Patient with severe heart failure d/t resistant hypertension (renal denervation therapy)

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Case Description

- 56 year old man
- Ischemic cardiomyopathy – S/P MI * 2, several PCIs
- Coronary risk factors: diabetes type II, long-standing uncontrolled HTN, hyperlipidemia, obesity (BMI = 34)
- Obstructive sleep apnea
- Moderate-severe LV dysfunction (LVEF=30-35%)
- NYHA FC 2-3 , complains of effort dyspnea

Case Description – cont.

- Meds: Carvedilol 12.5 mg bid, Enalapril 20 mg bid, Aldospirone 25 mg qd, Furosomide 40-80 mg qd, Lercanidipine (Vasodip) 10 mg qd, Cadex (Doxazocin) 4-8 mg qd

- Mean office BP = 180/100 , (HR= 65)
- ABP measurement mean = 150/100 similar at day time and night
- Complains also of strong head pounding pain with BP increase at night

Combination of systolic HF + uncontrolled HTN

- Not common → <10% of severe systolic LV dysfunction cases accompanied by high BP
- Generally caused by ↑ SVR + ↑ sympathetic tone
- Long standing HTN commonly leads to a combination of systolic + diastolic dysfunction (LVH)
- Patients with HF + systolic LV dysfunction with normal or increased BP have better prognosis than those with lower SBP (<100) + DBP (lower mean arterial pressure).
- However, ↑ PP in an independent predictor of mortality

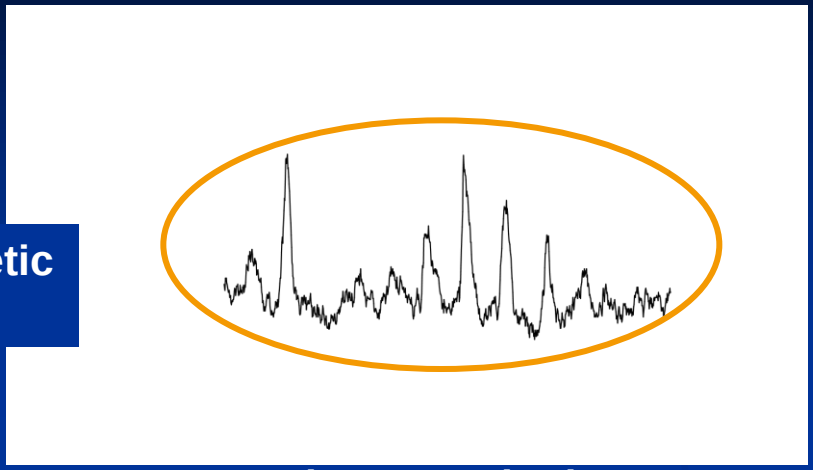
Domansky MJ et al, JACC 1999, Lee TT et al, AHJ 2006

Sympathetic activation: Common pathogenesis of HF and HTN

- Pivotal observation by Cohn et al that plasma concentration of noradrenaline was an independent predictor of HF patient survival *(Cohn et al, NEJM 1984)*
- High sympathetic activity, independent of HF severity caused death by arrhythmias and progressive LV failure *(Kaye et al, JACC 1995)*
- High renal sympathetic activity (renal noradrenaline spillover measur.) is a predictor of early death in HF pts, even those treated with β-blockers *(Peterson et al, EHJ 2005)*

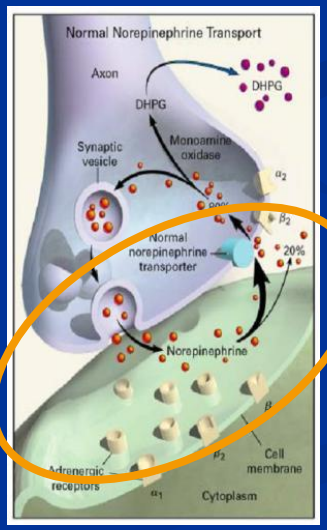
Quantifying Human SNS Activity

Central sympathetic nerve activity



Muscle sympathetic nerve activity (MSNA)
recording postganglionic nerve traffic

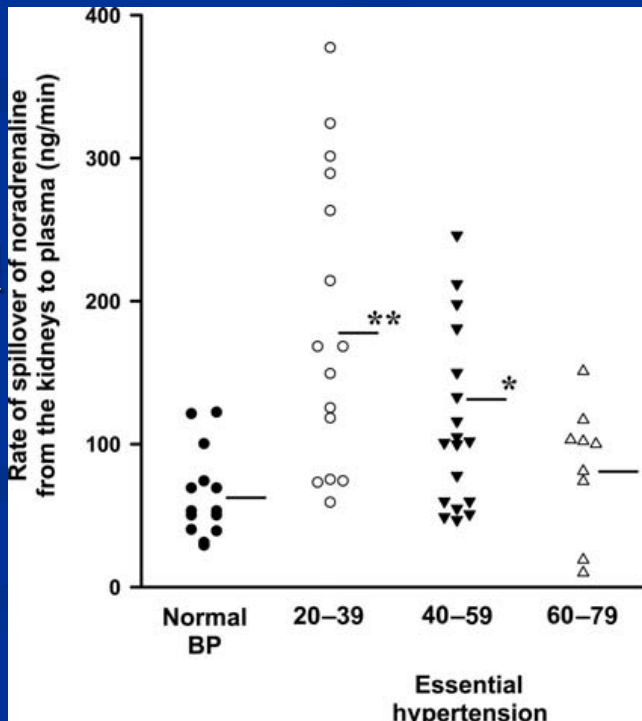
Renal sympathetic nerve activity



Norepinephrine spillover
measuring transmitter release from sympathetic nerves to plasma

