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Serviço de Medicina I
Serviço de Cardiologia I
C.H.L.N.

UNIDADE DE CARDIOLOGIA DE INTERVENÇÃO

HOSPITAL DE SANTA MARIA

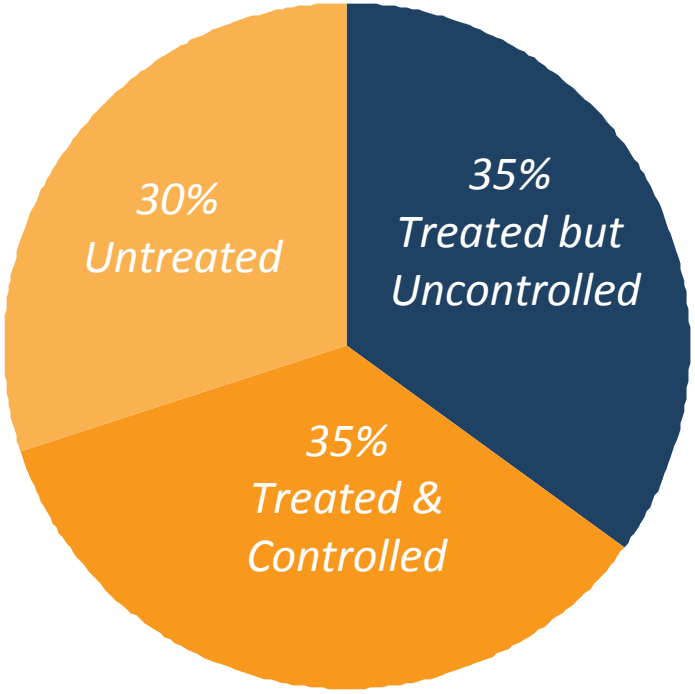
Sympathetic Renal Denervation

current state & future outlook

New Frontiers in Cardiology, 3rd edition

Ericeira, February 9th 2013

Hypertension Epidemiology



- Single largest contributor to death worldwide
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensives are controlled to established BP targets
- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025

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

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VOL. XX, NO. X, 2013
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http://dx.doi.org/10.1016/j.jcin.2012.09.005

STATE-OF-THE-ART PAPER

Endovascular Treatment of Resistant and Uncontrolled Hypertension

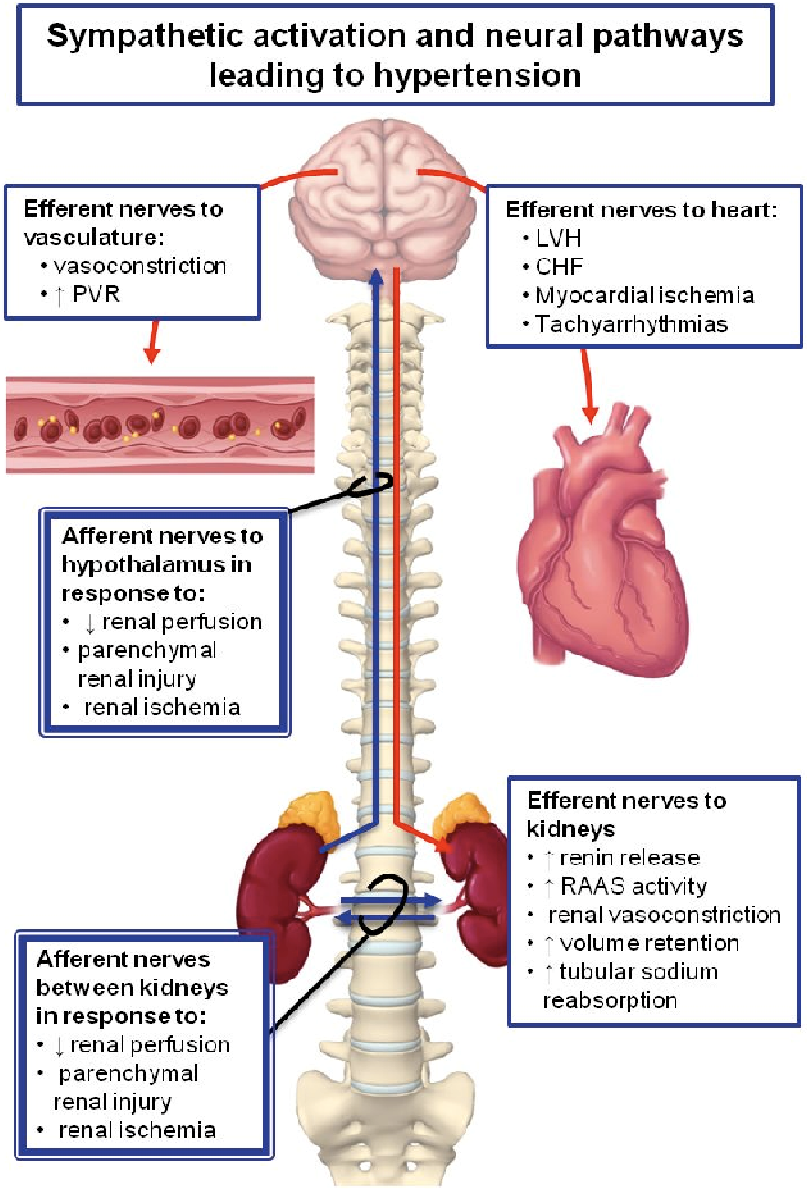
Therapies on the Horizon

Matthew C. Bunte, MD,* Eduardo Infante de Oliveira, MD,†
Mehdi H. Shishehbor, DO, MPH*

Cleveland, Ohio; and Lisbon, Portugal

Renal Sympathetic Afferent & Efferent Nerve Activity:

Kidney as Recipient and Producer of Sympathetic Signals



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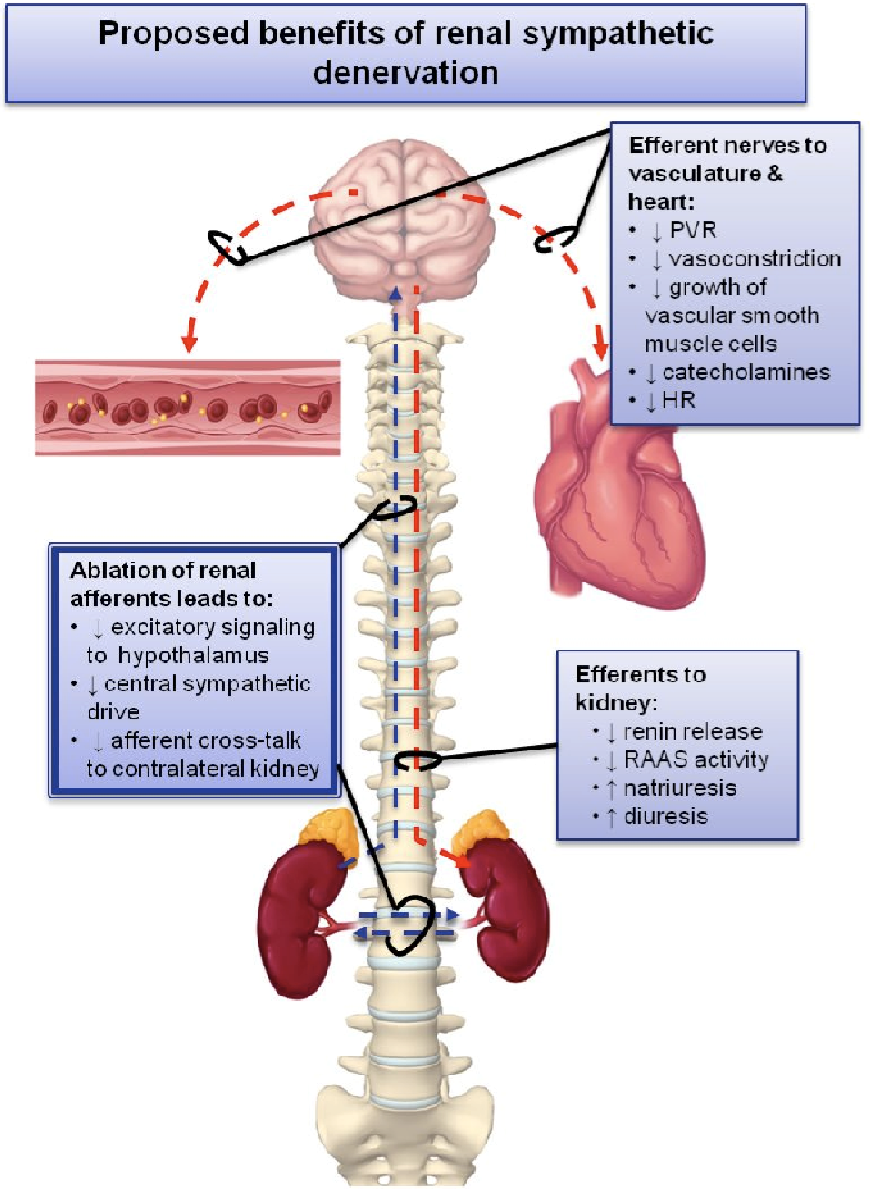
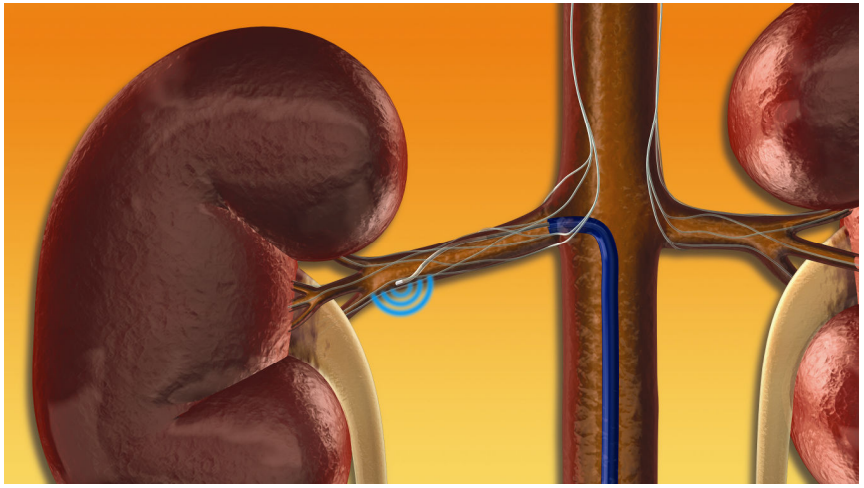
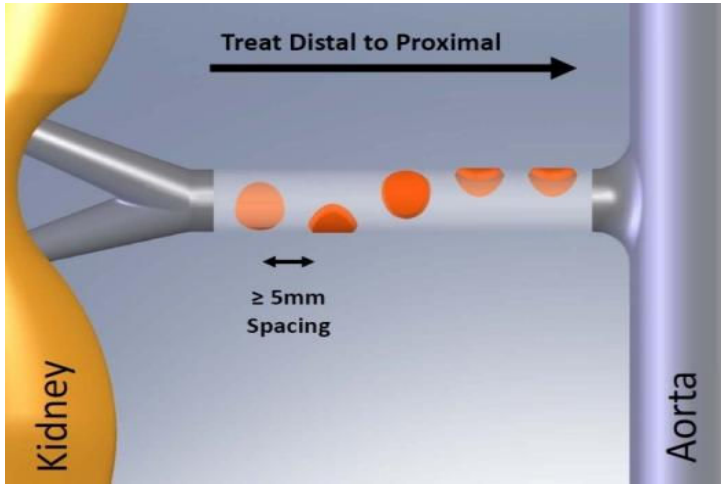


