Renal Denervation for Non-Hypertension Indications

Mechanisms and Evidence for Therapeutic Expansion

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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	Boston Scientific Corporation, Medtronic CardioVascular, Micell Technologies, Biotronik, Thoratec
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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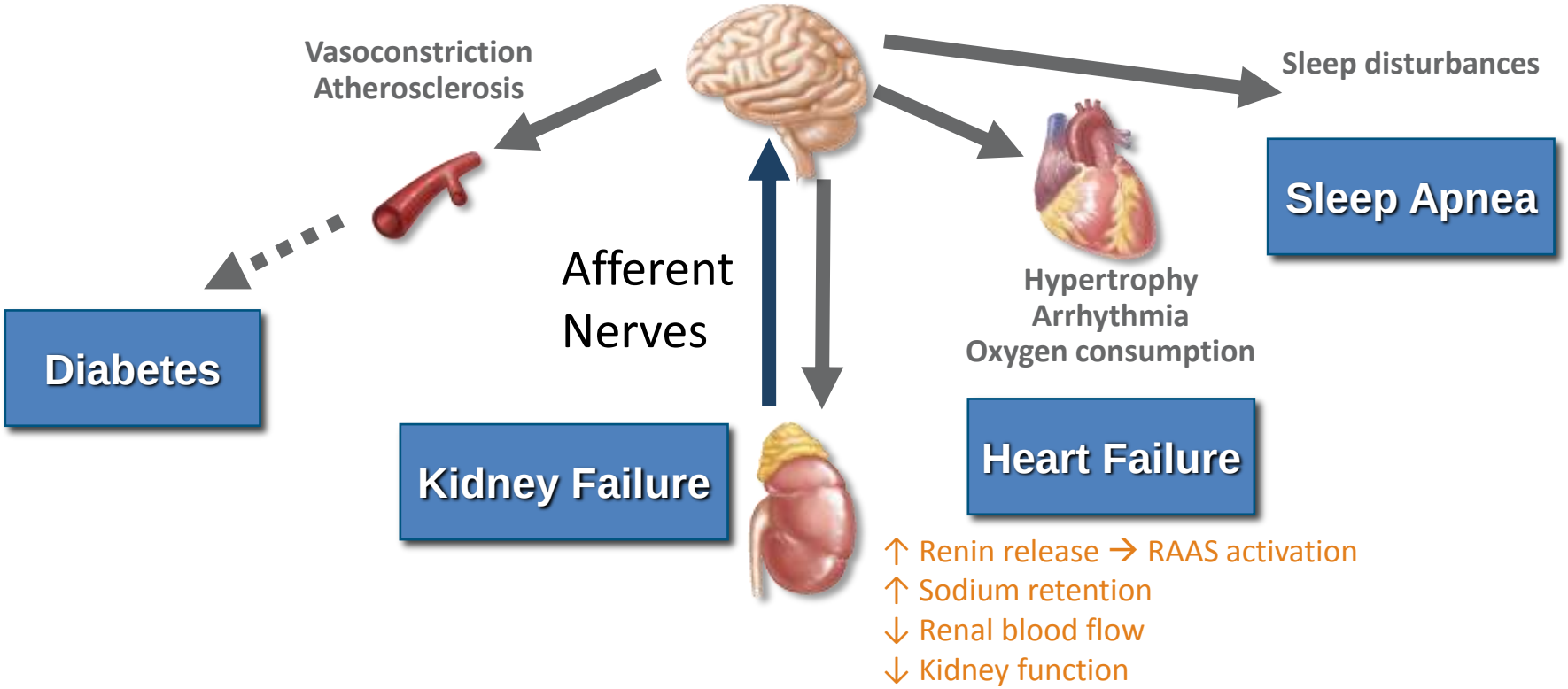
Future Directions for Research

- 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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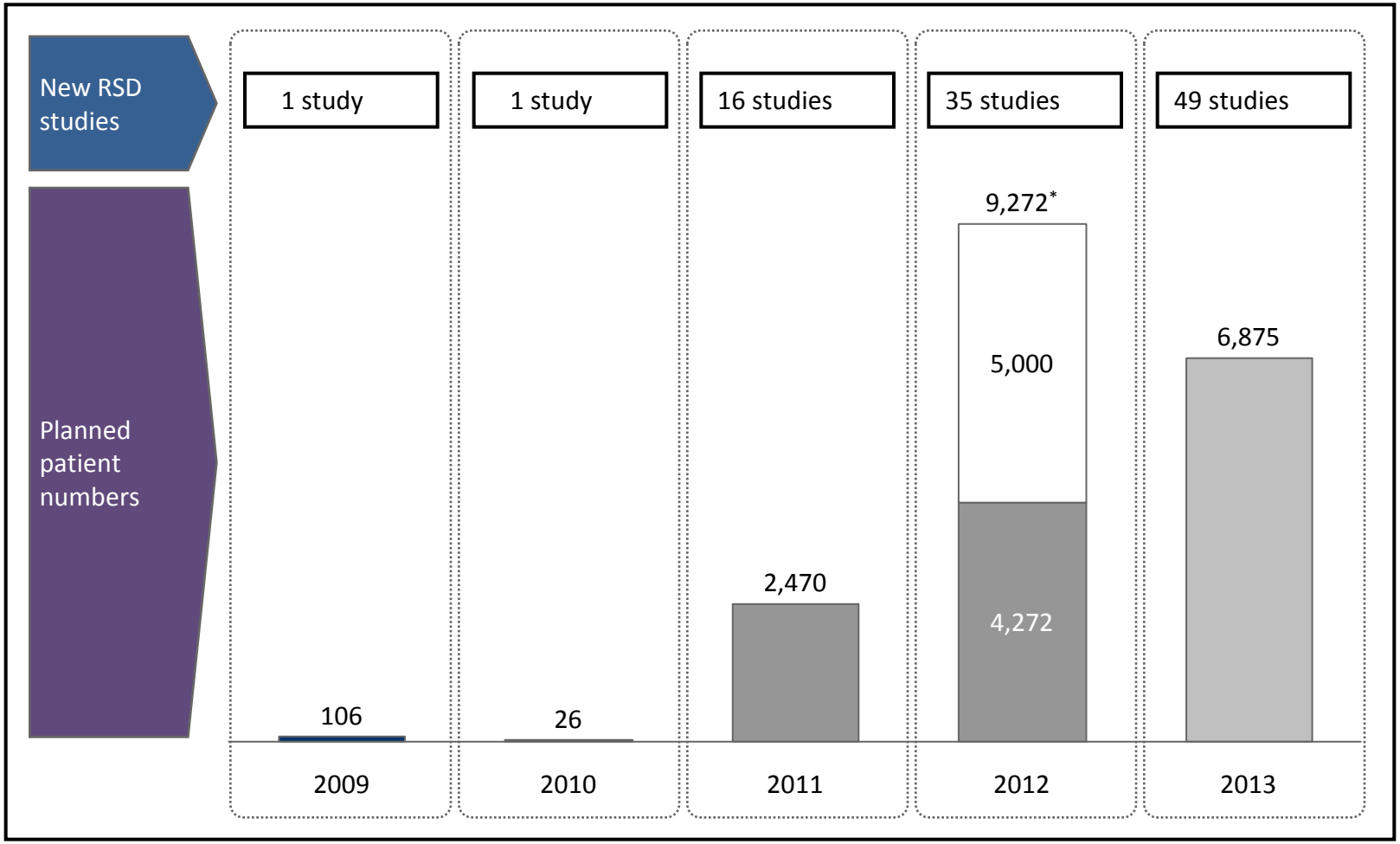
Annualized Increase in Number and Size of RDN Clinical Trials



