Catheter-Based Denervation for Resistant Hypertension

Therapeutic Options for Those Previously Without Alternative

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular,Boston Scientific Corporation, Medtronic CardioVascular
Consulting Fees/Honoraria	Abbott Vascular, Boston Scientific Corporation, Medtronic CardioVascular, Micell Technologies, Terumo Medical
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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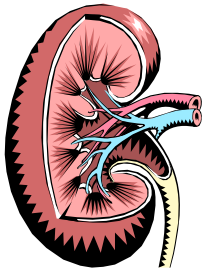
Renal Sympathetic Efferent Nerve Activity

Kidney as Recipient of Sympathetic Signals

Renal Efferent Nerves

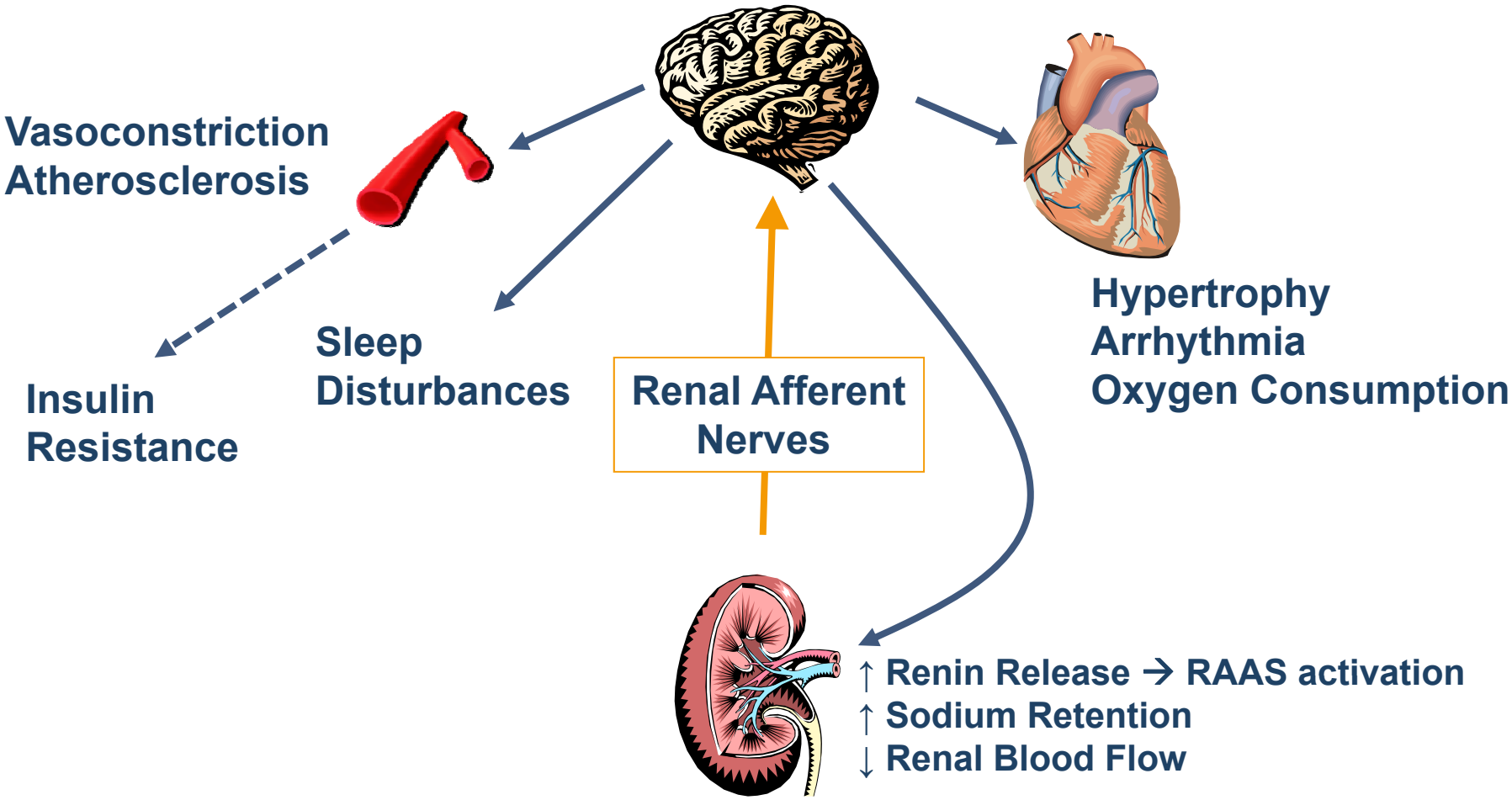


↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

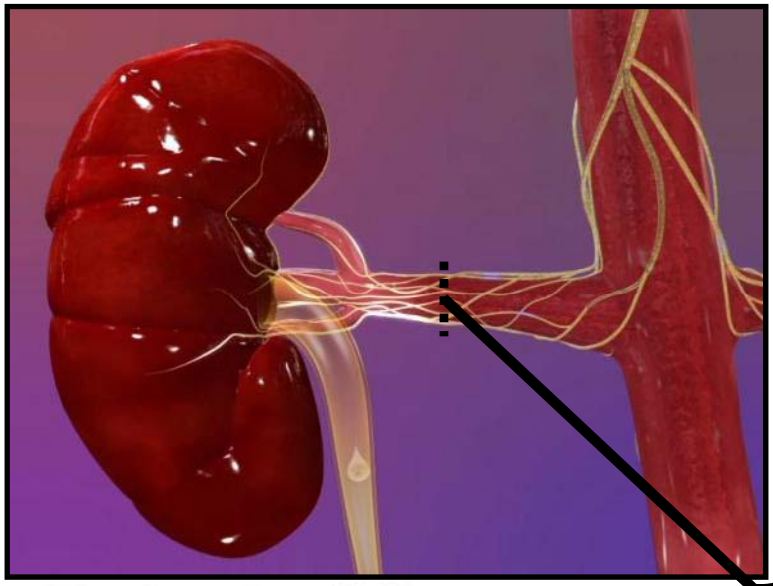
DiBona, Gerald F. *Am. J Physiol Regul Integr Comp Physiol.* 289: R633-R641, 2005