Renal Nerve Anatomy Allows a Catheter-Based Approach

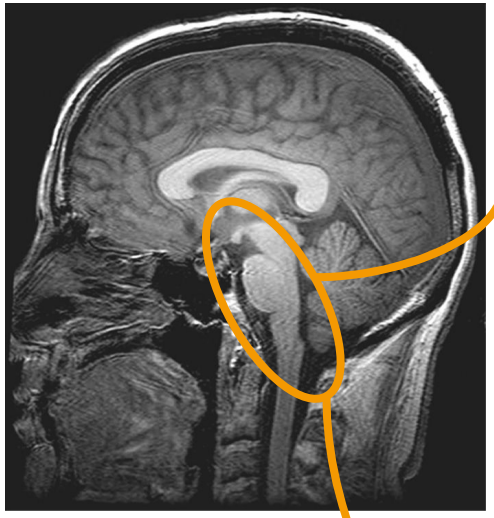




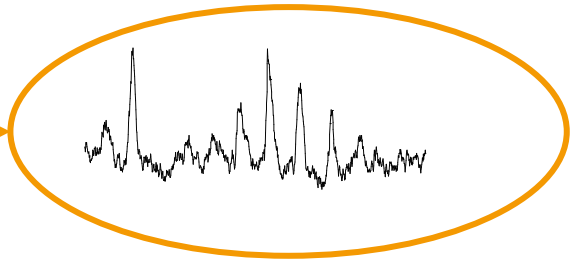
- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms

In the United States: Caution: Investigational Device. Limited by U.S. law to investigational use.

Proof of Principle

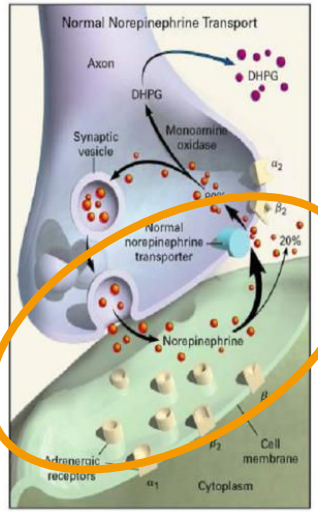


Central Sympathetic Nerve Activity



Muscle Sympathetic Nerve Activity (MSNA)

Renal Sympathetic Nerve Activity



Norepinephrine Spillover

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

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

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

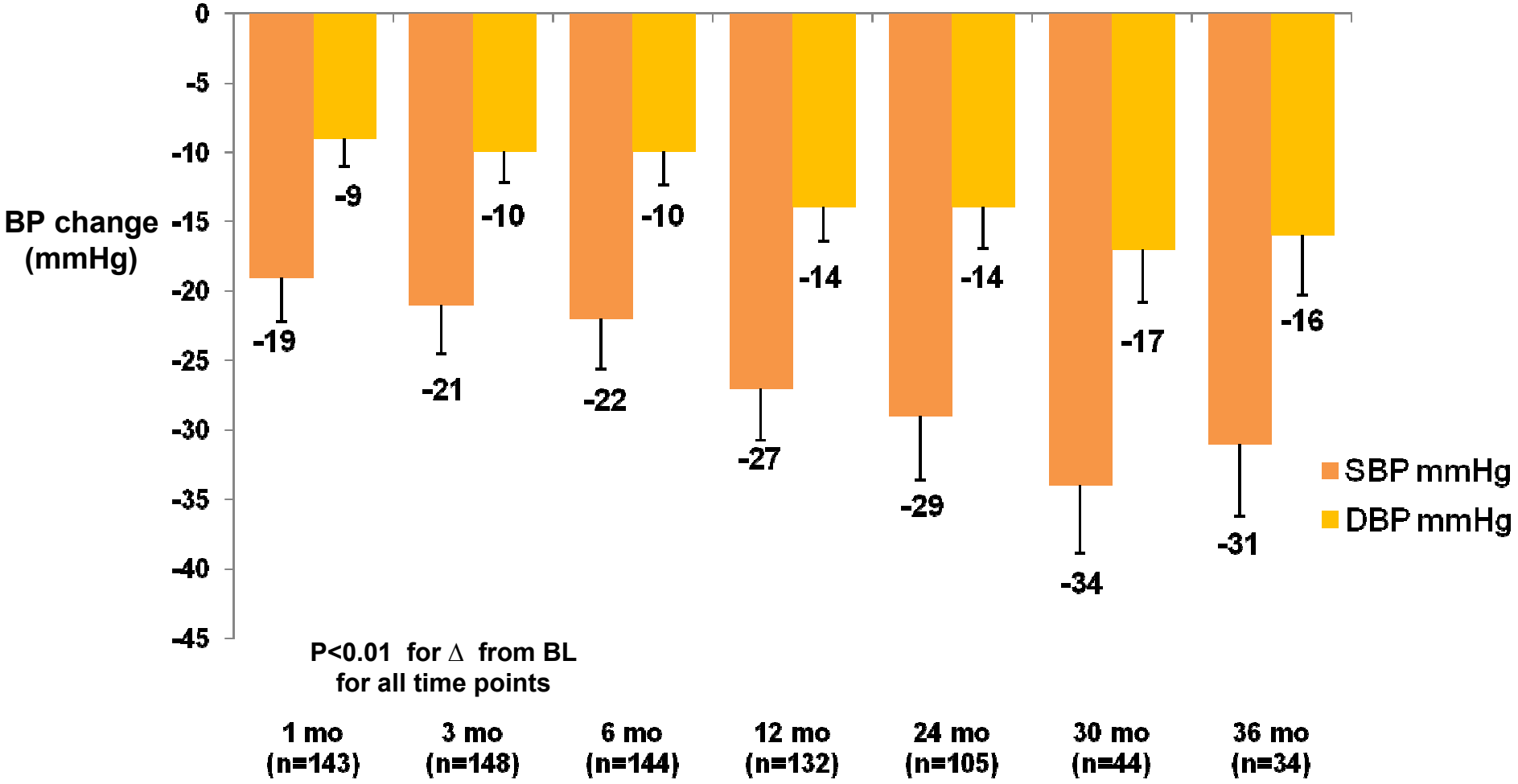
Expanded Cohort* – This Report (Symplicity HTN-1):

-Expanded cohort of patients (n=153)

