RENAL DENERVATION THERAPY FOR RESISTANT HYPERTENSION

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HA Convention, 7 May 2014

DRUGS:
MAINSTAY OF TREATMENT FOR HYPERTENSION

RENAL DENERVATION THERAPY FOR RESISTANT HYPERTENSION

V16 健康 爽報 SHARP DAILY 二〇一一年十一月八日

全新微創手術
切神經治高血壓

【本報訊】全港15歲以上人口中，有近三成人有高血壓，有人嚴重至服藥亦無法控制病情。仁安醫院最近便為7名這類嚴重個案，施行全新微創手術，切斷腎腦之間的交感神經，遏止血壓標升。

明報 2013.05.06 星期一 副刊 D6

與您談心 心臟科專科醫生，行醫逾廿年，最愛與人談「心」

高血壓——導管療法

高血壓非常普遍，有部分病人用了超過3至4種藥物，效果仍不理想，稱爲「抗藥性高血壓」。一般來說，這些病人的收縮壓（上壓），明顯地較舒張壓（下壓）高，反映他們的血管硬化及交感神經亢奮，高血壓的併發率也較高。

服4種藥無效 視網膜出血

導管療法
近年發展了利用導管進入血管，發放射頻來阻斷部分腎血管的交感神經，用以醫治抗藥性高血壓。

撰文：YAM
攝影：周耀忠、陸王術

說高血壓，標準是上壓超過140mmHg，或下壓高於90mmHg，論治療，建議指引是控制飲食+運動+減重+藥物。

怎麼看，這病都清清楚楚明明白白，既有目標亦有療法，但治療實況是，不少病人藥物用到三四五種仍無助降低血壓，潛藏引發中風、冠心病的風險……

近年本港引入新的高血壓手術療法——腎交感神經射頻消融治療，令頑治性高血壓病人的血壓受控機會大增。

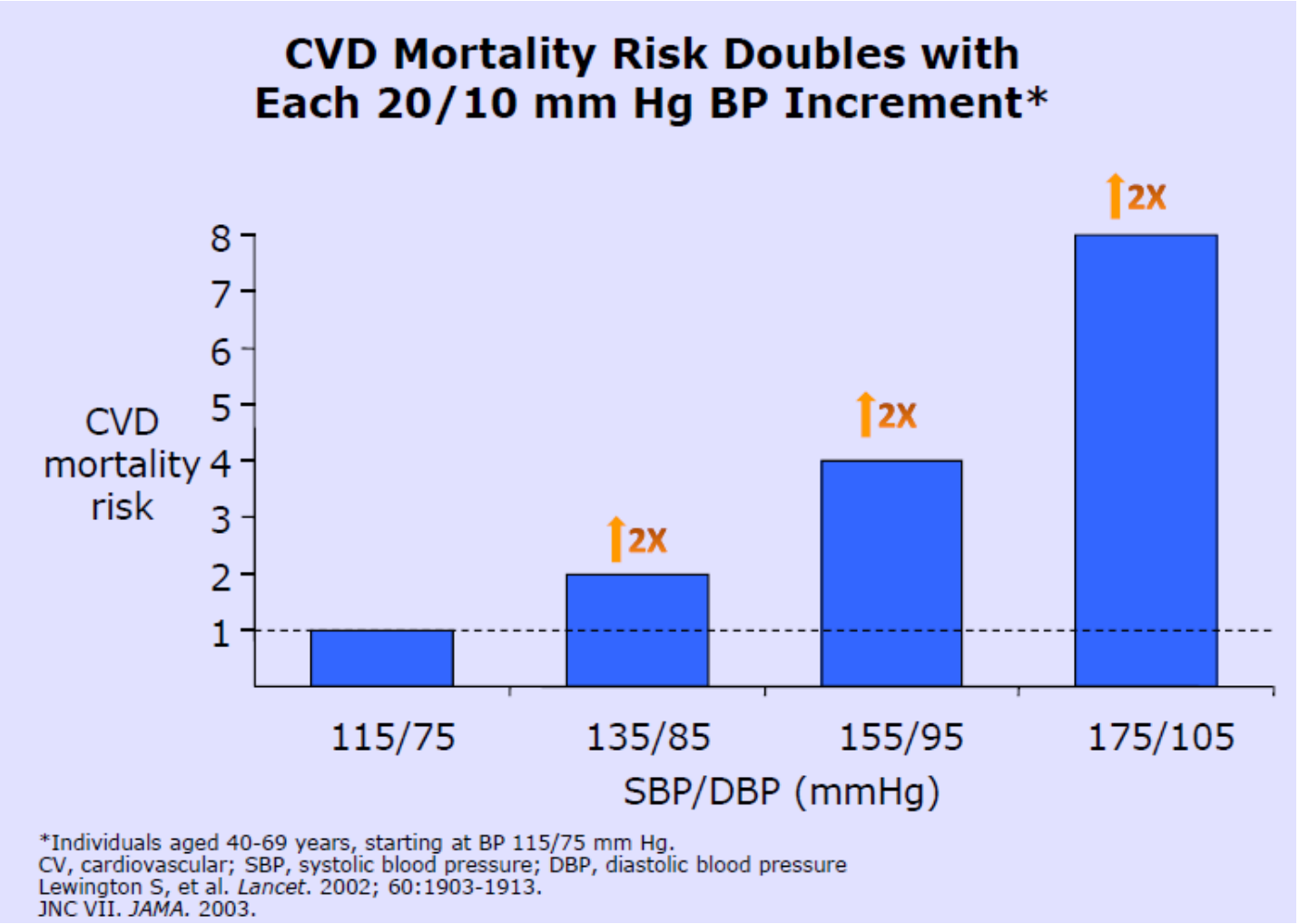
HEALTH FEATURE

消融手術 降頑治高血壓

FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Need of Change

HYPERTENSION:
A MAJOR PUBLIC HEALTH BURDEN

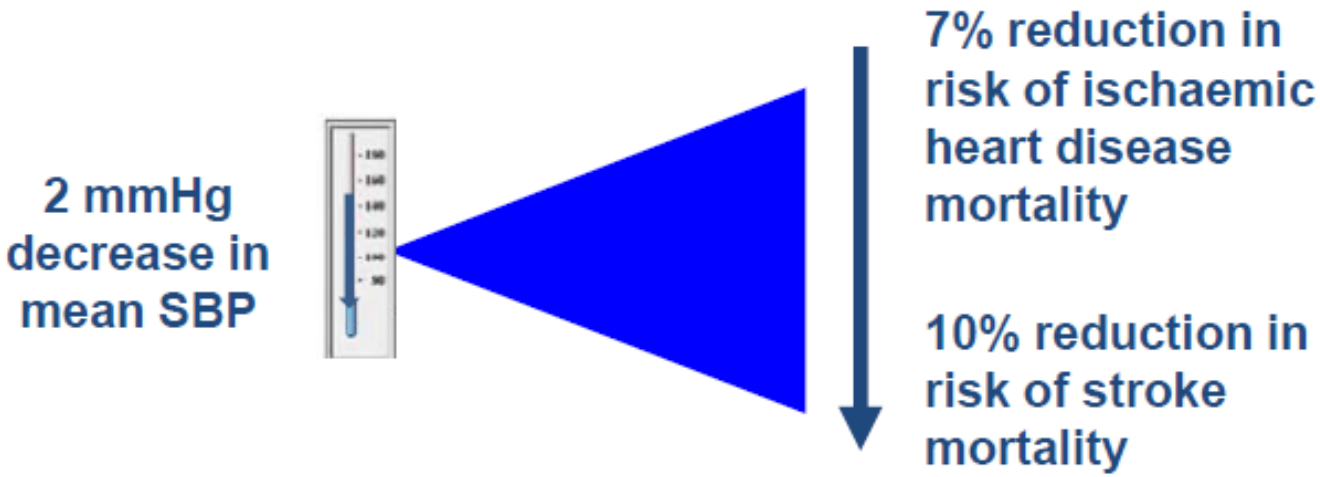


*Individuals aged 40-69 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure
Lewington S, et al. *Lancet*. 2002; 60:1903-1913.
JNC VII. *JAMA*. 2003.

BENEFITS OF BP CONTROL IN REDUCING COMPLICATIONS

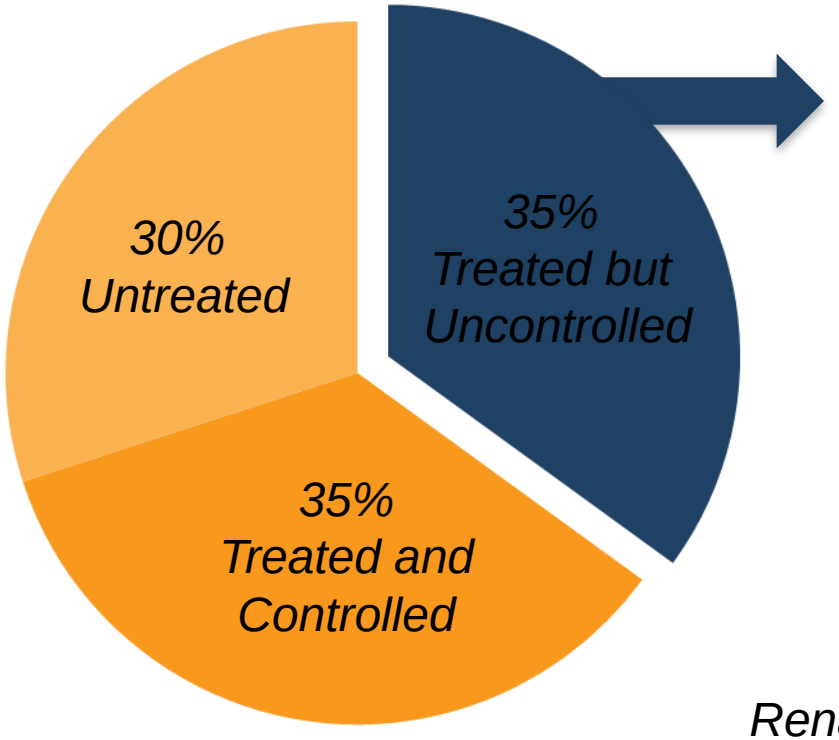
Meta-analysis of 61 prospective, observational studies which involve 1 million adults

Blood Pressure reduction of 2 mmHg decreases the risk of cardiovascular events by 7-10%



Lewington et al. Lancet 2002;360:1903-13

DRUGS WORK, BUT NOT AS WELL AS YOU MAY THINK



- Current approach failing:
  - Physician inertia
  - Patient compliance
  - Resistant HTN

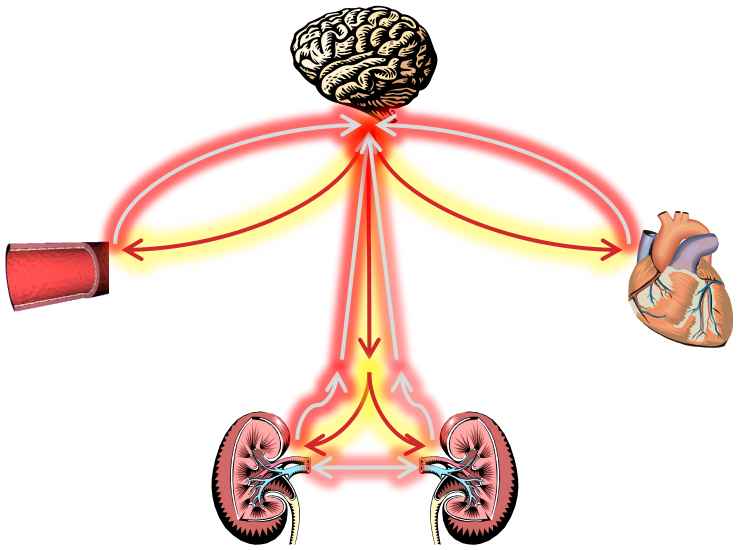
Renal denervation (RDN) =
potentially a compliance-independent therapy

FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Basis for Change

RENAL DENERVATION

WELL-ESTABLISHED SCIENTIFIC FOUNDATION

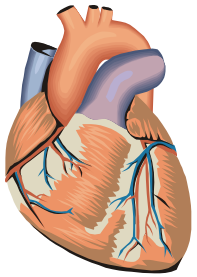


- Roles of kidneys and sympathetic nervous system in development and progression of HTN is well established
- Pharmaceuticals modify physiology at intermediate steps in pathway
- RDN attempts to break the cycle at its source

RENAL SYMPATHETIC NERVE ACTIVITY:

KIDNEY AS ORIGIN & RECIPIENT OF CENTRAL SYMPATHETIC DRIVE

- **Vasoconstriction**

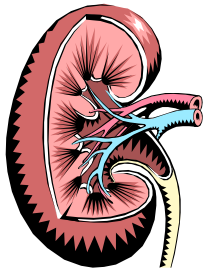


- ↑ **Contractility**
- ↑ Heart rate

Efferent Nerves

Afferent Nerves

Blood Pressure

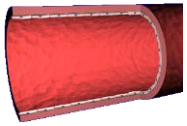


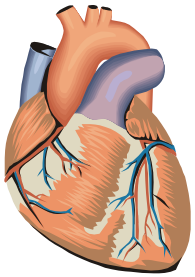
↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

Schlaich et al. Hypertension. 2009;54(6):1195-120

RENAL SYMPATHETIC NERVE ACTIVITY:

KIDNEY AS ORIGIN & RECIPIENT OF CENTRAL SYMPATHETIC DRIVE





- ↑ **Contractility**
- ↑ Heart rate
- **Hypertrophy**
- **Arrhythmia**
- **Heart Failure**

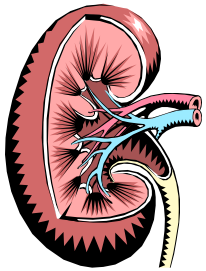
- **Vasoconstriction**
- **Atherosclerosis**

Efferent Nerves

Afferent Nerves

Blood Pressure

+ Increase co-morbidities



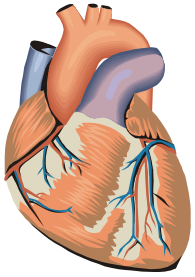
↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
↓ Kidney function

Schlaich et al. Hypertension. 2009;54(6):1195-120

RENAL SYMPATHETIC NERVE ACTIVITY:

RDN DISRUPTS RENAL NERVES, LOWERING SNS ACTIVITY

- **Vasoconstriction**
- **Atherosclerosis**



- **↑ Contractility**
- **↑ Heart rate**
- **Hypertrophy**
- **Arrhythmia**
- **Heart Failure**

