

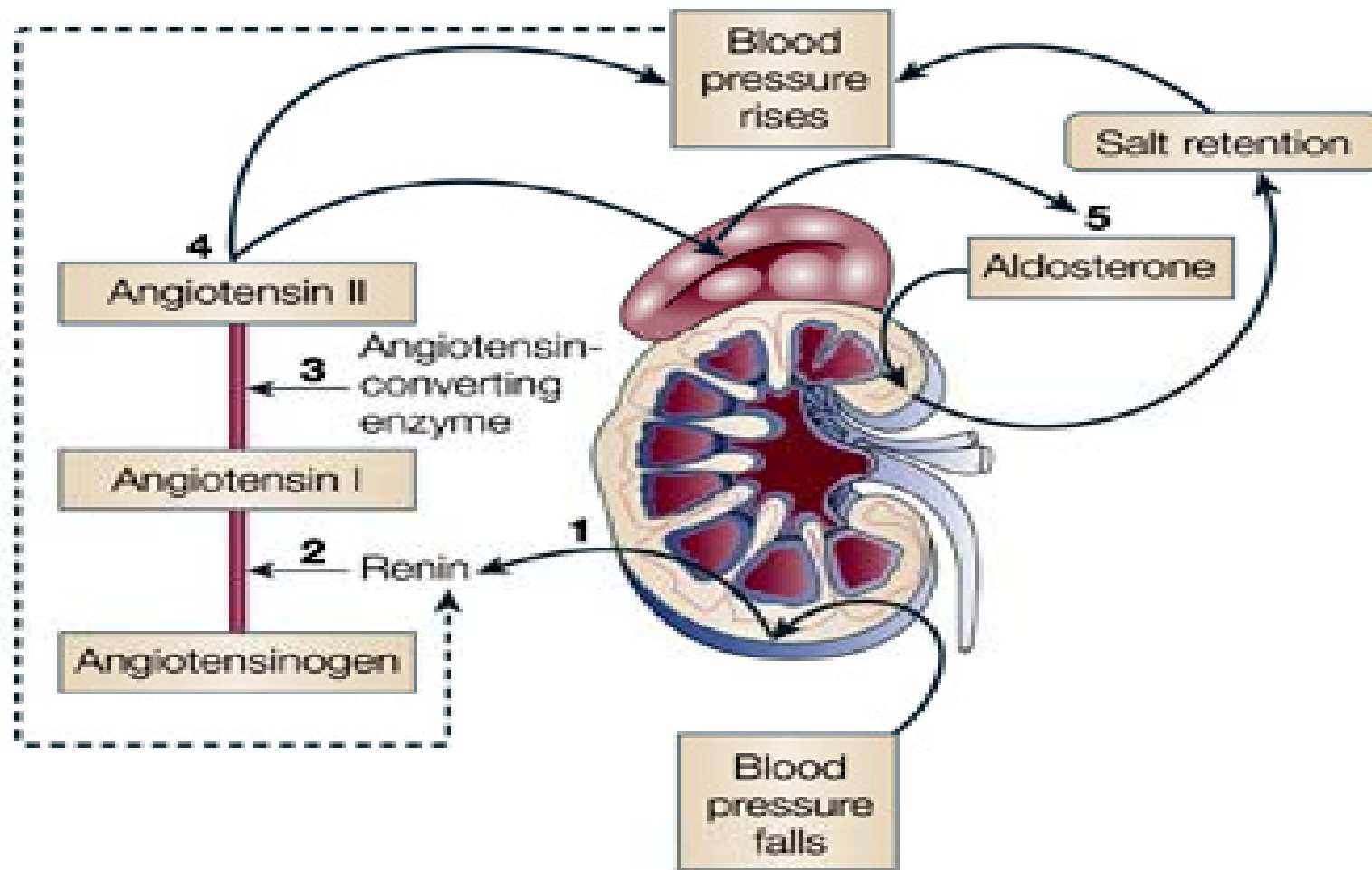
ANGIOPLASTY SUMMIT-TCTAP 2012  
Seoul, Korea, April 24-27, 2012

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# What We've Learned from Simplicity HTN-1,2, and Registries

Horst Sievert, Ann-Kathrin Ziegler, Benjamin  
Kaltenbach, Ilona Hofmann, Undine Pittl  
CardioVascular Center Frankfurt,  
Frankfurt, Germany

