Endovascular Renal Artery Denervation for Treatment of Therapy-Refractory Hypertension

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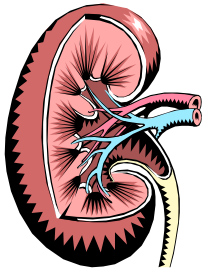
Renal Sympathetic Efferent Nerve Activity:
Kidney as Recipient of Sympathetic Signals

Renal Efferent Nerves

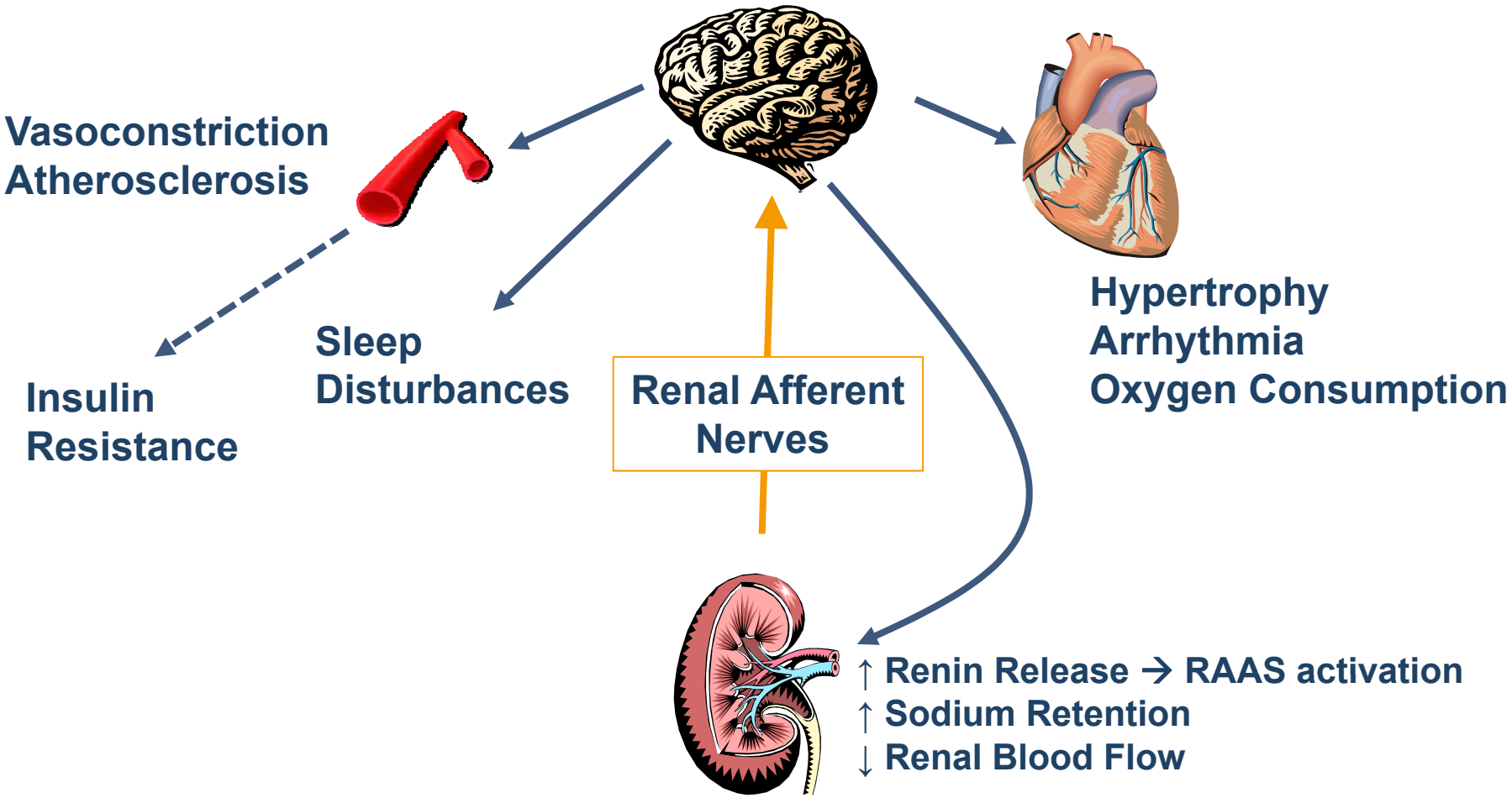


↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

Patients early in the course of hypertension often have been shown to have increased efferent sympathetic activity to the kidney.