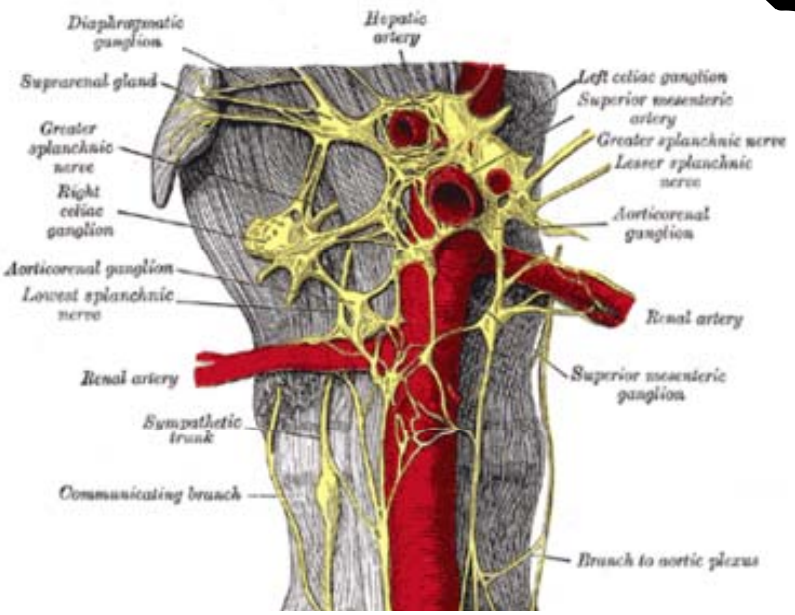
Renal Sympathetic Afferent Nerves

Kidney as Origin of Central Sympathetic Drive

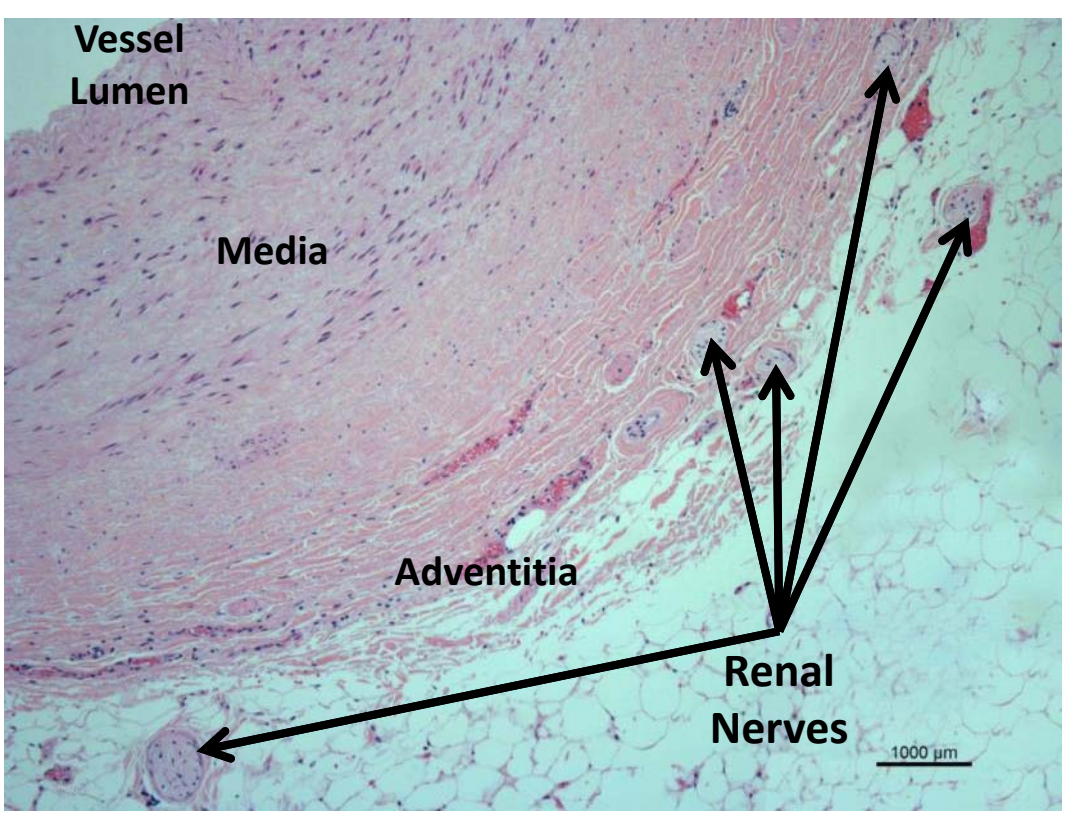


Renal Nerves as a Therapeutic Target





Arise from ~ T10-L2
Follow the renal artery to the kidney
Primarily lie within the adventitia



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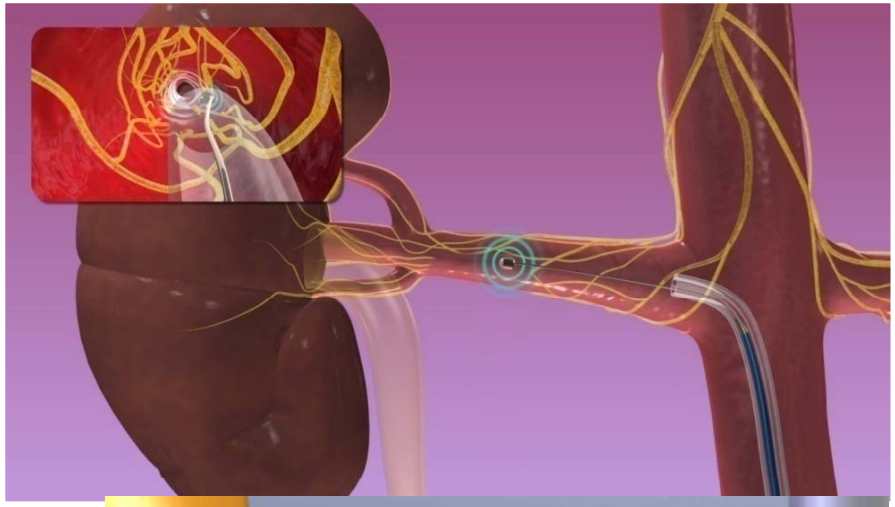
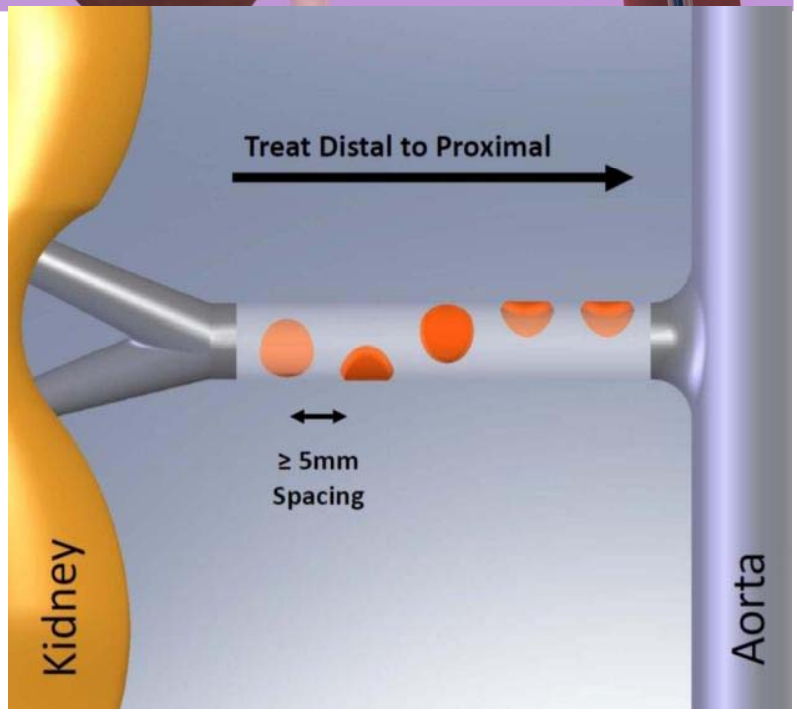
Renal Nerves as a Therapeutic Target

Symplicity® Catheter System™

- 6F catheter access
- Articulating tip with RF electrode

- Renal nerves lie in adventitia, encircling the renal arteries
- 4-6 focal 2-minute RF treatments along each renal artery



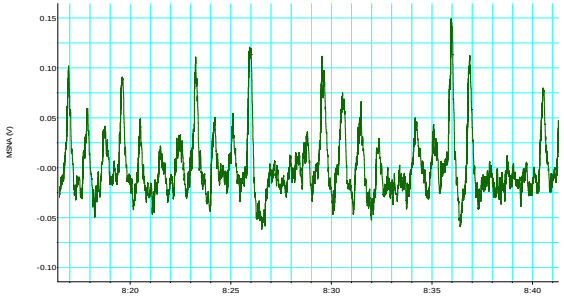


Proof of Principle: Therapeutic Renal Denervation and Reduction of Central Sympathetic Nerve Activity

Baseline

MSNA: 46 burst/min
BP: 155/95 mmHg

baseline MSNA: 46 burst/min



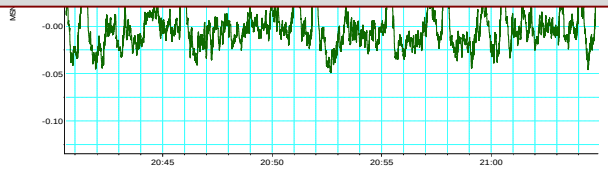
No impact on flight/fight "epinephrine" response

No blunting of baroreceptor function

Preserve central sympathetic homeostatic mechanisms

MSN

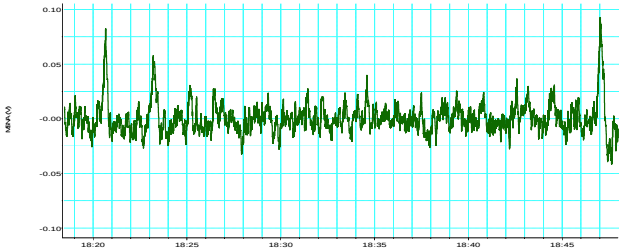
BP: 133/78 mmHg (↓22/17 mmHg)



12 Month Follow-up

MSNA: 21 burst/min (↓~54%)
BP: 132/75 mmHg (↓23/20 mmHg)

12 Months FU MSNA: 21 burst/min



Schlaich et al. *J Htn*. 2009; 27 (suppl 4):s437.

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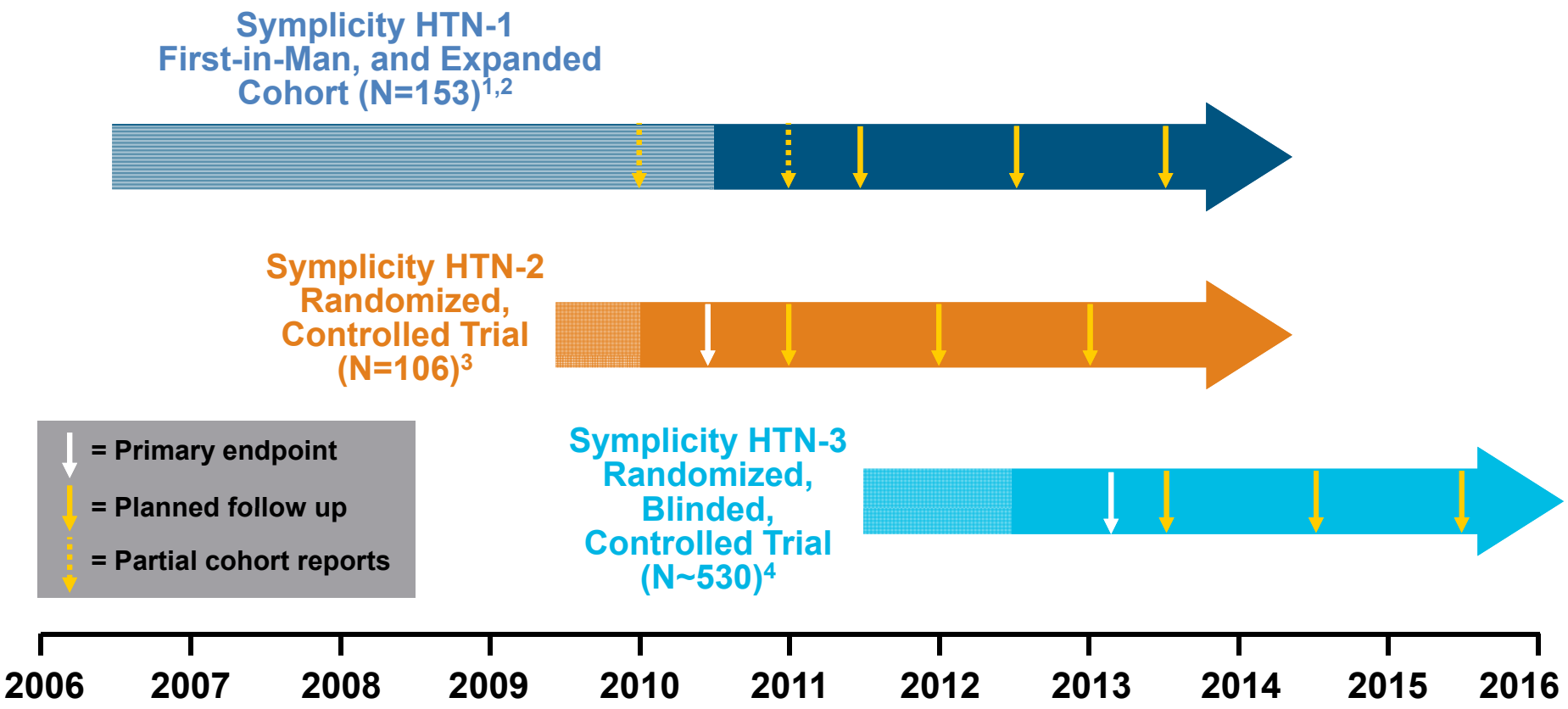
The Symplicity HTN Clinical Trial Program