* Includes MDT Global Symplicity RSD study with 5,000 planned patients

Source: Clinicaltrials.gov (search terms: “Renal denervation”, “Renal sympathetic denervation”, “RDN”, “RSD”)

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Renal Denervation Trials

Disease State	# Trials Listed
Hypertension	29
Heart Failure	6
CKD, ESRD	3
Atrial Fibrillation	2
Sleep Disordered Breathing	1
Metabolic Syndrome	1
Insulin Resistance	2
Diabetic Nephropathy	1

www.clinicaltrials.gov

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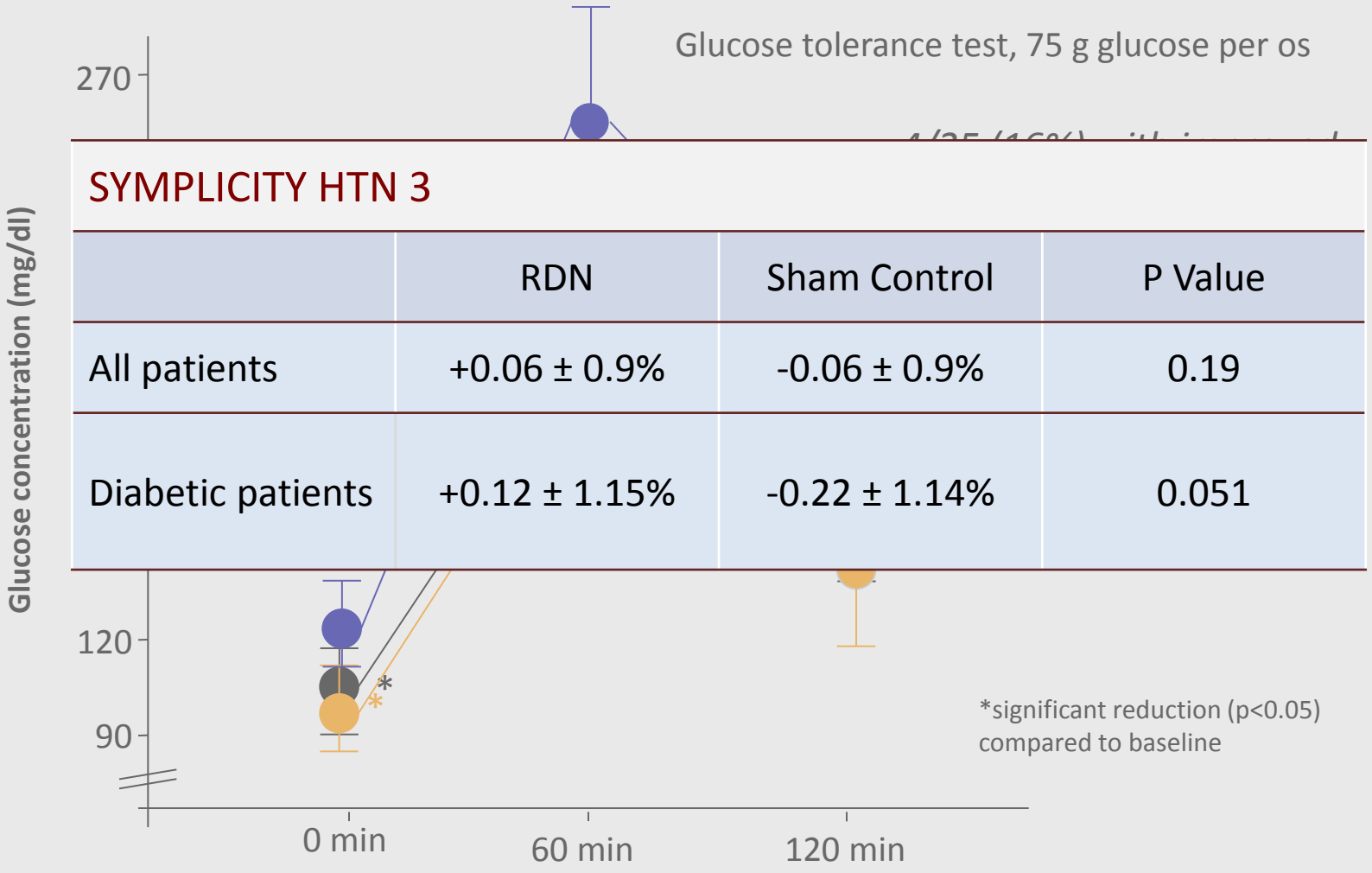
Improvement in Glucose Metabolism Following RDN