Katholi et al., *Curr Hypertens Rep* 2010

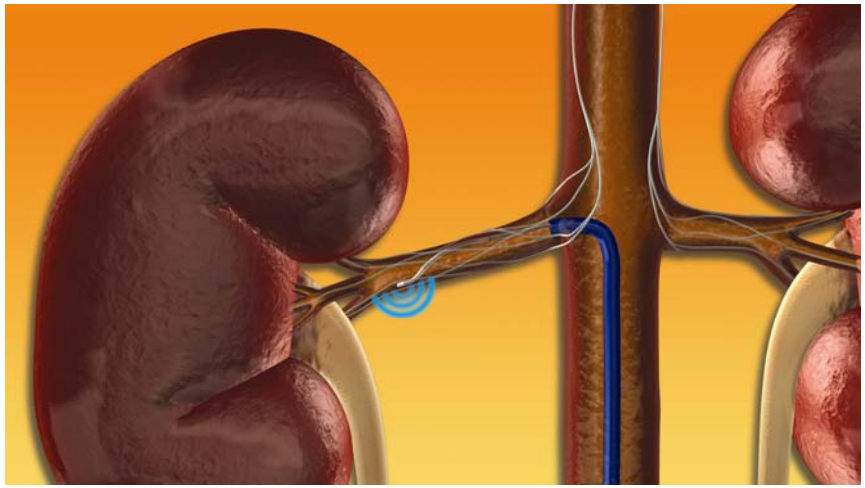
Renal Sympathetic Afferent Nerves:
Kidney as Origin of Central Sympathetic Drive

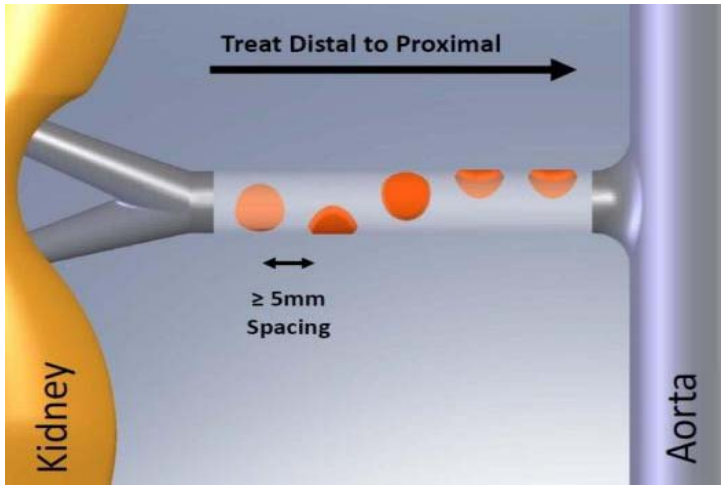


Patients with essential hypertension in the later course (with chronic renal disease) have been found to have increased centrally mediated sympathetic activity.

Katholi et al., *Curr Hypertens Rep* 2010

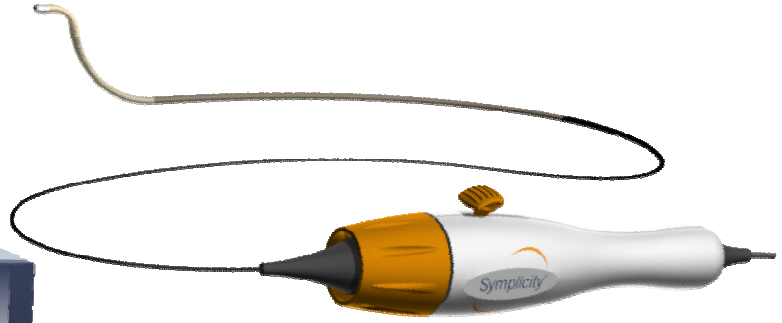
Renal Nerve Anatomy Allows a Catheter-Based Approach