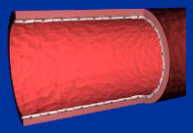
Sympathetic activation: Common pathogenesis of HF and HTN

- Application of norepinephrine spillover methodologies has demonstrated sympathetic activation to the kidneys and heart
- The majority of pts with essential HTN have demonstrable sympath. excitation
- The renal sympathetic nerves are pivotal in the pathogenesis of essential HTN through influence on renin release, GFR and renal reabsorption of sodium

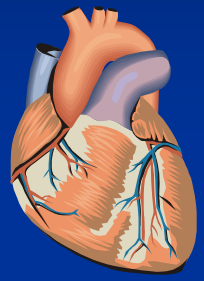


Parati et al, EHJ 2012

Renal Nerve and Sympathetic Activity:
Kidney as Origin and Recipient of Central Sympathetic Drive



• Vasoconstriction

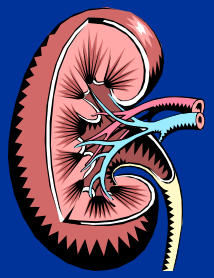


• ↑ Contractility
• ↑ Heart rate

Efferent nerves

Afferent nerves

Blood pressure

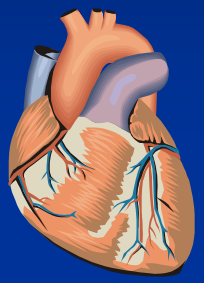


↑ Renin release → RAAS activation
↑ Sodium retention
↓ Renal blood flow

Schlaich M et al. *Hypertension.*2009;54:1195-1201.

Renal Nerve and Sympathetic Activity:
Kidney as Origin and Recipient of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis



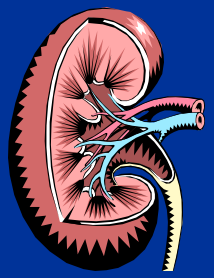
- ↑ Contractility
- ↑ Heart rate
- Hypertrophy
- Arrhythmia
- Heart failure

Efferent nerves

Afferent nerves

Blood pressure

+ Increase comorbidities



- ↑ Renin release → RAAS activation
- ↑ Sodium retention
- ↓ Renal blood flow
- ↓ Kidney function

Schlaich M et al. *Hypertension.*2009;54:1195-1201.

Physiology Supported 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

of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 152, NO. 16 — CHICAGO, ILLINOIS — AUGUST 15, 1953

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

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.

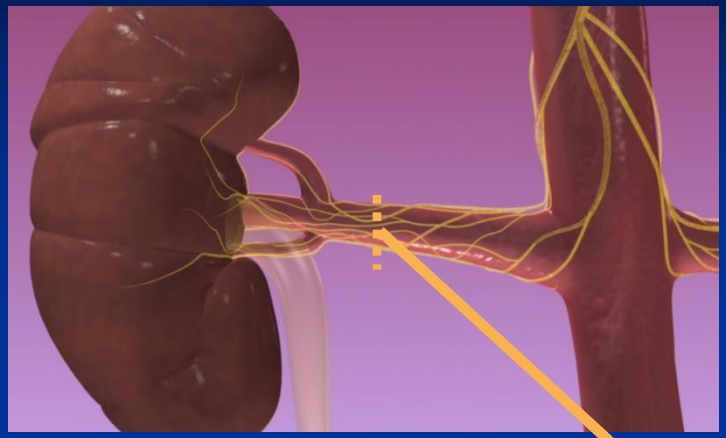
Transplanted kidneys:

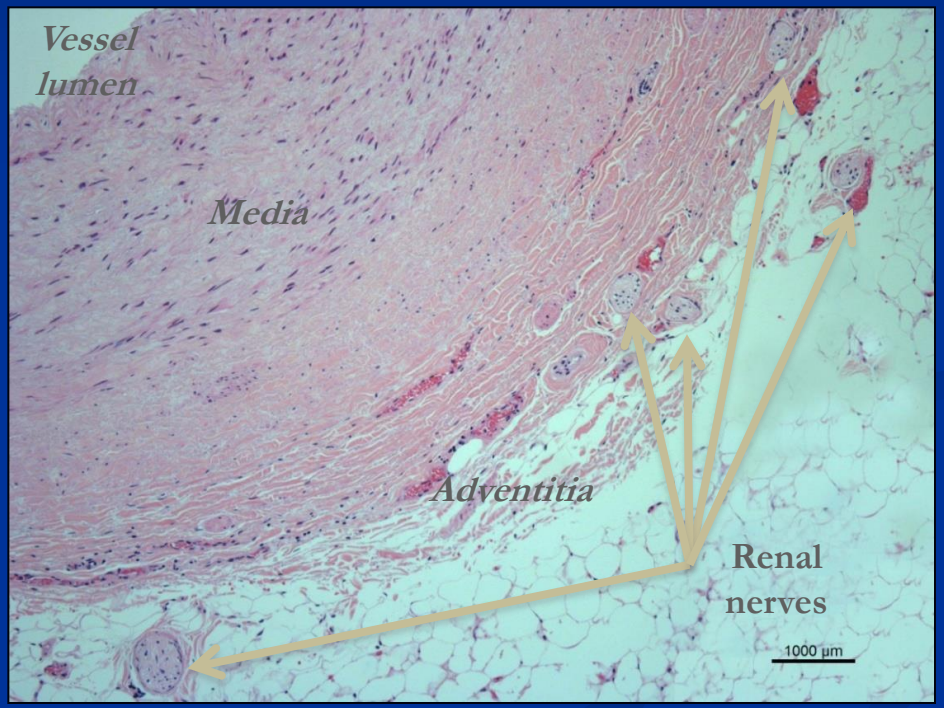
- Lack innervation
- Effectively maintain fluid and electrolyte balance