# The Renin-Angiotensin-System

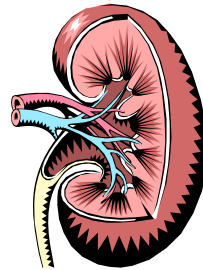


# Renal Sympathetic Efferent Nerves

Kidney as the recipient of central sympathetic signals



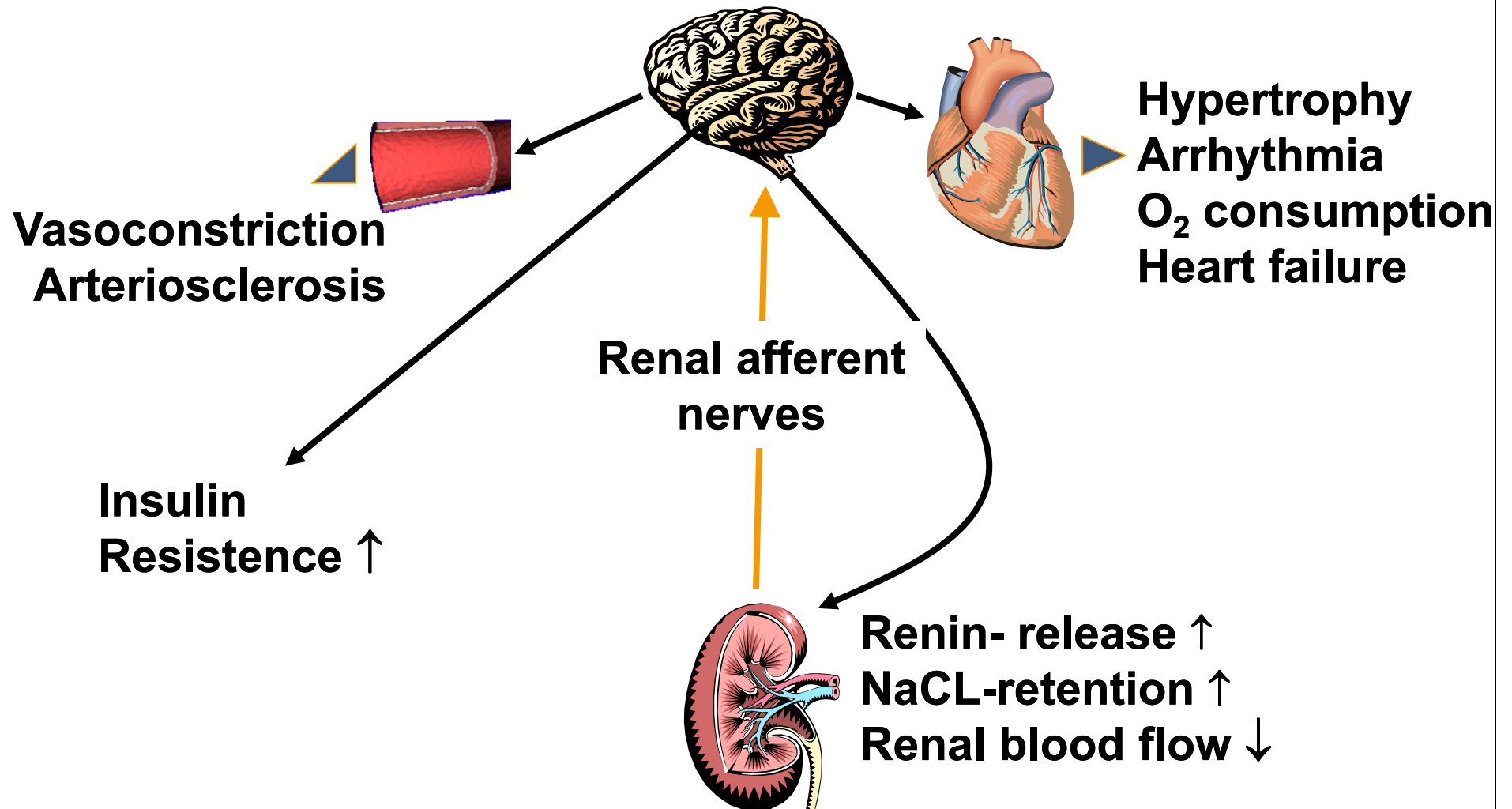
**Renal efferent nerves**



**Renin release ↑**  
**NaCl- retention ↑**  
**Renal blood flow ↓**

# Renal Afferent Nerves

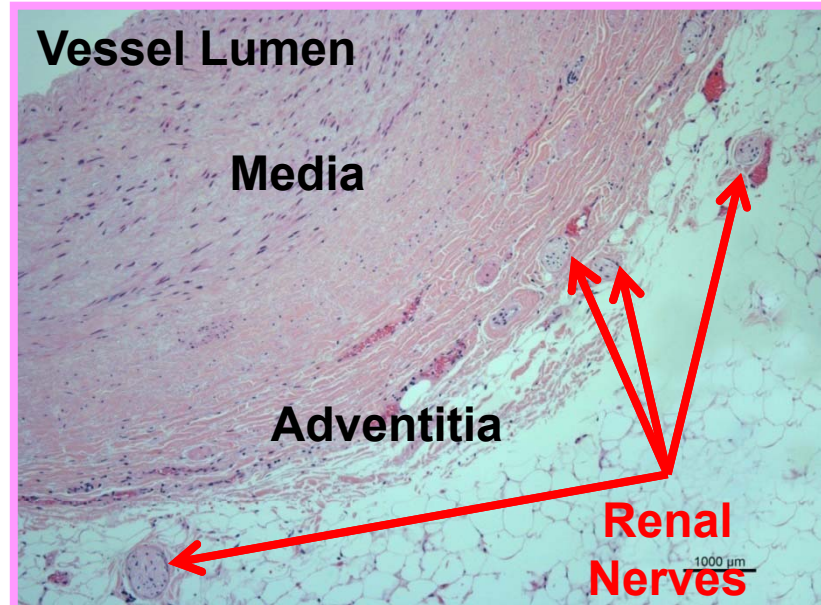
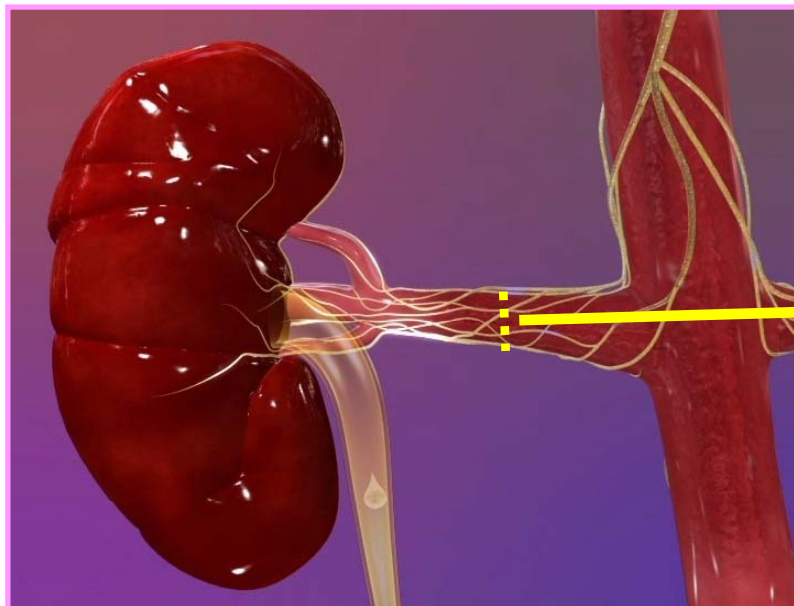
Kidney as the origin of central sympathetic drive



# The Renal Nerves

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- Follow the renal artery to the kidney
- Primarily lie within the adventitia



# Generator

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

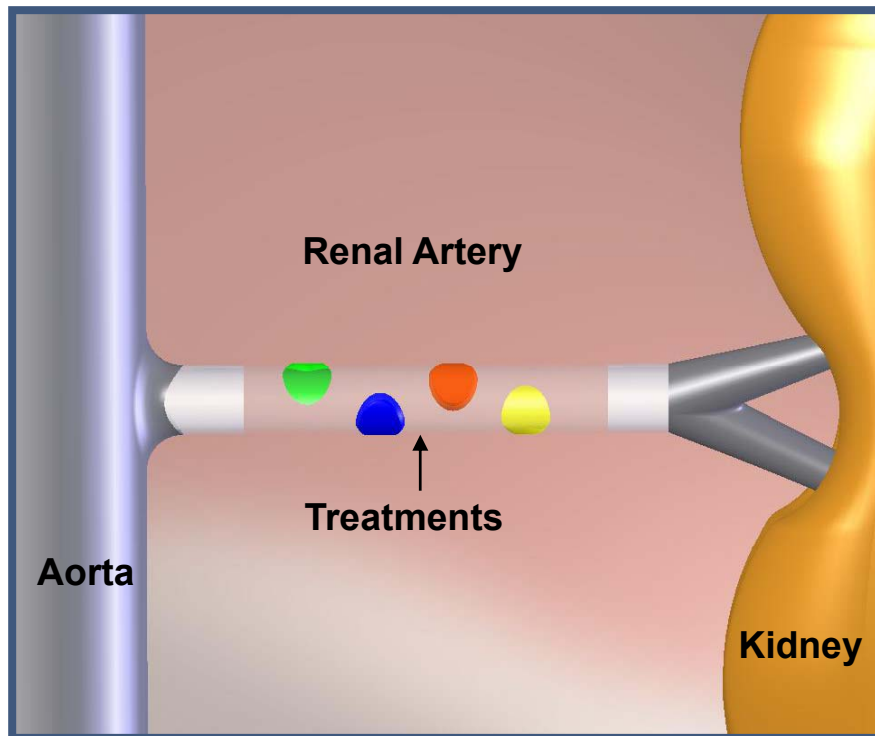


# Simplicity™ Catheter

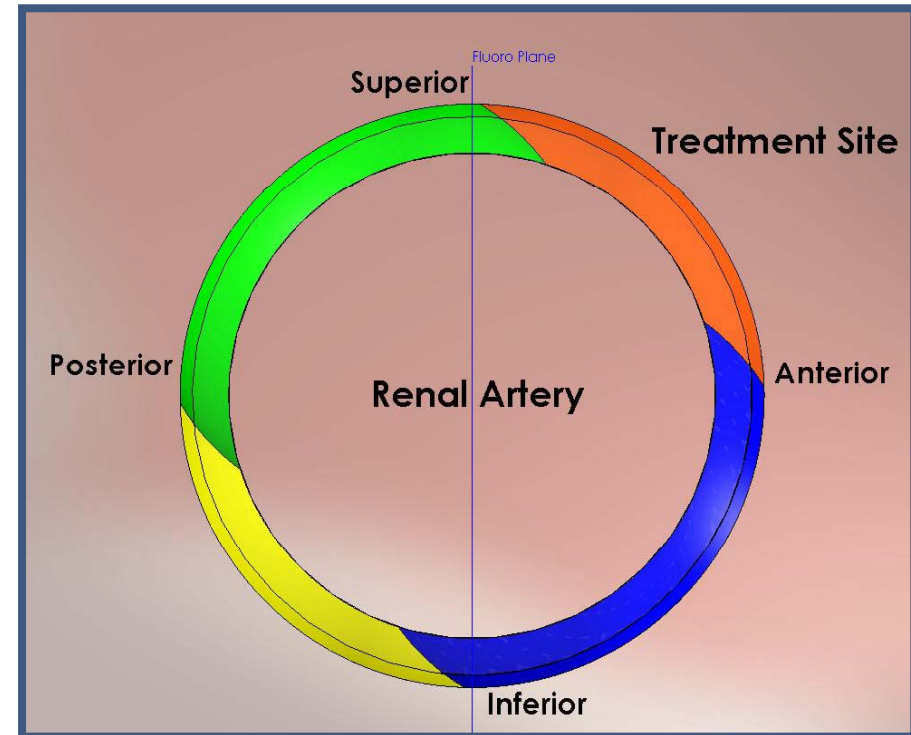
- Radiofrequency electrode tip
- Handle allows bending of the tip and rotation
- Compatible with a 6 F guiding catheter