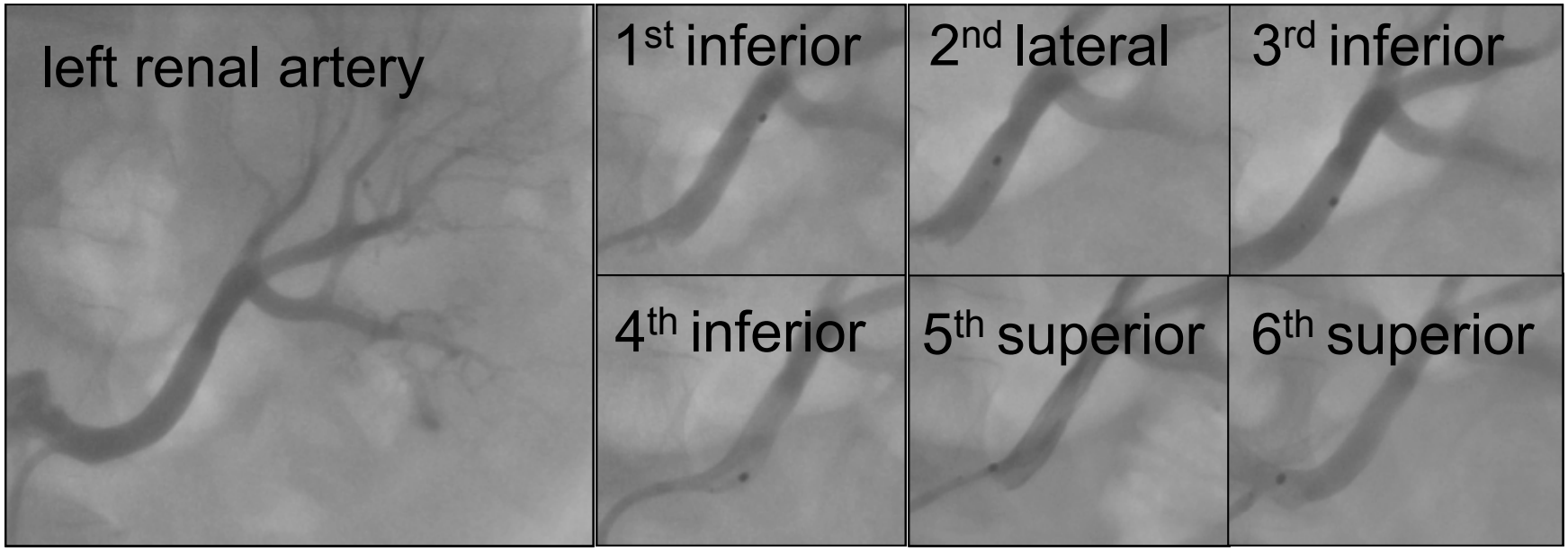


Sympathetic nerves lie within and immediately adjacent to the renal artery wall.

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



Renal Sympathetic Denervation

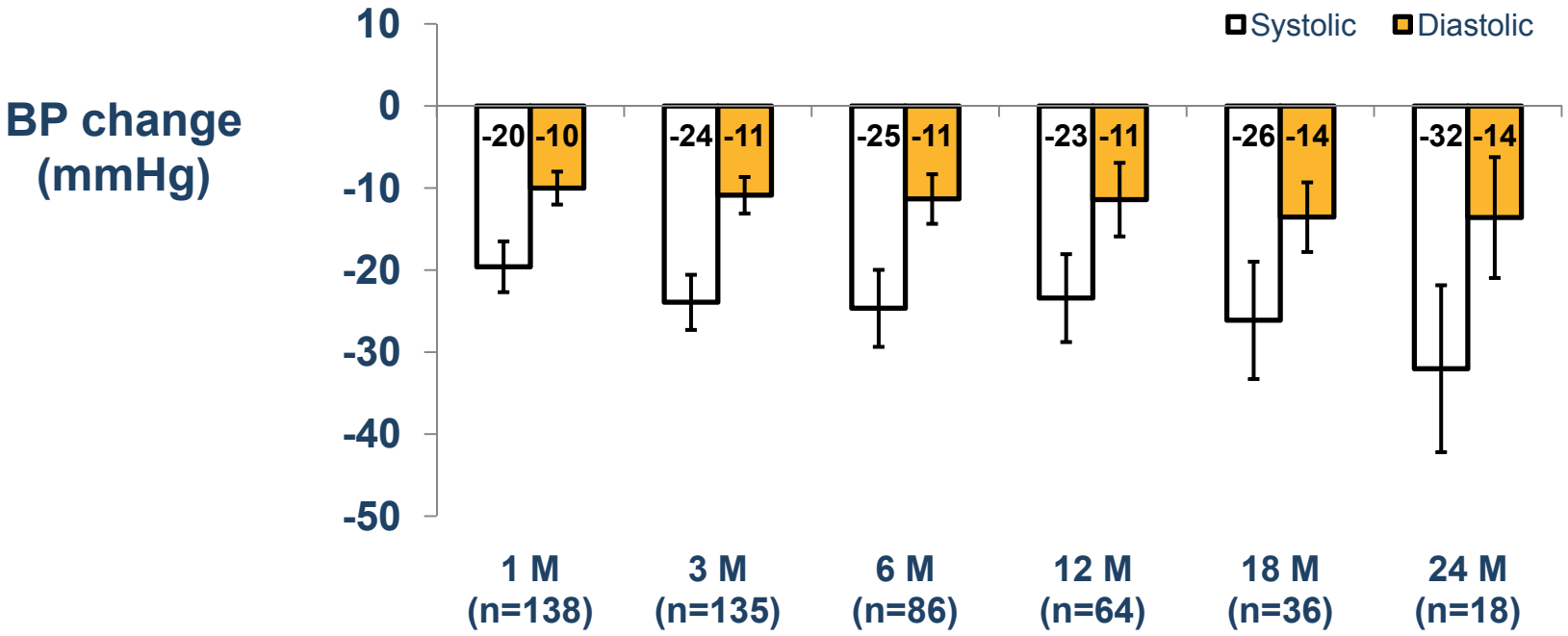


Male patient (56 yr)