Supports that sympathetic component of control represents "overdrive" system, rather than foundation of basic renal function

Blaufox et al. *N Engl J Med.* 1969;280(2):62–66.

Renal Anatomy Allows a Catheter-Based Approach



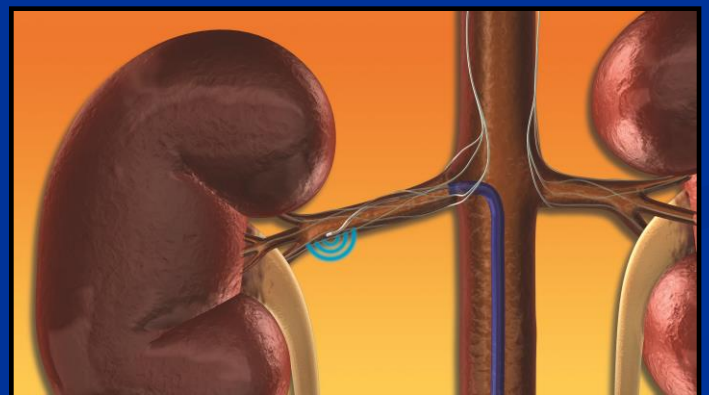


- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia*
- The only location that renal efferent and afferent nerves travel together†

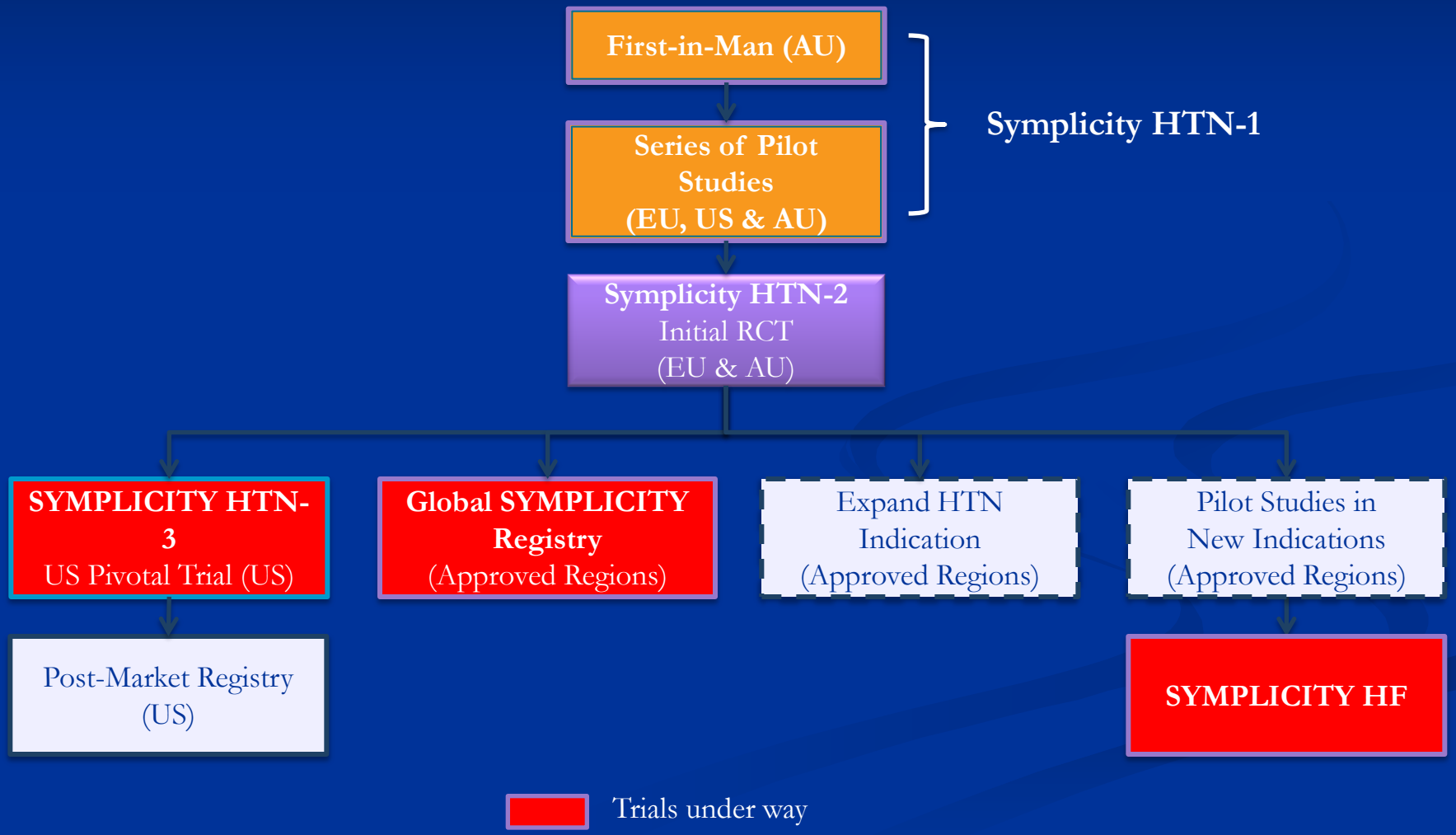
*Blaufox et al. *N Engl J Med.* 1969;280(2):62–66.
†Rippy et al. Clin Res. Cardiol. 2011;100:1095-1101