SYMPLICITY HTN 3

	RDN	Sham Control	P Value
All patients	+0.06 ± 0.9%	-0.06 ± 0.9%	0.19
Diabetic patients	+0.12 ± 1.15%	-0.22 ± 1.14%	0.051

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

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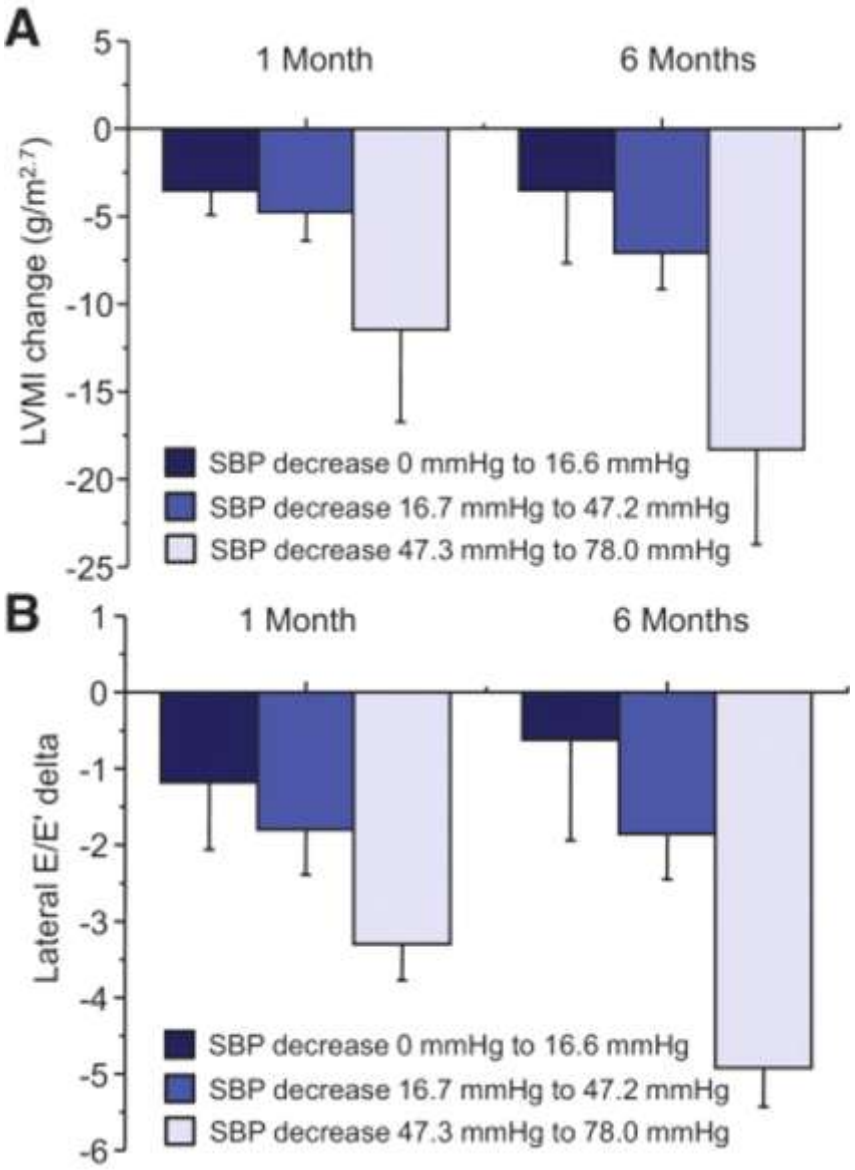
Regression of LVH and Improvement of Diastolic Function Relative to BP Reduction Achieved by Renal Denervation

Reduction in LV mass likely result of decreased LB workload and decreased sympathetic activity