-36-month follow-up

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

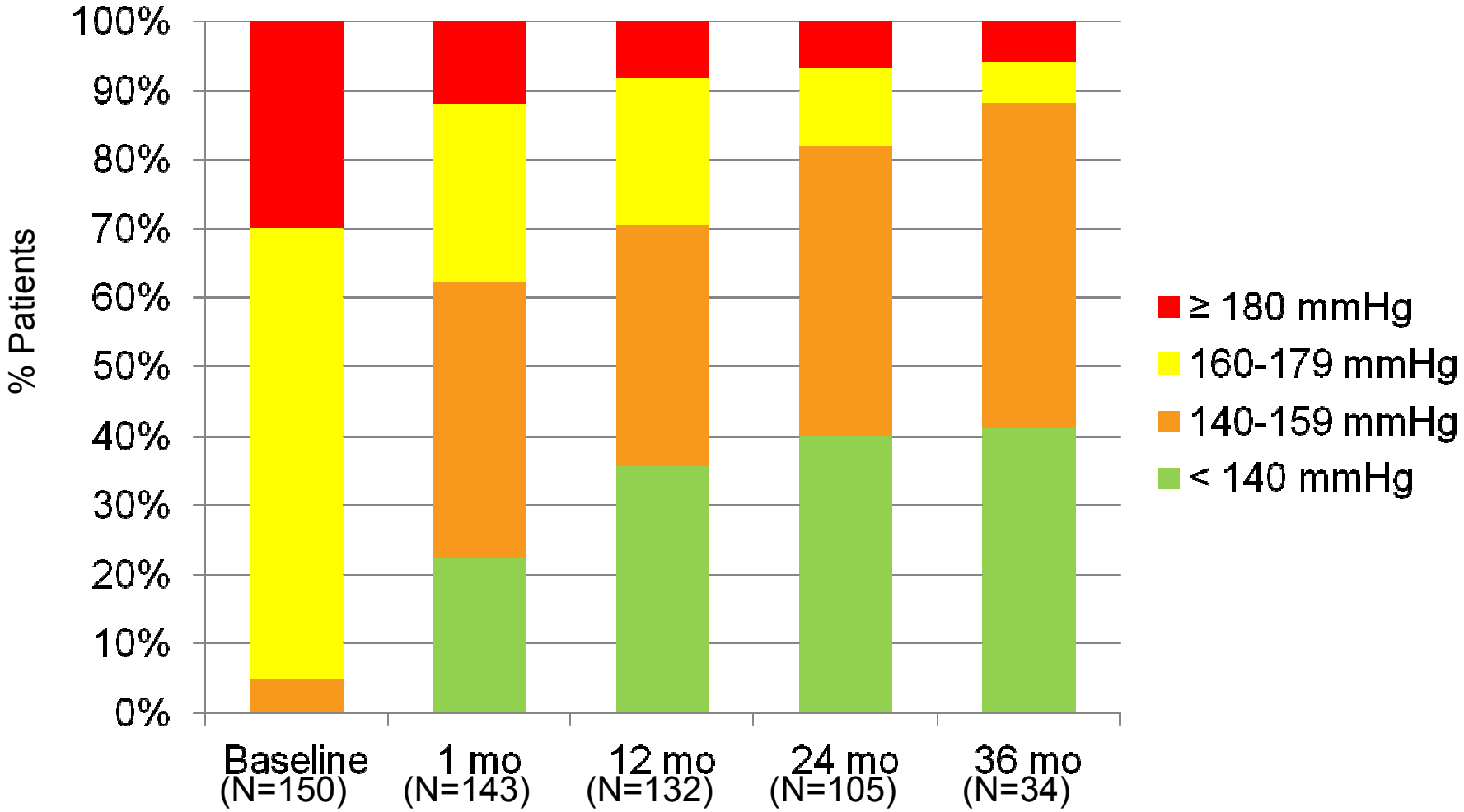
Symplicity HTN-1: BP Reductions 3 years



Reported as mean with 95% confidence intervals

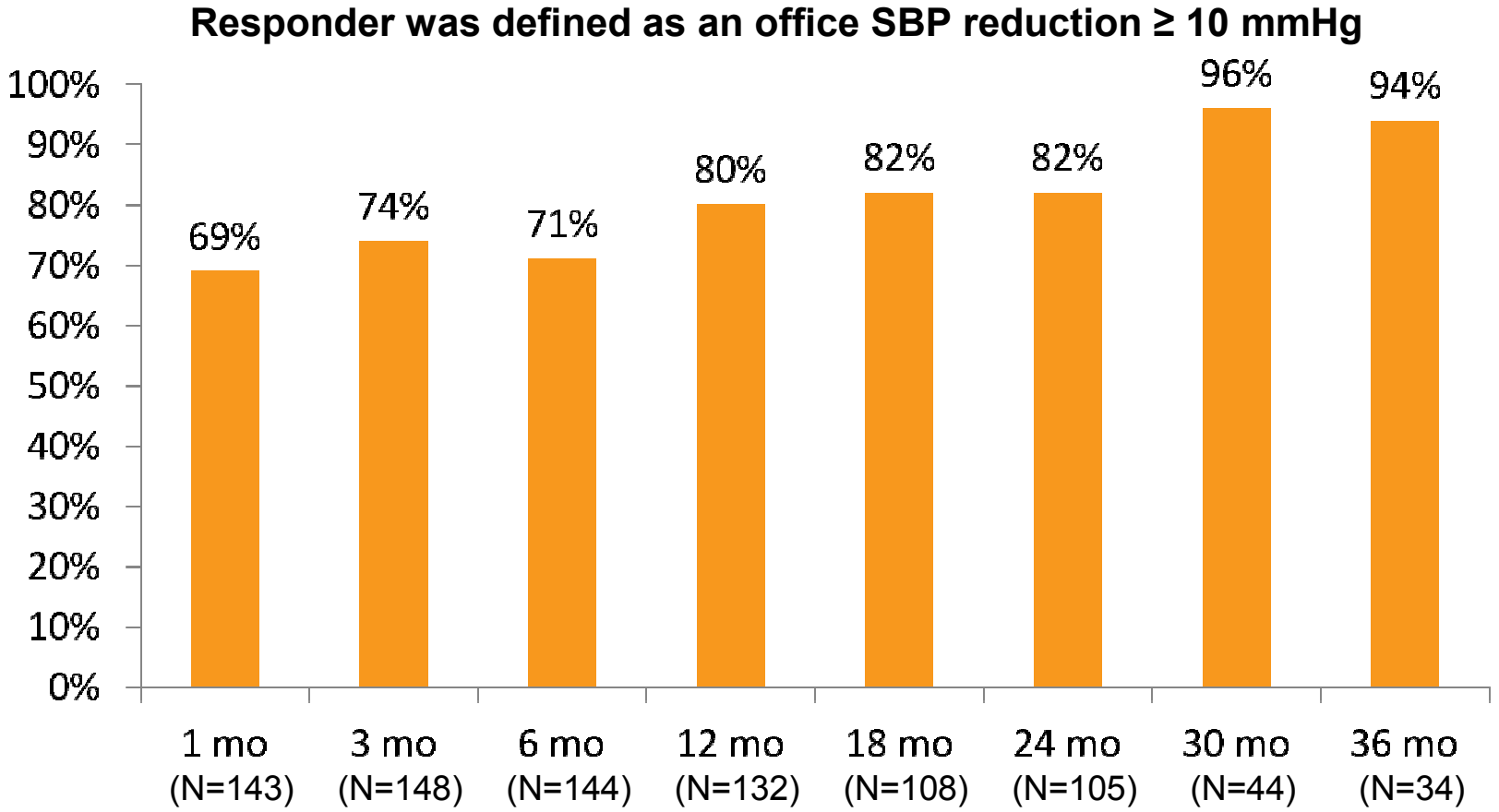
Schlaich M, TCT 2012

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



Schlaich M, TCT 2012

Symplicity HTN-1: Percentage Responders Over Time



*Full cohort has not yet been analyzed at all time points

Schlaich M, TCT 2012

Symplicity HTN-2 Trial

- Treatment-resistant HTN population
- BL OBP 178/97 mmHg
- 49 RDN, 51 Control
- Age 58 years
- BMI 31 kg/m²
- 40% with Diabetes
- eGFR 77*
- Avg # meds 5.2
- RDN and Control groups generally well-matched

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

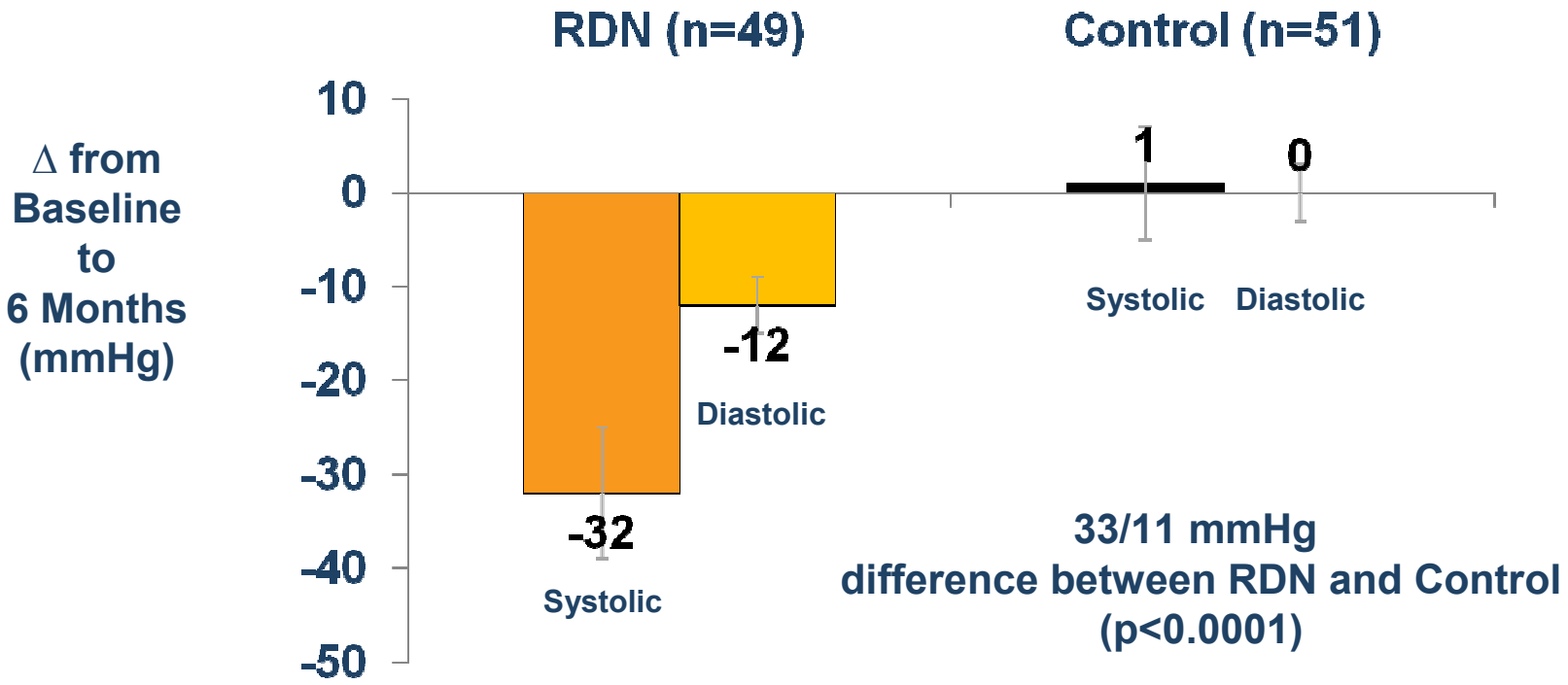
Exclusion Criteria:

- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m² (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

*MDRD, ml/min/1.73m²

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

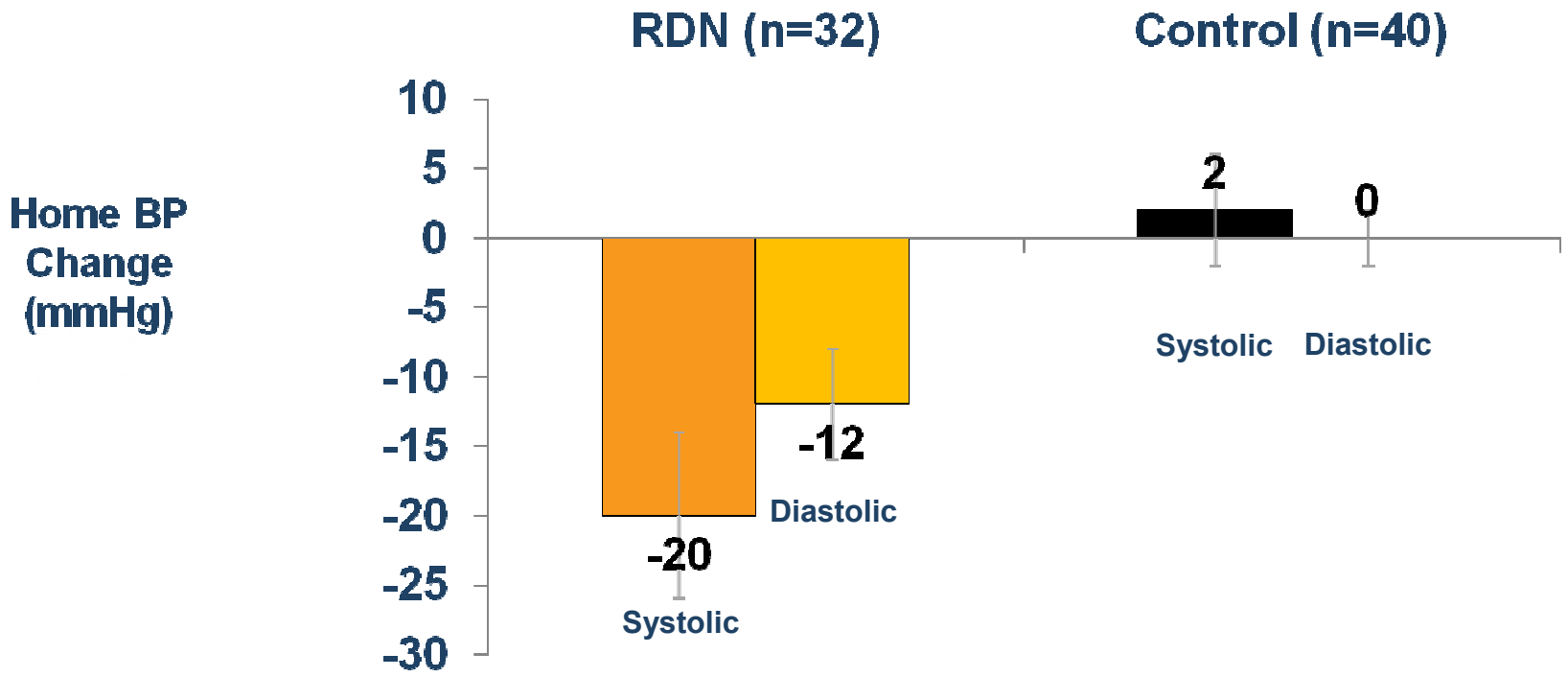
Primary Endpoint: 6-Month Office BP



- 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.

Home & 24 Hour Ambulatory BP



24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. The Lancet. 2010.

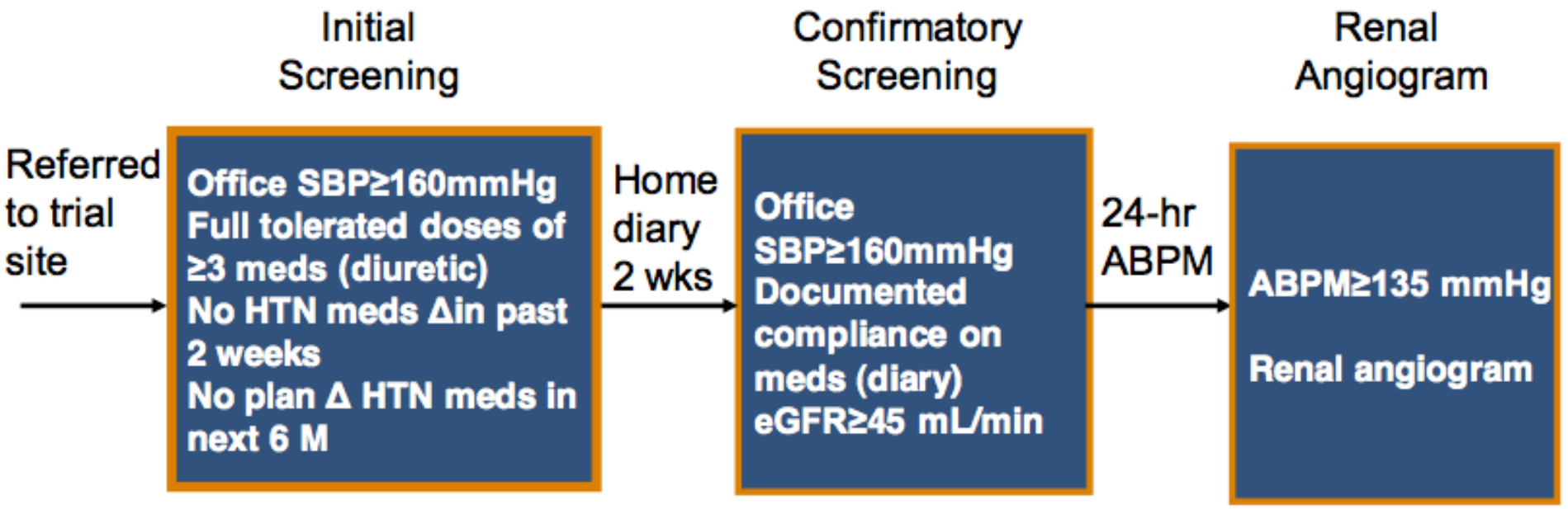
Symplicity HTN-3 Trial: Inclusion Criteria

- Average SBP ≥160mmHg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80
- eGFR ≥45mL/min

Randomization

- N = 530 randomized (enroll ~ 1060 at 530 sites)
- Randomization
  - —2:1 ratio – Treatment or Control
  - —Stratified by study center and by race (African American vs. non-African American)
- Single Blind
  - —Specific staff & subject until 6 months post randomization

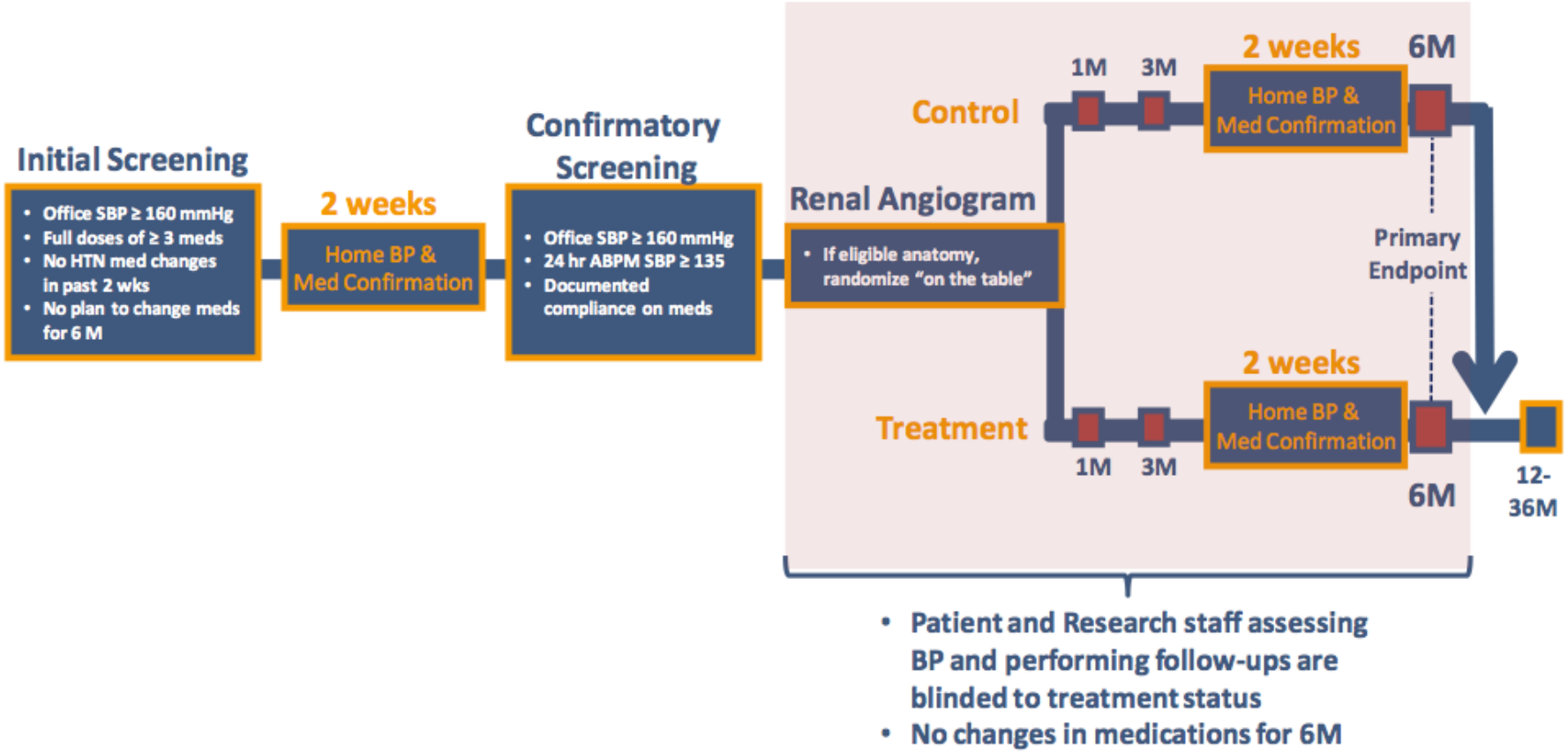
Symplicity HTN-3 Trial: Referral to Randomization Steps