Shading on bars indicates clinical trial enrollment periods.
Enrollment period for HTN-3 is estimated.

1. Krum H, et al. *Lancet*. 2009;373:1275-1281.
2. Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.
3. Esler et al. *Lancet*. 2010;376:1903-1909.
4. Data on file, Medtronic.

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SYMPLICITY I and Expanded Cohort Baseline Patient Characteristics

		N=153
Demographics	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
Co-morbidities	Diabetes Mellitus II (%)	32%
	CAD (%)	24%
	Hyperlipidemia (%)	72%
	eGFR (mL/min/1.73m^2)	81 ± 19
Blood Pressure	**Baseline BP (mmHg)**	**176/98 ± 17/15**
	Number of anti-HTN meds (mean)	**5.0 ± 1.4**
	ACE/ARB (%)	88%
	Beta-blocker (%)	79%
	Calcium channel blocker (%)	72%
	Vasodilator (%)	19%
	Diuretic (%)	96%
	Spironolactone (%)	24%

Krum et al. Lancet 2009; Schlaich et al. European Society of Hypertension 2010.

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SYMPLICITY HTN-1 Procedural Safety

- 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

Schlaich et al. European Society of Hypertension 2010; Esler ACC 2012

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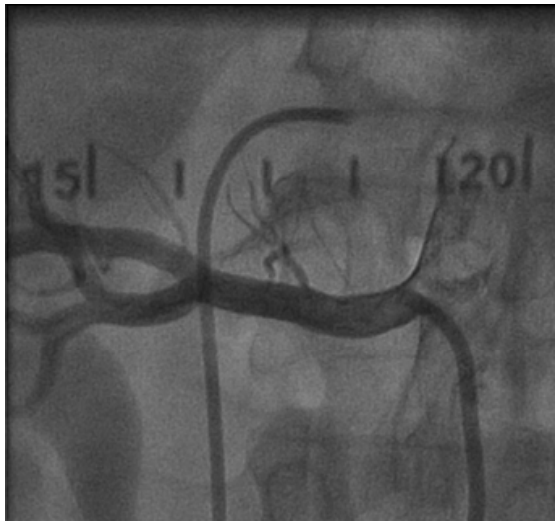
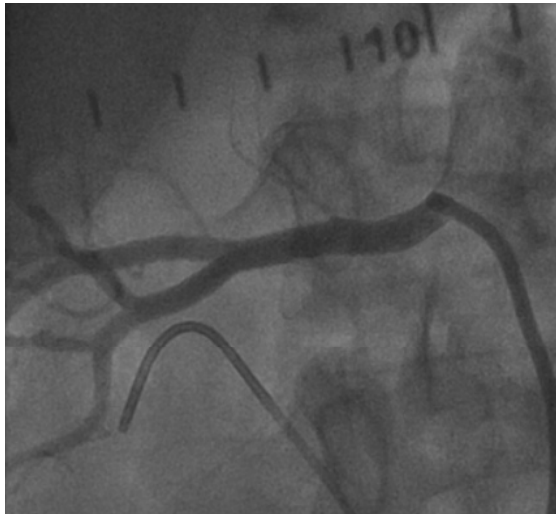
baseline right kidney