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

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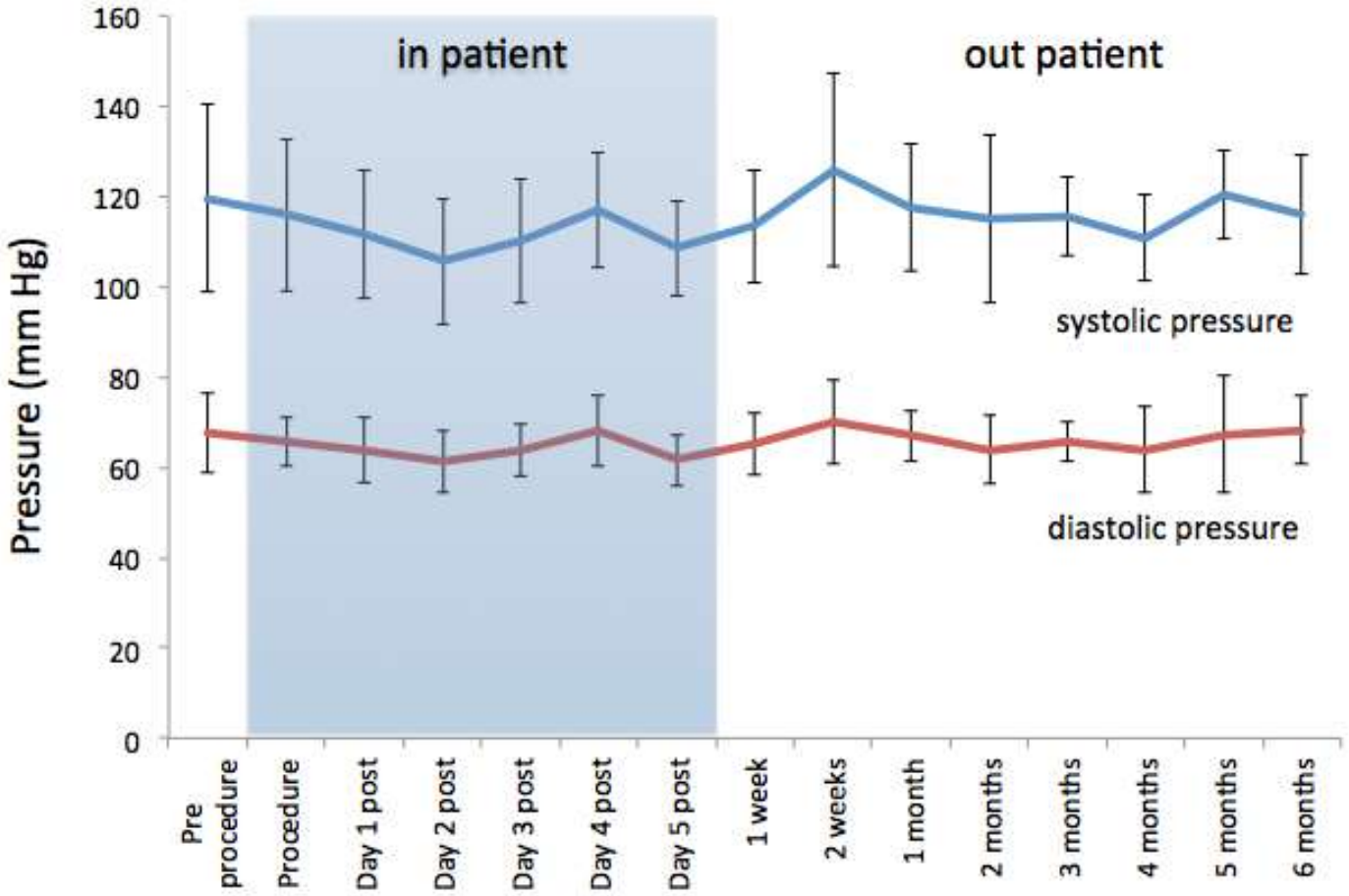
Blood Pressure Following RDN in Non-HTNsive Systolic HF



REACH-Pilot, Davies JE, Francis DP et al. International Journal of Cardiology (epub online)

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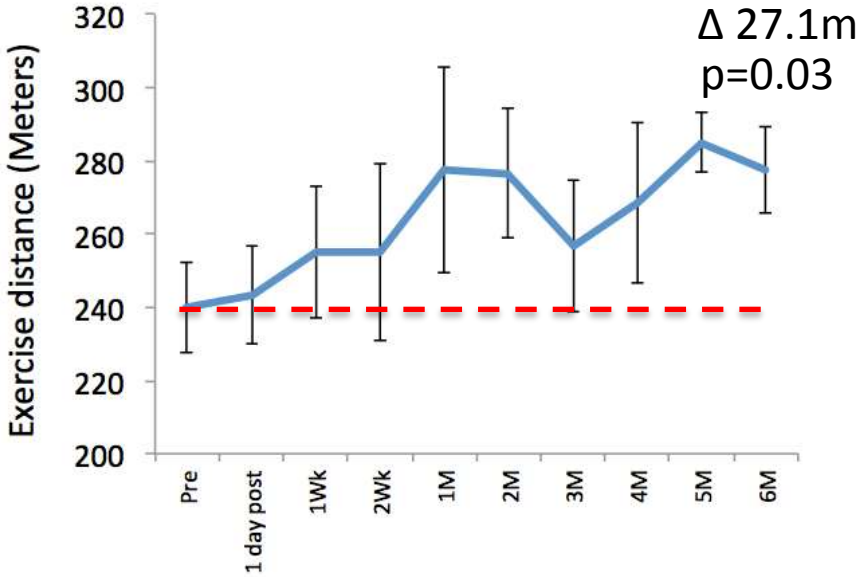
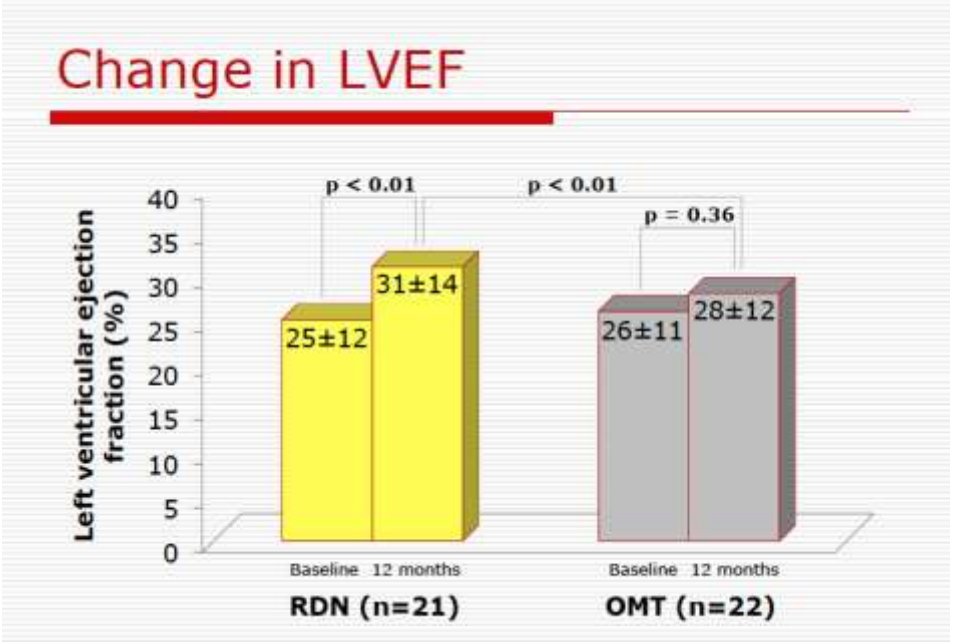
Potential Benefit of Renal Denervation in Heart Failure

