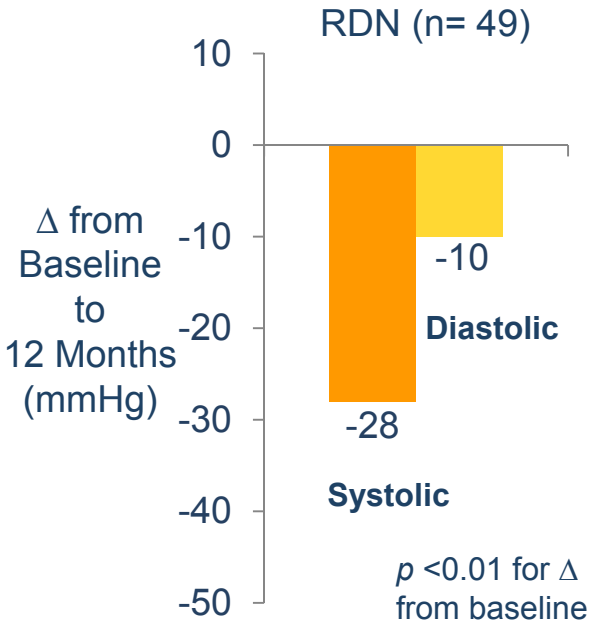
Primary Endpoint (6M post Randomisation)



Primary Endpoint:

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

Latest Follow-up (12M post Randomisation)



Latest Follow-up:

- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)

ACC 2012: Medication Changes at 6 and 12 Months Post-Renal Denervation

RDN (n=47)	6 month	12 months
Decrease (# Meds or Dose)	20.9% (9/43)	27.9% (12/43)
Increase (# Meds or Dose)	11.6% (5/43)	18.6% (8/43)

Crossover (n=35)	6 months post-RDN
Decrease (# Meds or Dose)	18.2% (6/33)
Increase (# Meds or Dose)	15.2% (5/33)

*Physicians were allowed to make changes to medications Once the 6 month primary endpoint was reached**

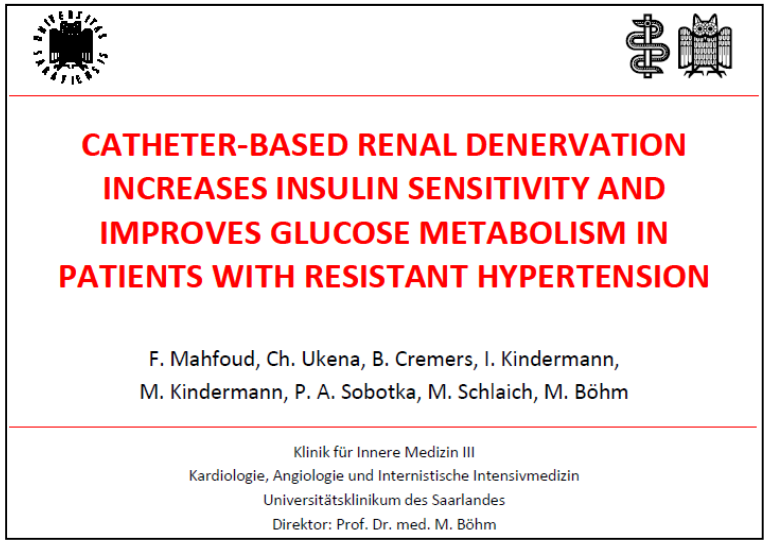
*Further analysis of Medications is ongoing

SNUH SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

RENAL DENERVATION & INSULIN RESISTANCE

Cardiovascular Center, Seoul National University Bundang Hospital

Effects of Renal Denervation on Glucose Handling in Patients with Resistant HTN



CATHETER-BASED RENAL DENERVATION INCREASES INSULIN SENSITIVITY AND IMPROVES GLUCOSE METABOLISM IN PATIENTS WITH RESISTANT HYPERTENSION

F. Mahfoud, Ch. Ukena, B. Cremers, I. Kindermann, M. Kindermann, P. A. Sobotka, M. Schlaich, M. Böhm

Klinik für Innere Medizin III
Kardiologie, Angiologie und Internistische Intensivmedizin
Universitätsklinikum des Saarlandes
Direktor: Prof. Dr. med. M. Böhm

- 25 Treatment, 11 Control
- Age 56.9 ± 10 years
- BMI 31.4 ± 5.5 kg/m²
- Type 2 DM on oral medication, n=15
- No patients on insulin treatment
- Baseline BP: 178/94 ± 16/13 mmHg
- 5.6 ± 1.4 antihypertensive meds

Mahfoud et al. European Society of Cardiology. 2010.

Reduction in HOMA Index at 1 & 3 Months following Renal Denervation

Treatment Group	Fasting Glucose (mg/dl)	Fasting Insulin (mU/l)	C-peptide (μg/l)	HOMA-IR
Baseline (25)	118 ± 20	20.7 ± 11.8	6.1 ± 3.6	6.1 ± 4.3
1 month (25)	110 ± 14*	12.9 ± 7.3*	3.3 ± 1.5*	3.5 ± 1.8*
3 months (25)	106 ± 12*	11.1 ± 4.8*	3.1 ± 1.1*	2.9 ± 1.3*

*significant reduction ($p<0.05$) compared to baseline
HOmeostasisModelAssessment-InsulinResistance (HOMA-IR) = (FPI x FPG)/405

Mahfoud et al. European Society of Cardiology. 2010.

Symplicity HTN-1 Three year and Symplicity HTN-2 Full year Summary

- **Sustained BP Reductions to Three Years**
  - First Symplicity HTN-1 patient treated June 2007
  - Three year reporting shows no diminishment of effect and impressive long term safety
  - For patients that have completed 3 year follow up, 100% have been classified as responders (>10 mmHg reduction), while at 6 months 71% of patients were classified as responders.

- **Superior Results Confirmed in Randomised Study**
  - Symplicity HTN-2 treatment population shows sustained treatment effect at 12 month follow-up
  - Control cross-over patients also show significant BP reduction

Only the Symplicity™ renal denervation system has proven safe, superior and sustained BP reductions

Comprehensive SYMPLICITY Clinical Trial Program follows over 5000 patients across multiple indications