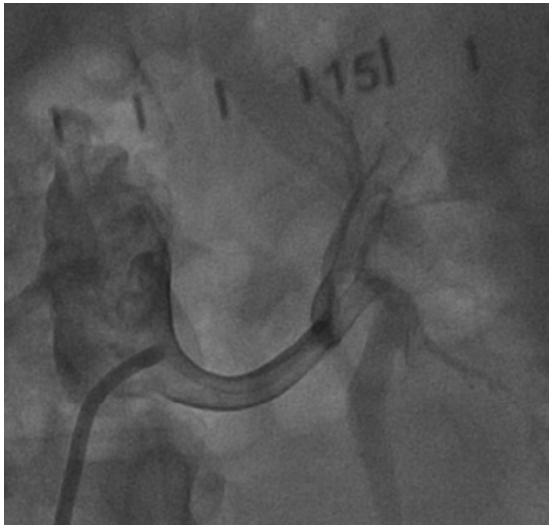


acute post treatment right

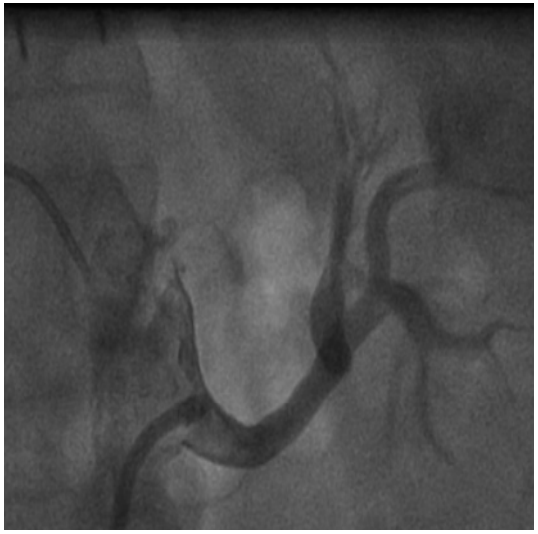
30 day post treatment right



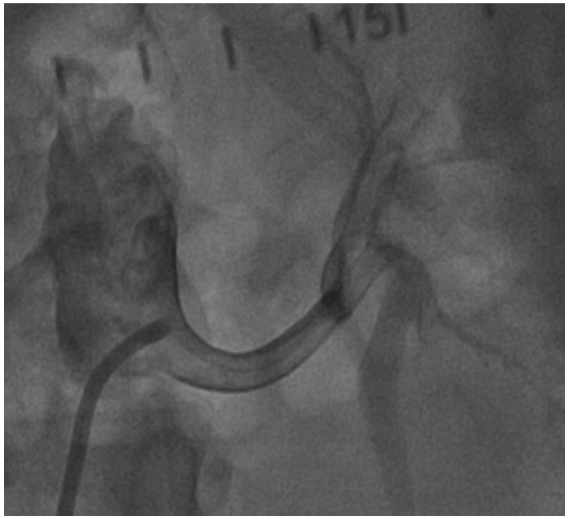
baseline left kidney



acute post treatment left

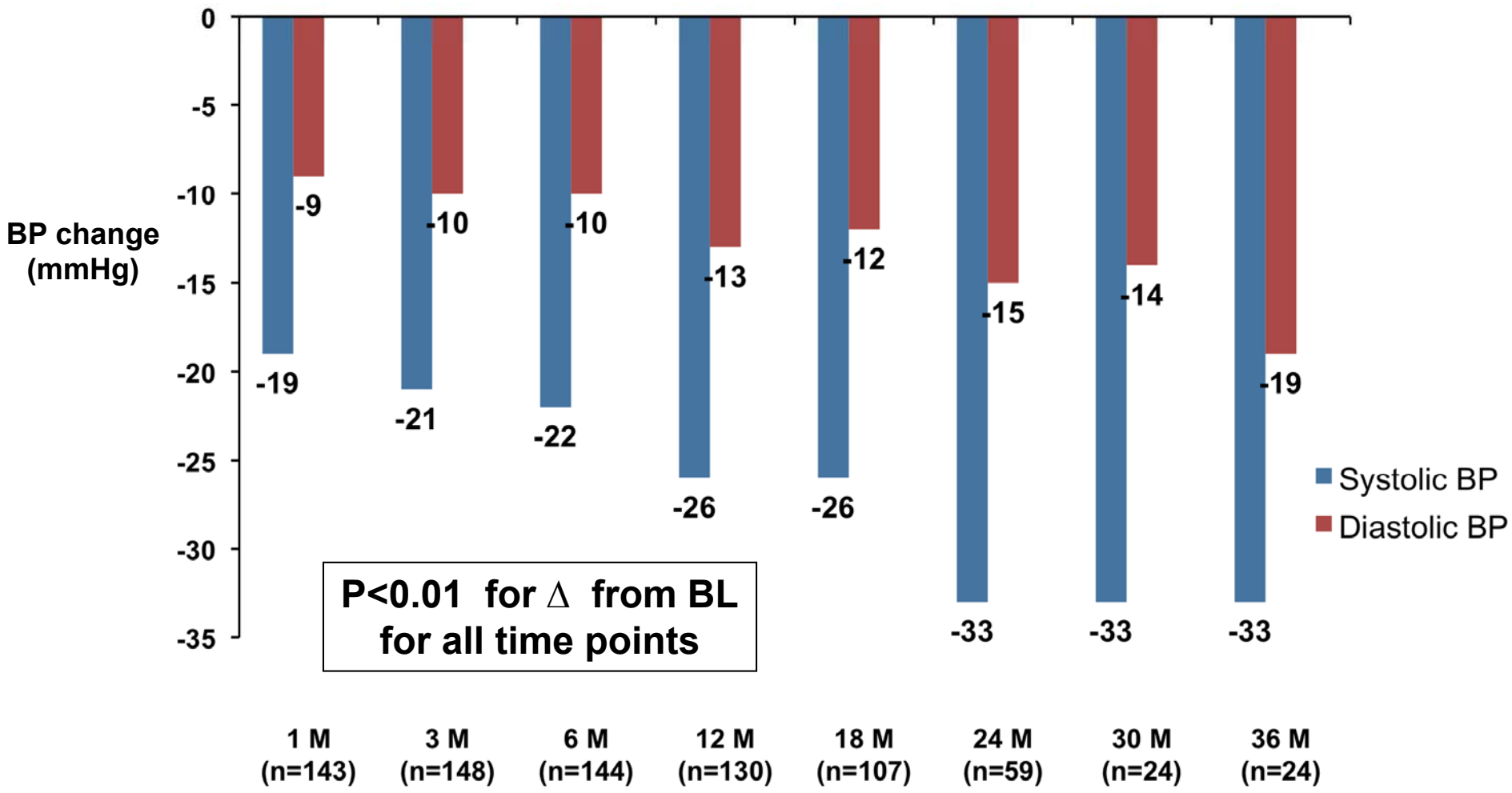


30 day post treatment left



SYMPLICITY HTN 1

Change in Office Blood Pressure Through 36 Months



Sobotka et al. ACC 2012

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SYMPLICITY HTN-1 Late-Term Safety (3 Years)

- No RF treatment related vascular complications
  - One progression of a pre-existing renal artery stenosis (40%→80%), possibly related to catheter manipulation, successfully stented
  - 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
- No orthostatic hypotension
- No electrolyte disturbances
- There was no significant change in mean electrolytes or eGFR

Esler ACC 2012

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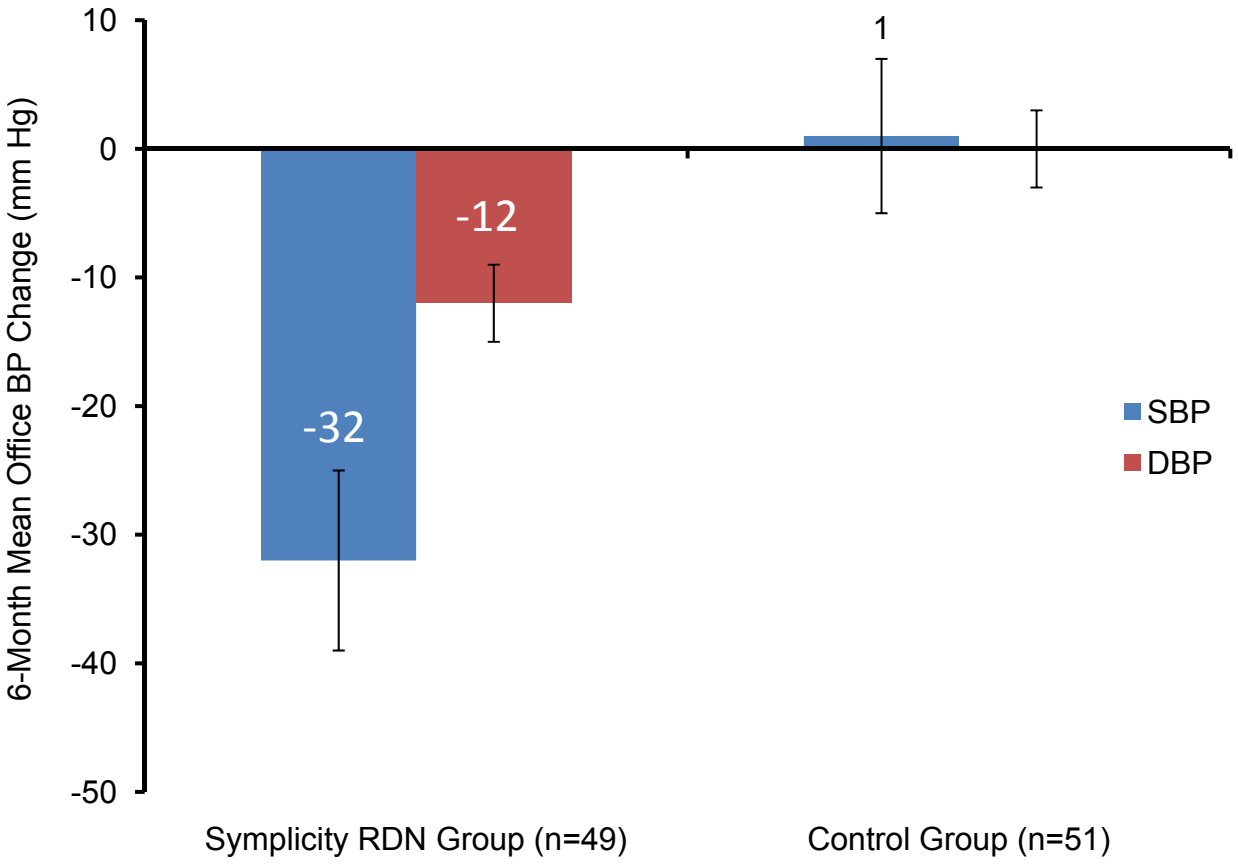
Primary Endpoint
6-Month Office Blood Pressure



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. The Lancet 2010: 376:1903-1909

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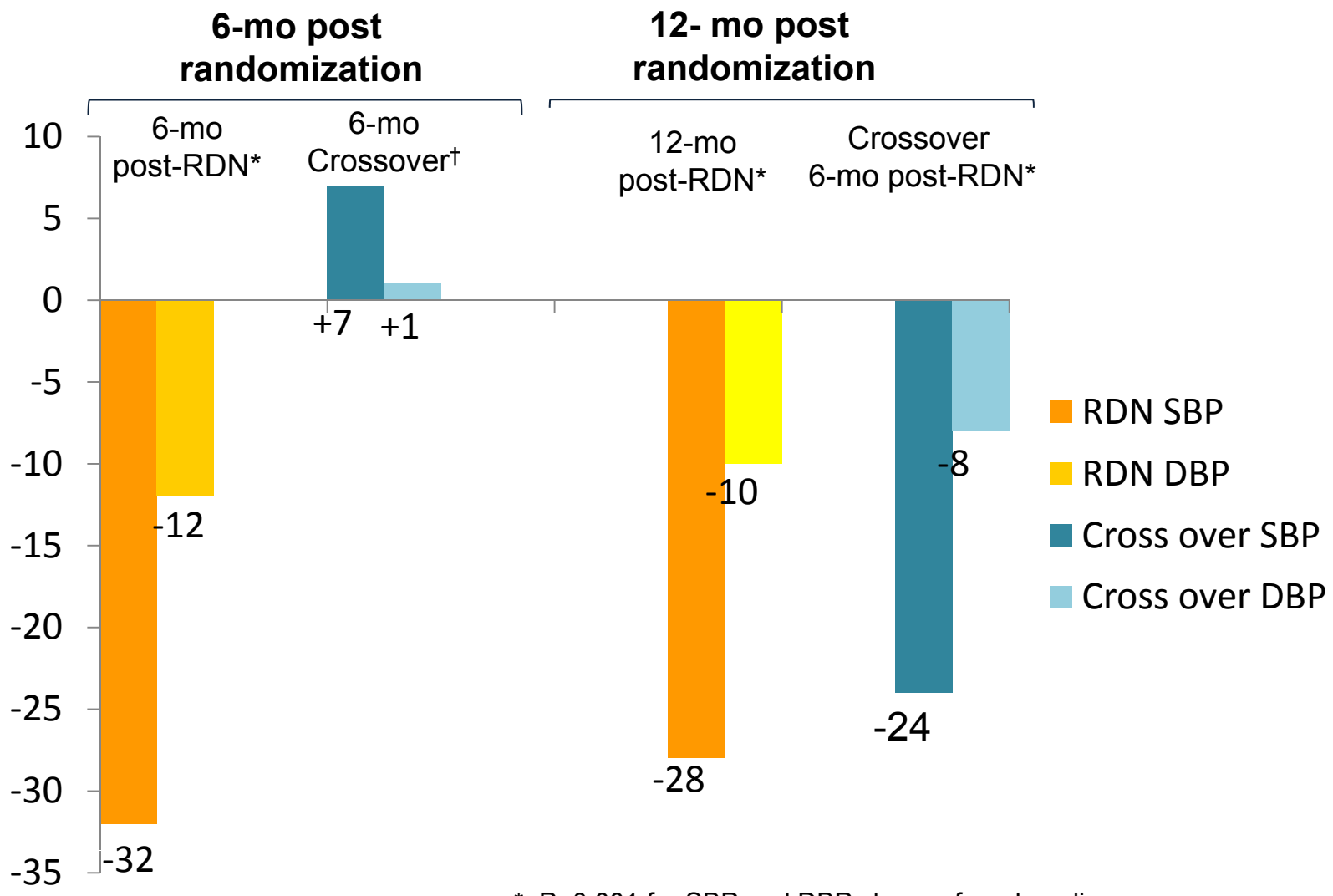
Change in Office Blood Pressure (mm Hg)