Improvement in exercise capacity
REACH-Pilot



Improvement in ejection fraction
OLOMOUC I Study



REACH-Pilot, Davies JE, Francis DP et al. International Journal of Cardiology (epub online)
OLOMOUC I Study, ESC 2012

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SYMPLICITY Heart Failure Study

Goal

Evaluate safety of the ***Symplicity Catheter System*** and efficacy of renal denervation for improving cardiac & renal function in patients who have Chronic Heart Failure with Renal impairment

Study Design

Multicenter prospective, non-randomized, open-label study

Enrollment

40 subjects NYHA Class II-III, EF<40%, eGFR 30-75 mL/min/1.73m^2
< 8 sites in Australia and Europe

Australia

- First 5 subjects undergo unilateral RDN with 4 week interval before Tx other kidney
- 10/40 subjects undergo:
  - **Right Heart Catheterization**
  - **Cardiac and Renal Noradrenaline Spillover**
  - **Holter Monitor**
  - **Muscle Sympathetic Nerve Recordings**
  - **Mag3 Nuclear Imaging**

Australia + Europe

- All subjects
  - **CBC and blood chemistries** (Baseline, 1, 3, 6, 9, & 12, 24, 36month)
  - **Angiogram** (Baseline)
  - **Renal artery duplex ultrasound** (Baseline & 6 month)
  - **GFR** (Baseline, 1, 3, 6 & 12 month, 24 and 36 month
  - **Echocardiography** (Baseline, 6 & 12 month)

Major Assessments:

- Cardiac ventricular function by Echocardiography - 6 & 12 months
- Renal function by GFR - 1, 3, 6, & 12 months

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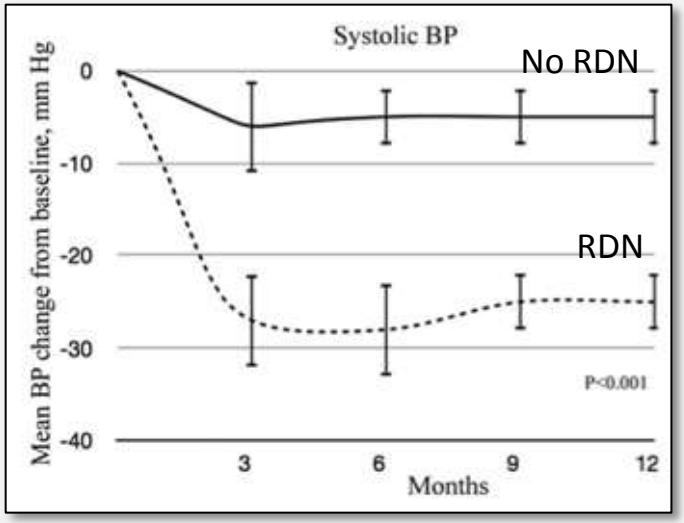
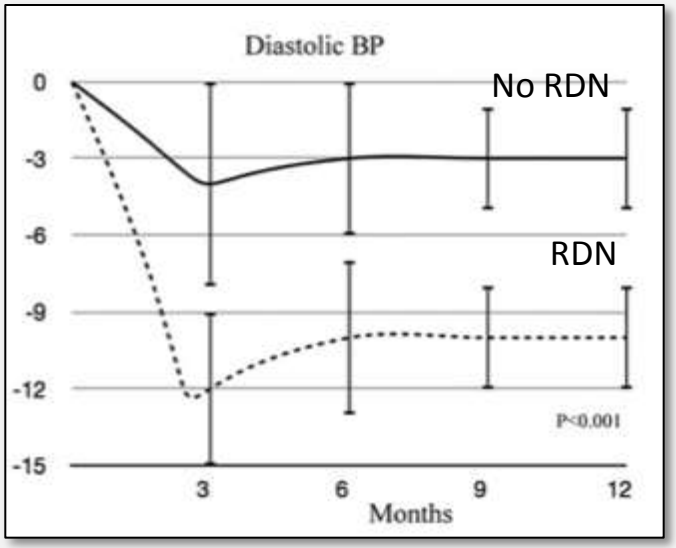
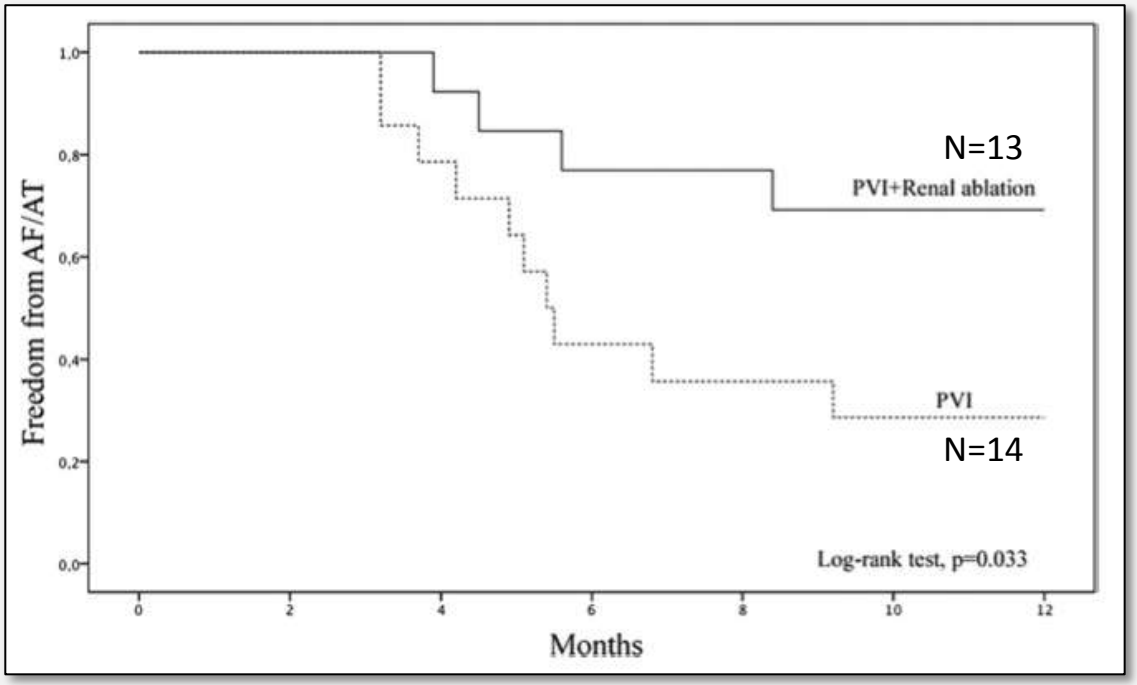
Preserving Renal Sodium Excretion by Renal Sympathetic Denervation in Congestive Heart Failure (PRESERVE)