# Treatment Strategy



Focal ablations  
spaced along vessel



Multiple focal ablations  
↑ circumferential coverage



# Procedural details

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

# Example Treatment Locations in a Right Renal Artery

Treatment #1



Treatment #4



Treatment #2



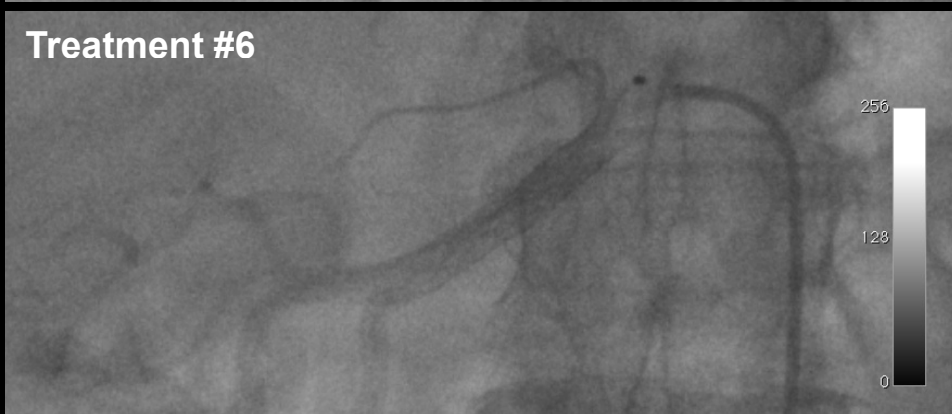
Treatment #5



Treatment #3



Treatment #6





TREND ASIA-PACIFIC  
CSI FOCUS



LIVE  
CASES

# TREND 2012 ASIA-PACIFIC

SEPTEMBER 29, 2012 | HONG KONG

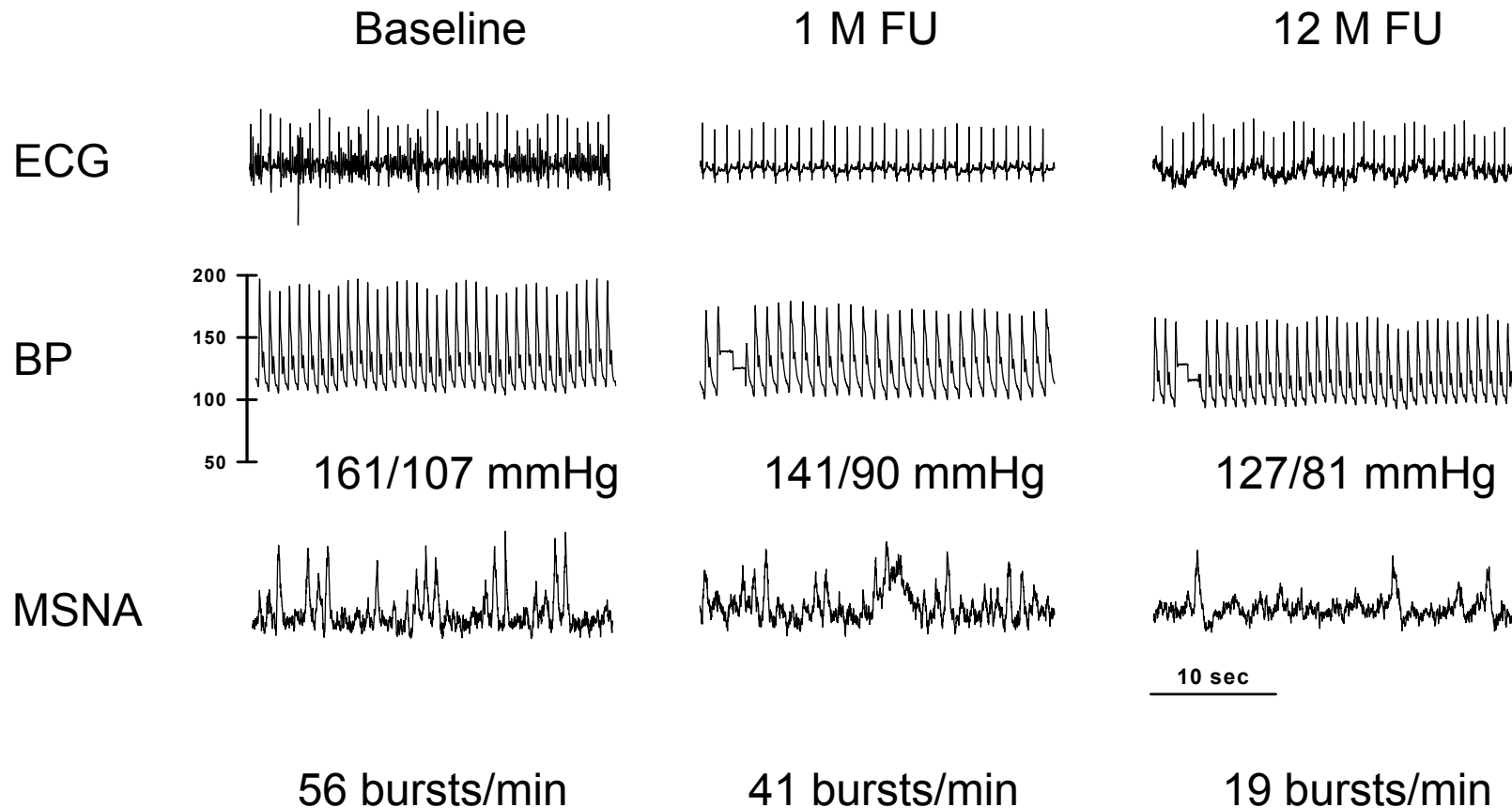


Neuro-Humoral Interventions  
Catheter and Device Based Treatment of Hypertension and Heart Failure  
Transcatheter Renal Denervation

[www.csi-trend.org](http://www.csi-trend.org)

TREND Frankfurt, Germany, Frankfurt, March 1-2. 2013

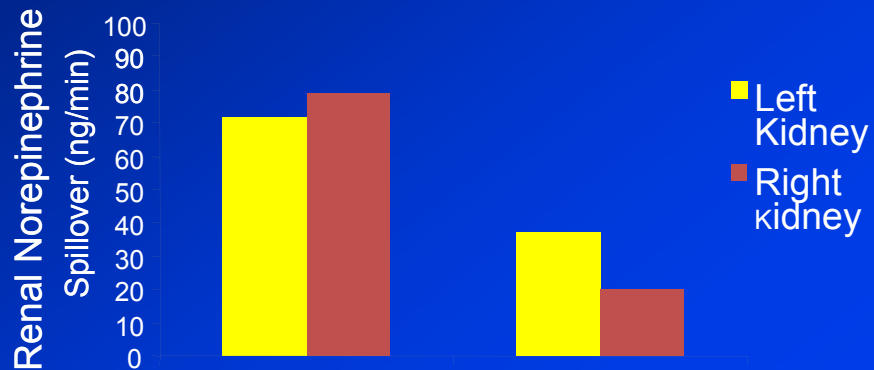
# Reduction of sympathetic activity: MSNA in a patient with resistant hypertension



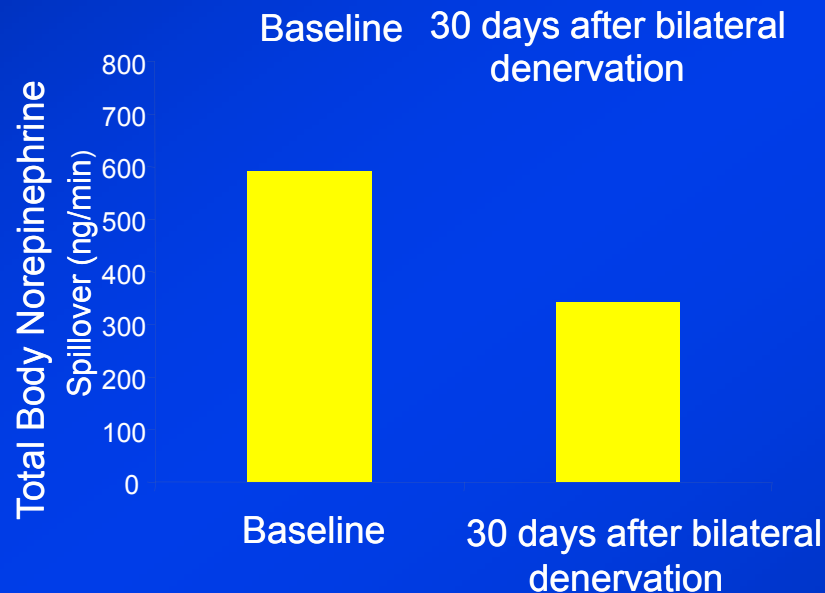
Improvement in cardiac baroreflex sensitivity after renal denervation  
(from 7.8 to 11.7msec/mmHg).

# Effects of renal denervation on renal and total body NA spillover

Mean office blood pressure  
**161/107**                      **141/90**



47% reduction in renal noradrenaline spillover (p<0.05)



28% reduction in total body NA spillover (p<0.05)

Clinical studies

Renal denervation

# 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

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

- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP  $\geq$ 160 mmHg on  $\geq$ 3 anti-HTN drugs, including a diuretic; eGFR  $\geq$  45 mL/min)
- 12-month data

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

- Expanded cohort of patients (n=153)
- 24-month follow-up

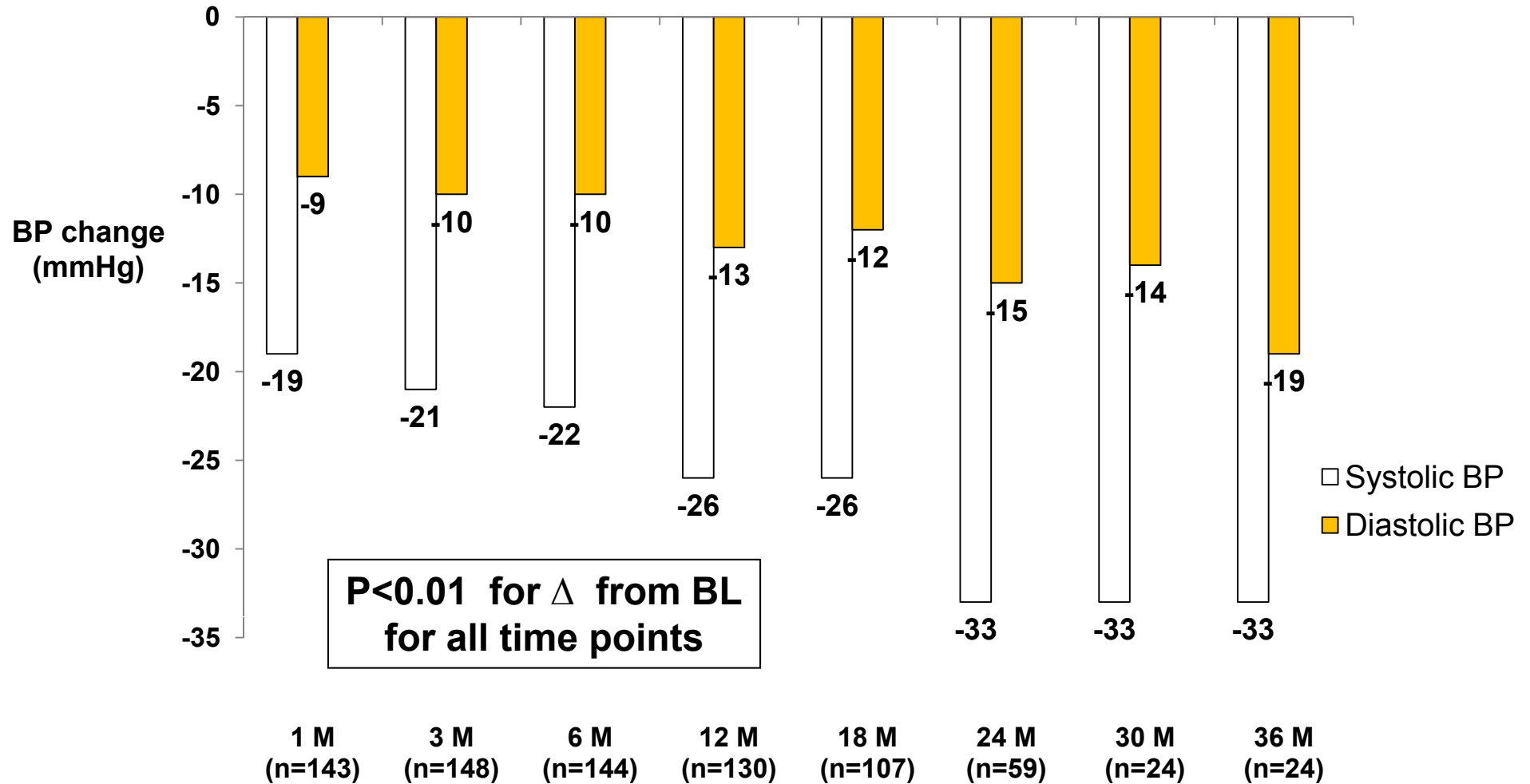
# Baseline Patient Characteristics

<b>Demographics</b>	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
<b>Co-morbidities</b>	Diabetes Mellitus II (%)	31%
	CAD (%)	22%
	Hyperlipidemia (%)	68%
	eGFR (mL/min/1.73m <sup>2</sup> )	83 ± 20
<b>Blood Pressure</b>	<b>Baseline BP (mmHg)</b>	<b>176/98 ± 17/15</b>
	<b>Number of anti-HTN meds (mean)</b>	<b>5.0 ± 1.4</b>
	ACE/ARB (%)	90%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Vasodilator (%)	19%
	Diuretic (%)	95%
	Spirolactone (%)	21%