Poorly controlled BP - 7 antihypertensive drugs

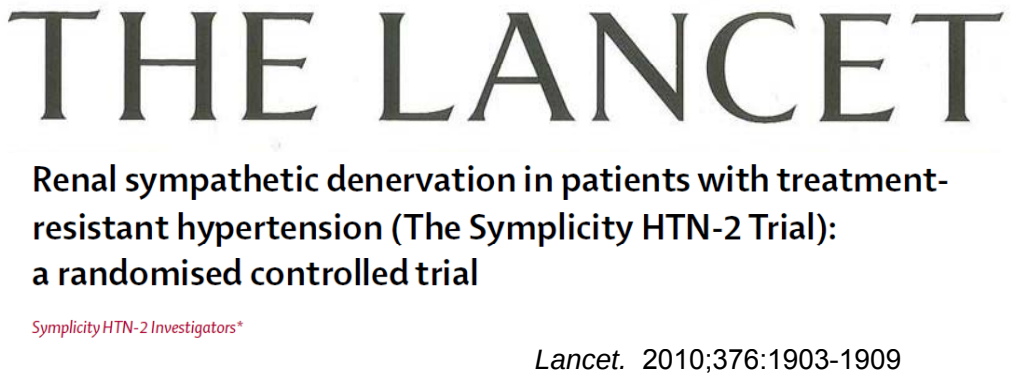
Symplicity HTN-1

- N=153 Patients; SBP ≥160 mmHg on ≥3 anti-HTN drugs; eGFR ≥ 45 mL/min
- 81 patients with 6-month renal CTA/MRA/Duplex - no vascular abnormalities at any site of RF delivery