* P<0.001 for SBP and DBP change from baseline
† P=0.026 for SBP change from baseline

Esler et al. ACC 2012

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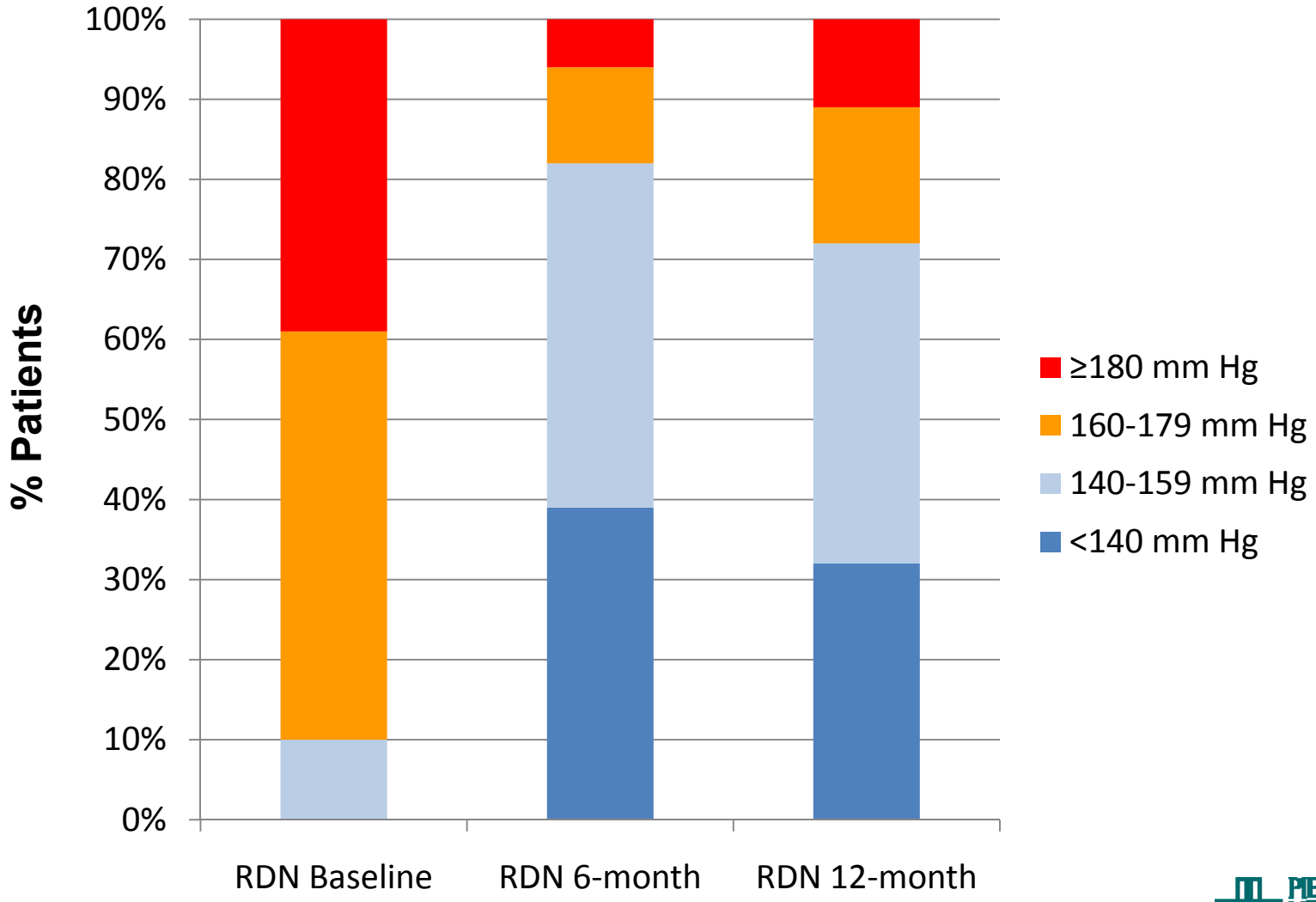
Distribution of Office SBP for RDN Group



Esler et al. ACC 2012

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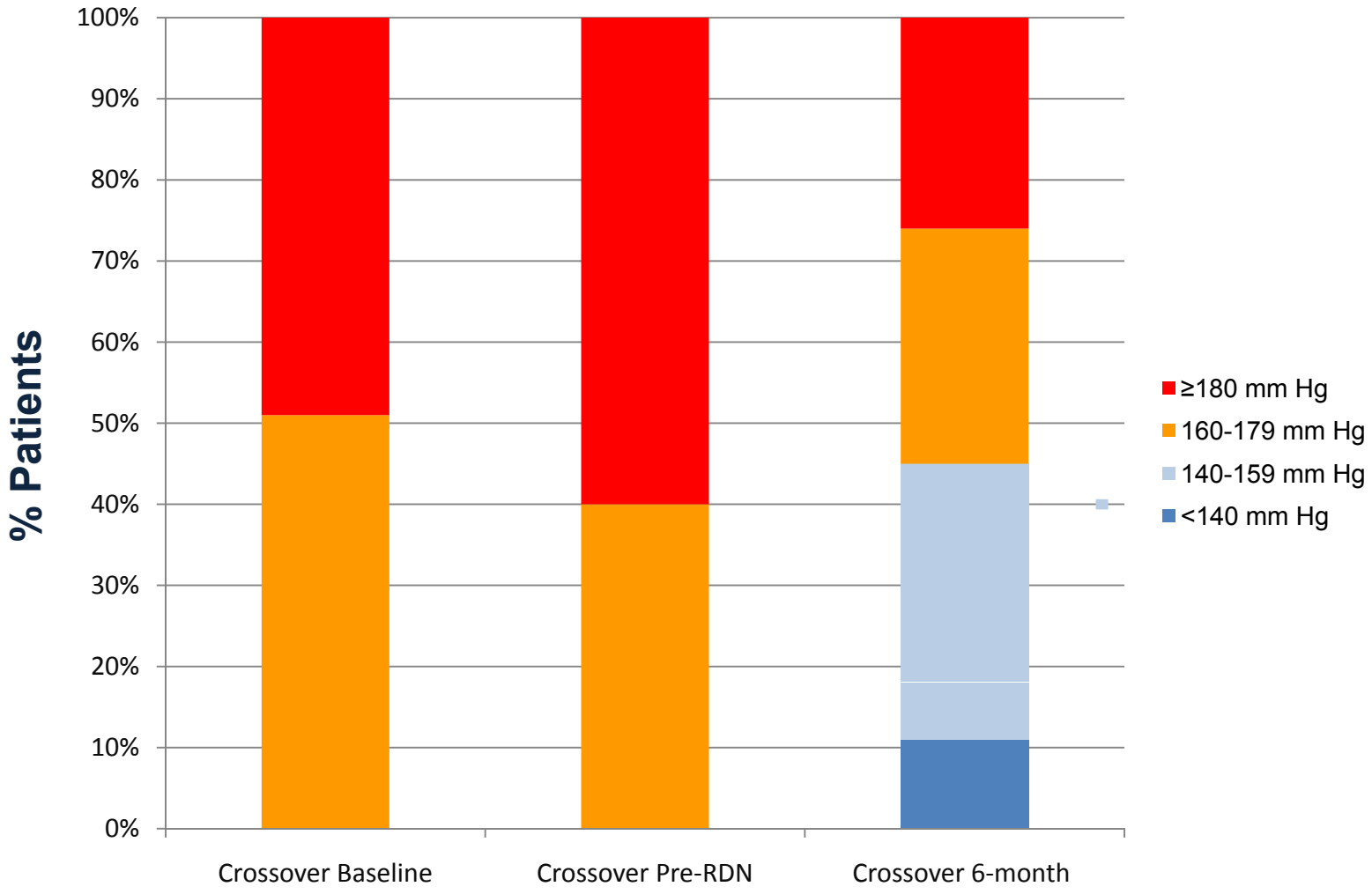
Distribution of Office SBP For Crossover Group



Esler et al. ACC 2012

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SYMPLICITY HTN-2
Renal Function in RDN and Crossover Groups

