Disclosure Statement of Financial Interest

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

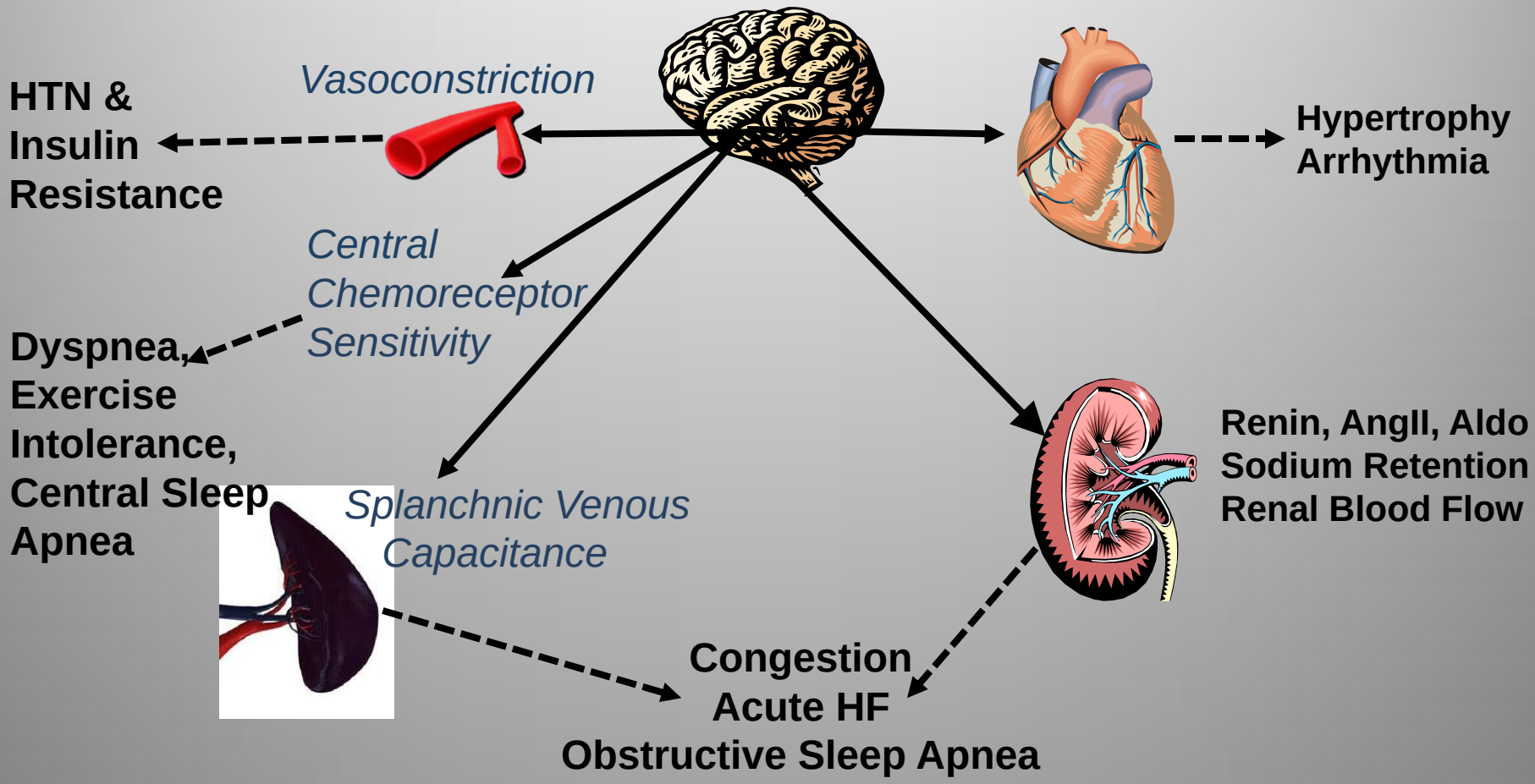
Affiliation/Financial Relationship	Company
• Consulting Fees/Honoraria	• Ardelyx Inc. • Medtronic, Inc. • Rox Medical, Inc.
• Royalty Income	• Ardian, Inc.
• Ownership/Founder/Salary	• Cibiem, Inc.

Time To Generalize

Paul A. Sobotka, M.D., F.A.C.P.,F.A.C.C., F.A.H.A.
Professor of Medicine/Cardiology
The Ohio State University

Chief Medical Officer
Cibiem, Inc.