Symplicity™ Renal Denervation System (Medtronic)

- Low-profile, electrode-tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Access via standard interventional access 6 F
- Approximately 40 minutes from first to last RF delivery



SYMPLICITY Clinical Trial Program follows over 5000 patients



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


Hypertension

Celebrating 30 Years: 1979 to 2009

Journal of the American Heart Association

24 month extended follow-up

Hypertension. 2011;57:911-917.

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)

-36-month follow-up

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

Baseline Patient Characteristics (n=153)

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)	**5.1 ± 1.4**
	Diuretic (%)	95%
	Aldosterone blocker(%)	22%
	ACE/ARB (%)	91%
	Direct Renin Inhibitor	14%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Centrally acting sympatholytic (%)	33%
	Vasodilator (%)	19%
	Alpha-1 blocker	19%

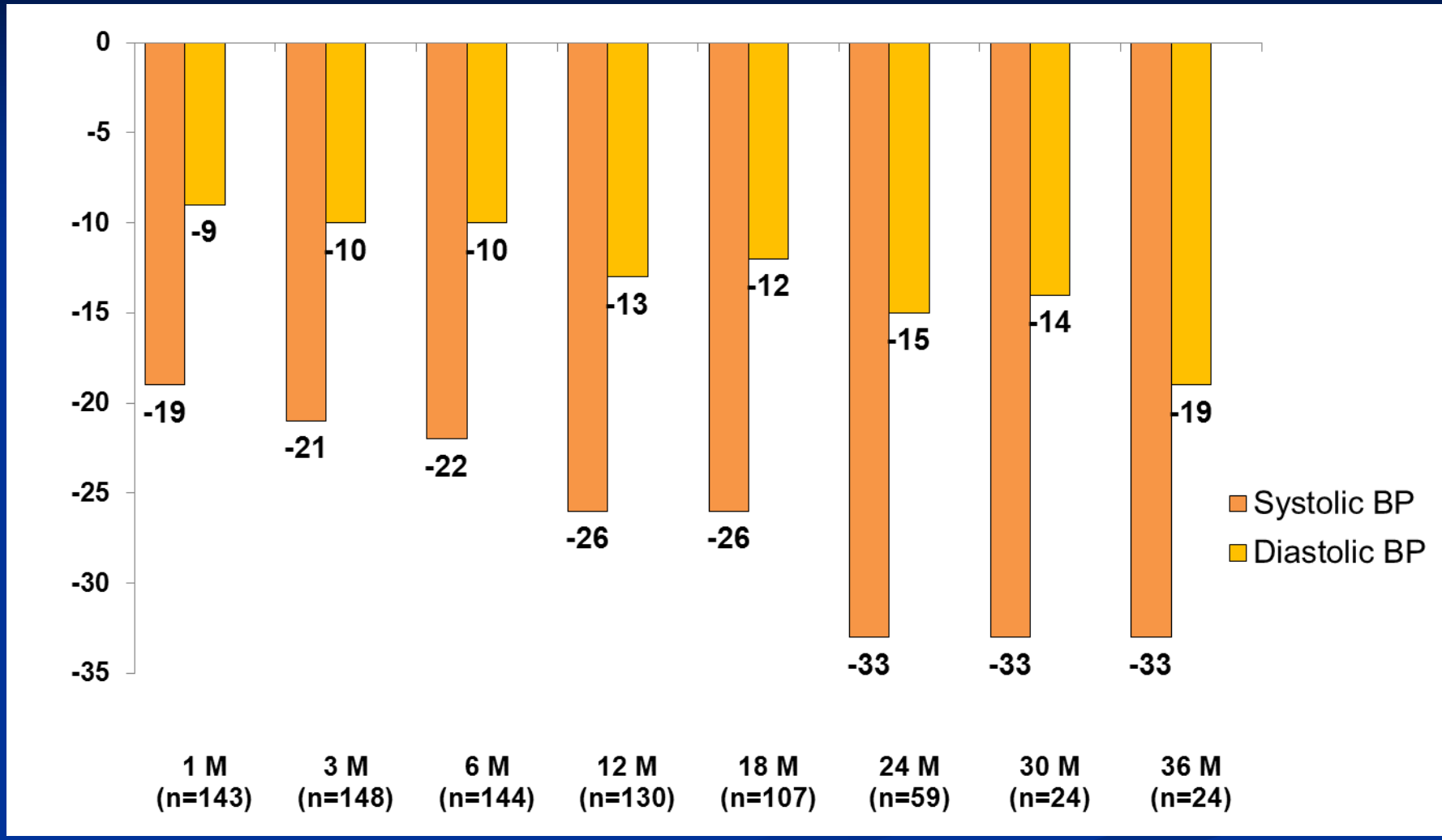
Symplicity HTN-1 Investigators. *Hypertension*. 2011;57:911-917.