RDN
N=47

Treated at Randomization ↓

	Baseline		6 month		12 months
eGFR (ml/min/1.73m²)	76.9 ±19.3 (n= 49)		77.1±18.8 (n=49)		78.2±17.4 (n=45)
Cystatin C (mg/L)	0.91±0.25 (n=38)		0.98±0.36 (n=40)		0.98±0.30 (n=38)

Crossover
N=35

Treated after 6-mo Follow-up ↓

	Baseline		6 month		12 months
eGFR (ml/min/1.73m²)	88.8 ± 20.7 (n = 35)		89.3±19.5 (n = 35)		85.2±18.3 (n = 35)
Cystatin C (mg/L)	0.78 ± 0.17		0.82±0.16 (n=26)		0.89±0.20 (n=26)

Esler et al. ACC 2012

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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*

Esler et al. ACC 2012

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SYMPLICITY Global Registry

- Prospective, multi-center, global registry
- Minimum 5,000 pts
- Evaluate safety in ‘real world’ population of patients treated with RDN using the Symplicity® Renal Denervation System™
- Attention to treatment-resistant hypertension, heart failure, insulin resistance, chronic kidney disease, and sleep apnea

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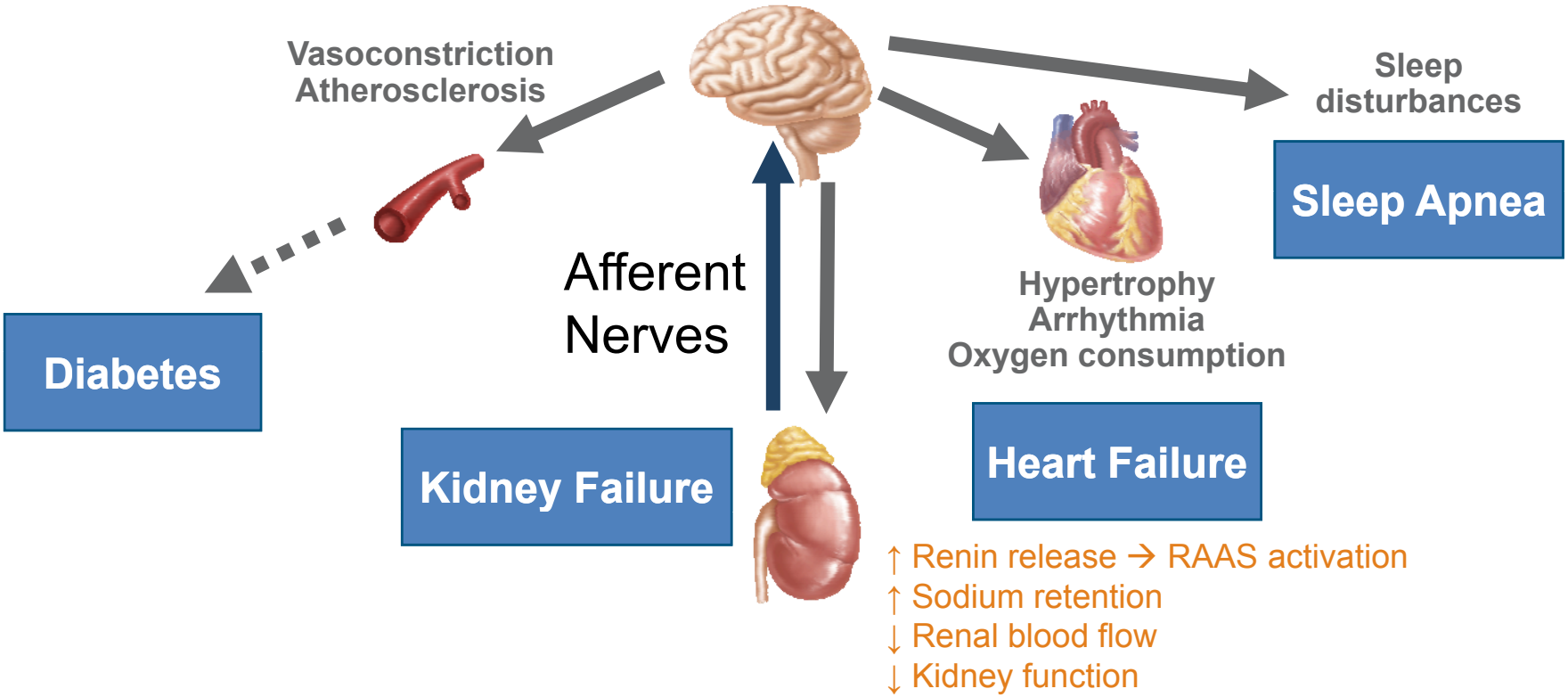
Future Directions for Research

- Chronic activation of renal nerves is common in multiple conditions/disease states[1,2]
- Future research may be warranted in disease states characterized by hyperactive afferent and efferent renal nerves



RAAS = renin-angiotensin-aldosterone system.

1. Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.
2. Blankestijn PJ, et al. *Nephrol Dial Transplant*. 2011;26:2732-2734.

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Pilot Study in Heart Failure with Reduced LVEF

- 40 patients at up to 5 international centers
- Inclusion Criteria:
  - Heart Failure patients NYHA Class II or III
  - Renal Impairment Left Ventricular Ejection Function <40%
  - GFR 30 to 75 mL/min/1.73m2
  - Optimal stable medical therapy

- Exclusion Criteria:
  - Renal artery anatomy must be eligible for treatment as determined by Angiography, and
  - History of prior renal artery intervention
  - Single functioning kidney.
  - Myocardial Infarction, unstable angina pectoris or cerebrovascular Accident within 3 months
  - Systolic BP <110mmHg

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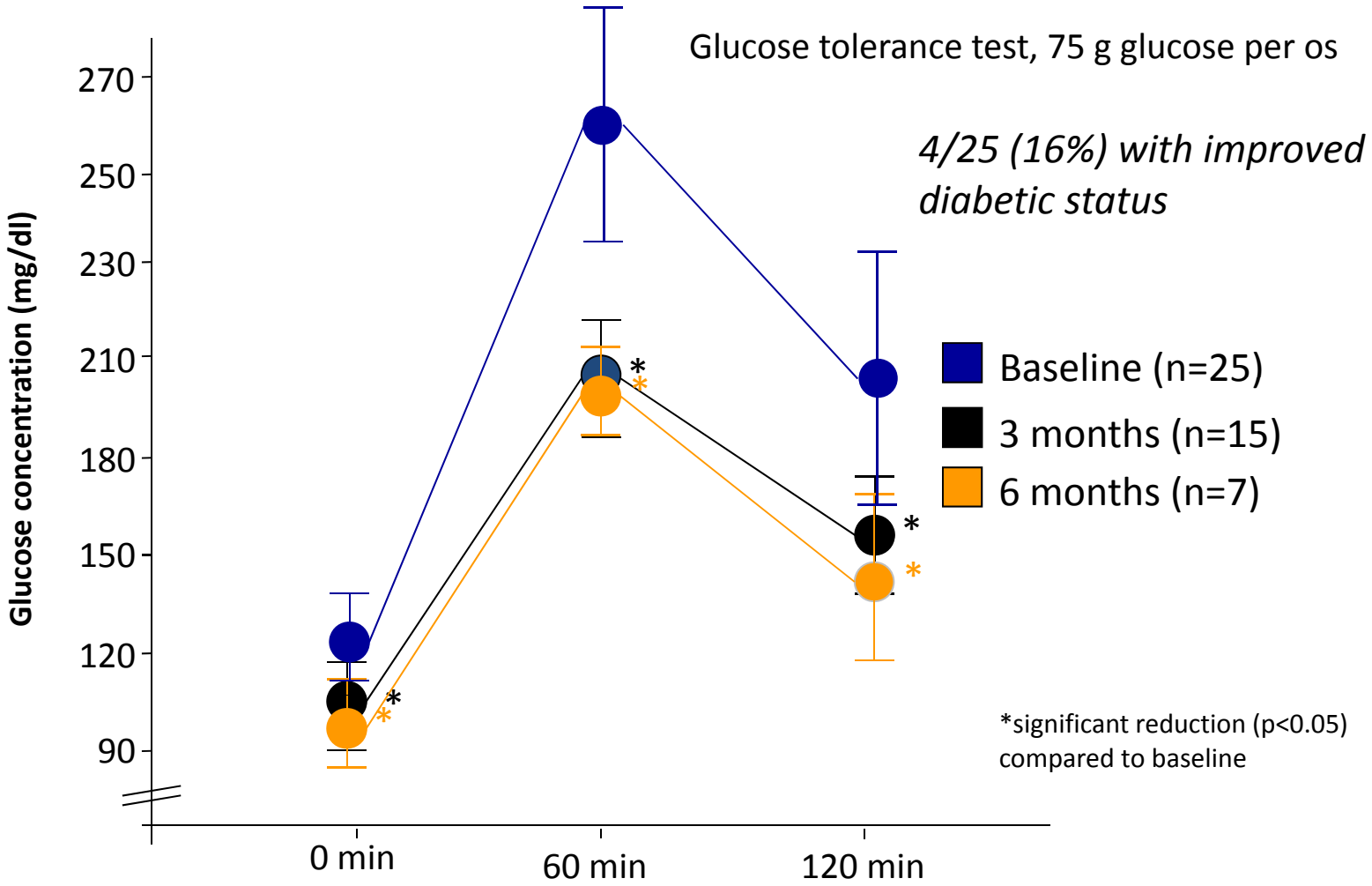
Improvement in Glucose Metabolism