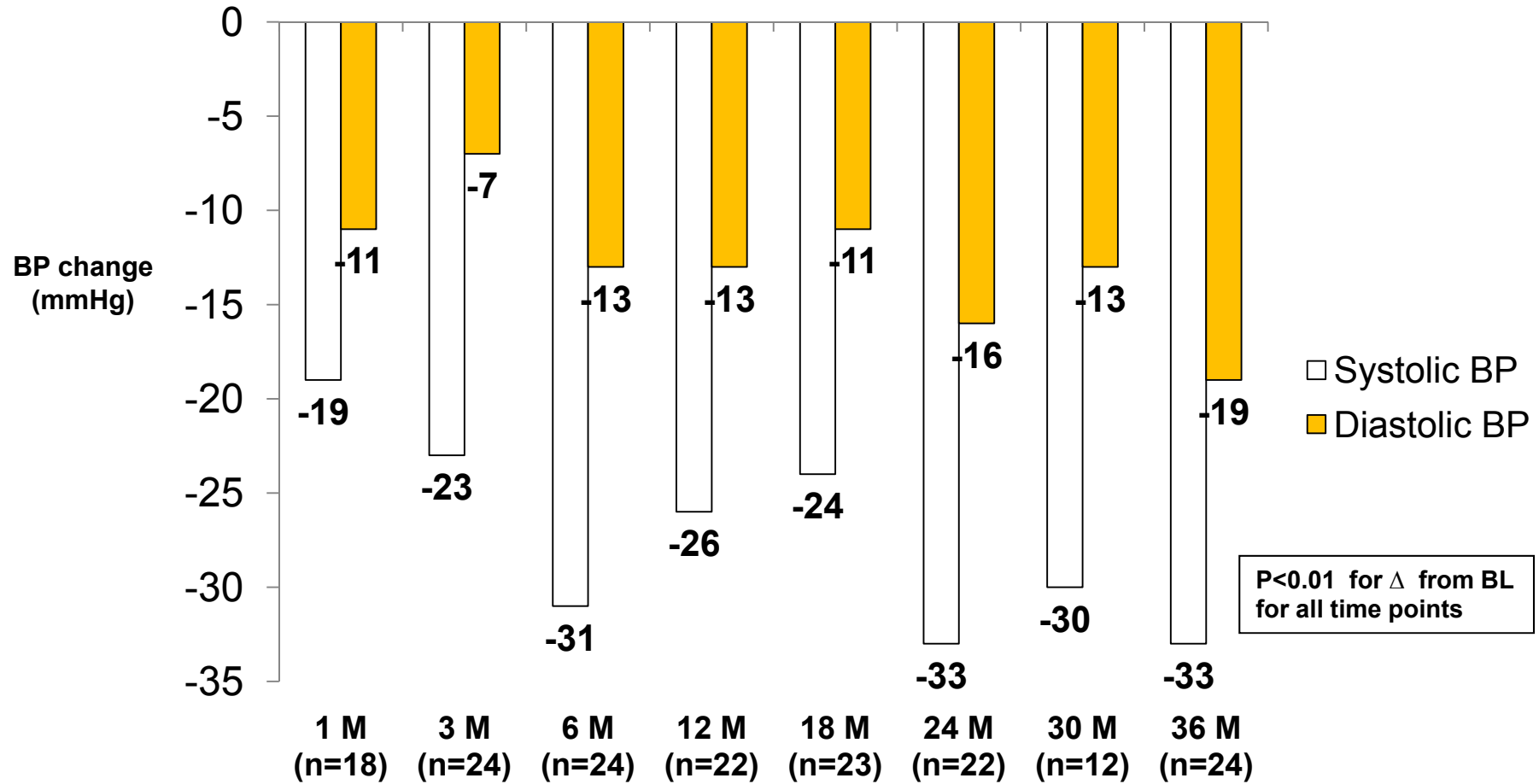
# Symplicity HTN-1

## Significant, Sustained BP Reduction through 3 yrs

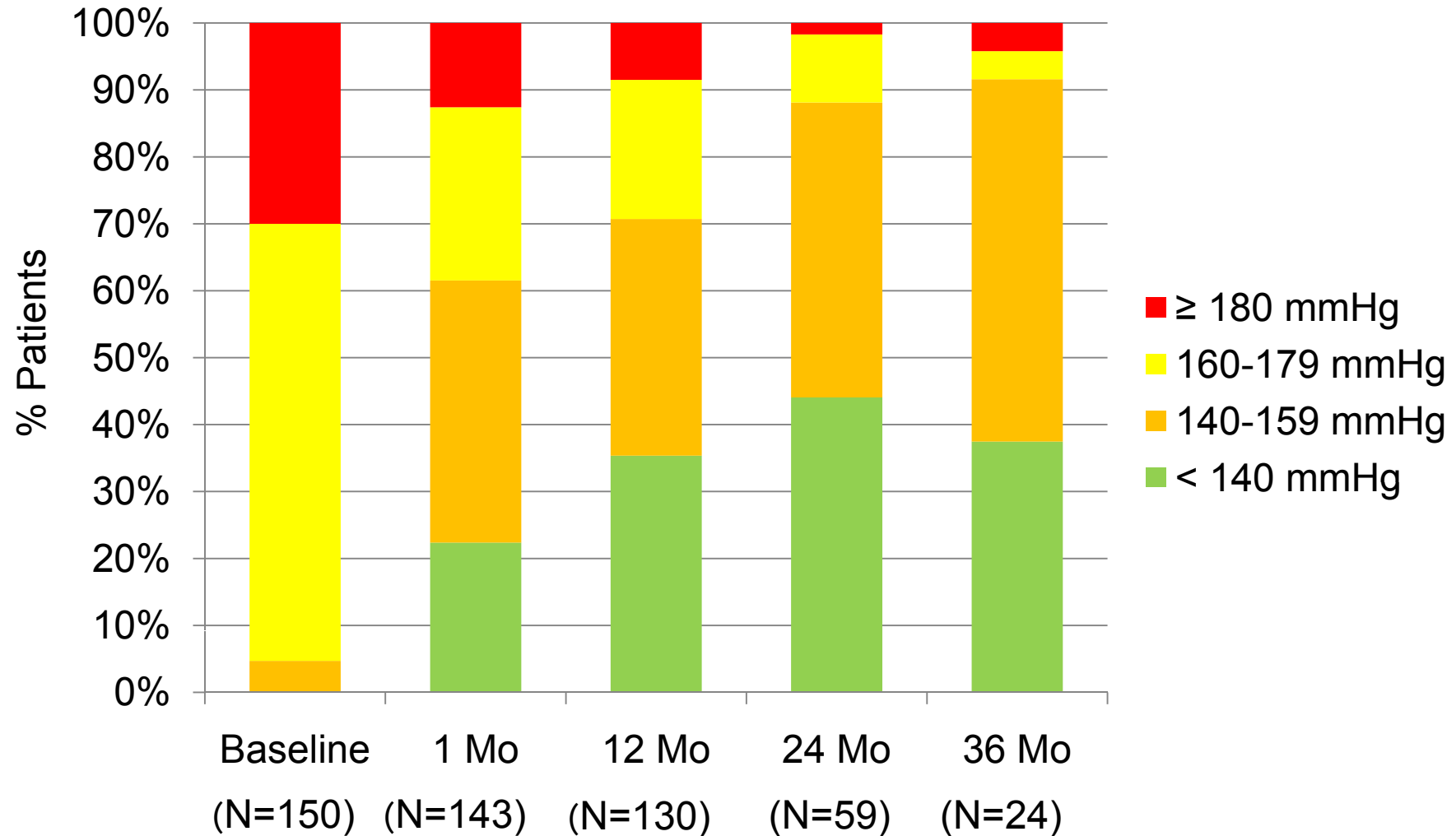


# Symplicity HTN-1

## Change in Office Blood Pressure for 24 Pts with 3 yrs Follow-up



# Distribution of SBP Change at BL, 1, 12, 24, and 36 Months



# HTN-1: Adverse Events Out to 3 Years

- One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- One new moderate stenosis which was not hemodynamically relevant and no treatment
- 3 deaths within the follow-up period; all unrelated to the device or therapy
- No hypotensive events that required hospitalization
- There were no observed changes in mean electrolytes or eGFR

# Symlicity HTN-2

## THE LANCET

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

SymlicityHTN-2 Investigators\*

*Lancet.* 2010;376:1903-1909

- **Study design:** 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

# Symlicity HTN-2 Trial

## **Inclusion Criteria:**

- Office SBP  $\geq$  160 mmHg  
( $\geq$  150 mmHg with type II diabetes mellitus)
- 3+ more anti-HTN medications
- Age 18-85 years

## **Exclusion Criteria:**

- Significant renal artery abnormalities or prior renal artery intervention
- eGFR  $<$  45 mL/min/1.73m<sup>2</sup> (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

# 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 <sup>2</sup> )	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 <sup>2</sup> )	77 ± 19	86 ± 20	0.013
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.003
eGFR 45-60 (% patients)	21%	11%	0.19
Urine Alb/Creat Ratio (mg/g) <sup>†</sup>	128 ± 363	109 ± 254	0.64
Cystatin C (mg/L) <sup>††</sup>	0.9 ± 0.2	0.8 ± 0.2	0.16
Heart rate (bpm)	75 ± 15	71 ± 15	0.23