The Procedure

- 38 minute median procedure time
  - Average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- 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

Symplicity HTN-1 Investigators. *Hypertension.* 2011;57:911-917.

Symplicity HTN-1: BP Reductions through 3 yrs

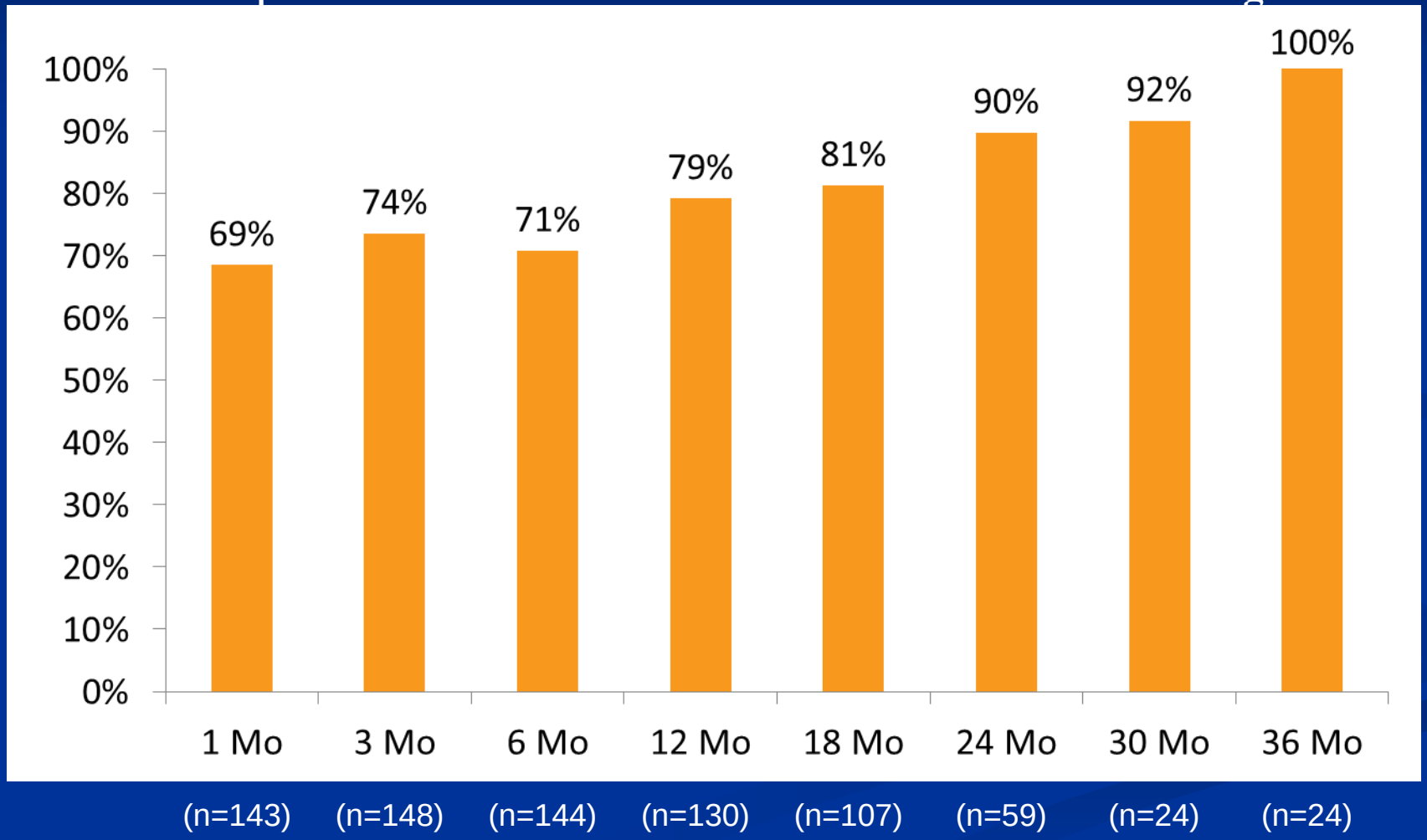


P<0.01 for Δ from BL for all time points

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

Symplicity HTN-1: Percentage Responders Over Time

Responder was defined as an office SBP reduction ≥ 10 mmHg



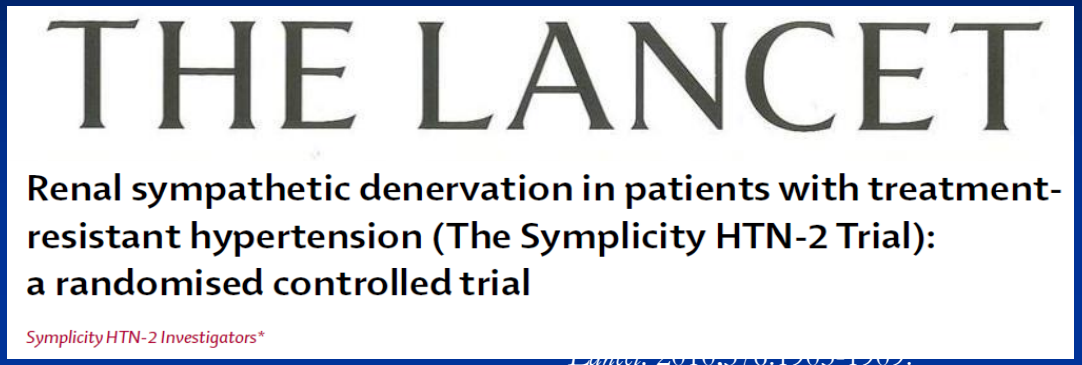
*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Conclusions from Symplicity HTN-1

- The magnitude of clinical response is significant and sustained through 3 years
- Increasing responder rates indicate:
  - no loss of treatment effect out to 36 months
- The treatment effect was consistent across subgroups (age, diabetes status, and baseline renal function)
- No late adverse events were seen

*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*

- **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: main renal arteries <4 mm in diameter or <20 mm in length
- 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.