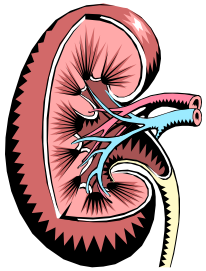
Efferent Nerves

-- Renal Denervation (RDN)--

Afferent Nerves

Blood Pressure

+ Increase co-morbidities



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

Schlaich et al. Hypertension. 2009;54(6):1195-120

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

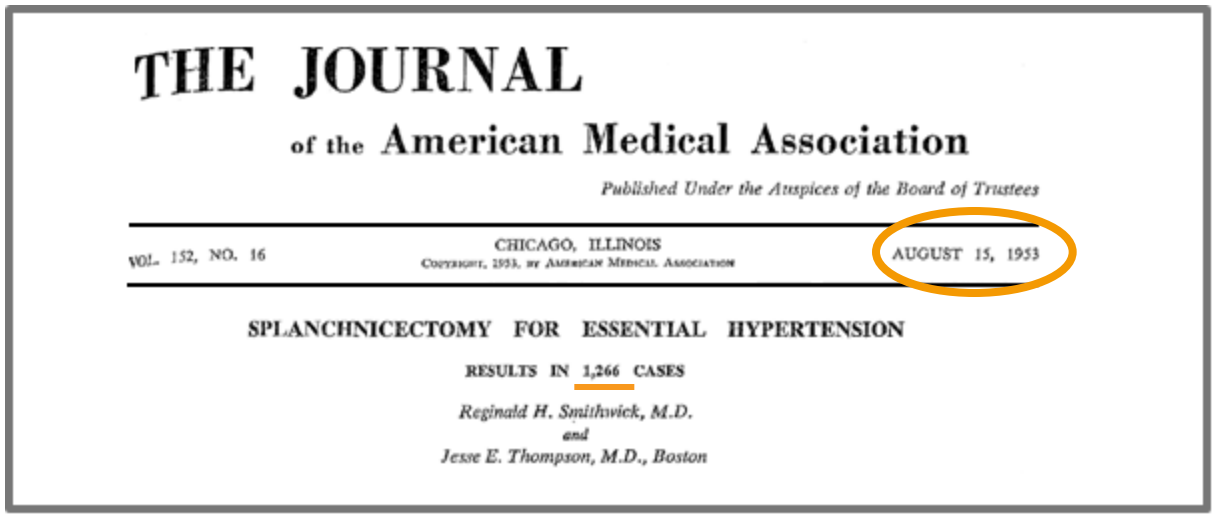
THE BRITISH JOURNAL OF SURGERY

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

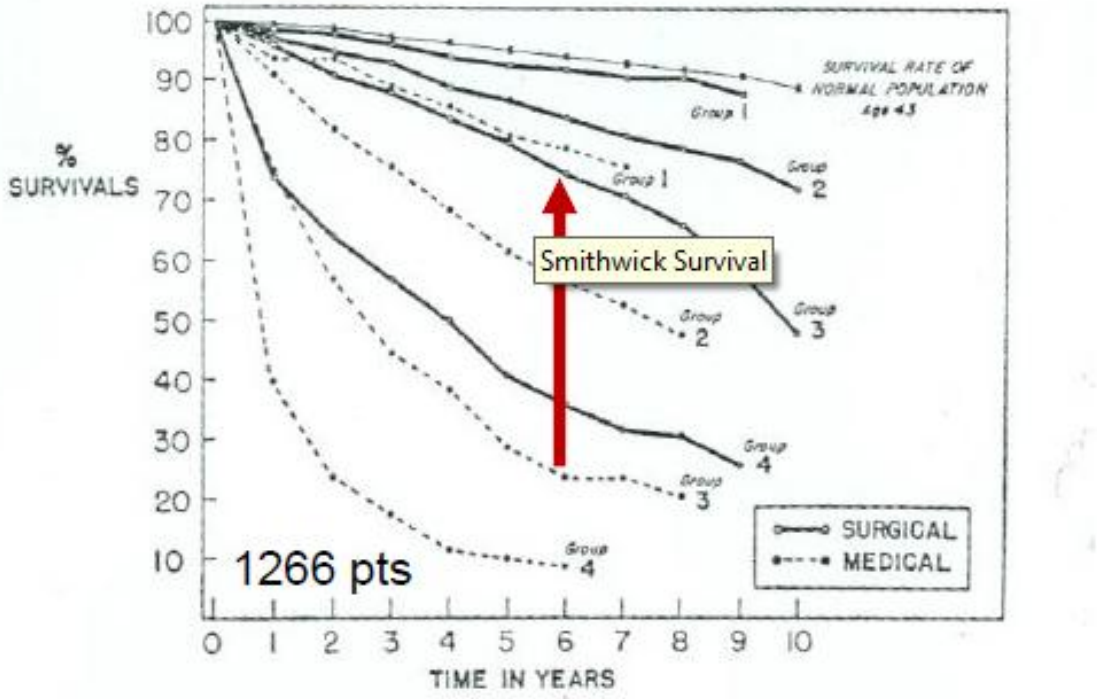
SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

Effective, but significant, morbidity

Sympathectomy in Hypertension:
Effects on survival, but side effects and complications



Denervating lower half of the body produced:

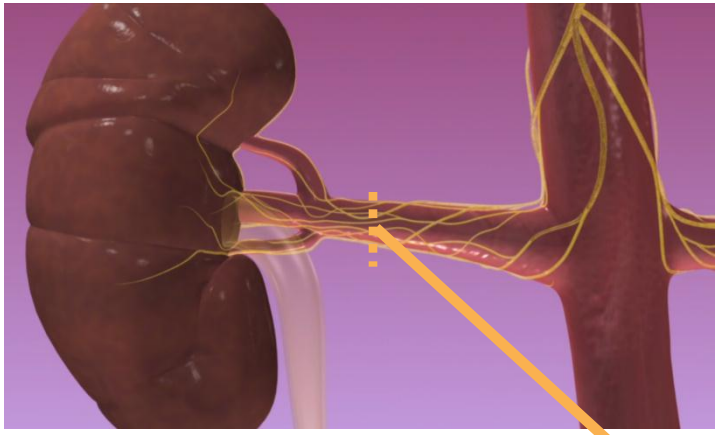
- **Mortality benefit**
- **Inconsistent BP results**
- **Significant morbidity including orthostatic hypotension, bowel & bladder dysfunction**

Smithwick RH, *J Am Med Assoc*. 1953;152:1501-1504

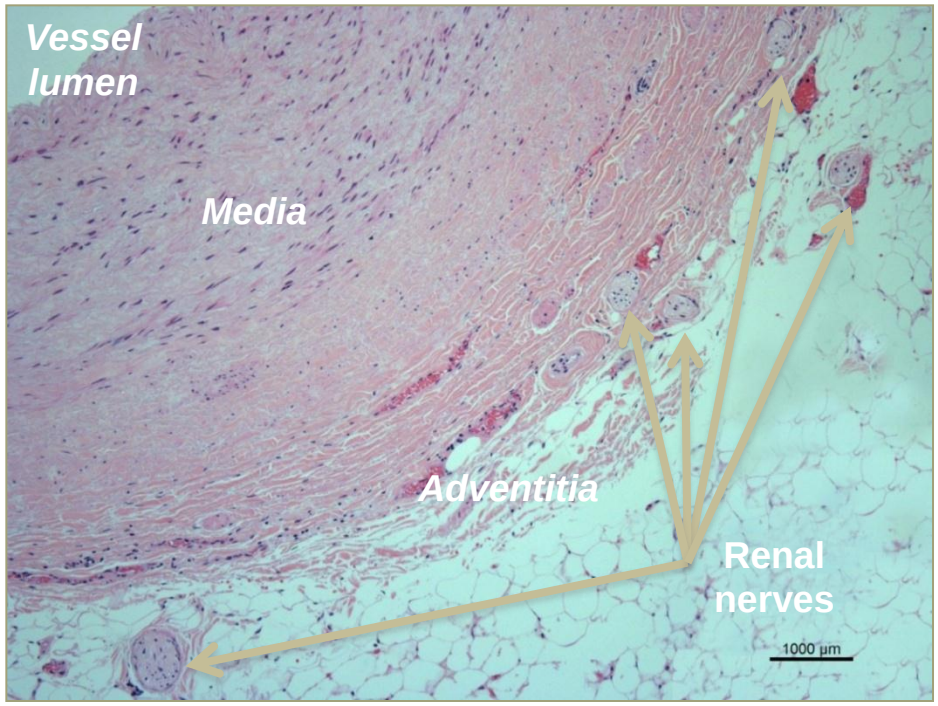
FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