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

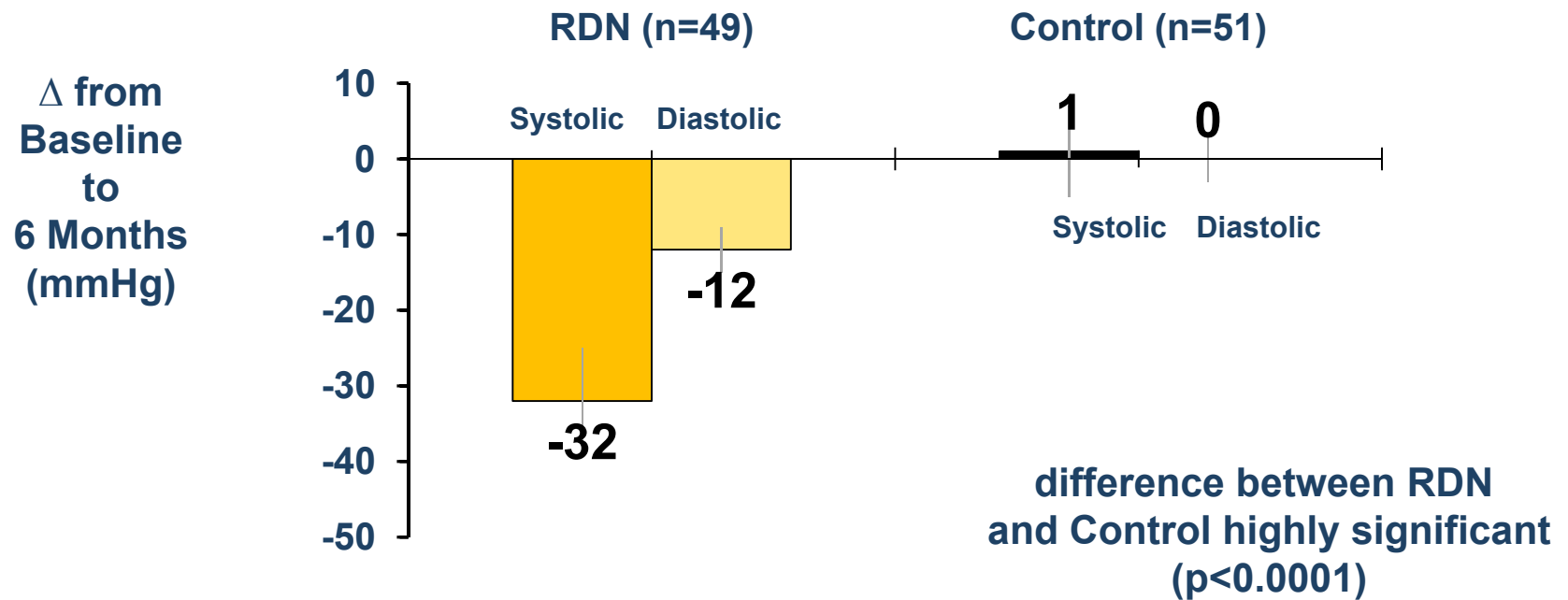
<sup>††</sup> n=39 for RDN and n=42 for Control

# 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

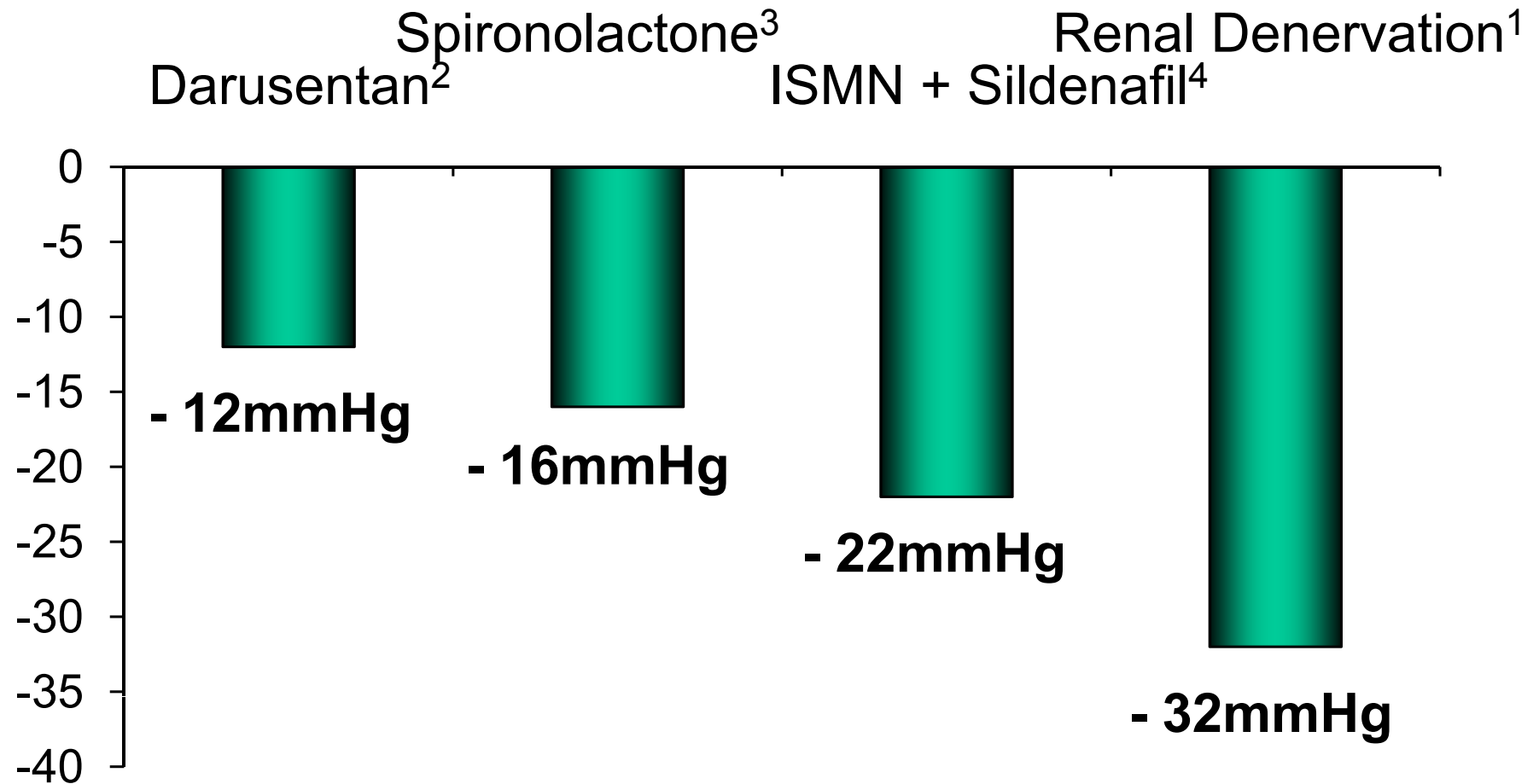


- 84% of RDN patients had  $\geq 10$  mmHg reduction in SBP
- Only 10% of RDN patients had no reduction in SBP

How does this compare  
to medical treatment?

# Randomized Trials in Resistant Hypertension

## Mean Reduction in Systolic BP



<sup>1</sup>Lancet. 2010

<sup>2</sup>Curr Hypertens Rep. 2008 Dec;10(6):429-31.

<sup>3</sup>Hypertension. 2010 Jan;55(1):147-52

<sup>4</sup>Hypertension. 2010 Jul;56(1):22-3.

## Adverse events

- No serious device or procedure related adverse events (n=52)
- Minor adverse events (all unrelated to RF)
  - 1 femoral artery pseudoaneurysm → 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)

# No Change in Renal Function

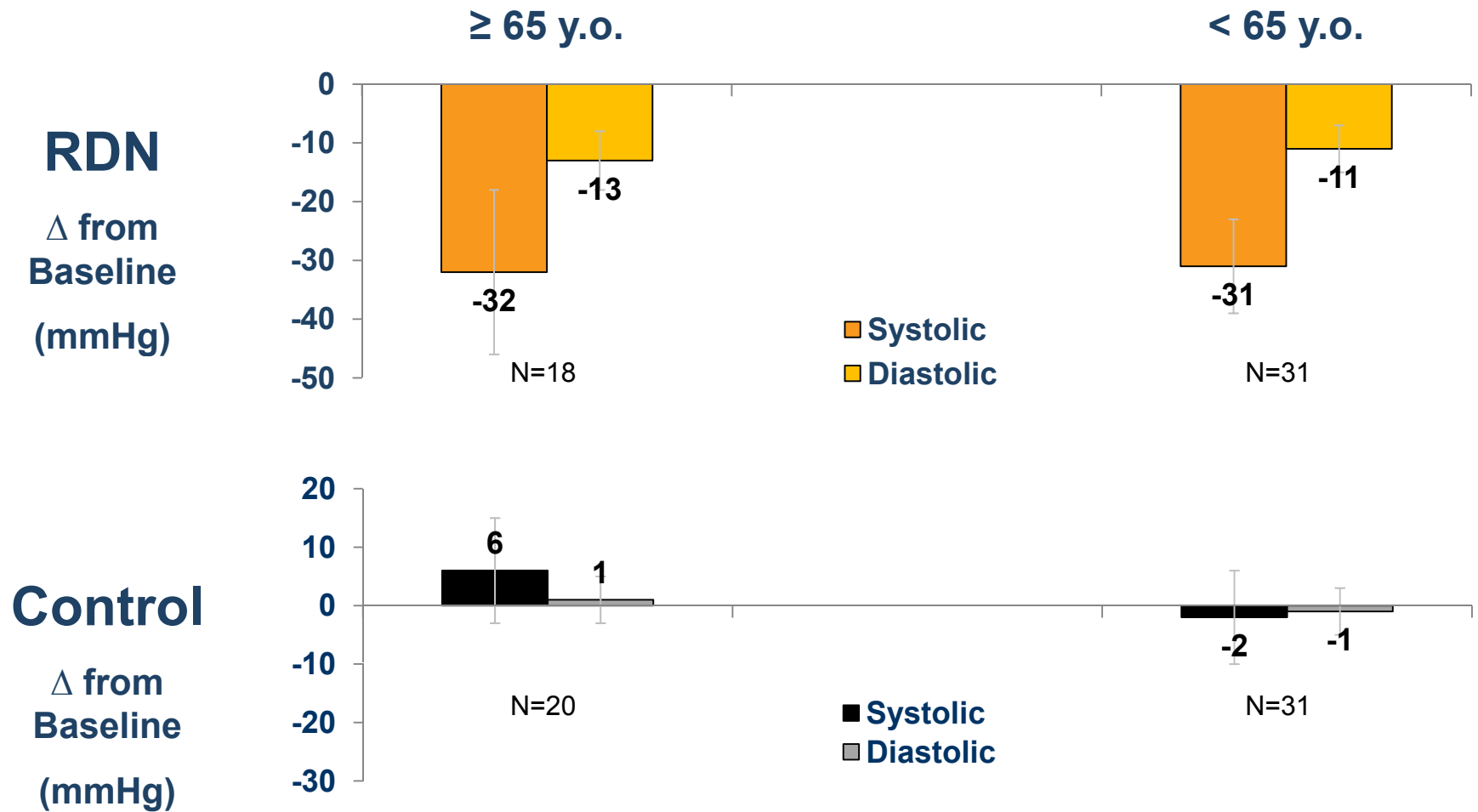
<b>Δ Renal Function (baseline - 6M)</b>	<b>RDN Mean ± SD (n)</b>	<b>Control Mean ± SD (n)</b>	<b>Difference (95% CI)</b>	<b>p-value</b>
<b>eGFR (MDRD)</b> (mL/min/1.73m <sup>2</sup> )	<b>0 ± 11</b> (49)	<b>1 ± 12</b> (51)	<b>-1</b> (-5, 4)	<b>0.76</b>
<b>Serum Creatinine</b> (mg/dL)	<b>0.0 ± 0.2</b>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