Simplicity HTN-1 Investigators Hypertension 2011

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

Symplicity HTN-2 Study Centers

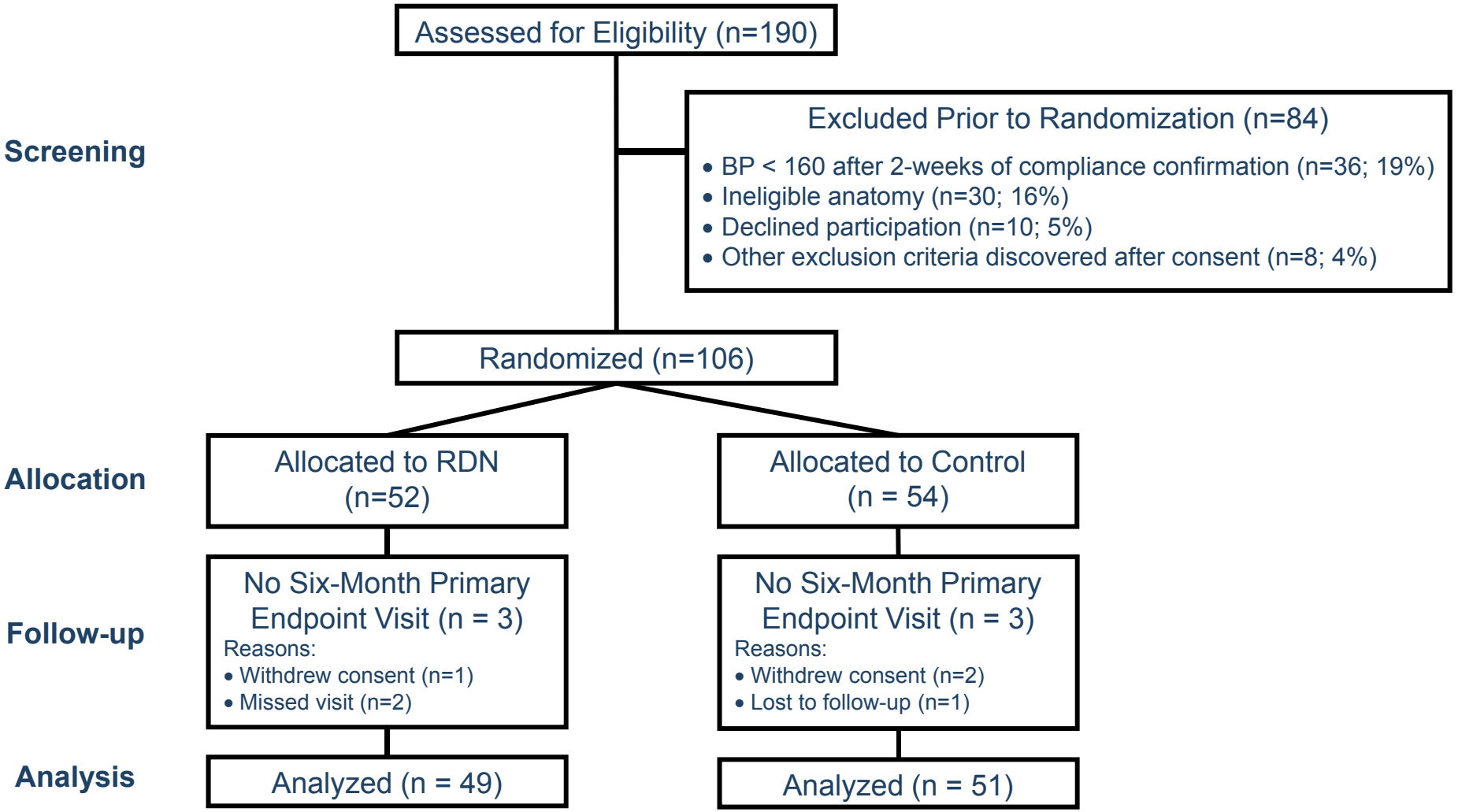
Europe & Australia/NZ

PI: Prof. Murray Esler

Universitätsklinikum des Saarlandes, Homburg, Germany
CardioVascular Center Frankfurt, Frankfurt, Germany
Universitätsklinikum Düsseldorf, Düsseldorf, Germany
Universität Erlangen-Nürnberg, Erlangen, Germany
William Harvey Research Institute, Queen Mary University of London and Barts, London, UK
Pauls Stradins Clinical University Hospital, Riga, Latvia
Assistance Publique des Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France
John Hunter Hospital, Newcastle, Australia
Cliniques Universitaires Saint-Luc, Brussels, Belgium
Universitaetsklinikum Schleswig-Holstein, Lübeck, Germany
Universität zu Köln, Köln, Germany
The Alfred Hospital, Melbourne, Australia
Universität Leipzig – Herzzentrum, Leipzig, Germany
Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria
Samodzielna Pracownia Hemodynamiczna, Warsaw, Poland
Hospital 12 de Octubre, Madrid, Spain
St. Vincent's Hospital, Melbourne, Australia
Universitätsklinikum Essen, Essen, Germany
Kent and Canterbury Hospital, Canterbury, UK
University Hospital Zurich, Zurich, Switzerland
University of Glasgow, Glasgow, UK
Auckland City Hospital, Auckland, New Zealand
Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany
The John Paul II Hospital, Krakow, Poland

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

Patient Disposition



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

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**
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
eGFR 45-60 (% patients)	21%	11%	0.19
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

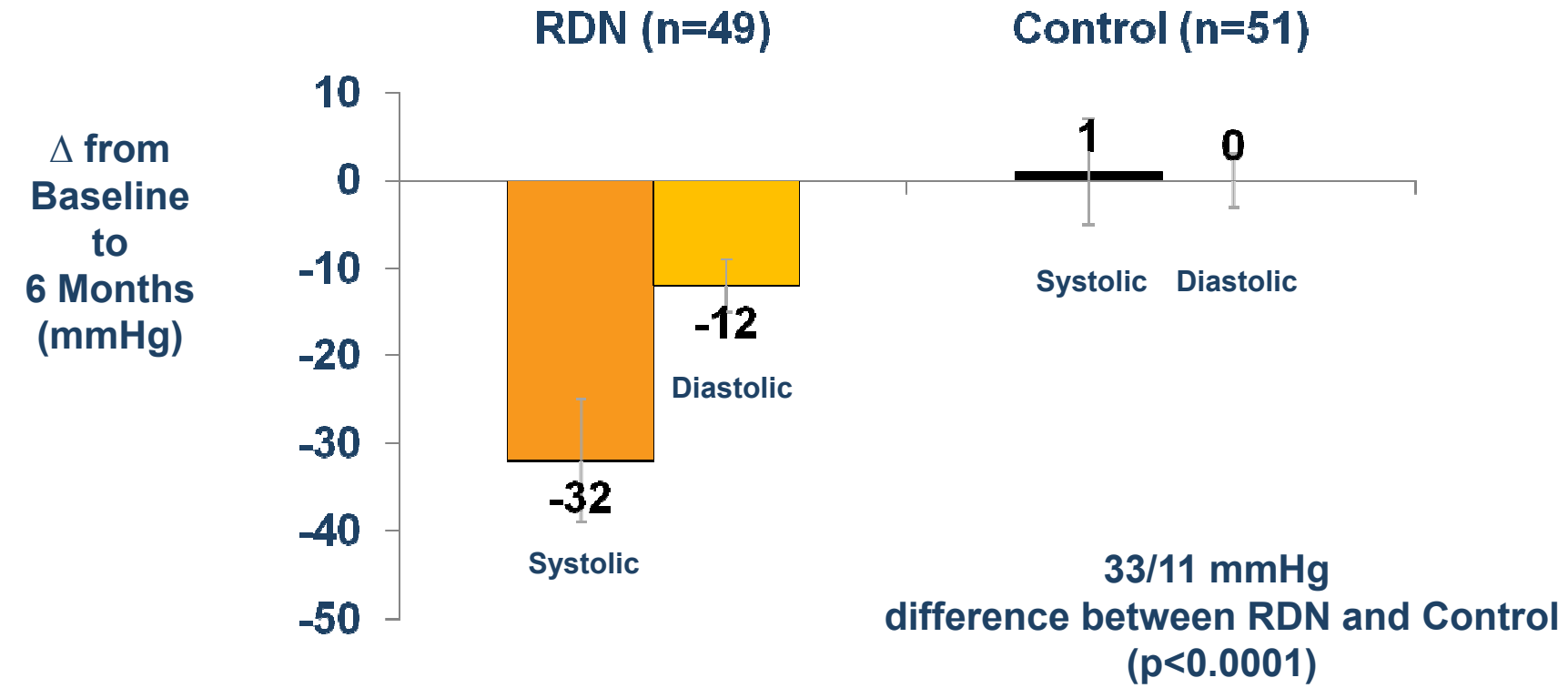
Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909