A Way to Change

RENAL ANATOMY ALLOWS A CATHETER-BASED APPROACH

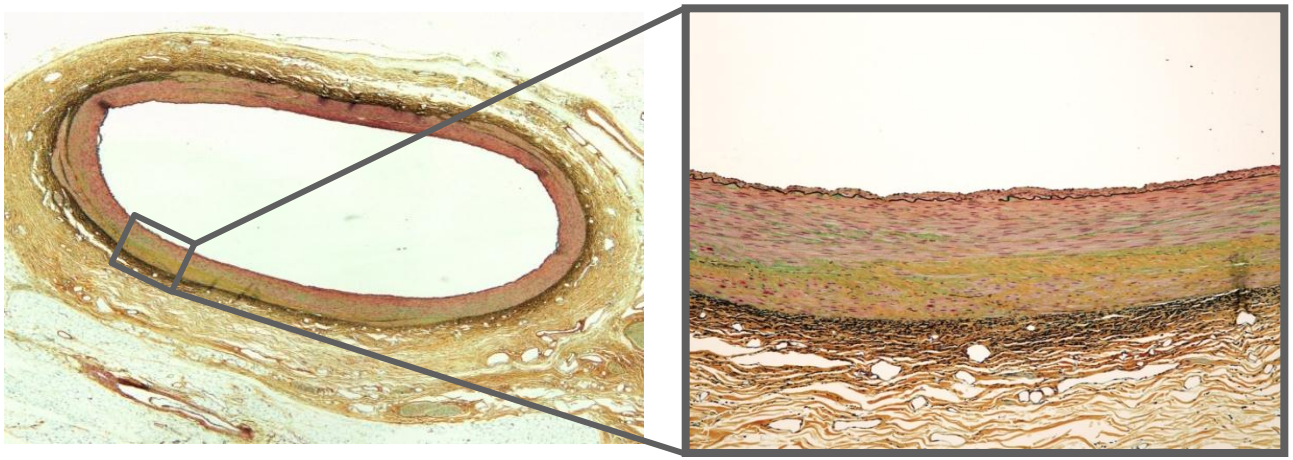


- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent and afferent nerves travel together



VASCULAR SAFETY PREDICTED BY PRECLINICAL STUDIES

- **Extensive research in >300 swine**
- **Angiography and pathology at 7, 30, 60 and 180 days**
- **No stenosis or luminal reduction seen in treated arteries**
- **RF generator algorithm optimized to minimize vascular injury**