Consequences of Chronically Elevated Sympathetic Activity



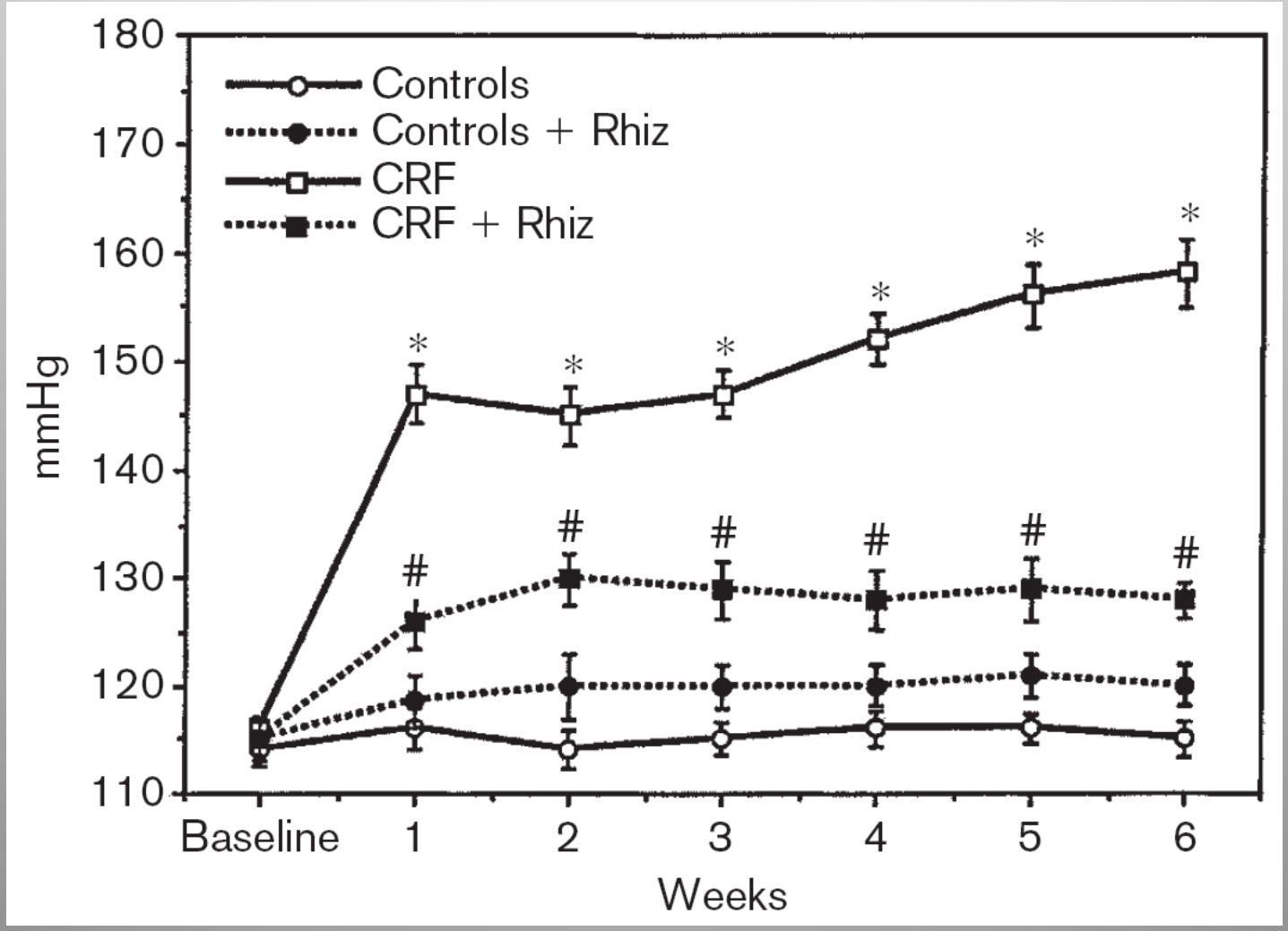
Adrenergic Stimulation

Acute Adrenergic Stimulation is critical for survival

Chronic Adrenergic Stimulation is maladaptive