E. Infante de Oliveira, V. Ramalhinho, A. Bordalo, P. Canas da Silva, F. Pinto, J. Braz Nogueira, A. Nunes Diogo

Symplicity-3 Design

Study Design Flow Chart



Endpoints

- Primary efficacy endpoint: Change in office SBP from baseline to 6 months post randomization
- Secondary efficacy endpoint: Change in 24hr ABPM SBP average from baseline to 6 months
- Primary safety endpoint: Mortality, ESRD, or procedural complications w/in 1 month or new RAS w/in 6 months post randomization

E. Infante de Oliveira, V. Ramalhinho, A. Bordalo, P. Canas da Silva, F. Pinto, J. Braz Nogueira, A. Nunes Diogo

Medtronic Global SYMPLICITY Registry

Objectives:

- Assess procedural and long term safety of renal denervation
- Evaluate effectiveness of renal denervation on clinical outcomes
- Establish procedural benchmarking & physician practice patterns
- Evaluate the effect of geographical variations in patients and procedural characteristics on clinical outcomes
- Perform Quality of Life analysis

First enrollment
February 2nd, 2012

Scope:

- Over 200 sites world wide; at least 5000 patients
- Prospective, single-arm, open-label, non-interventional registry
- In accordance with *Instructions For Use*
- Geographies with commercial availability of Medtronic Symplicity Renal Denervation System

Renal denervation reduces left ventricular mass and improves diastolic function

JACC

Journal of the American College of Cardiology

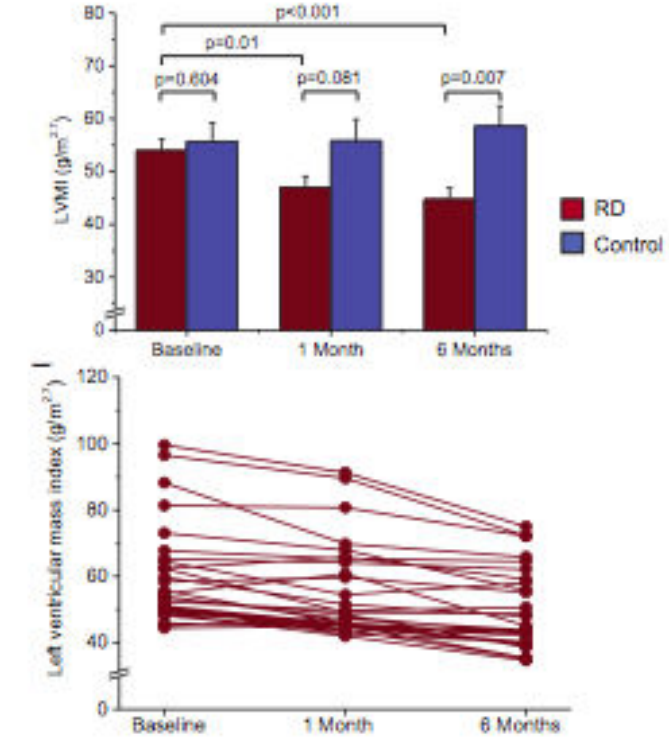
CLINICAL RESEARCH — Interventions in Hypertension

Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

Mathias C. Brandt, MD,*† Felix Mahfoud, MD,§ Sara Reda, MD,*†
Stephan H. Schirmer, MD, PhD,§ Erland Erdmann, MD,† Michael Böhm, MD,§
Uta C. Hoppe, MD*†‡

Salzburg, Austria; and Cologne and Homburg/Saar, Germany

JACC 2012;59:901–9



n=64 (46 RDN vs 18 control)

Renal Denervation in Chronic Kidney Disease

J Am Soc Nephrol. 2012 Jul;23(7):1250-7. Epub 2012 May 17.

Renal Denervation in Moderate to Severe CKD.

Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, Sobotka PA, Böhm M, Cremers B, Esler MD, Schlaich MP.

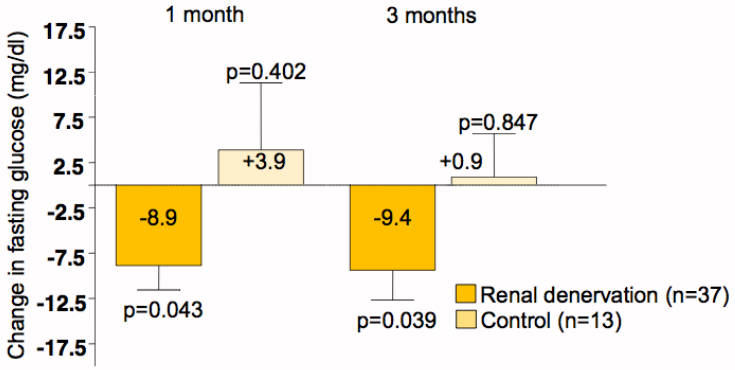
Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, P.O. Box 6492, St Kilda Road Central, Melbourne, Victoria 8008, Australia. markus.schlaich@bakeridi.edu.au.

Abstract

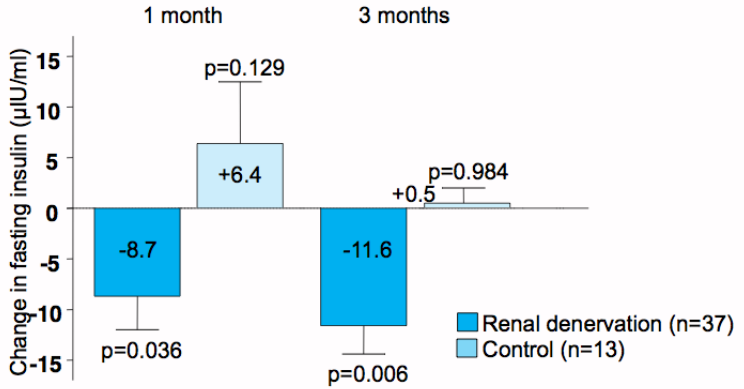
Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) < 45 ml/min per 1.73 m(2) is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3-4 CKD (mean eGFR, 31 ml/min per 1.73 m(2)). We used CO(2) angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO(2) angiography. Mean baseline BP ± SD was 174±22/91±16 mmHg despite the use of 5.6±1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were -34/-14, -25/-11, -32/-15, and -33/-19 mmHg, respectively. Night-time ambulatory BP significantly decreased (P<0.05), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3-4 CKD and resistant hypertension.

PMID: 22595301 [PubMed - in process] PMCID: PMC3380649 [Available on 2013/7/1]

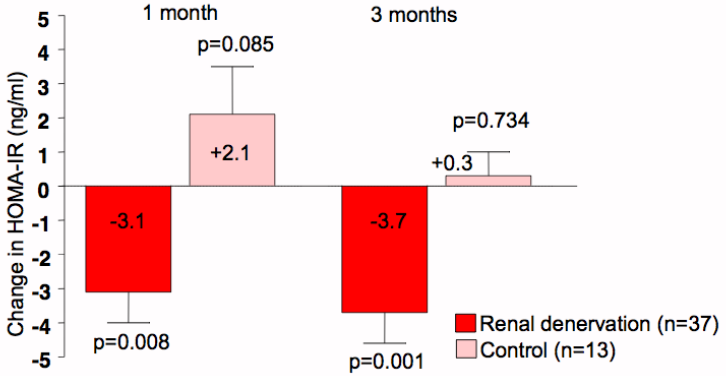
RD reduces fasting glucose



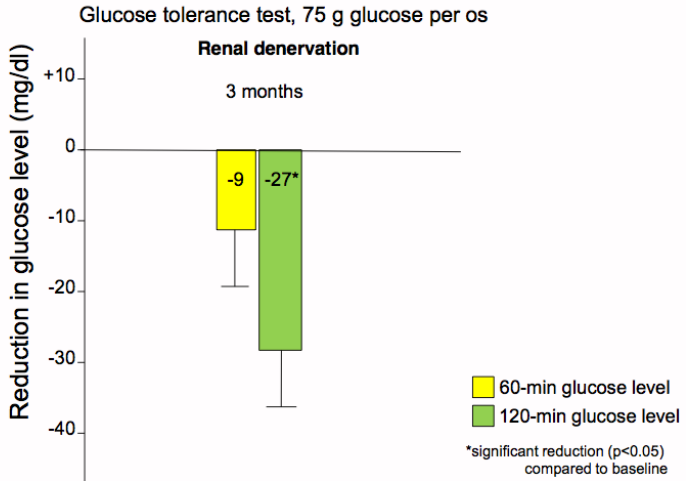
RD reduces fasting insulin



RD improves insulin sensitivity



RD improves glucose tolerance



Mahfoud F. Circulation. 2011; 123:1940-1946

Hospital Santa Maria

Renal Denervation Program

	Baseline	1-month	*p*-Value
Systolic BP (mmHg)	180 ± 27	161 ± 29	0.04
Diastolic BP (mmHg)	104 ± 8	95 ± 4	0.04
Fasting glucose (mg/dL)	129 ± 66	120 ± 36	NS
HbA1C (%)	7.0 ± 0.8	6.7 ± 0.9	NS
Fasting Insulin (mU/mL)	19 ± 11	18 ± 11	NS
Fasting C-peptide (ng/mL)	2.5 ± 1.3	2.2 ± 1.0	NS
HOMA-IR (%S)	2.3 ± 1.4	1.8 ± 0.9	0.04
Glucose tolerance test (mg/dL)	256 ± 142	173 ± 52	< 0.001