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

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

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

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

Medication Changes

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

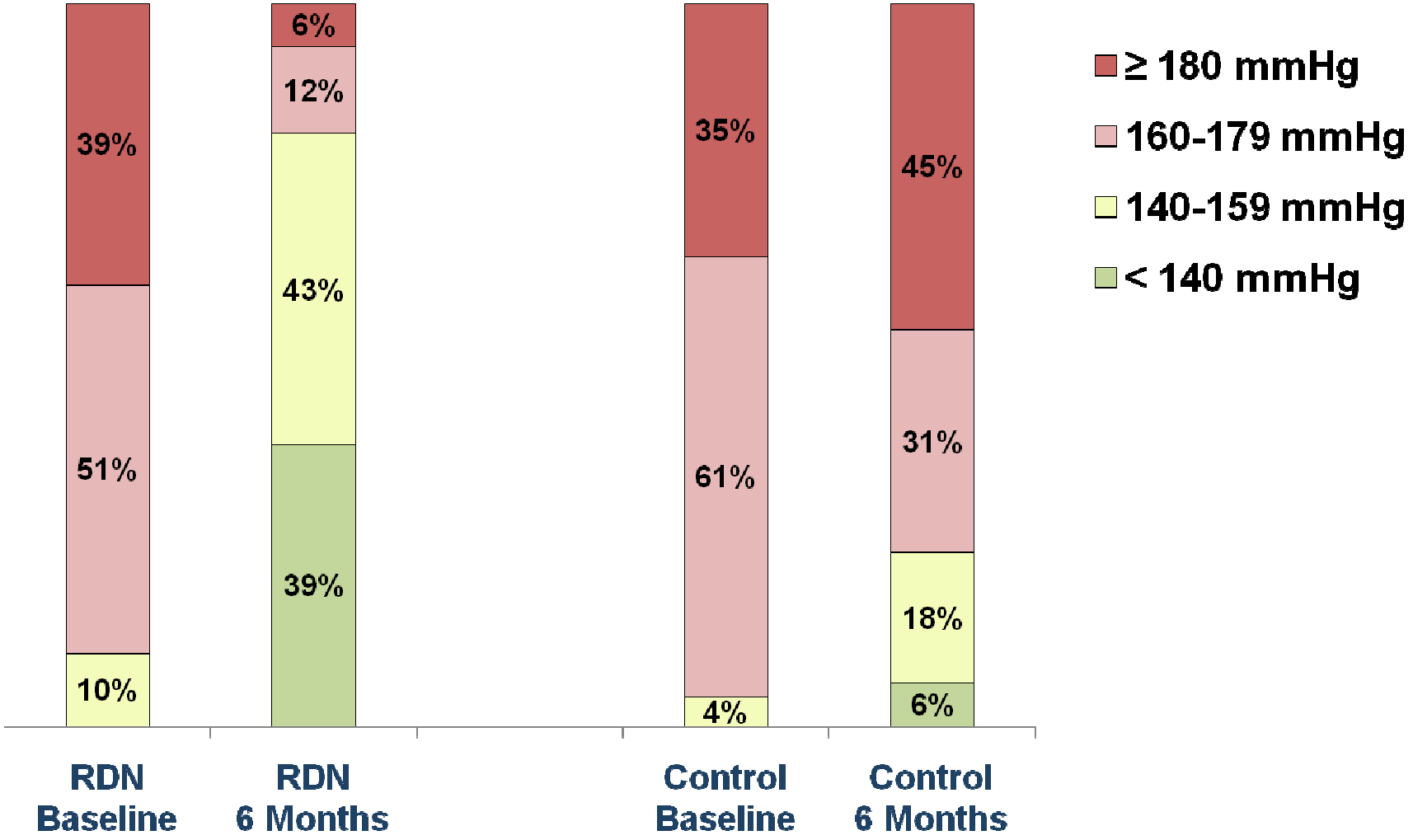
	RDN (n=49)	Control (n=51)	P-value
# Med Dose Decrease (%)	10 (20%)	3 (6%)	**0.04**
# Med Dose Increase (%)	4 (8%)	6 (12%)	0.74