Zebra’s don’t get ulcers, we do

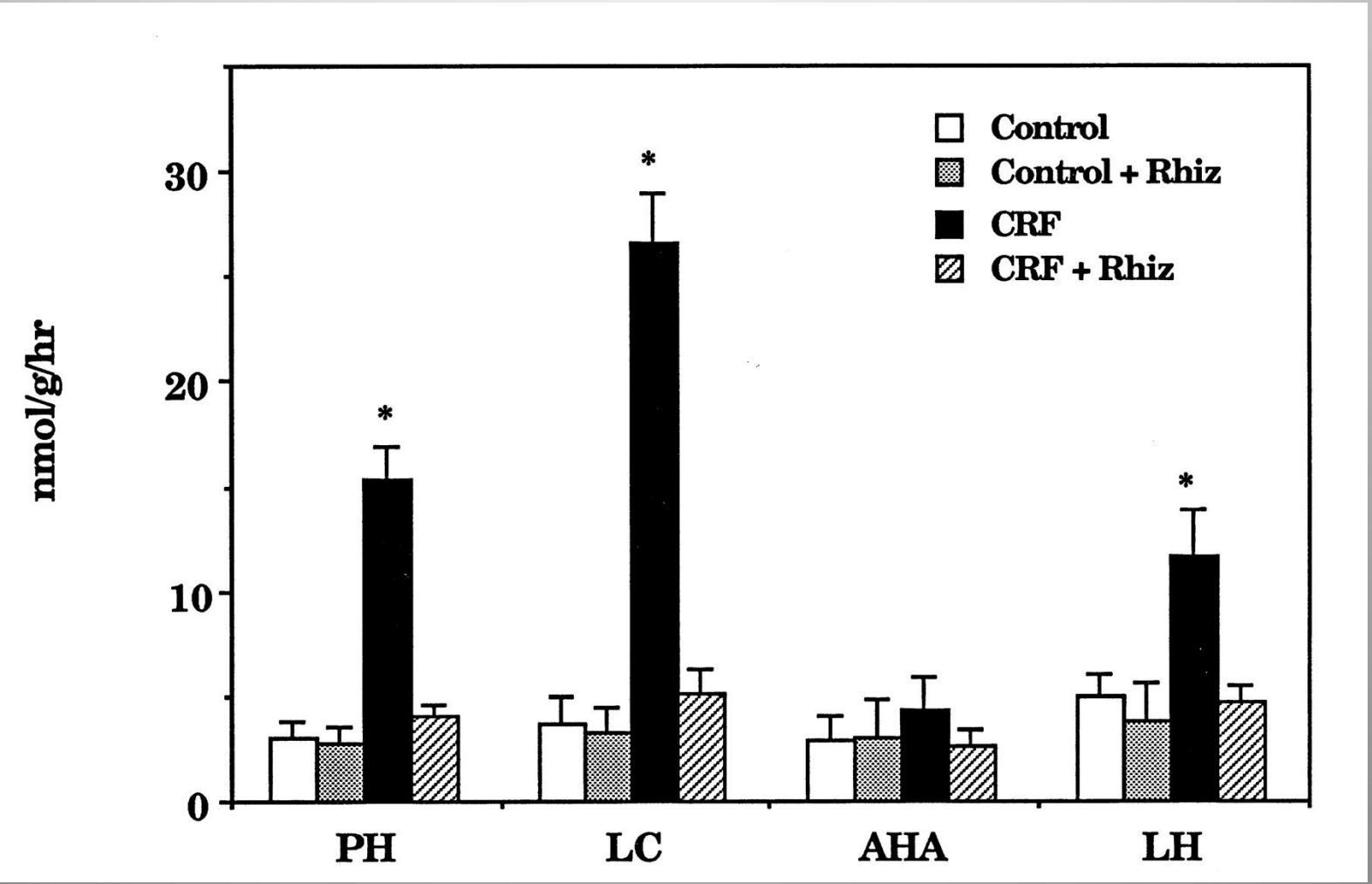
Pressor Response to Renal Injury (5/6 Nx) Blocked by Afferent Renal DNX (rhizotomy)



Campese V, et. al. Hypertension 1995;25:878-82.