# Subgroup analyses

- Age
- Gender
- Diabetes

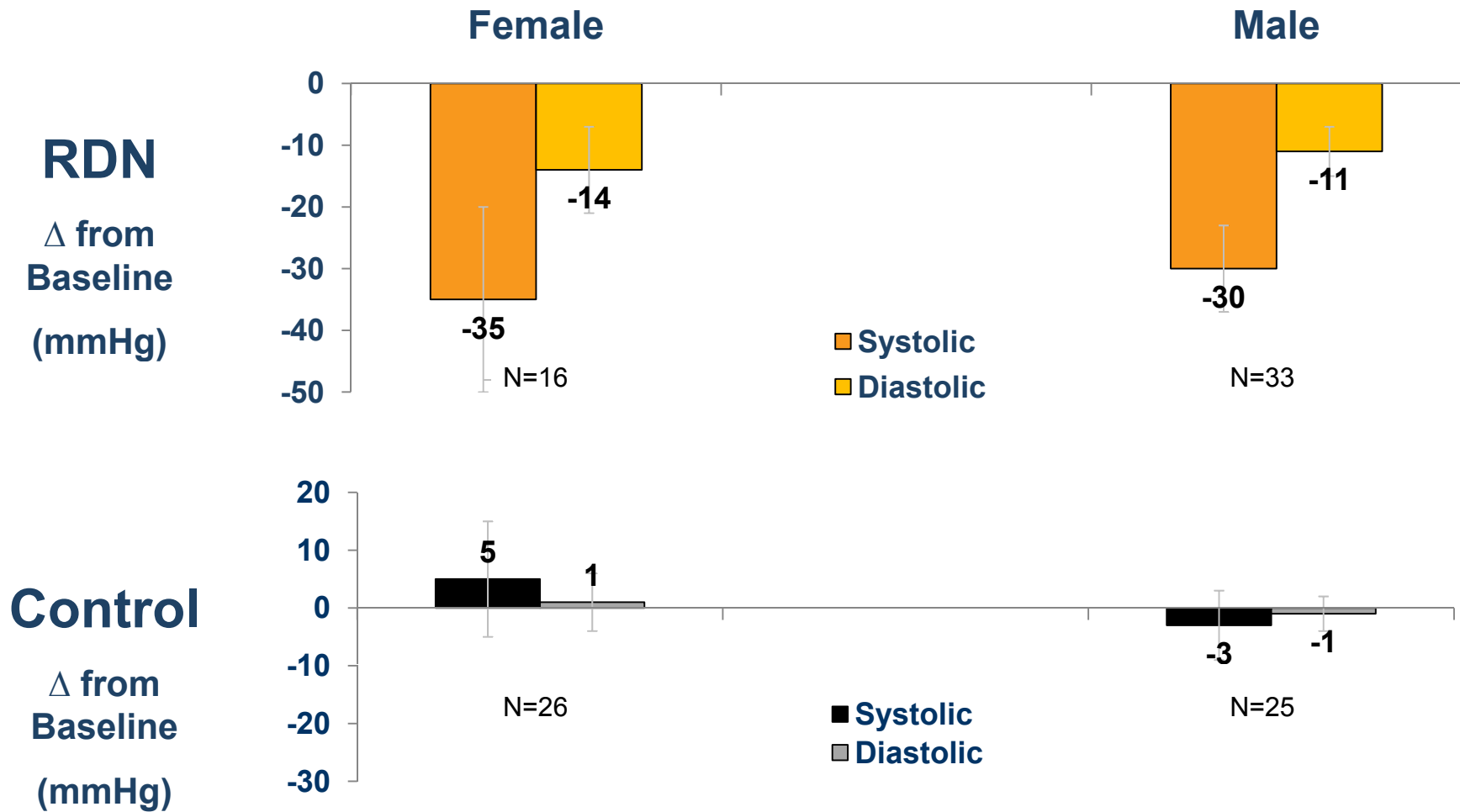
—————→ no differences

# 6-month Office BP Change by Age ( $\geq 65, < 65$ )



All between-age p-values = NS

# 6-month Office BP Change by Gender

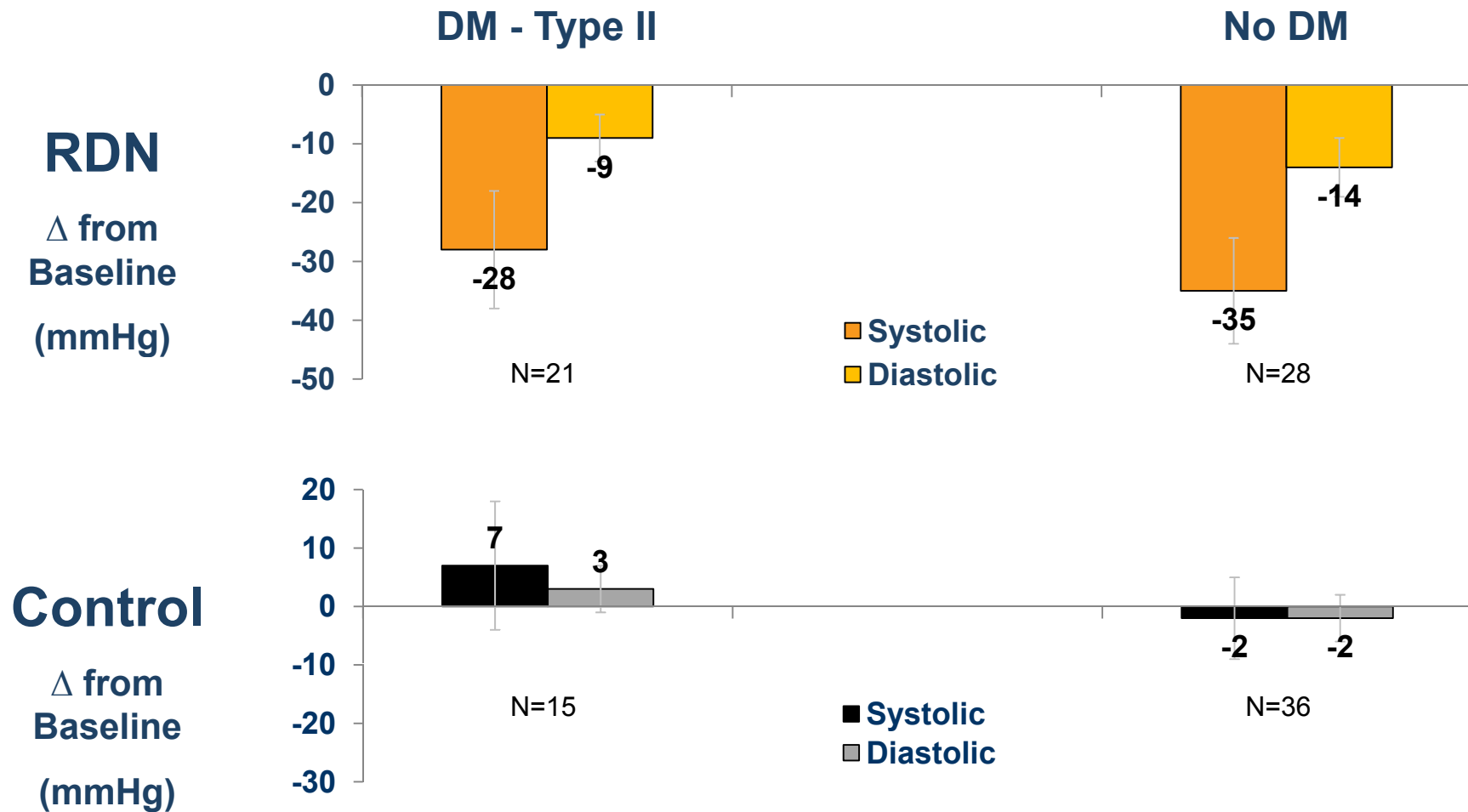


All between-gender p-values = NS



# 6-month Office BP Change by DM Status

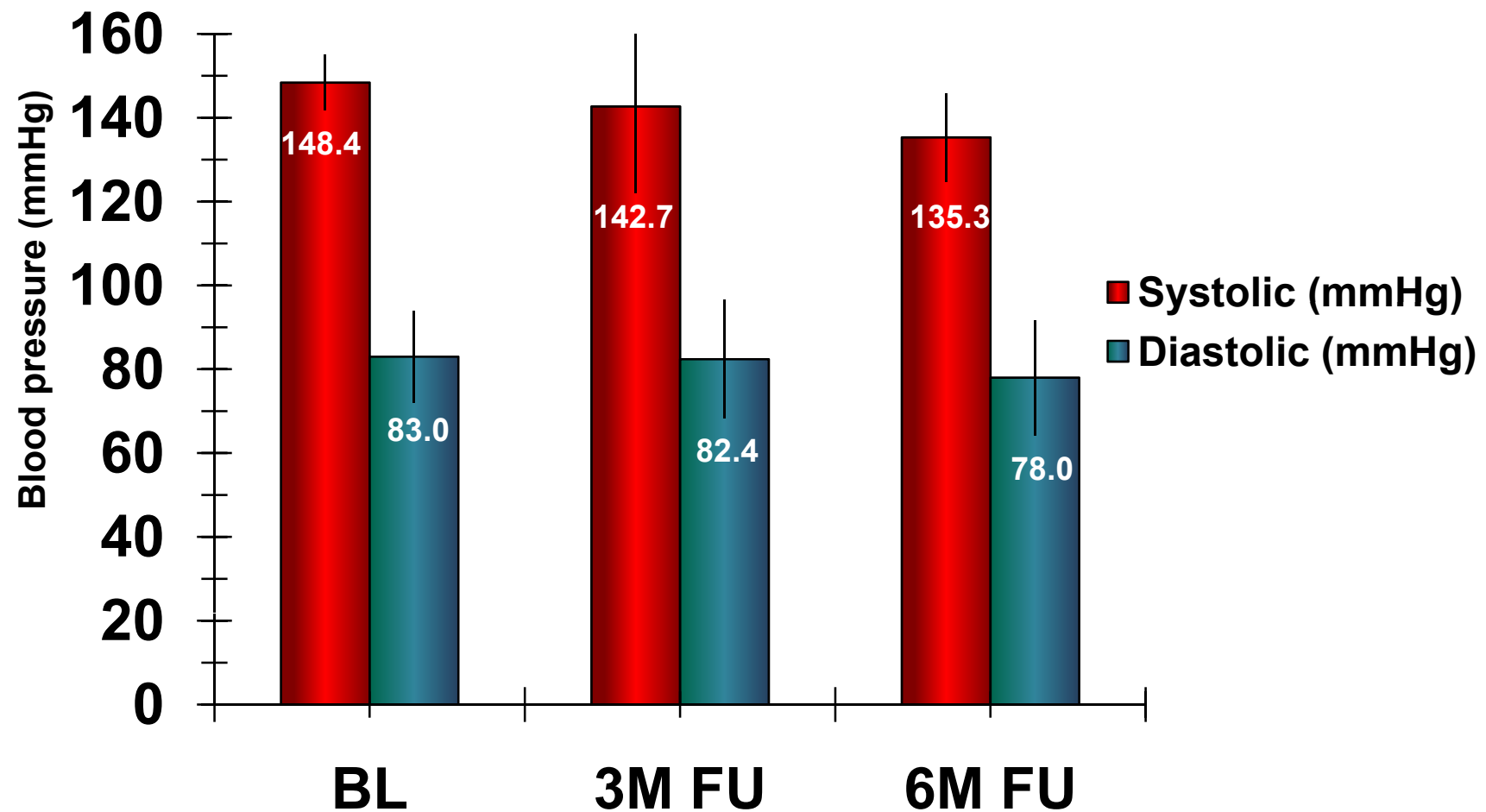
Diabetes type II only



All between-DM group p-values = NS

Does it work in less severe  
resistant hypertension?

# Renal Denervation in Borderline Hypertension - Mean Office BP



# Other potential indications

- Sleep apnea syndrom