- **Study Population:** Stable chronic heart failure with reduced ejection fraction with mild-moderate renal impairment; n=60
- **Hypothesis:** RDN improves renal sodium handling via reduced renal sympathetic outflow in patients with symptomatic heart failure and renal impairment
- **Design:** Multi-Center, prospective, randomized (1:1); crossover (3 Mo); "Early RDN" versus "Late RDN"
- **Primary Endpoint:** *Within-subject comparison* of urine sodium excretion following saline loading
- **Key Inclusion Criteria:**
  - History of chronic heart failure with current NYHA II-III symptoms.
  - LV ejection fraction ≤ 40%
  - Receiving guideline-recommended medical therapy for heart failure
  - Systolic BP ≥110 mmHg
  - eGFR 30-80 ml/min/1.73m^2
  - Able to maintain stable medications and non-added salt diet (120 mEq sodium/day) for 24 weeks

Pulmonary Vein Isolation With or Without Concomitant RDN







Pokushalov et al. JACC 2012

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SYMPLICITY AFib

- **Study Population:** Paroxysmal atrial fibrillation with hypertension; N=87
- **Objective:** Evaluate feasibility, safety, and effectiveness of the addition of RDN to PVI in preventing recurrence of paroxysmal atrial fibrillation
- **Design:** Multi-Center, prospective, randomized (2:1) study
- **Primary Endpoint:**
  - Effectiveness: freedom of chronic treatment failure through at least six months of follow-up
  - Safety: composite safety endpoint for both PVI and RDN
- **Key Secondary Endpoints:**
  - Office and ABPM systolic and diastolic blood pressure at 6 months compared to baseline
  - Heart rate at 6 months
  - LVEF, LVH, mitral valve regurgitation and LA size at 6 months
  - Procedural measures (procedure times, contrast dye usage)
  - Symptoms at 6 months
  - Quality of life at 6 months
- **Key Inclusion Criteria:**
  - Drug refractory recurrent symptomatic paroxysmal atrial fibrillation
  - Office-based systolic blood pressure of ≥140 mm Hg despite treatment with ≥2 antihypertensive medications of different classes
  - Ambulatory Blood Pressure Monitoring (ABPM) average systolic blood pressure ≥135 mmHg
  - Estimated Glomerular Filtration Rate (eGFR) of >45 mL/min/1.73m^2

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RDN Effects on Atrial and Ventricular Electrophysiology

- Significant decline in 24 hr Holter heart rate (~6 bpm), supraventricular and ventricular premature complexes

Tsioufis et al. J Hum Hypertens 2014

- Significant attenuation of ventricular tachycardia among 2 pts with cardiomyopathy and refractory ventricular arrhythmias

Ukena et al. Clin Res Cardiol 2011

- Atrial fibrillation episodes and ventricular rate reduced after RDN in preclinical model but no effect on atrial effective refractory period or AF inducibility