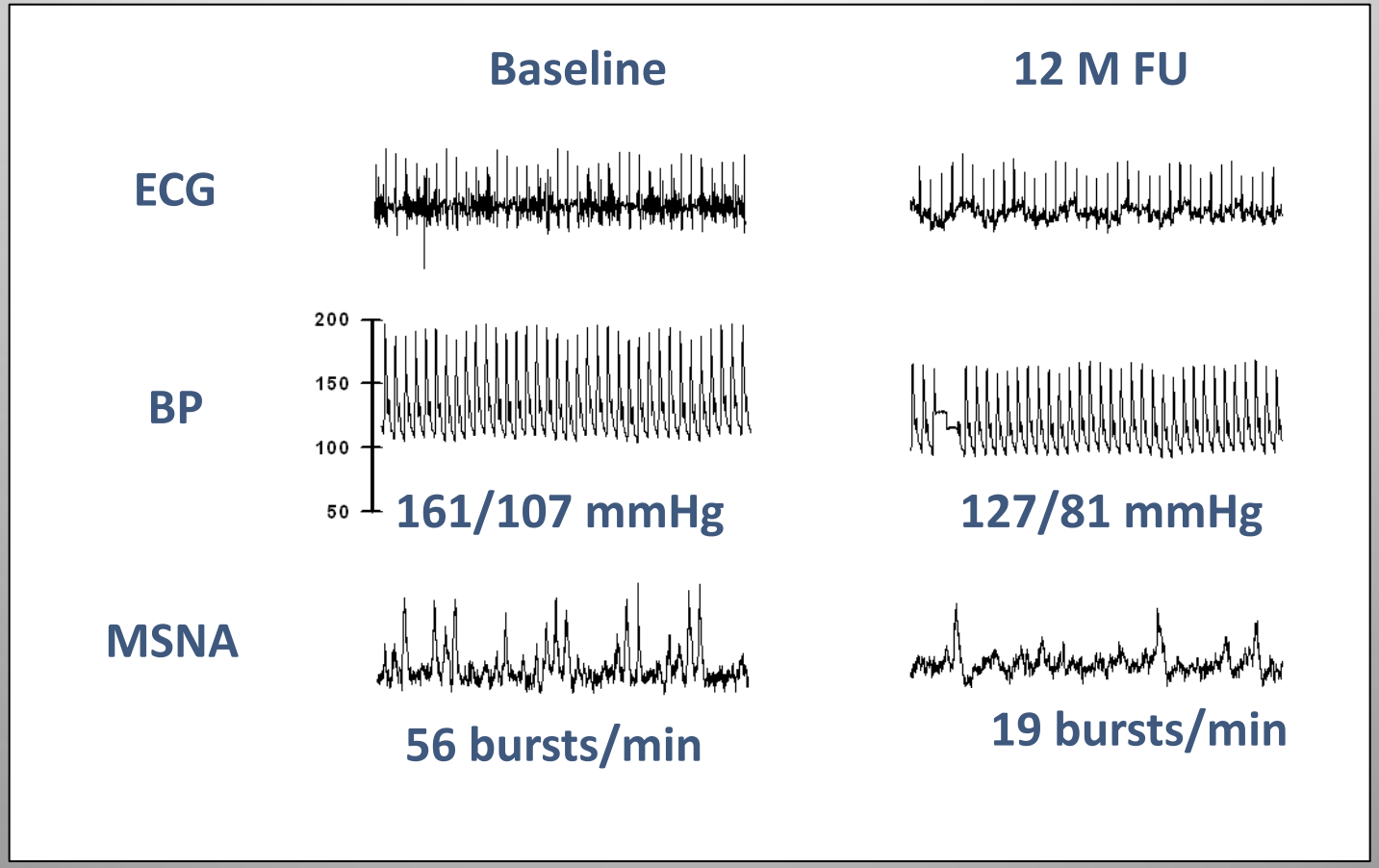
Norepinephrine Turnover Rate in Posterior (PH), Anterior (AHA), and Lateral (LH) Hypothalamic Nuclei and Locus Coeruleus (LC)

Afferent renal DNX (rhizotomy) reverses central activation of CRF



Campese V, et. al. *Hypertension* 1995;25:878-82.

Therapeutic Renal Denervation Resistant Hypertension



Improvement in cardiac baroreflex sensitivity after renal denervation 7.8 to 11.7msec/mmHg

Schlaich, Krum, Walton, Sobotka, et al. NEJM. 2009; 36(9): 932-934

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 ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)

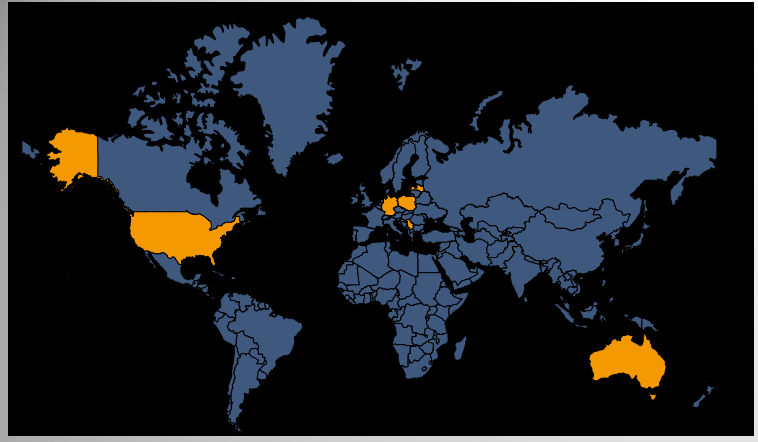
- 12-month data

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

-Expanded cohort of patients (n=153)

-24-month follow-up

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension: Durability of Blood Pressure Reduction Out to 24 Months.
Symplicity HTN-1 Investigators.
Hypertension. 2011 Mar 14.