HOMA – Homeostatic model assessment

Effects of Renal Sympathetic Denervation on Blood Pressure, Sleep Apnea Course, and Glycemic Control in Patients With Resistant Hypertension and Sleep Apnea

Adam Witkowski, Aleksander Prejbisz, Elżbieta Florczak, Jacek Kądziela, Paweł Śliwiński, Przemysław Bieleń, Ilona Michałowska, Marek Kabat, Ewa Warchoł, Magdalena Januszewicz, Krzysztof Narkiewicz, Virend K. Somers, Paul A. Sobotka, Andrzej Januszewicz

	Baseline	3 months	6 months
Improvement in AHI	-	7/10 patients	8/10 patients
AHI, events/hr	30.7 ± 26.5	20.0 ± 25.3 (p=ns)	16.1 ± 22.2 (p=ns)
Epworth Sleepiness Scale Score, points	9	6.5 (p=ns)	7 (p<0.05)
120 min glucose level OGTT, mmol/l	8.4 ± 3.3	6.8 ± 2.5 (p=0.051)	6.8 ± 2.9 (p<0.05)
HbA1C, %	6.4 ± 0.8	6.0 ± 0.7 (p<0.05)	5.9 ± 0.7 (p<0.05)

Witkowski A. Hypertension. 2011;

Chronic heart failure with renal impairment
SYMPLICITY HF 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

Major Assessments:

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

Sympathetic renal denervation – current state & future outlook

E. Infante de Oliveira, V. Ramalhinho, A. Bordalo, P. Canas da Silva, F. Pinto, J. Braz Nogueira, A. Nunes Diogo

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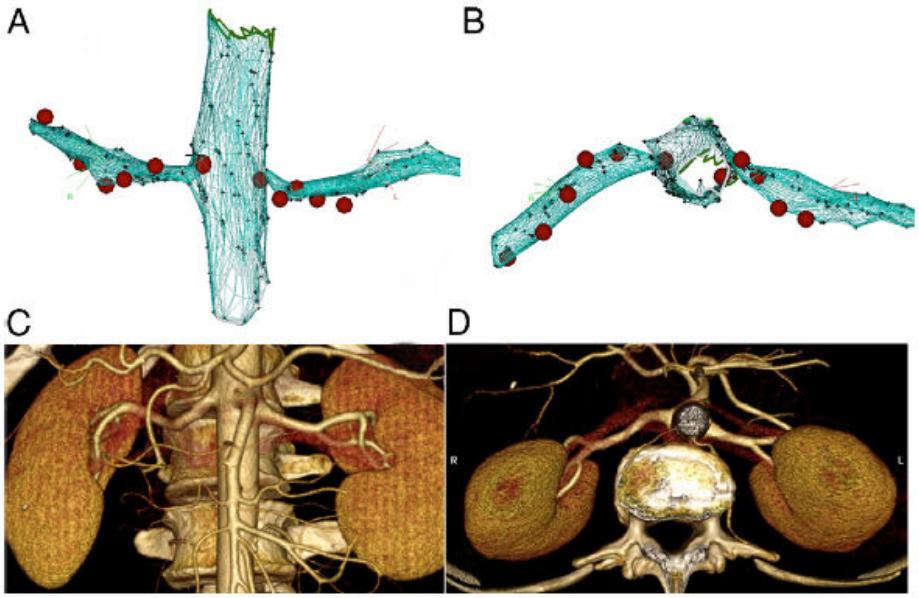
http://dx.doi.org/10.1016/j.jacc.2012.05.036

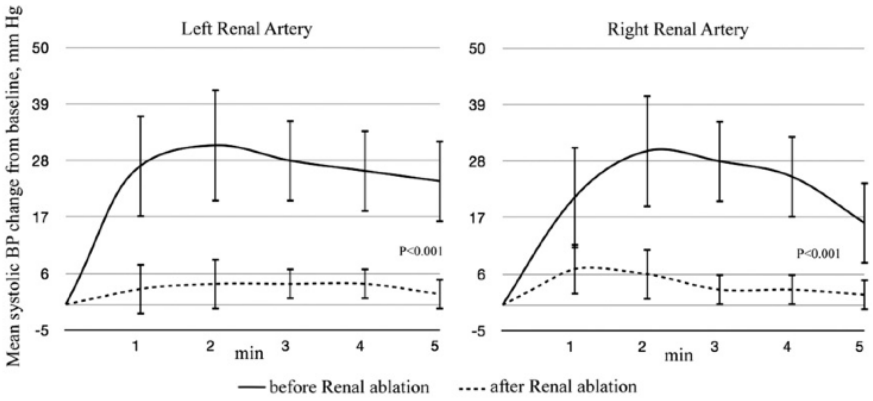
Heart Rhythm Disorders

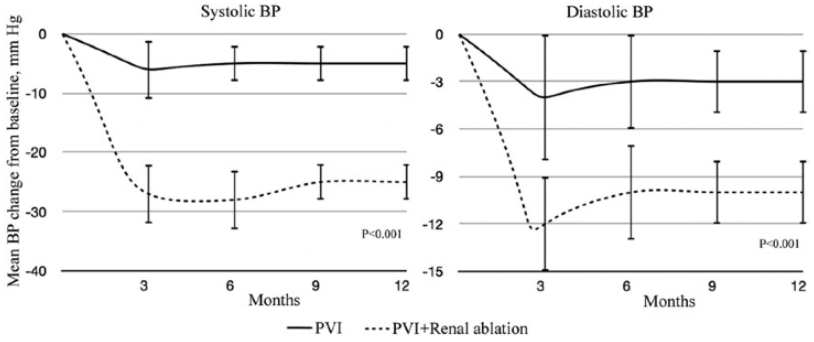
A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension

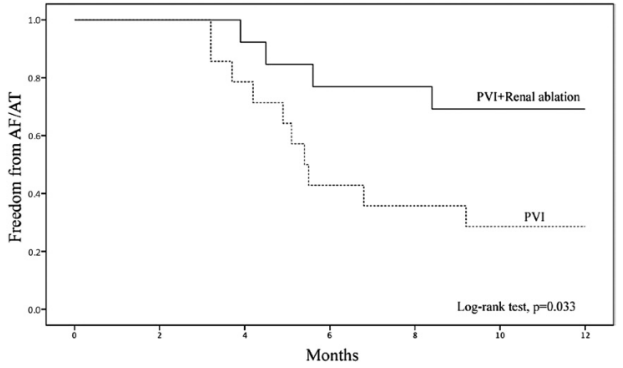
Evgeny Pokushalov, MD, PhD,* Alexander Romanov, MD,* Giorgio Corbucci, PhD,†
Sergey Artyomenko, MD,* Vera Baranova, MD,* Alex Turov, MD,* Natalya Shirokova, MD,*
Alexander Karaskov, MD, PhD,* Suneet Mittal, MD,‡ Jonathan S. Steinberg, MD‡

Novosibirsk, Russia; Maastricht, the Netherlands; and New York, New York



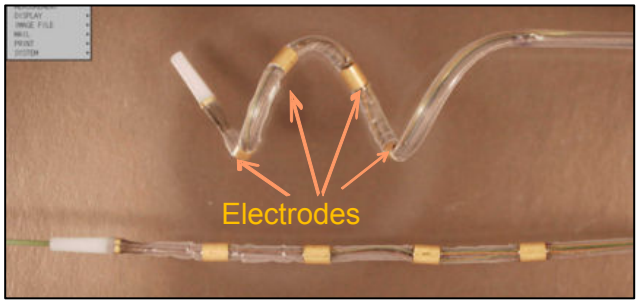


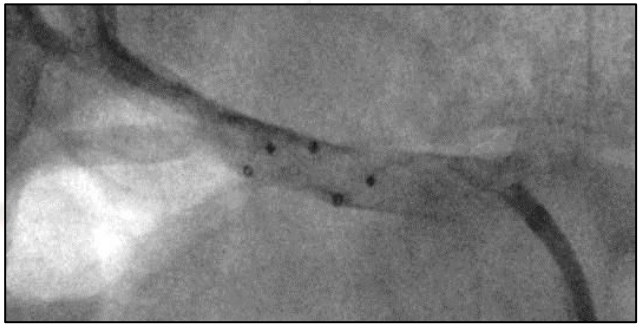




New Multi-Electrode System Design Goals

- Reduced Ablation Time
- Multi-Electrode
- 6F Guide Compatible
- Monorail Delivery
- Non-Occlusive
- Vessel Conformability



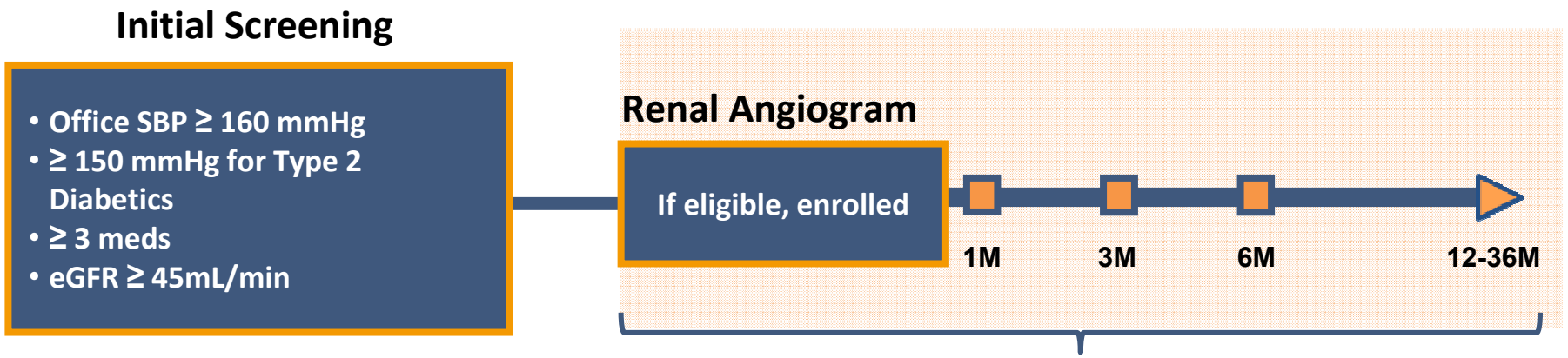


Medtronic RDN Technology Comparison

Technology	Single Electrode	Multi-Electrode
Delivery Access	Direct	Monorail
Guide Catheter Compatability	6F	6F
# Electrodes	1	4
Electrode Selectability	1	4/ 3/ 2/ 1
# of Placements/Artery	4-6	1
Energy Delivery Time per Placement	2 mins	1 min
Total Energy Delivery Time	16-24 mins	2 mins