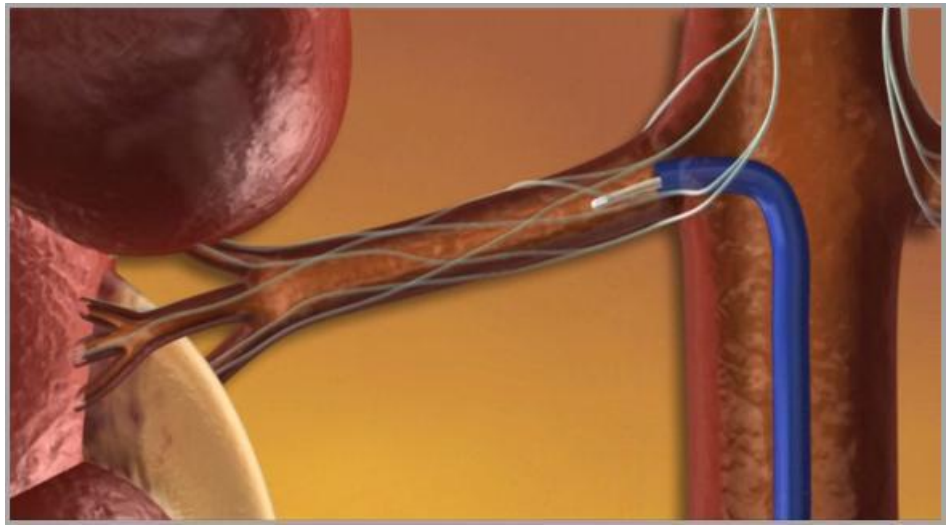


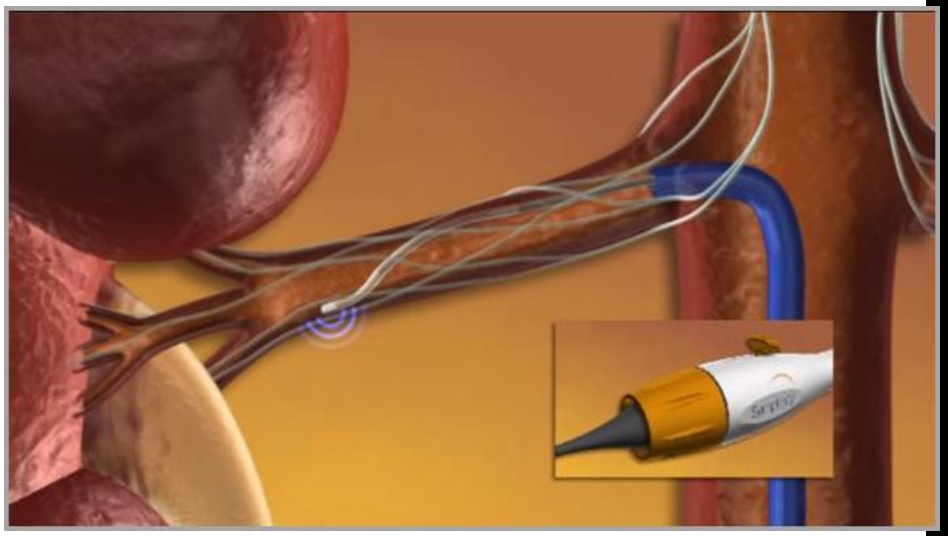
COMMERCIALLY AVAILABLE RENAL DENERVATION SYSTEM

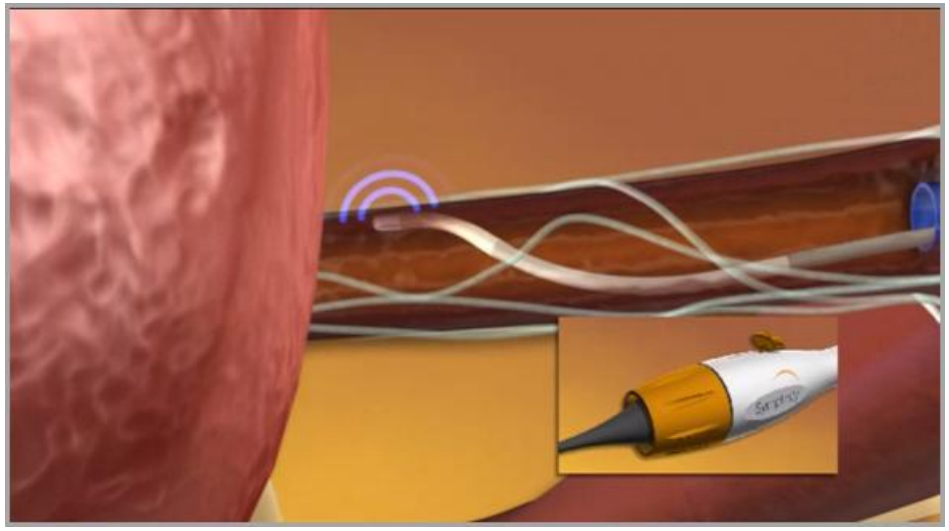
MEDTRONIC SYMPLICITY

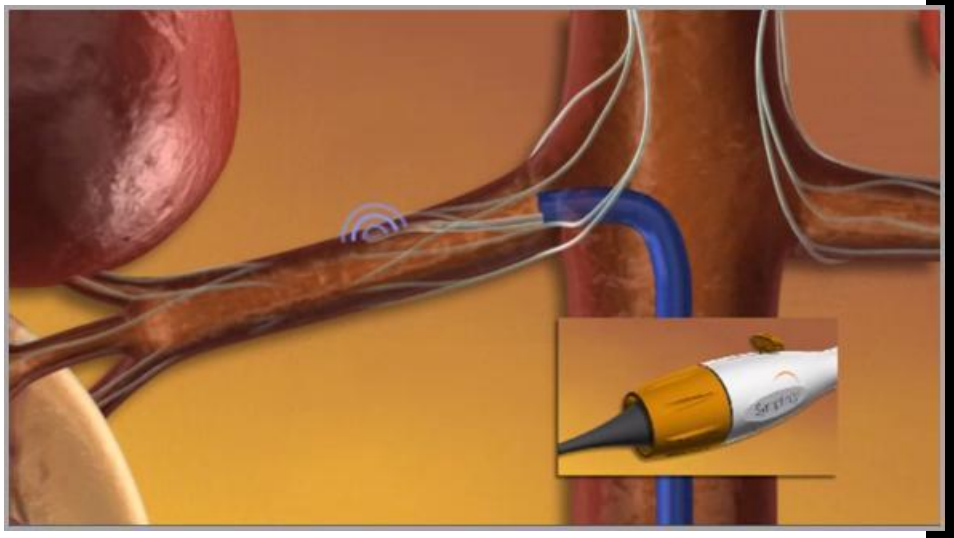
- Low-profile, electrode tipped catheter
- Delivers RF energy to treatment site
- Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
- Standard interventional technique
- 40 minutes from first to last RF delivery