Symplicity HTN-1 Study Centers

Australia, Europe, and USA

The John Paul II Hospital, Krakow, Poland	Jerzy Sadowski
Prairie Education and Research Cooperative, Springfield, IL, USA	Krishna Rocha-Singh
Universitätsklinikum des Saarlandes, Homburg, Germany	Michael Böhm
Samodzielna Pracownia Hemodynamiczna, Warsaw, Poland	Andrzej Januszewicz & Adam Witkowski
The Alfred Hospital, Melbourne, Australia	Henry Krum
CardioVascular Center Frankfurt, Frankfurt, Germany	Horst Sievert
St. Vincent's Hospital, Melbourne, Australia	Robert Whitbourn
Universitätsklinikum Düsseldorf, Düsseldorf, Germany	Lars Christian Rump
MetroHealth System, Cleveland, OH, USA	Mark Dunlap
John Hunter Hospital, Newcastle, Australia	Suku Thambar
Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany	Thomas Zeller
Pauls Stradins Clinical University Hospital, Riga, Latvia	Andrejs Erglis
Dedinje Cardiovascular Institute, Belgrade, Serbia	Boško Đukanović
Klinikum Coburg, Coburg, Germany	Johannes Brachmann
Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany	Gerhard Adam & Ulrich Wenzel
Hennepin County Medical Center, Minneapolis, MN, USA	Bradley Bart
Universität Erlangen-Nürnberg, Erlangen, Germany	Roland Schmieder
Universität Leipzig – Herzzentrum, Leipzig, Germany	Dierk Scheinert
St. Josef und St. Elisabeth Hospital, Bochum, Germany	Jan Börgel

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)**	**175/98 ± 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%

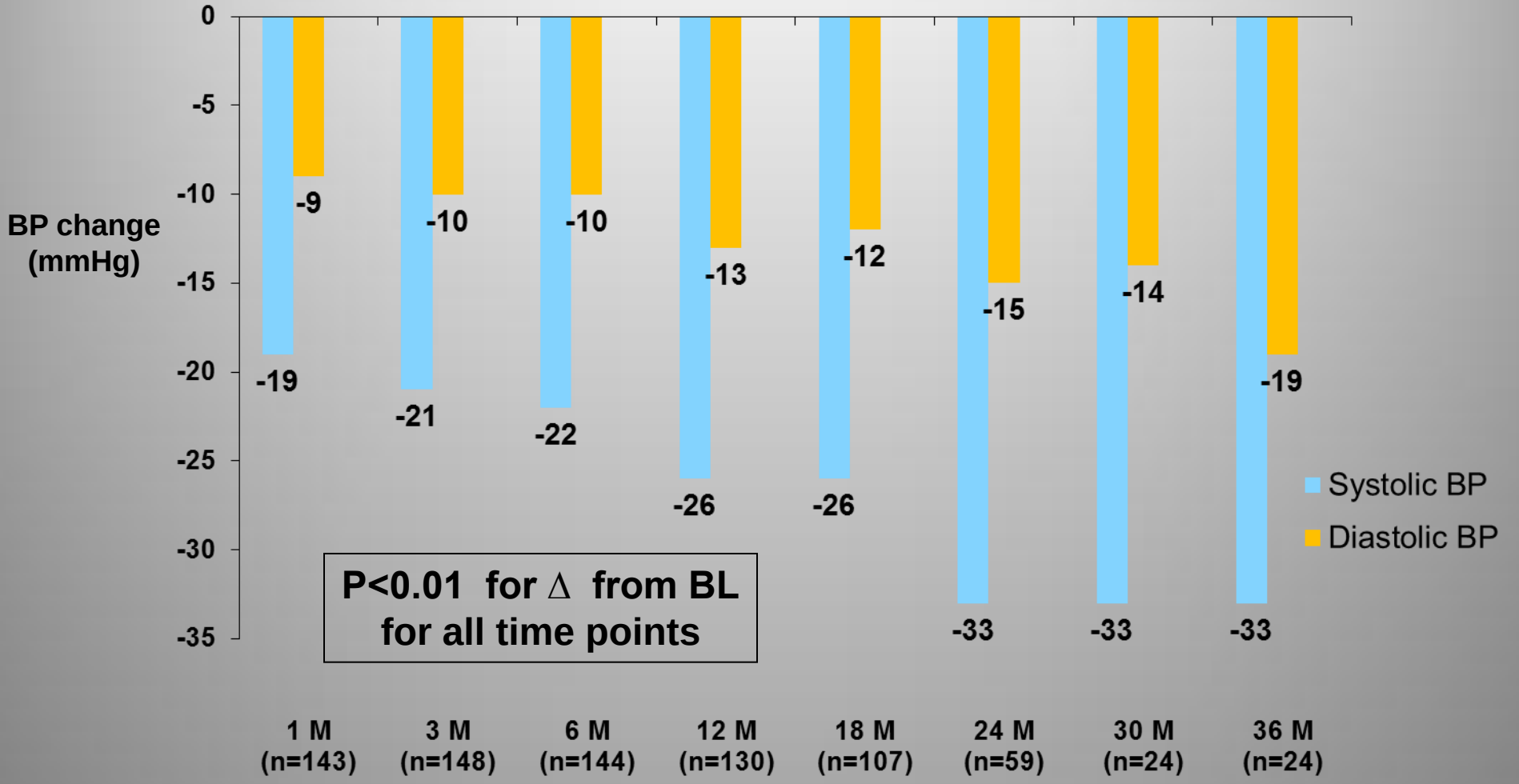
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Procedure Detail & Safety