RDN and Control Populations Well-matched, Severe Treatment Resistant Hypertensives

	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

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

Symplicity HTN-2: Procedural Safety

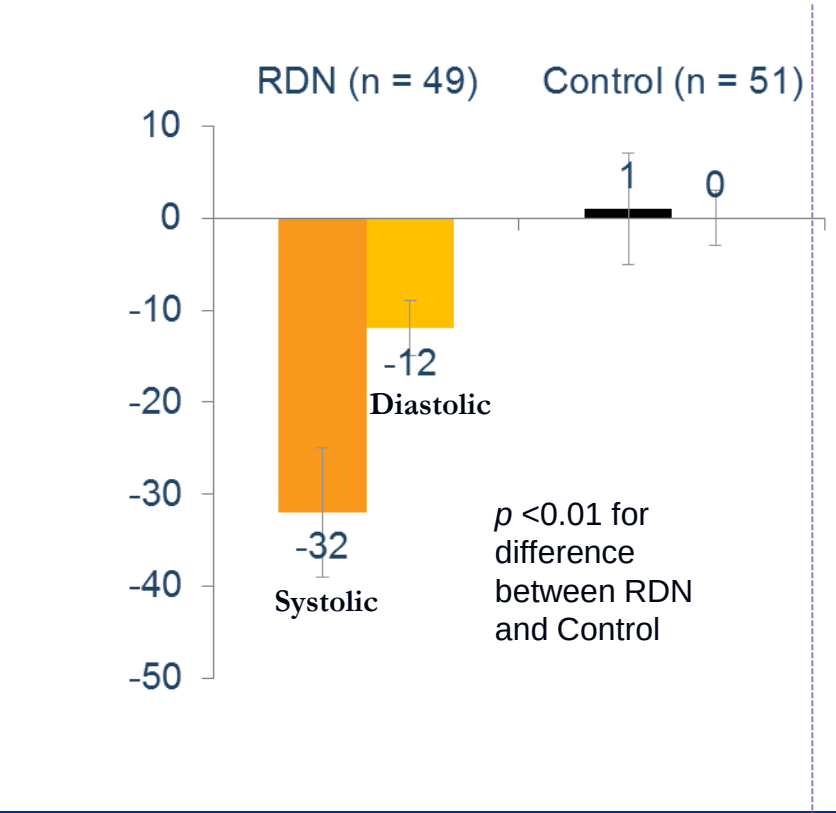
- One renal artery dissection. The lesion was stented without further consequences
- One hospitalization prolonged due to hypotension following the RDN procedure. IV fluids administered, anti-hypertensive medications decreased and patient discharge without further incident
- No radiofrequency-related renal artery stenosis or aneurysm occurred in either Randomised group
- Minor adverse events (full cohort)
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 postprocedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalisation for evaluation of paraesthesias
  - 1 back pain treated with pain medications and resolved after 1 month

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

Symplicity HTN-2: Primary Endpoint and 1 year Follow-up

Primary Endpoint
(6M post Randomisation)

Δ from Baseline to 6 Months (mmHg)



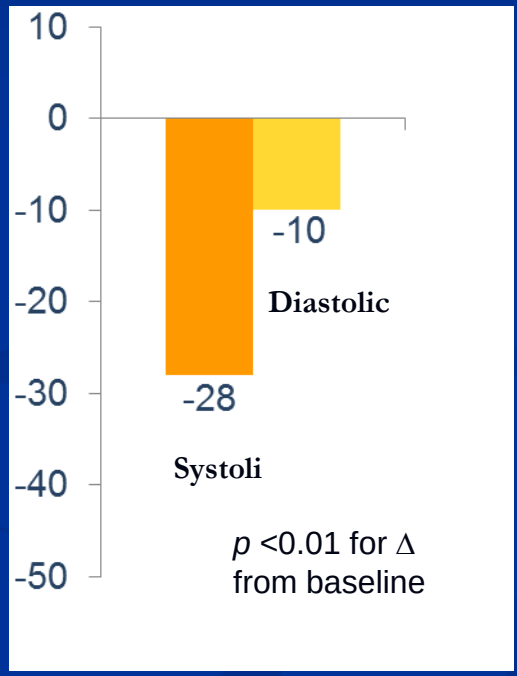
Primary Endpoint:

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

1 year Follow-up

RDN (n= 47)

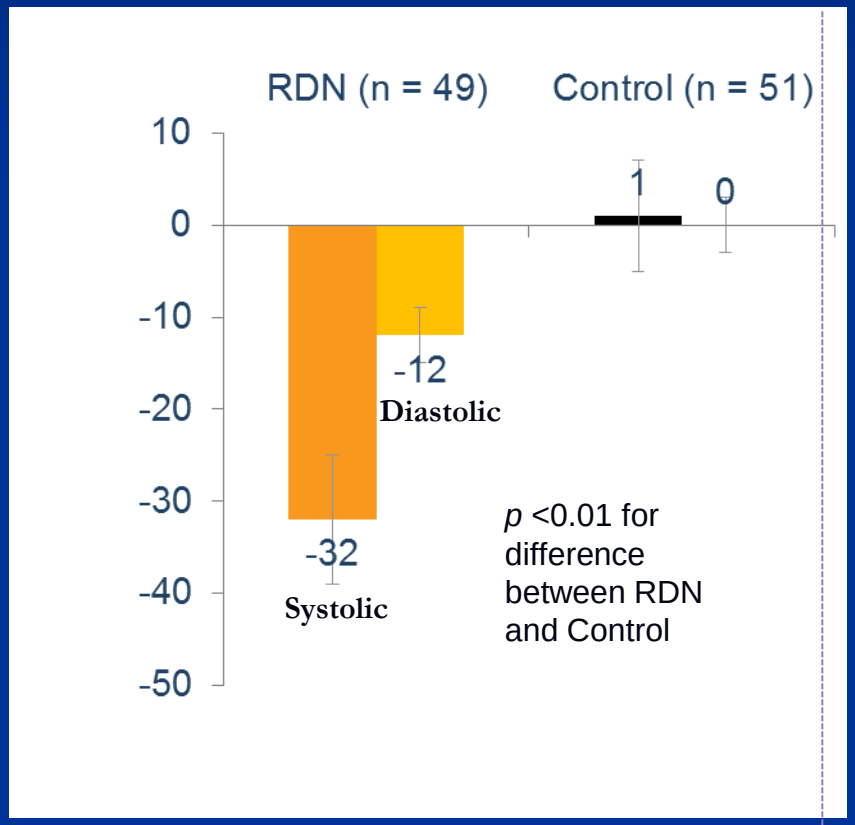
Δ from Baseline to 12 Months (mmHg)



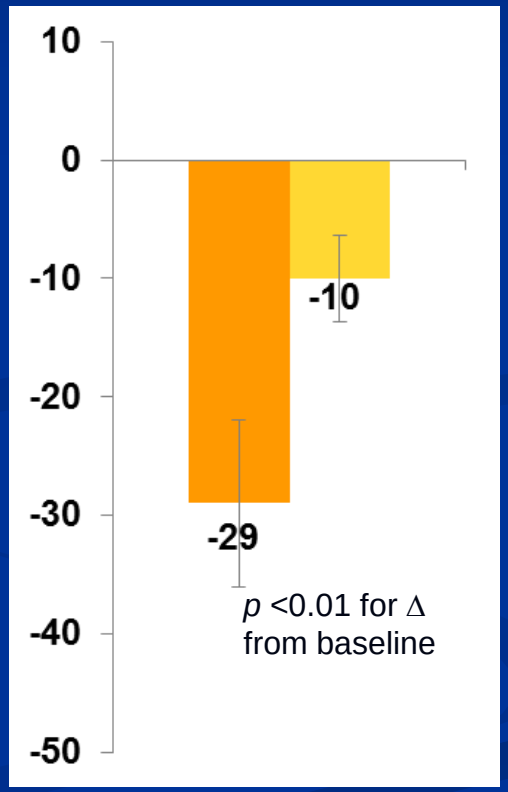
Expanded results presented at the *ACC Annual Meeting 2012* (Esler, M.)

Symplicity HTN-2: Primary Endpoint and 2 year Follow-up – results maintained

Primary Endpoint
(6M post Randomisation)



Latest Follow-up:
24 mo. post randomization
RDN (n= 40)



Presented at ACC 2013

Catheter-based renal denervation is beneficial and results in significant and sustained BP reductions in patients with treatment-resistant essential HTN

Symplicity HTN-2: 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)

Symplicity HTN-2: Renal Function Results

	Baseline		6 month		12 months
eGFR (ml/min/1.73m^2)	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)

Symplicity HTN-2 Investigators. *The Lancet*. 2010.

Proof of Principle

Related Changes in Underlying Physiology

		Baseline	1 Month	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 mo.