- Heart failure
- Ventricular arrhythmias
- Diabetes

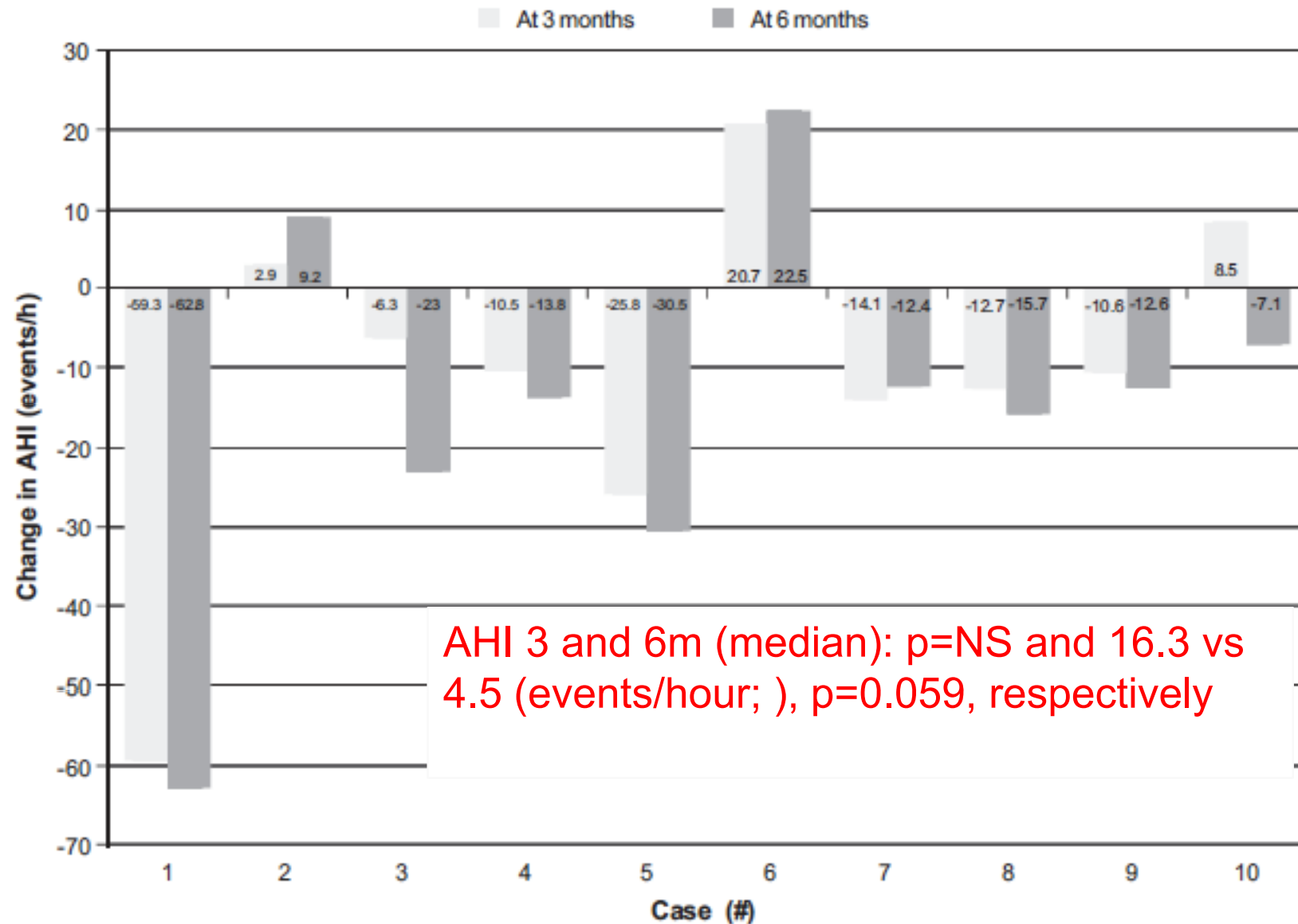
# Sleep apnea syndrome

- ... is considered to be a causal factor for hypertension
- Frequent in resistant hypertension
- Sympathetic activity is increased
- Renal denervation
  - reduces sympathetic activity
  - may be beneficial in sleep apnea syndrome

# Sleep apnea syndrome

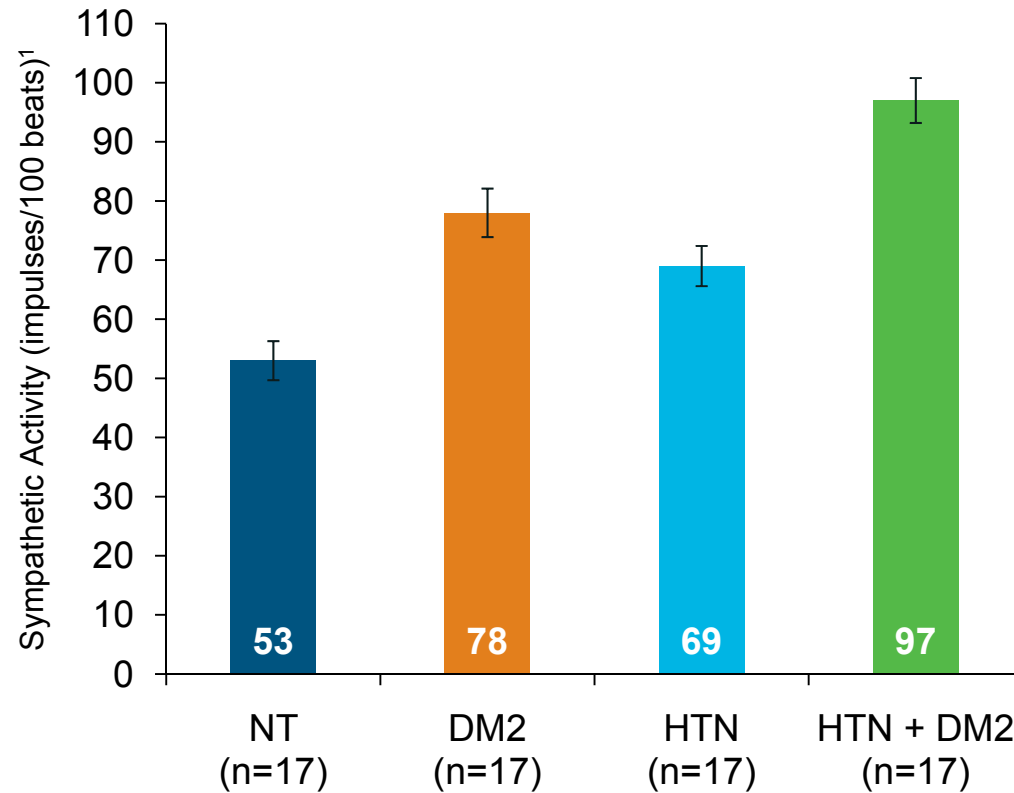
- 10 patients with sleep apnea who participated in the Simplicity trial
- AHI (Apnea-Hypopnea Index) before and at 3 and 6 months after denervation