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)

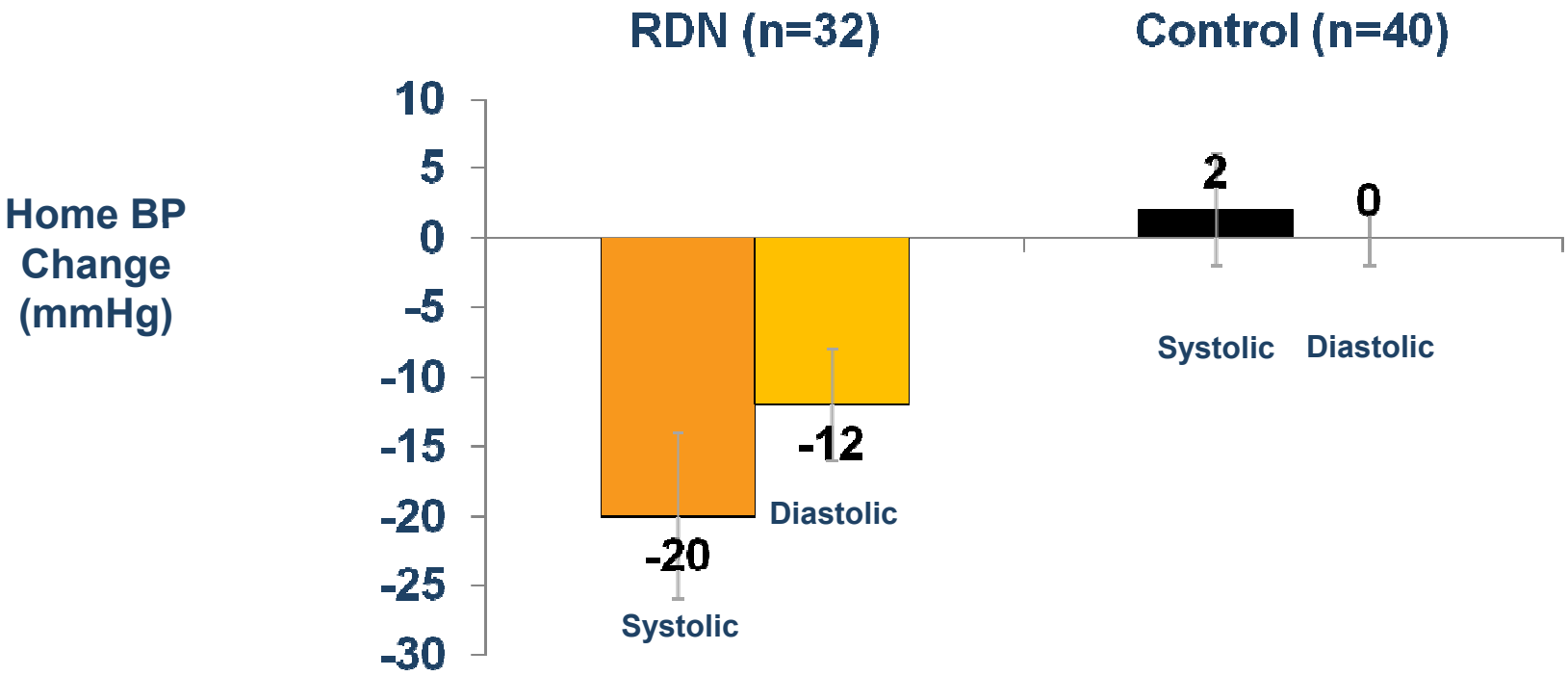
Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909