Linz et al. Hypertension 2013

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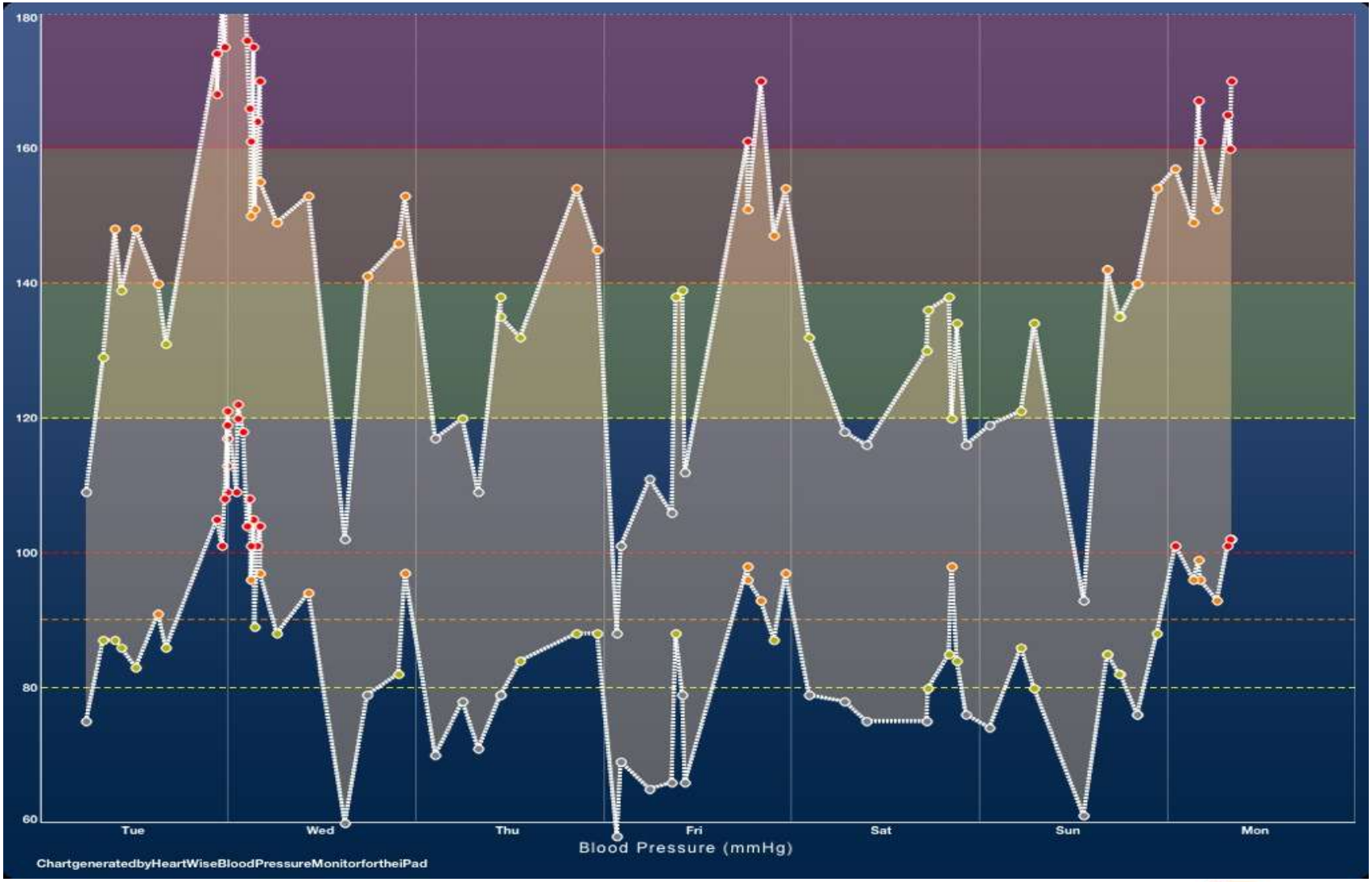
Blood Pressure Variation and Obstructive Sleep Apnea



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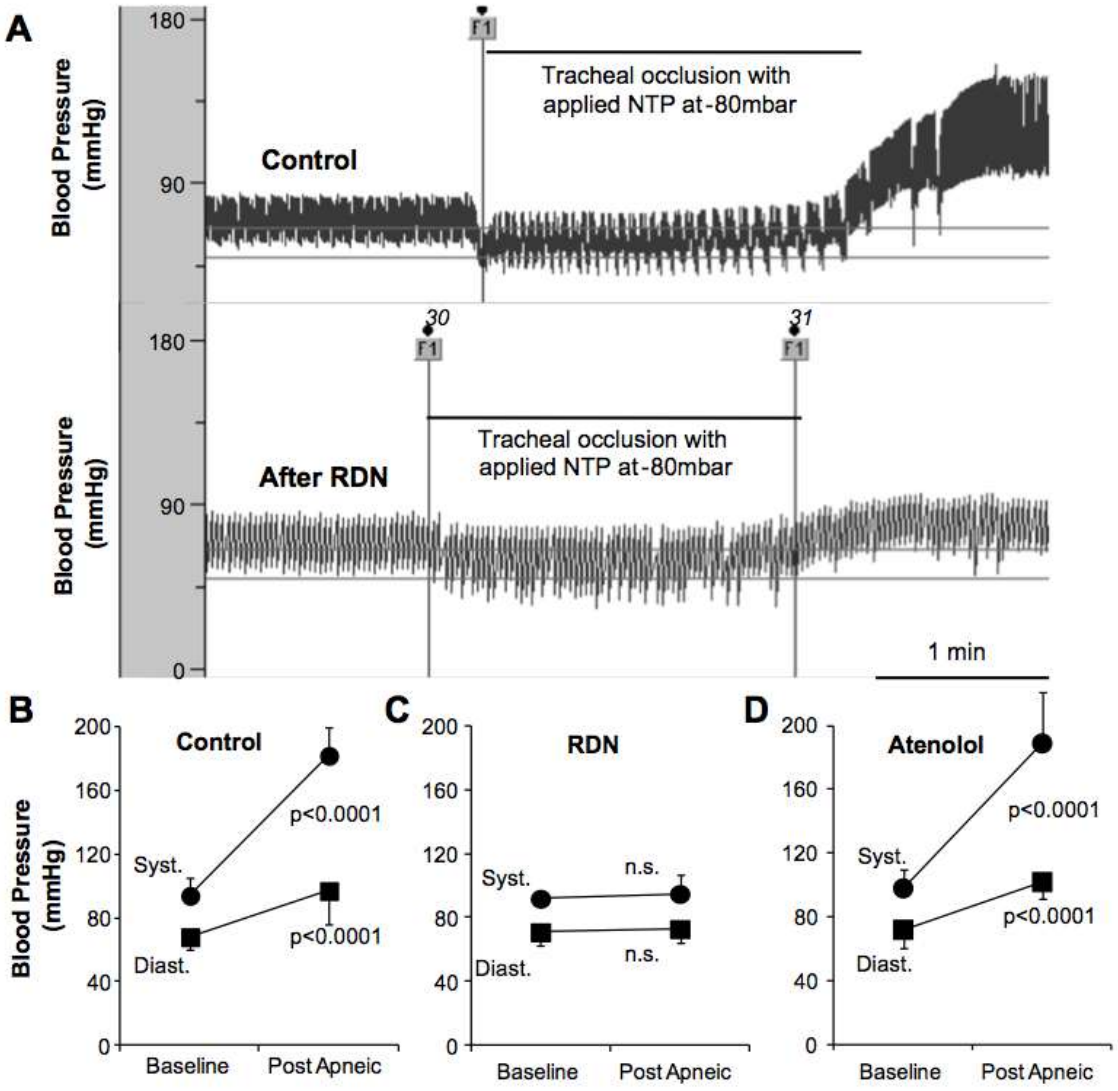
RDN Suppression of Postapneic Blood Pressure Increase and Atrial Fibrillation