Multi-Electrode System FIM Phase II Design

Purpose: To assess performance of Medtronic multi-electrode RDN system



- Up to 50 Patients (*9 completed*)
- Inc/Excl criteria similar to Symplicity HTN-1
- No Confirmatory BP screenings or ABPM
- Renal artery anatomy eligibility
  - ≥4mm diam, ≥ 20mm treatable length
  - No stenosis > 50%
  - No prior stent/angioplasty
- Primary Goal: Acute procedural safety assessment
- Secondary Goals:
  - Δ in office BP at all f/u time-points
  - AE evaluation at all f/u time-points
  - Duplex Ultrasound at 3M or 6M –further evaluation if indicated

Sympathetic renal denervation – current state & future outlook

E. Infante de Oliveira, V. Ramalhinho, A. Bordalo, P. Canas da Silva, F. Pinto, J. Braz Nogueira, A. Nunes Diogo

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Endovascular Treatment of Resistant and Uncontrolled Hypertension

Therapies on the Horizon

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Table 1: Overview of clinical trials enrolling hypertensive patients for endovascular renal nerve ablation.

Product Name	Product Design	Clinical Trial Name	Hypertension Type Studied	Trial Status	Clinical Trial ID*	Sponsor
RADIOFREQUENCY ABLATION						
Symplicity RFA catheter	Single-electrode RFA catheter	SYMPLICITY HTN-1	Resistant	Active, not recruiting	NCT00664638	Medtronic, Inc.
		SYMPLICITY HTN-2	Resistant	Active, not recruiting	NCT00888433	
		SYMPLICITY HTN-3	Resistant	Recruiting	NCT01418261	
		Effect of Renal Denervation on Biological Variables	Resistant	Recruiting	NCT01427049	
		Renal nerve ablation in CKD Patients	Resistant, with stage III – V CKD	Recruiting	NCT01442883	
		PRAGUE – 15	Uncontrolled	Recruiting	NCT01560312	
		Renal Denervation in Patients with RH and OSA	Uncontrolled, with OSA	Recruiting	NCT01366625	
EnligHTN RFA catheter	Multi-electrode RFA catheter	ARSENAL	Resistant	Active, not recruiting	NCT01438229	St. Jude, Inc.
Vessix V2 RFA catheter	Balloon-mounted RFA catheter	REDUCE-HTN	Resistant	Recruiting	NCT01541865	Vessix Vascular, Inc.
OneShot RFA catheter	Irrigated, balloon-mounted RFA catheter	RAPID	Resistant	Recruiting	NCT01520506	Maya Medical, Inc.
THERMOCOOL cryoablative catheter	Irrigated RFA catheter	SWAN HT	Uncontrolled	Recruiting	NCT01417221	Biosense Webster, Inc.
		SAVE	Uncontrolled	Recruiting	NCT01628198	
		RELIEF	Uncontrolled	Recruiting	NCT01628172	
Chilli II cryoablative catheter	Irrigated RFA catheter	SAVE	Uncontrolled	Recruiting	NCT01628198	Boston Scientific, Inc
ULTRASONIC ABLATION						
PARADISE ultrasonic catheter	Ultrasonic balloon catheter	REALISE	Resistant	Recruiting	NCT01529372	ReCor Medical, Inc.
TIVUS ultrasonic catheter	Ultrasonic auto-regulating balloon catheter	In development.				Cardiosonic, Ltd.
Kona Medical ultrasonic system	Low-intensity external ultrasonic ablation system	In development.				Kona Medical, Inc.
TISSUE-DIRECTED PHARMACOLOGIC ABLATION						
Bullfrog Microinfusion catheter	Microneedle-equipped balloon catheter	In development.				Mercator MedSystems, Inc.

*Available at www.clinicaltrials.gov; RFA: radiofrequency ablation; CKD: chronic kidney disease; OSA: obstructive sleep apnea

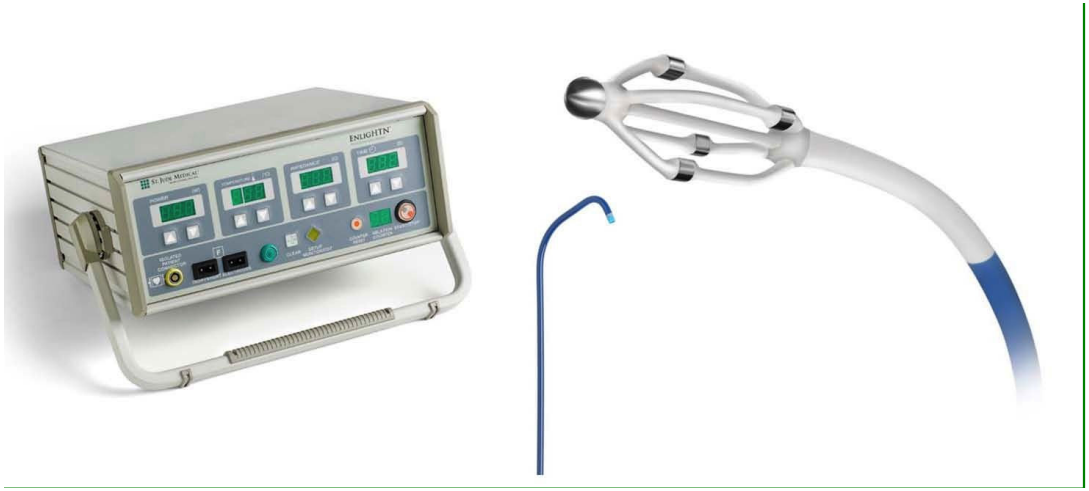
EnligHTN

Monopolar RF

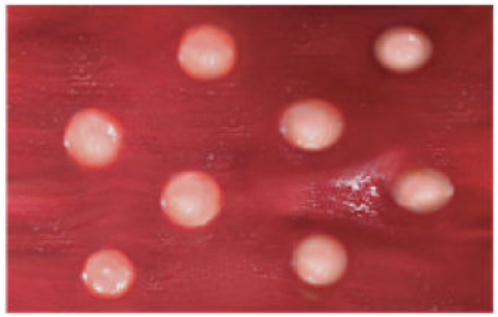
Multi-ablation basket

90 sec energy per electrode

8 Fr compatible

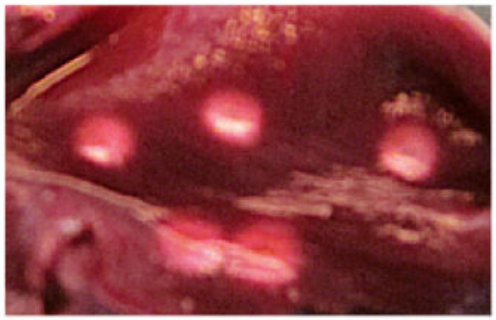


ENLIGHTN MULTI-ELECTRODE ABLATION[1]



Precision Pattern

SINGLE-ELECTRODE ABLATION[1]