PROCEDURE OVERVIEW

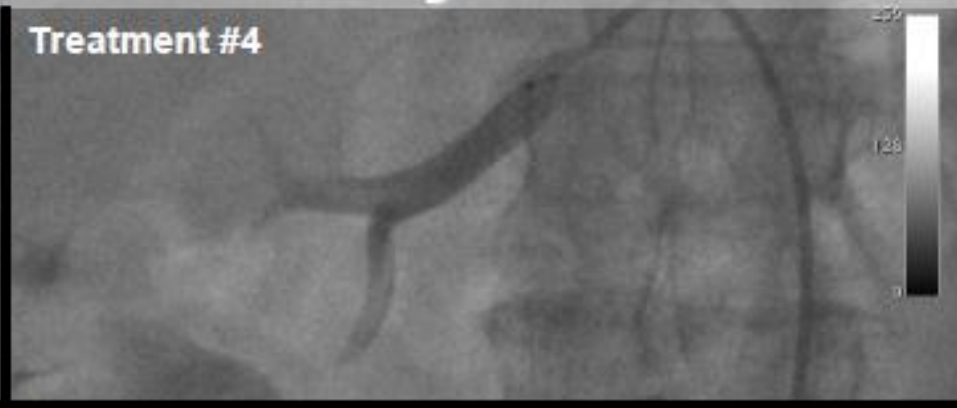


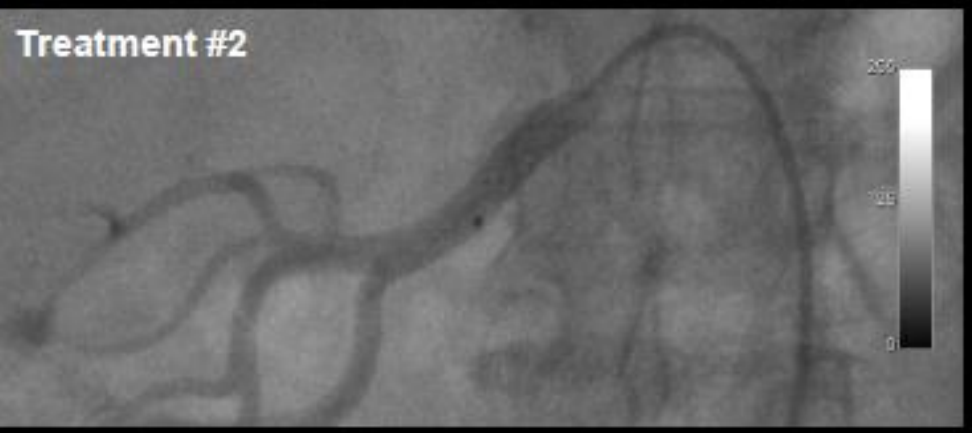


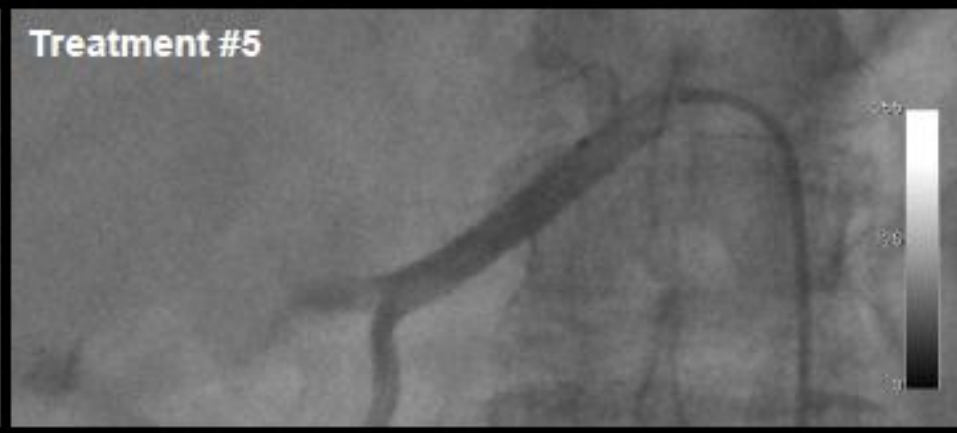


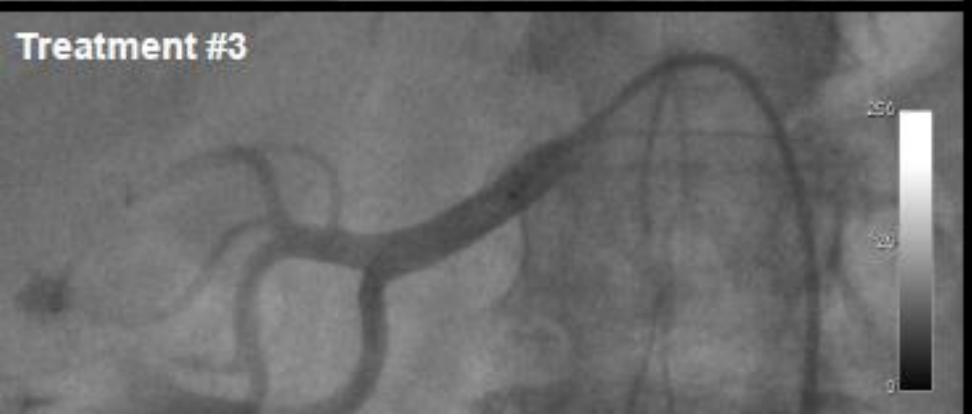


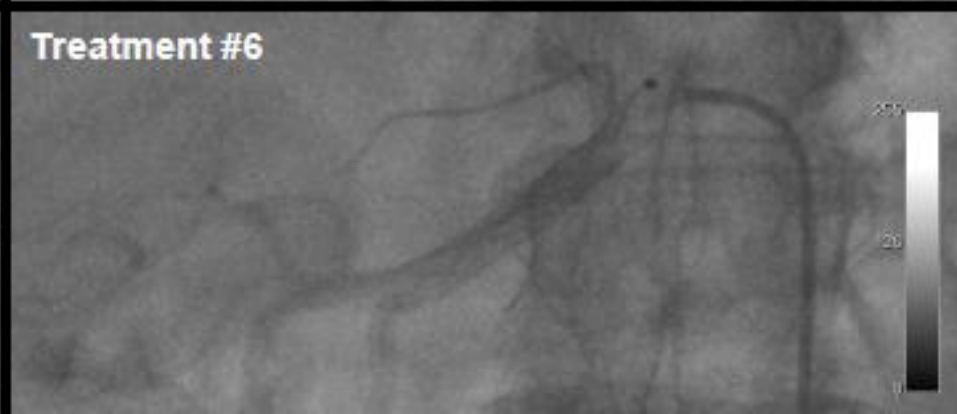
Example Treatment Locations in a Right Renal Artery









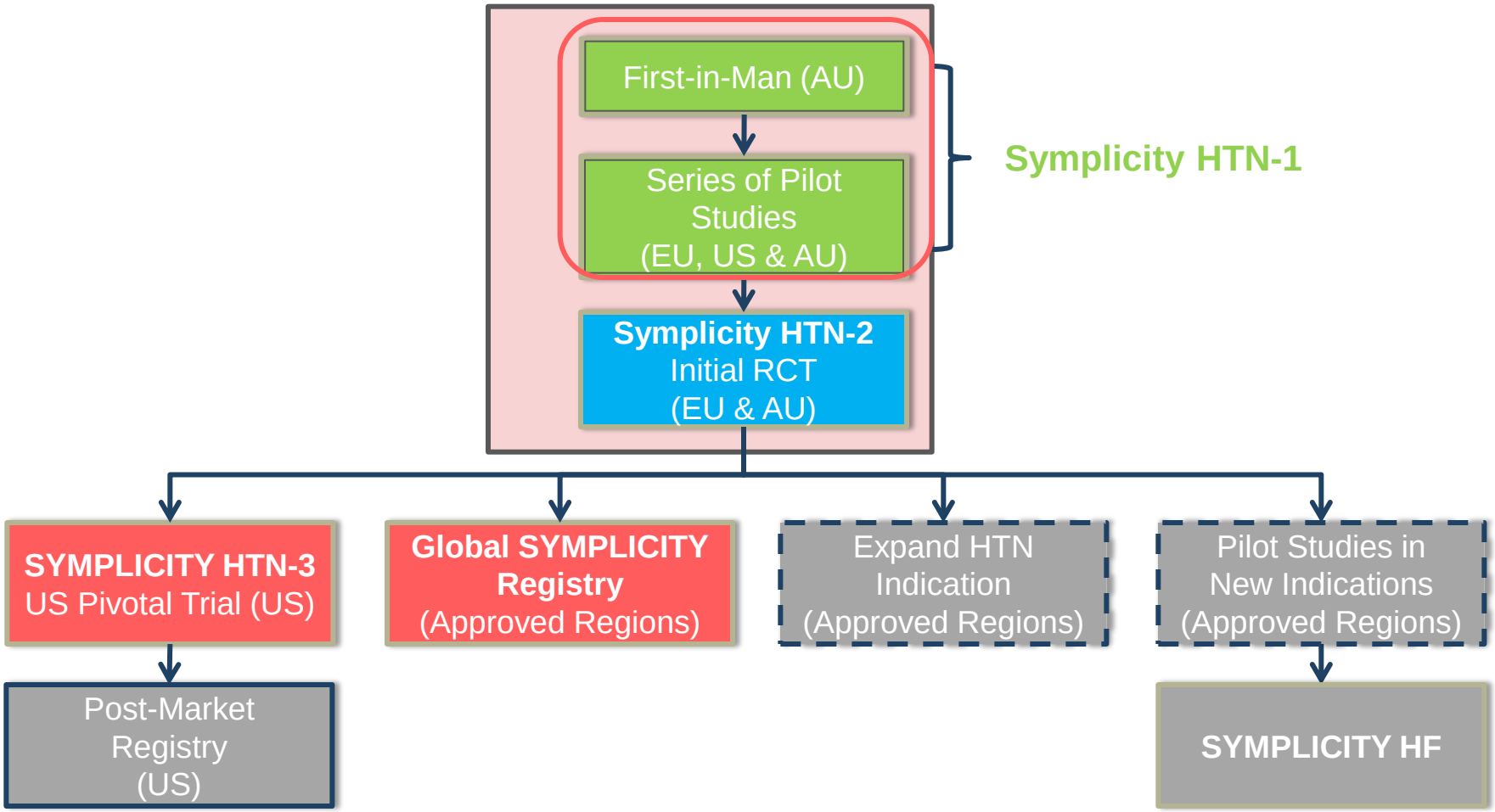


FROM DRUGS TO RENAL DENERVATION: WHAT BROUGHT THE CHANGE?