Mahfoud et al., German Society of Cardiology, 2010; Circulation 2011;123:1940-1946

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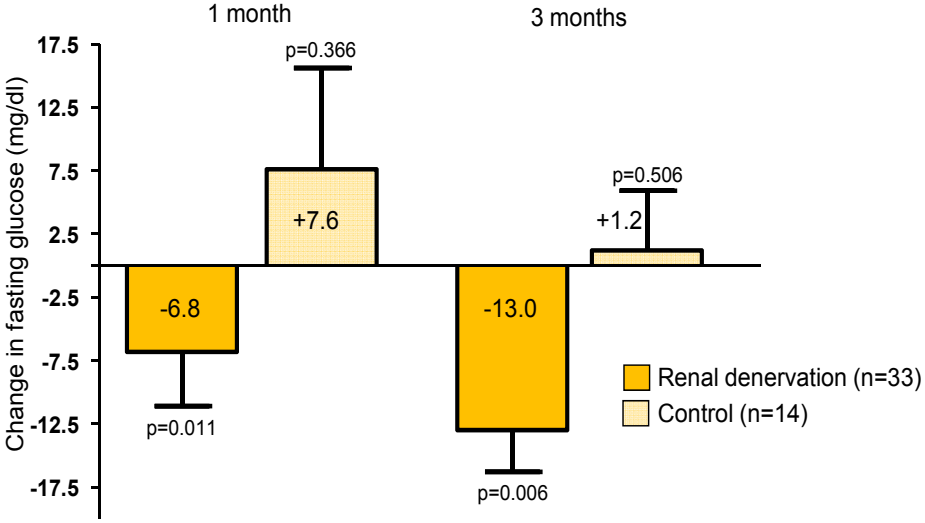
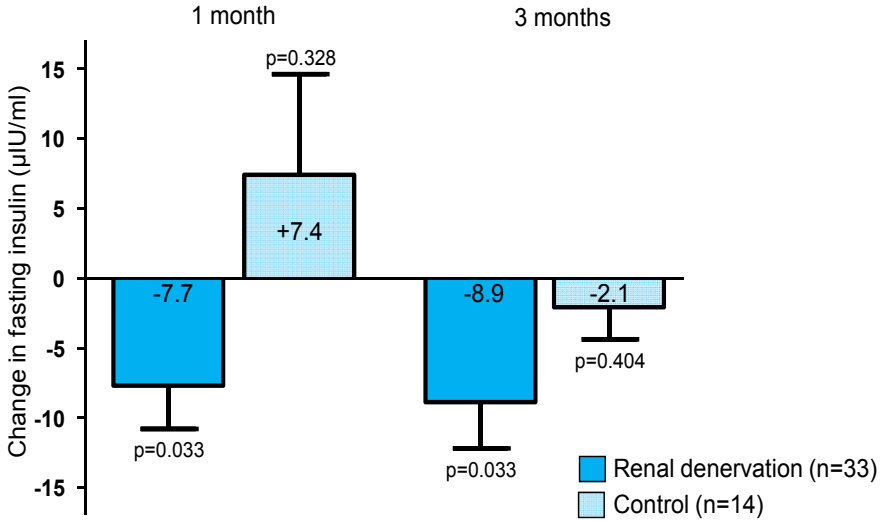
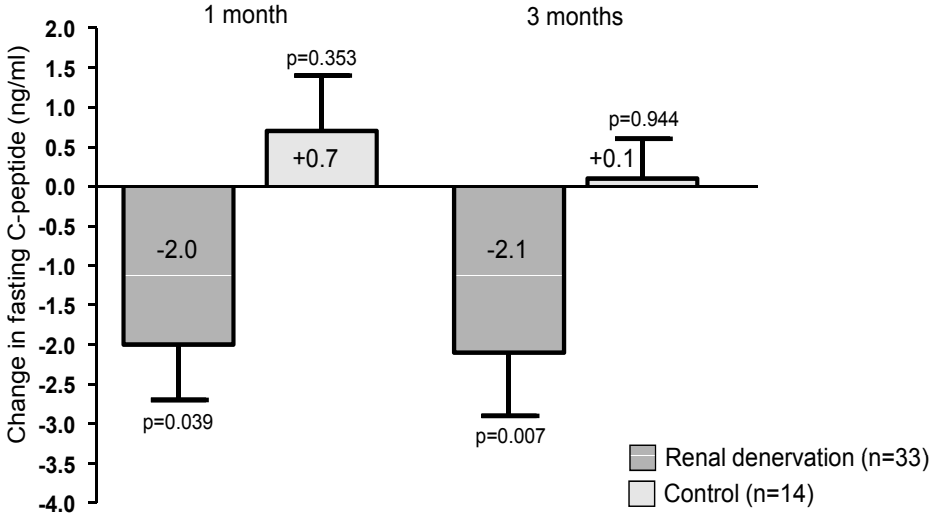
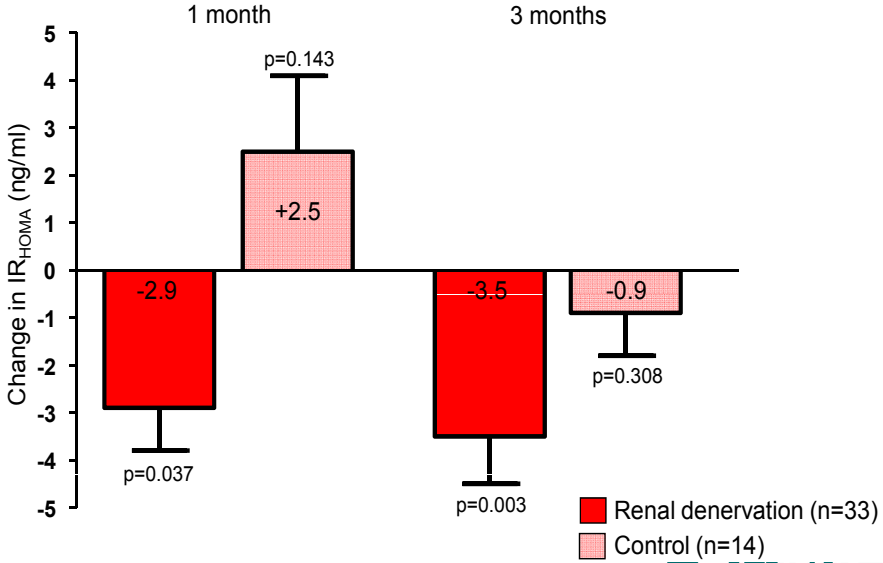
Changes in Glucose Metabolism with Renal Denervation









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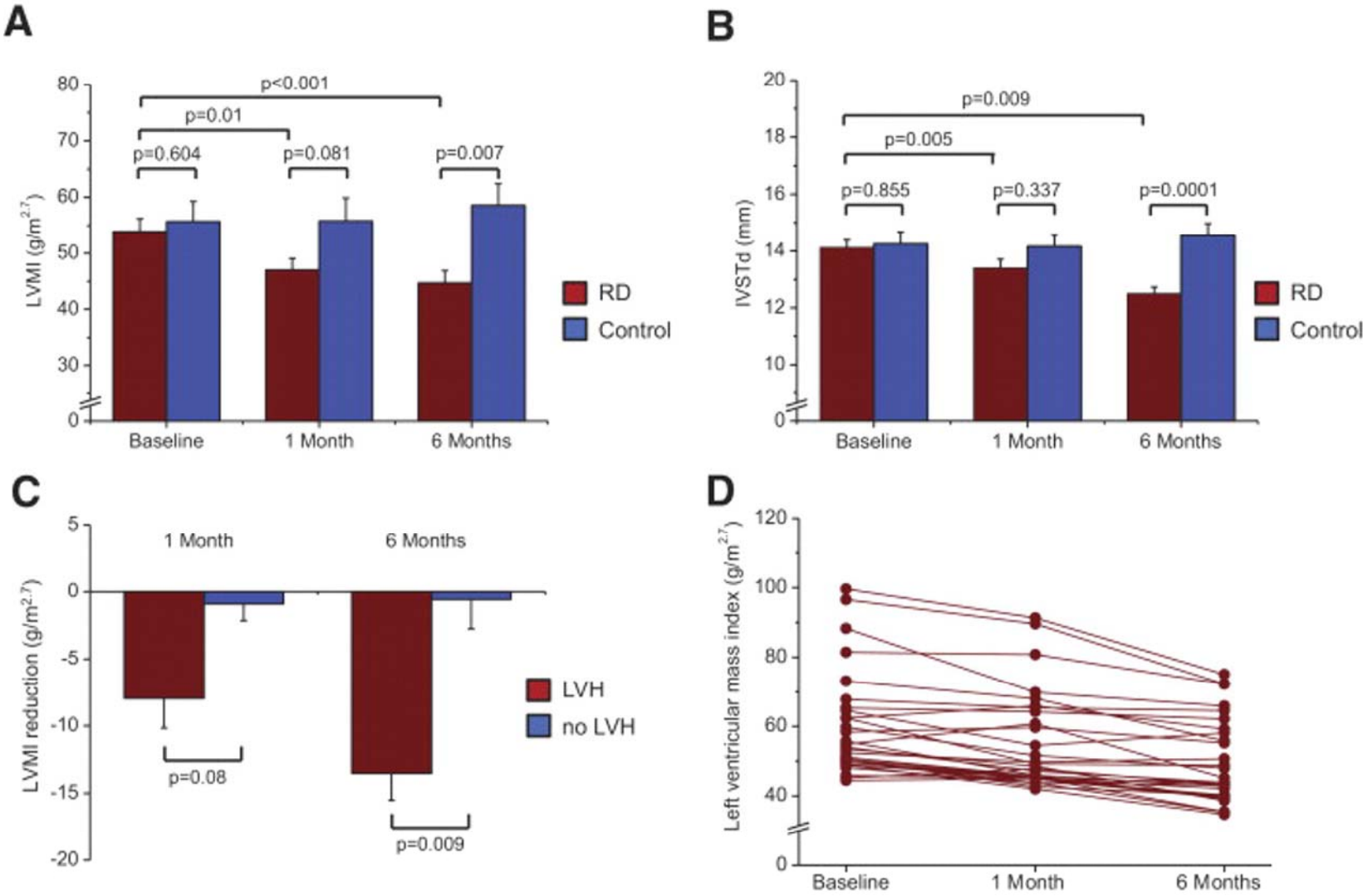
Influence of Renal Denervation on Regression of LVH and Improvement of Diastolic Function