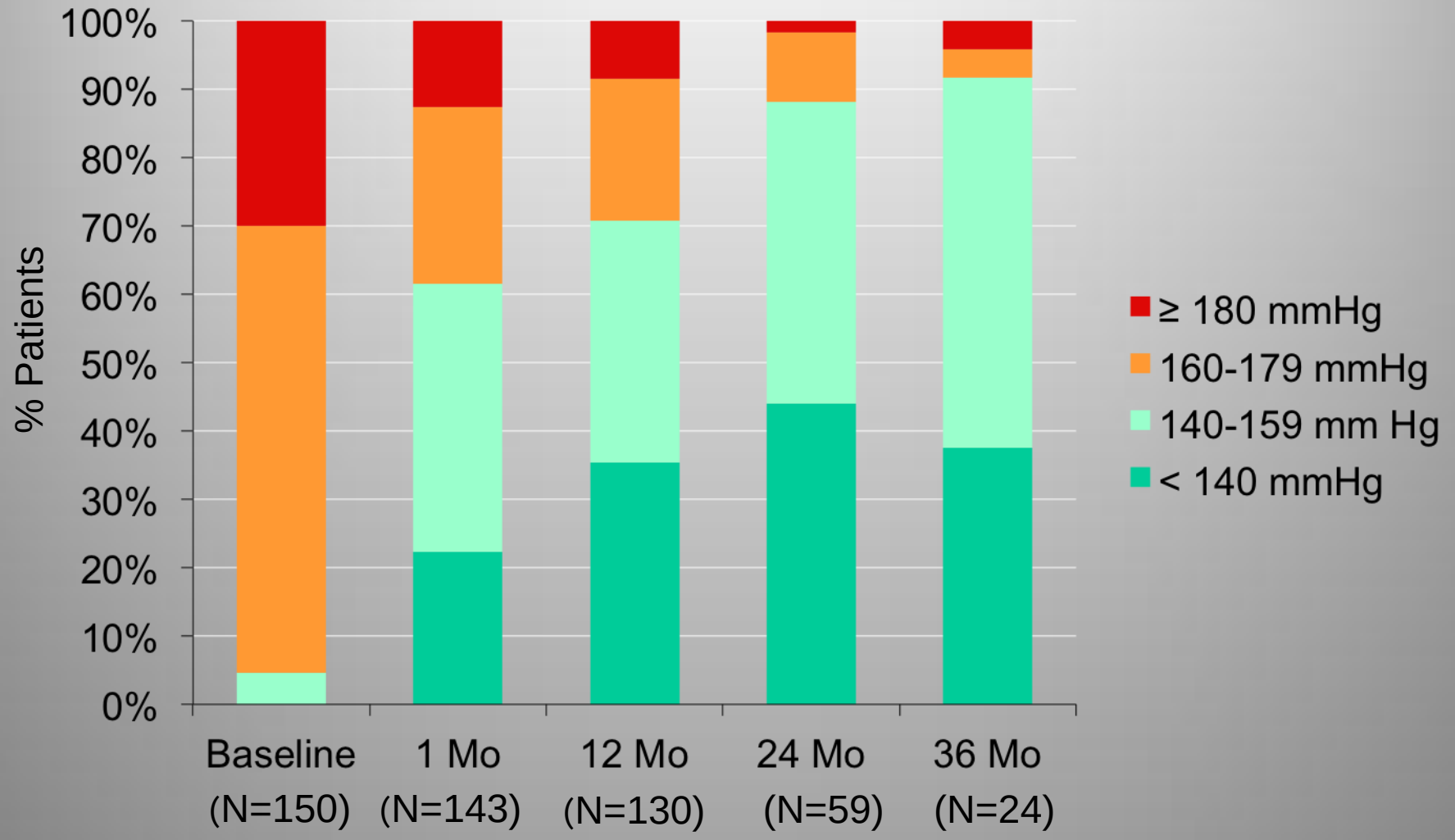
- 38 minute median procedure time
  - Average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- Minor complications 4/153:
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further aftereffect