Linz et al. Hypertension 2012

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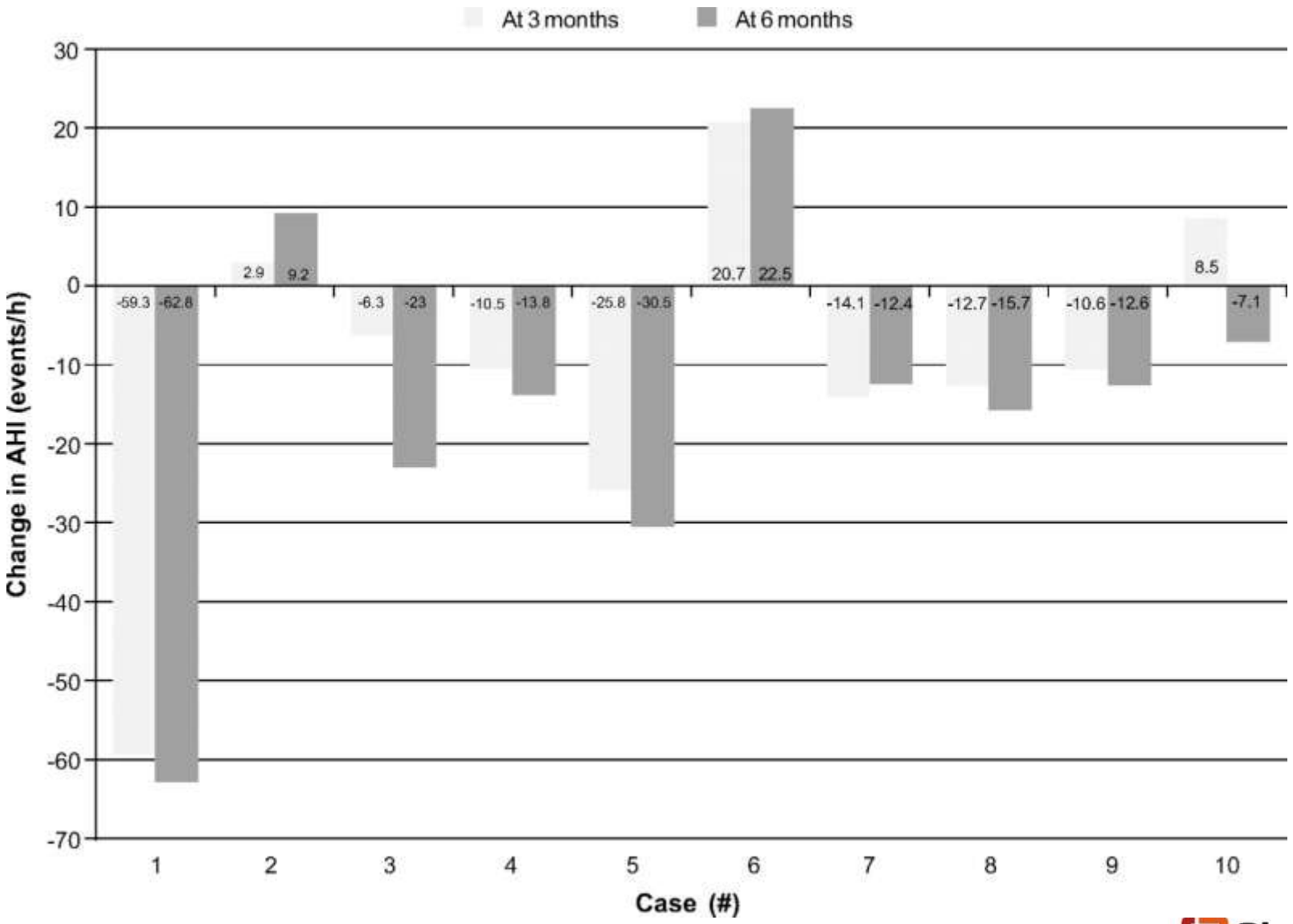
Change In Apena/Hypopnea Index at 3 and 6 months Following Renal Denervation



Witkowski et al. Hypertension 2011

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Is the Reduction in Afferent Activity Following RDN Sustained?

Parameter	Baseline	3 Months	6 Months	12 Months	*P* value
SBP, mm Hg	166 ± 22	154 ± 24	150 ± 27	144 ± 24	<0.001
DBP, mm HG	88 ± 19	82 ± 17	79 ± 16	77 ± 13	<0.001
HR, bpm	66 ± 14	66 ± 14	65 ± 14	67 ± 13	0.66
MSNA, bursts/min	51 ± 11	43 ± 14	45 ± 13	45 ± 15	0.001
MSNA, bursts/100 heartbeats	80 ± 16	69 ± 17	70 ± 16	69 ± 18	<0.001

Hering, Esler, Schlaich et al. Hypertension 2014 *In press*

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Catheter-Based Renal Denervation for Non-HTN Indications
Opportunities for Disease Management

- Initial concept of eliminating renal efferent traffic would turn off renin-angiotensin-aldosterone system thereby reducing blood pressure
- Refocus of attention toward sympathoexcitatory renal afferents in resistant HTN
- Reduction in hypersympathetic signature may effect pleiotropic effects on disease conditions not intuitively related to HTN but rather hypersympathetic activity
- Decline in afferent sympathetic activity may be durable following renal denervation
- Studies examining pleitropic effects of reducing sympathetic signature must and will be held to same standard and ideally be supported by measures independent of BP lowering

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