Brandt, M. C. et al. J Am Coll Cardiol 2012;59:901-909

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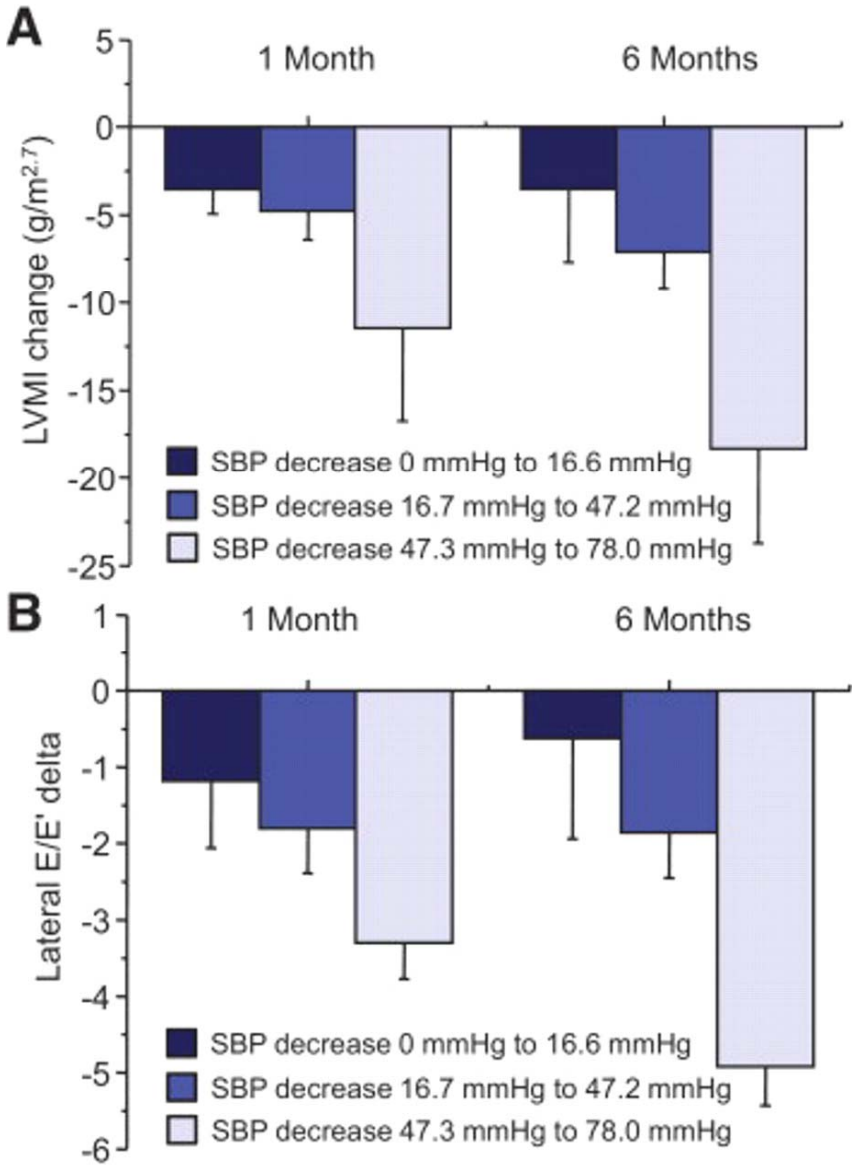
Regression of LVH and Improvement of Diastolic Function Relative to BP Reduction Achieved by Renal Denervation

Reduction in LV mass likely result of decreased LB workload <u>and</u> decreased sympathetic activity



Brandt, M. C. et al. J Am Coll Cardiol 2012

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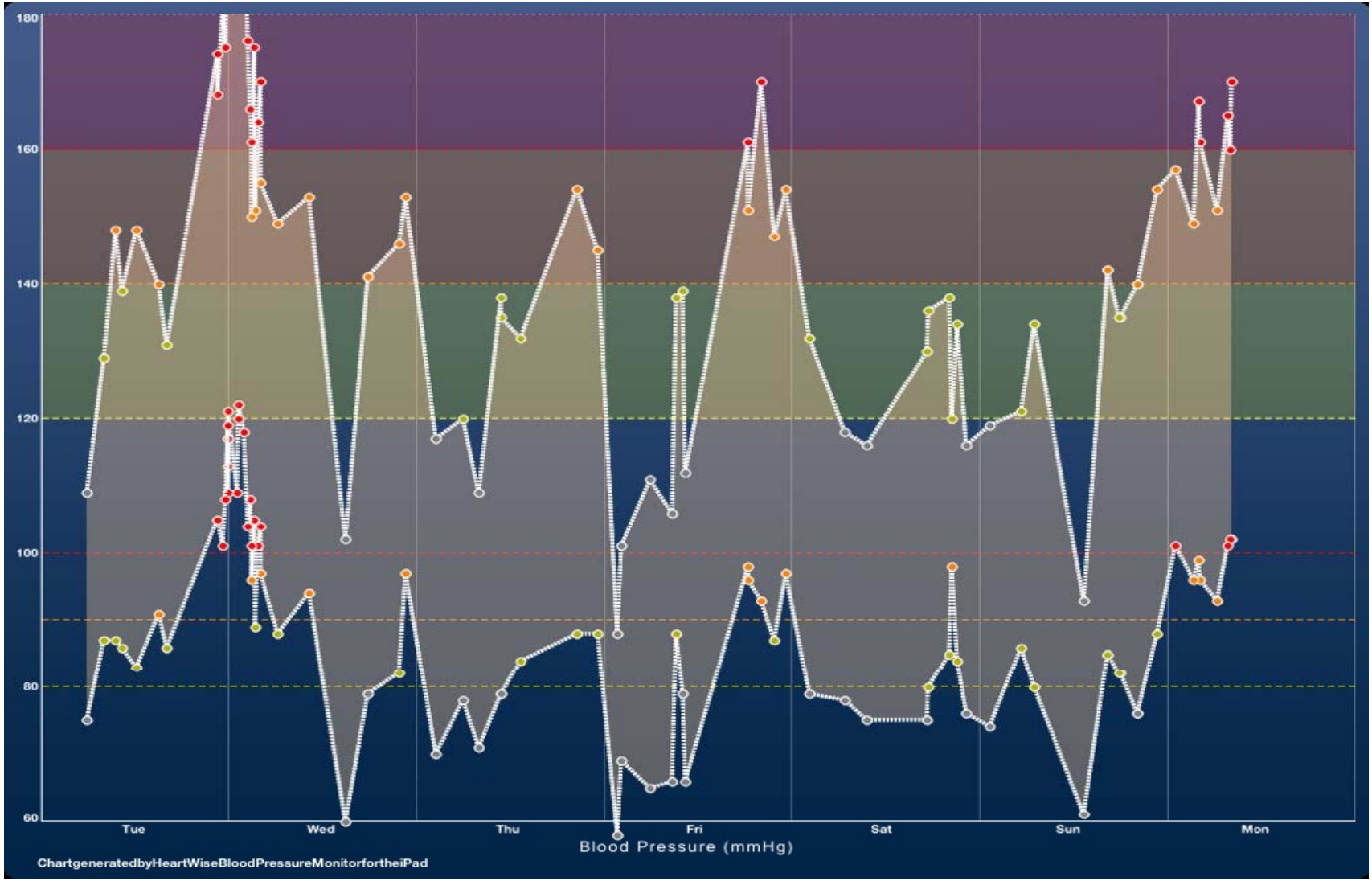
Blood Pressure Variation and Obstructive Sleep Apnea



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Catheter-Based Renal Denervation Opportunities for Disease Management

- RDN for resistant HTN is associated with
  - Significant and durable reductions in blood pressure
  - Procedural and intermediate-term safety
  - Preservation of electrolyte and hemodynamic homeostasis
- Ongoing evaluation in both RCT and observational studies may confirm and expand upon RDN effectiveness in both selected and broader patient populations
- Evolving applications in disease conditions related to hypersympathetic activity may expand therapeutic opportunities