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

Blood Pressure Change Following RDN



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

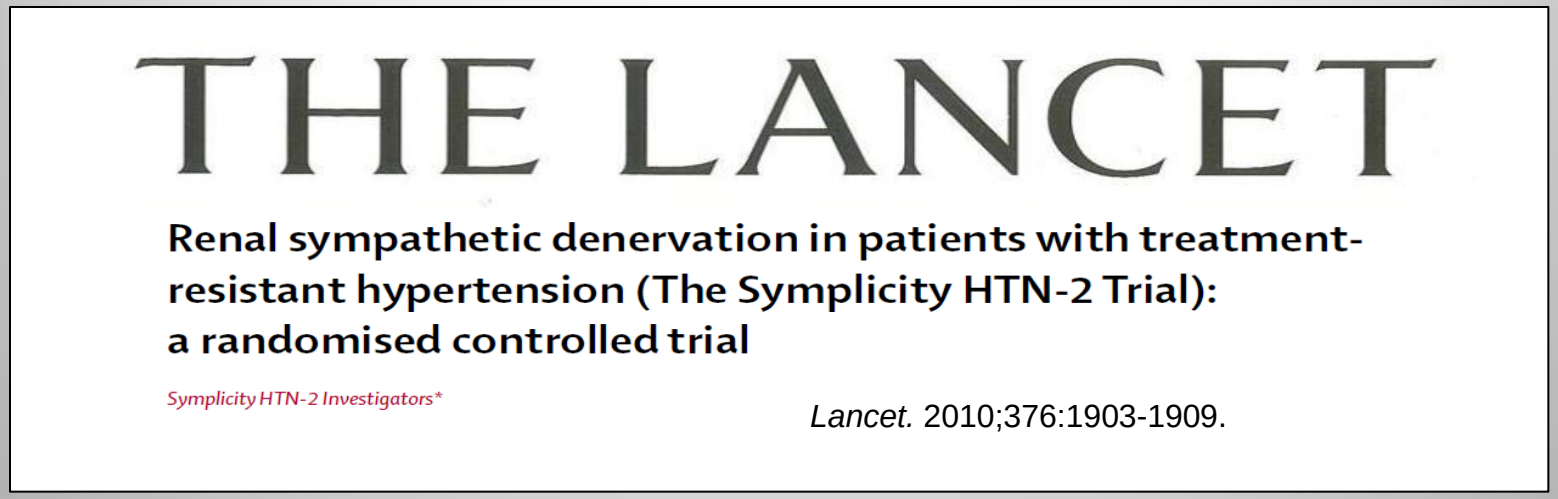


Chronic Safety Out to 3 Years

- 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 was no significant change in mean electrolytes or eGFR

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

Symplicity HTN-2 Design


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 (RDN) for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- Patients: 106 patients with drug-resistant hypertension randomized 1:1 to treatment with RDN vs. control
- Clinical Sites: 24 centers in Europe, Australia, & New Zealand
  - 67% were designated hypertension centers of excellence
- Primary Endpoint: Office systolic BP change from baseline at 6 months

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

Participating Centers: HTN-2 Randomized Controlled Trial

- Universitätsklinikum des Saarlandes
  Homburg, Germany (Michael Böhm)
- CardioVascular Center Frankfurt
  Frankfurt, Germany (Horst Sievert)
- Universitätsklinikum Düsseldorf
  Düsseldorf, Germany (Lars Christian Rump)
- Universität Erlangen-Nürnberg
  Erlangen, Germany (Roland Schmieder)
- Barts and The London
  London, UK (Mel Lobo)
- Pauls Stradins Clinical University Hospital Riga,
  Latvia (Andrejs Erglis)
- L'Hôpital Européen Georges Pompidou
  Paris, France (Guillaume Bobrie)
- John Hunter Hospital
  Newcastle, Australia (Suku Thambar)
- Cliniques Universitaires Saint-Luc
  Brussels, Belgium (Alexandre Persu)
- Universitaetsklinikum Schleswig-Holstein Lübeck,
  Germany (Heribert Schunkert)
- Universität zu Köln
  Köln, Germany (Uta Hoppe)
- The Alfred Hospital
  Melbourne, Australia (Henry Krum)
- Universität Leipzig – Herzzentrum
  Leipzig, Germany (Dierk Scheinert)
- Allgemeines Krankenhaus der Stadt Wien Vienna,
  Austria (Thomas Binder)
- Samodzielna Pracownia Hemodynamiczna Warsaw,
  Poland (Andrzej Januszewicz & Adam Witkowski)
- Hospital 12 de Octubre
  Madrid, Spain (Luis Ruilope)
- St. Vincent's Hospital
  Melbourne, Australia (Robert Whitbourn)
- Universitätsklinikum Essen
  Essen, Germany (Heike Bruck)
- Kent and Canterbury Hospital
  Canterbury, UK (Mark Downes)
- University Hospital Zurich
  Zurich, Switzerland (Thomas Lüscher)
- University of Glasgow
  Glasgow, UK (Alan Jardine)
- Auckland City Hospital
  Auckland, New Zealand (Mark Webster)
- Herz-Zentrum Bad Krozingen
  Bad Krozingen, Germany (Thomas Zeller)
- The John Paul II Hospital
  Krakow, Poland (Jerzy Sadowski)

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. The Lancet 2010: 376:1903-1909