Krum et al, Lancet 2009

Glucose Metabolism Improved Following RDN in Subset of Symplicity HTN-2 Patient Population

Timepoint	Fasting Glucose (mg/dl)	Insulin (mU/l)	C-Peptide (µg/l)	HOMA-IR
Baseline (n = 25)	118±20	22.3±14.8	6.2±3.6	6.2±4.3
1 Month (n = 21)	113±14	10.9±7.3*	3.2±1.5*	3.0±1.8*
3 Months (n = 15)	102±12*	8.4±4.8*	3.0±1.1*	2.1±1.3*
6 Months (n = 7)	99±18*	8.8±4.6	3.1±1.1	2.2±1.4

*Significant reduction (p <0.05) compared with baseline.
Homeostasis model assessment-insulin resistance (HOMA-IR) = (insulin x blood glucose)/405

Mahfoud et al. Deutsche Gesellschaft Für Kardiologie: Jahrestagung Mannheim. April 2010.

Renal sympathetic denervation reduces LVH and improves cardiac function in pts with resistant HTN

- 46 patients underwent bilateral RD, and 18 patients served as controls. TTE was performed at baseline, and after 1 and 6 mo.
- Besides reduction of systolic and diastolic BP, RD significantly reduced mean interventricular septum thickness and LV mass index (53.9 ± 15.6 g/m(2.7) → 47.0 ± 14.2 g/m(2.7), $p < 0.001$).
- Reduction of LV filling pressures, isovolumic relaxation time shortened, and EF significantly increased after RD (baseline: 63.1 ± 8.1% → 70.1 ± 11.5% at 6 months, $p < 0.001$).
- No significant changes were obtained in control patients.
- RD sig. reduces LV mass and improves diastolic function

Brandt MC, JACC 2012

First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study

- **Aim:** To evaluate the safety of renal denervation for heart failure
- 7 patients with chronic systolic HF (mean BP 112/65 mmHg) on max. tolerated HF therapy underwent bilateral RD.
- No haemodynamic disturbances, hypotensive or syncopal episodes were noted during the acute phase or 6 mo. f/u post RD.
- Over 6 mo. there was a non sig. trend to BP reduction (Δ -7.1 syst, -0.6 mmHg diast). Renal function remained stable . All pts described improved symp. The 6 min. walk distance at 6 mo. was sig. increased
- This study found no procedural or post-procedural complications following RD in patients with chronic systolic HF

Davies et al, Int J Cardiol 2013

Our patient

- Underwent bilateral renal denervation using the Simplicity Renal denervation system (Medtronic)
- After 2 months: mean ABP recording decreased to 130/80, office measurements decreased to 130-150 systolic over 75-85 diastolic
- Decreased number and dosages of HTN meds
- Significant improvement in sleep quality, functional class, HF symptoms, and glucose control !!

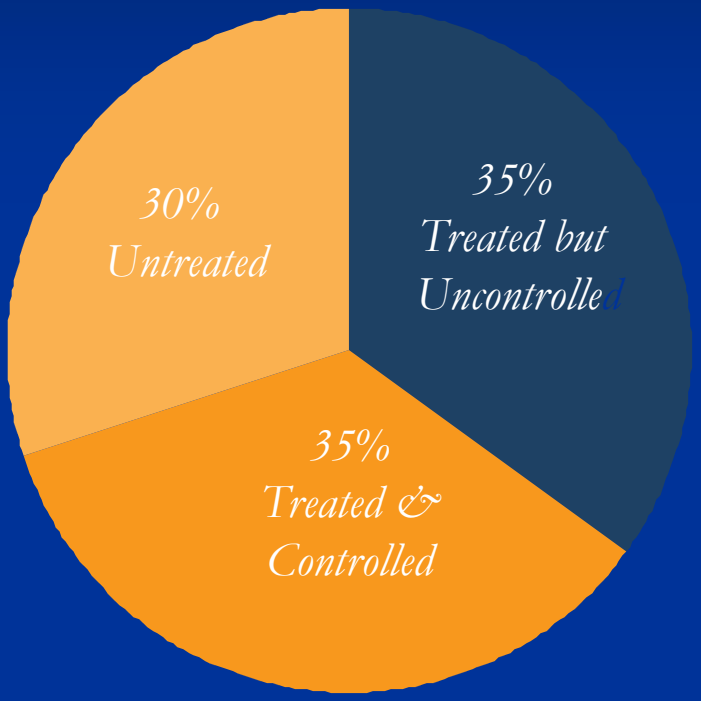
Conclusion

- Reduction of sympathetic activation via renal denervation can potentially benefit patients with heart failure + uncontrolled HTN, possibly also normotensive HF patients, through:

- Reduction in SVR
- Reduction in LV mass and improvement in diastolic function
- Improvement in glucose metabolism, exercise capacity, sleep indices, possibly also reduced risk of arrhythmias
- Reduction on number and/or dose of anti-HTN meds

THANK YOU

Hypertension Epidemiology



- Single largest contributor to death worldwide
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Less than half of all treated hypertensives are controlled to established BP targets

Chobanian et al. Hypertension. 2003;42(6):1206–1252.

Proof of Principle

Direct Measurement of Reduced Central Sympathetic Nerve Activity

Denervation of Patient with Essential HTN

59-Year-Old Male on 7 HTN Meds

	MSNA (burst/min)		BP (mmHg)
Baseline	**56**	→	**161/107**
1 Month	**41** (-27%)	→	**141/90** (-20/-17)
12 Month	**19** (-66%)	→	**127/81** (-34/-26)

Schlaich M et al. *NEJM*. 2009;36(9):932-934.