Random Pattern

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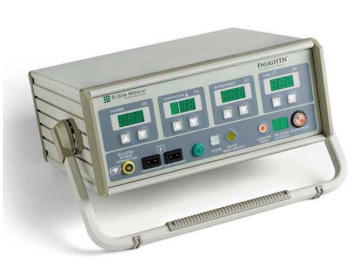
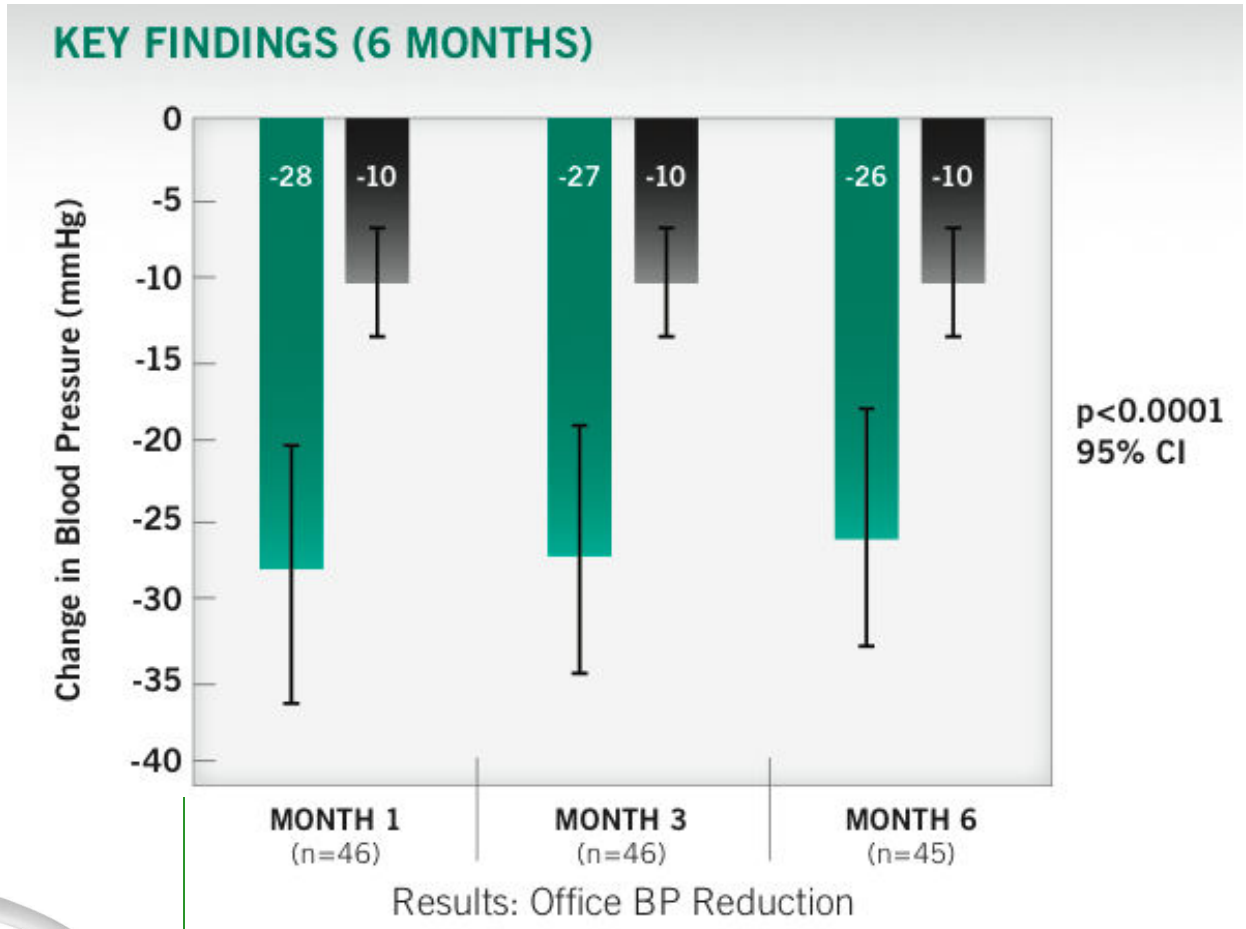
EnligHTN I
(n=46)





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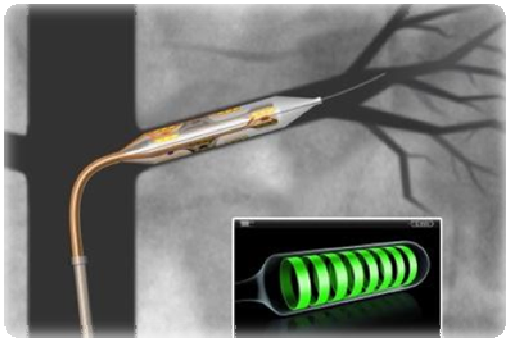
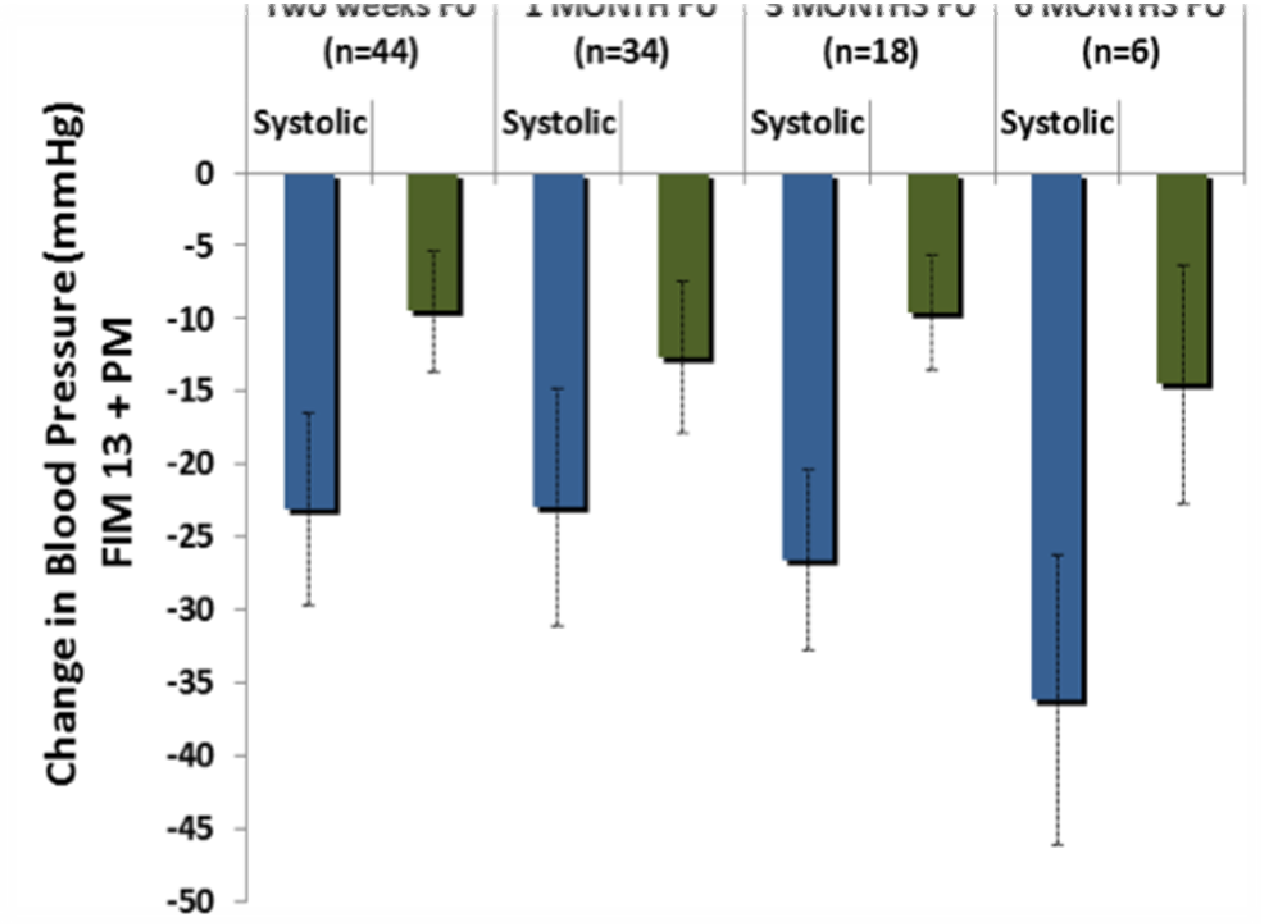
Vessix – pilot study & post market



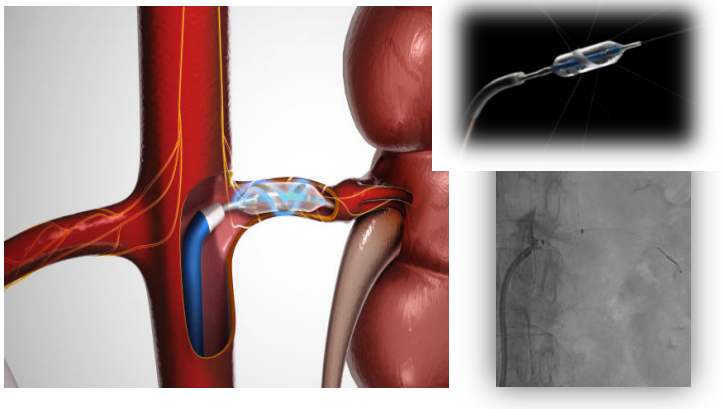


Vessix, Symplicity & EnligHTN comparison

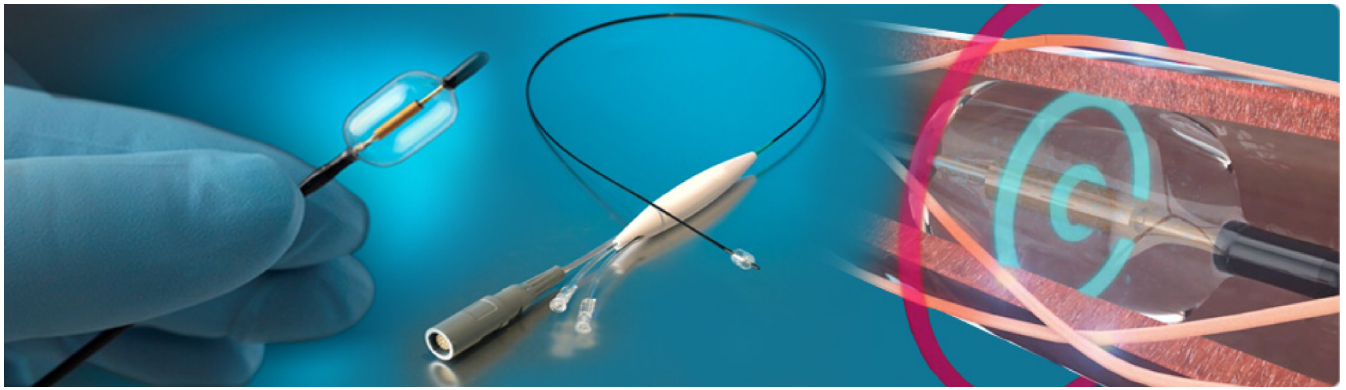


	V2	Symplicity	EnligHTN
Total therapy time for both arteries (minutes)	1-2	24-40	24-34
Technology type	Bipolar RF	Mono RF	Mono RF
Power (watts) per electrode	**0.7**	8.0	6.0
Extensive pre-clinical package	**Yes**	Yes	-
Capable of treating ≤ 4 mm diameter renal arteries?	**Yes**	-	-
Technology lessens pain for patient	**Yes**	-	-
Technology lessens fluoroscopy time	**Yes**	-	-
Technology eliminates need for grounding pad on patient	**Yes**	-	-

One-Shot
Covidien



Paradise
ReCor Medical



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