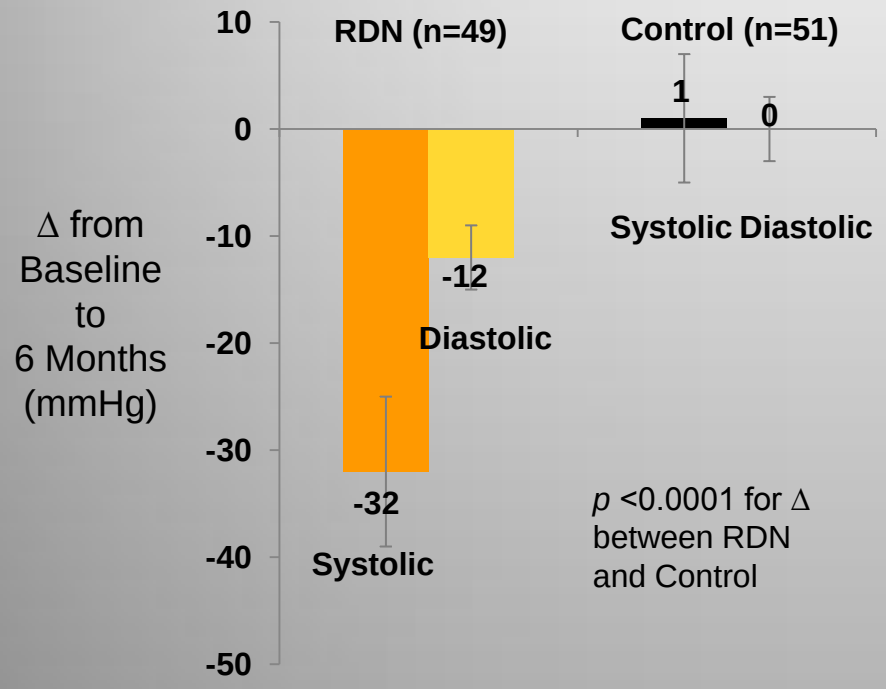
Baseline Medications

	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

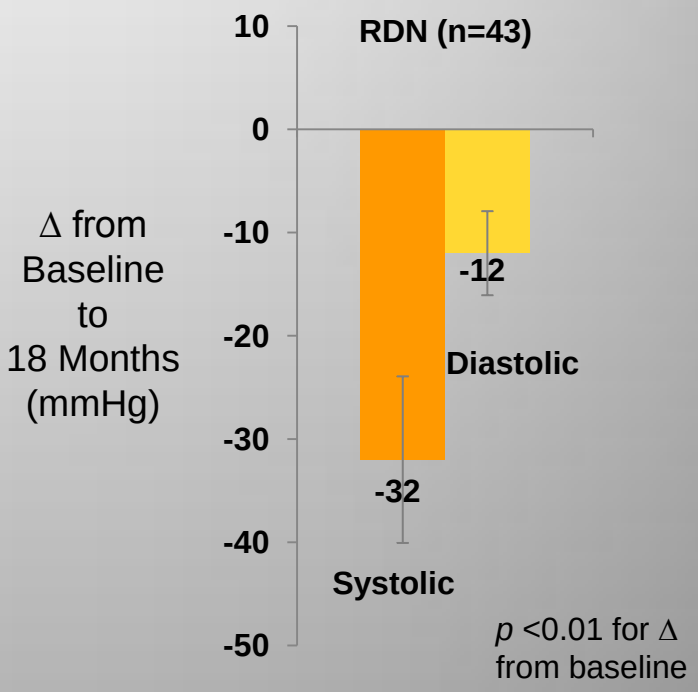
Symplicity HTN-2 Investigators. The Lancet 2010: 376:1903-1909

Symplicity HTN-2: RDN Superior to Medical Management, Reductions Sustained to 18M

Primary Endpoint (6M post Randomisation)



Latest Follow-up (18M post Randomisation)



Primary Endpoint:

- >80% of RDN patients had ≥10 mmHg reduction in SBP
- 5 patients had ≤ 5mmHG reduction in SBP

Real World Outcomes

- 35 sequential rHTN patients
  - 63.6 ± 11.7 years
  - 36% women
  - 36% diabetic
  - 15% eGFR < 60ml/min/m2
  - Office BP: 181 mmHg ± 21.9
  - ABPM : 171.6 mmHg ± 19.6
- At 6 months
  - BP reduced 30.3 ± 21.6
  - ABPM reduced 23.3 ± 12.1

Darren Mylotte et. al. 2012 ACC; 2012 ESC

How do we choose between pills and interventional therapy

- Why restrict availability of interventional therapy to those with highest pressures or those failing all medications?
- Does patient preference between life long polypharmacy versus a therapy matter?
- Can we exclude non-compliant patients from receiving interventional therapy?

Are there exploitable differences between renal denervation devices?

- Does the mode of renal denervation change:
  - Mix of afferent/efferent denervation
    - Does this make a difference?
  - Risk of early or late complications
  - Responder rate
  - Absolute response

Is there value to screening RDN patients?

- What is the value of screening…
  - If complications of RDN are scarce?
  - If the RDN response rate is high?
  - If screening tests are imperfect?

Terminal Thoughts