## Results (2): AHI before and at 3 and 6 months after denervation. Data of individual cases



# Impact of Type 2 Diabetes Mellitus on Sympathetic Neural Mechanisms in Hypertension

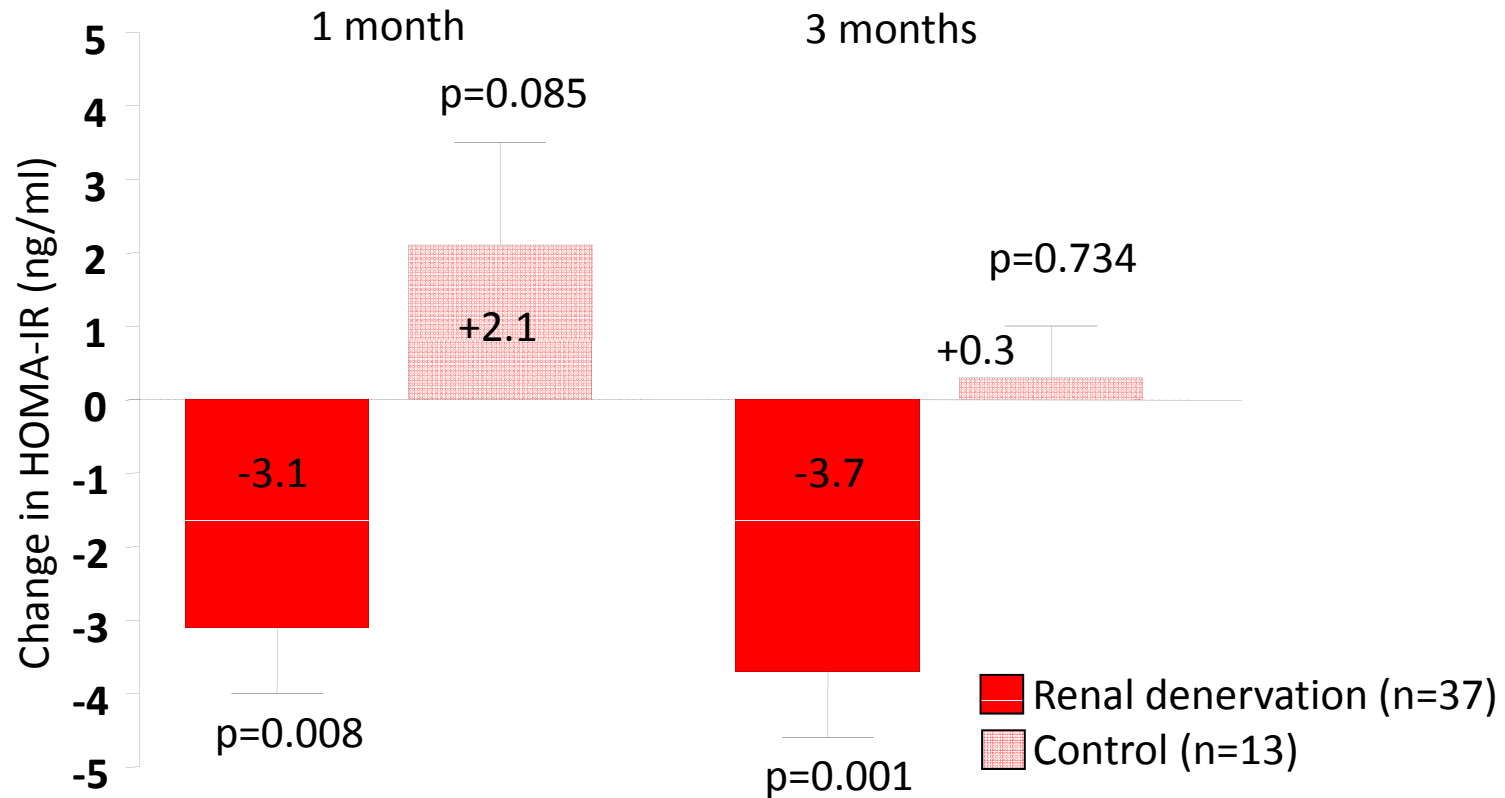
Robert J. Huggett, MB, BS; Eleanor M. Scott, BM, BS, MD; Stephen G. Gilbey, BA, MD;  
John B. Stoker, BSc, MB, ChB; Alan F. Mackintosh, MA, MD; David A.S.G. Mary, MB, ChB, PhD



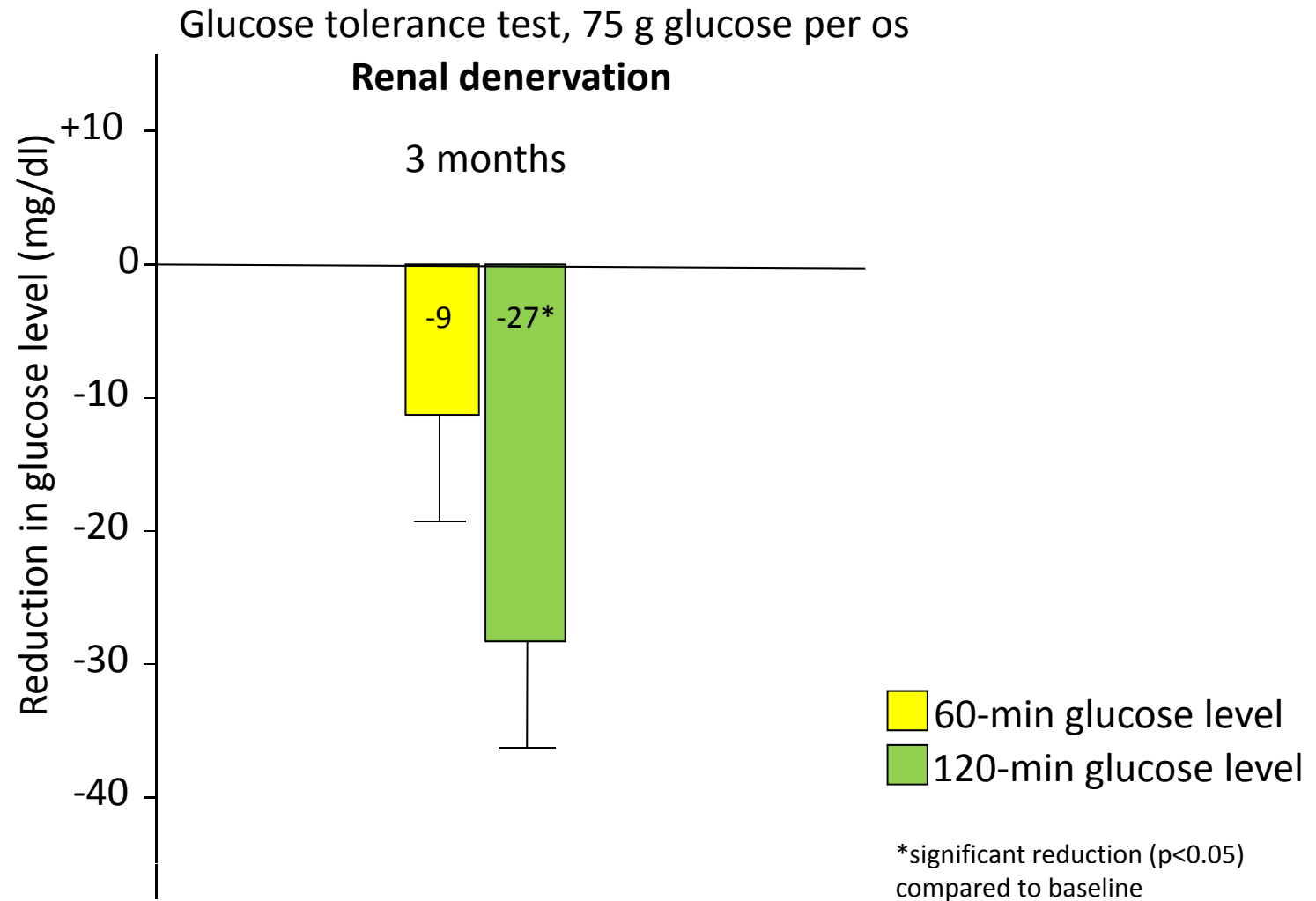
NT: normo tensive controls; DM: diabetes; HTN: hypertension; HTN+DM: hypertension+diabetes



# RD improves insulin sensitivity



# RD improves glucose tolerance



# Take Home Messages

- Transcatheter Renal Denervation results in significant reductions in BP
- The procedure seems to be very safe
- The effect is sustained up to 3 years
- It may also be beneficial in patients with diabetes, sleep apnea, heart failure and other diseases