Office Systolic BP Distribution



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

Home & 24 Hour Ambulatory BP

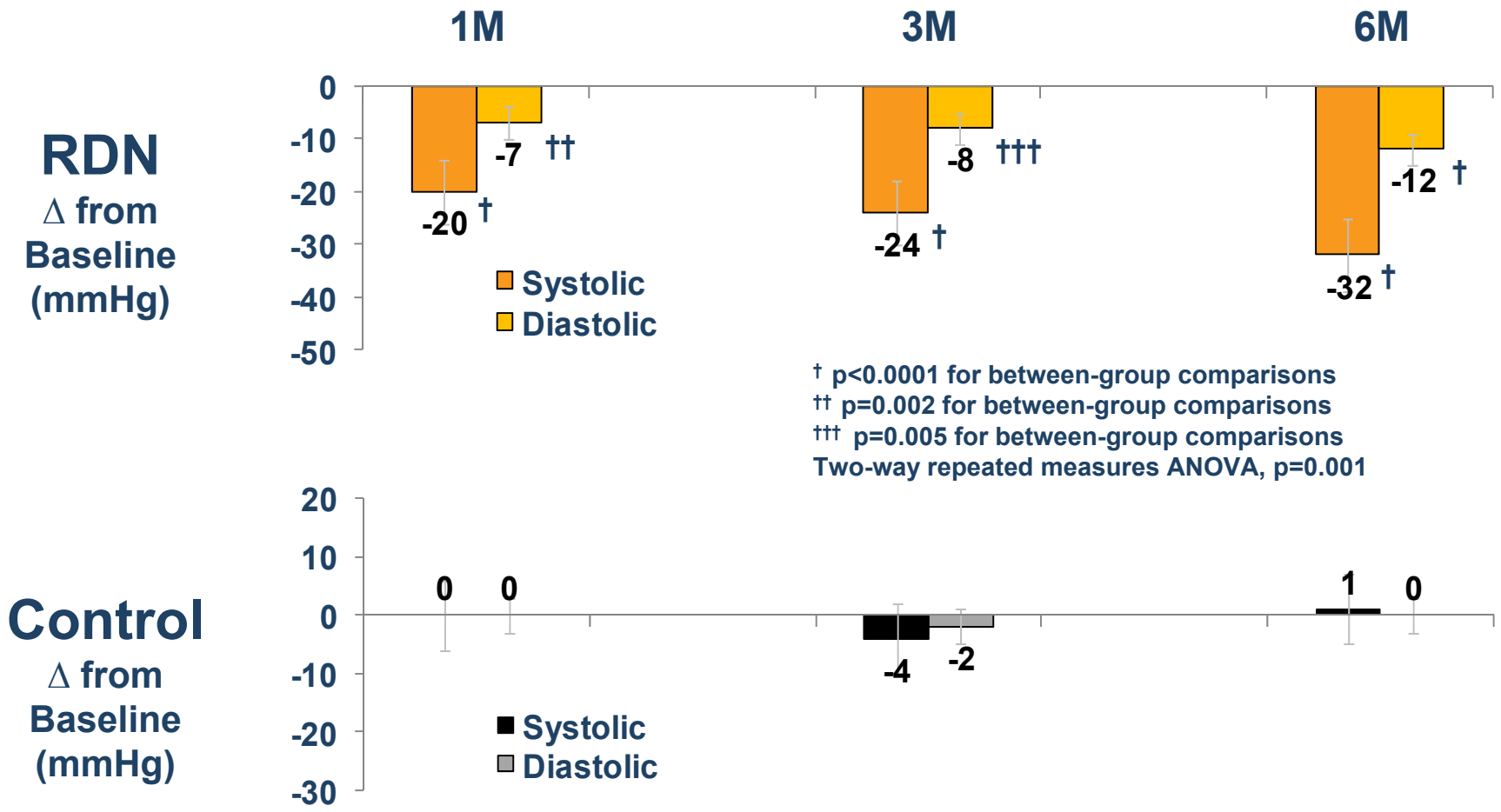


24-h ABPM:

- 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

Time Course of Office BP Change



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)

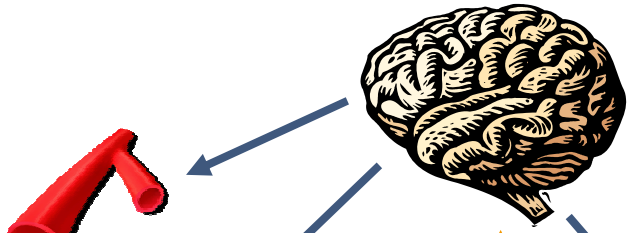
Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909

Renal Function

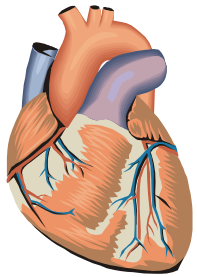
Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0,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

Symplicity HTN-2 Investigators. The Lancet. 2010.

Possible Areas for Future Research…



Vasoconstriction
Atherosclerosis

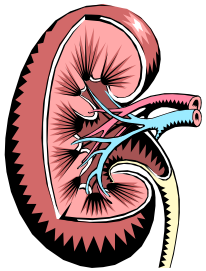


Hypertrophy
Arrhythmia
Oxygen Consumption

Insulin
Resistance

Sleep
Disturbances

Renal Afferent
Nerves



↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

Key Topics of Future Research:

1) Insulin Resistance / Diabetes
2) HF / Cardiorenal Syndrome
3) Arrhythmia
4) Sleep Apnea

Conclusions

- 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 can be applied without major complications
- This new option for treatment-resistant hypertension may also play a role in other co-morbid diseases driven by elevated central sympathetic drive