An Effect from the Change

CLINICAL RESULTS

SYMPLICITY Clinical Trial Programs:
over 5000 patients across multiple indications



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

The Lancet. 2009;373:1275–1281.

Key Inclusion Criteria

- Office SBP ≥160 mmHg
- Stable drug regimen of 3+ more anti-HTN medications (including diuretic)
- eGFR ≥45 mL/min/1.73m^2

Non-randomized

Initial cohort： 45 patients

Expanded cohort: 153 patients

36-month follow-up

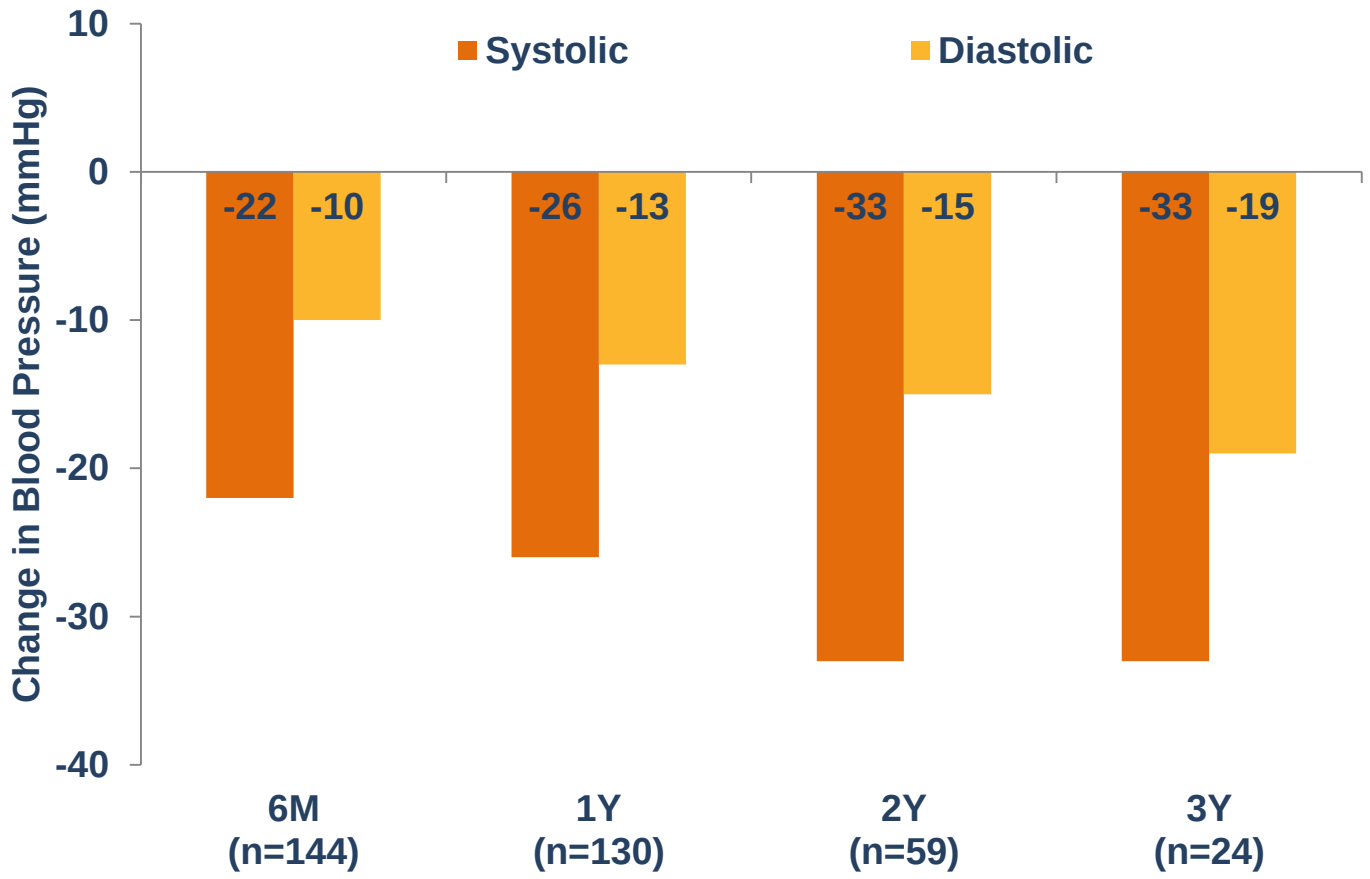
* Symplicity HTN-1 Investigators. *Hypertension*. 2011

BASELINE PATIENT CHARACTERISTICS

Demographics	Age (yr)	57 ± 11
	Gender (female) (%)	39
	Race (noncaucasian) (%)	5
Comorbidities	Diabetes mellitus type 2 (%)	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)	**5.0 ± 1.4**
	ACE/ARB (%)	90
	Beta blocker (%)	82
	Calcium channel blocker (%)	75
	Vasodilator (%)	19
	Diuretic (%)	95
	Spironolactone (%)	21

Symplicity HTN-1 Investigators. *Hypertension*. 2011.

SIGNIFICANT, SUSTAINED BLOOD PRESSURE REDUCTIONS TO AT LEAST 3 YEARS



p <0.01 for Δ from baseline for all time points

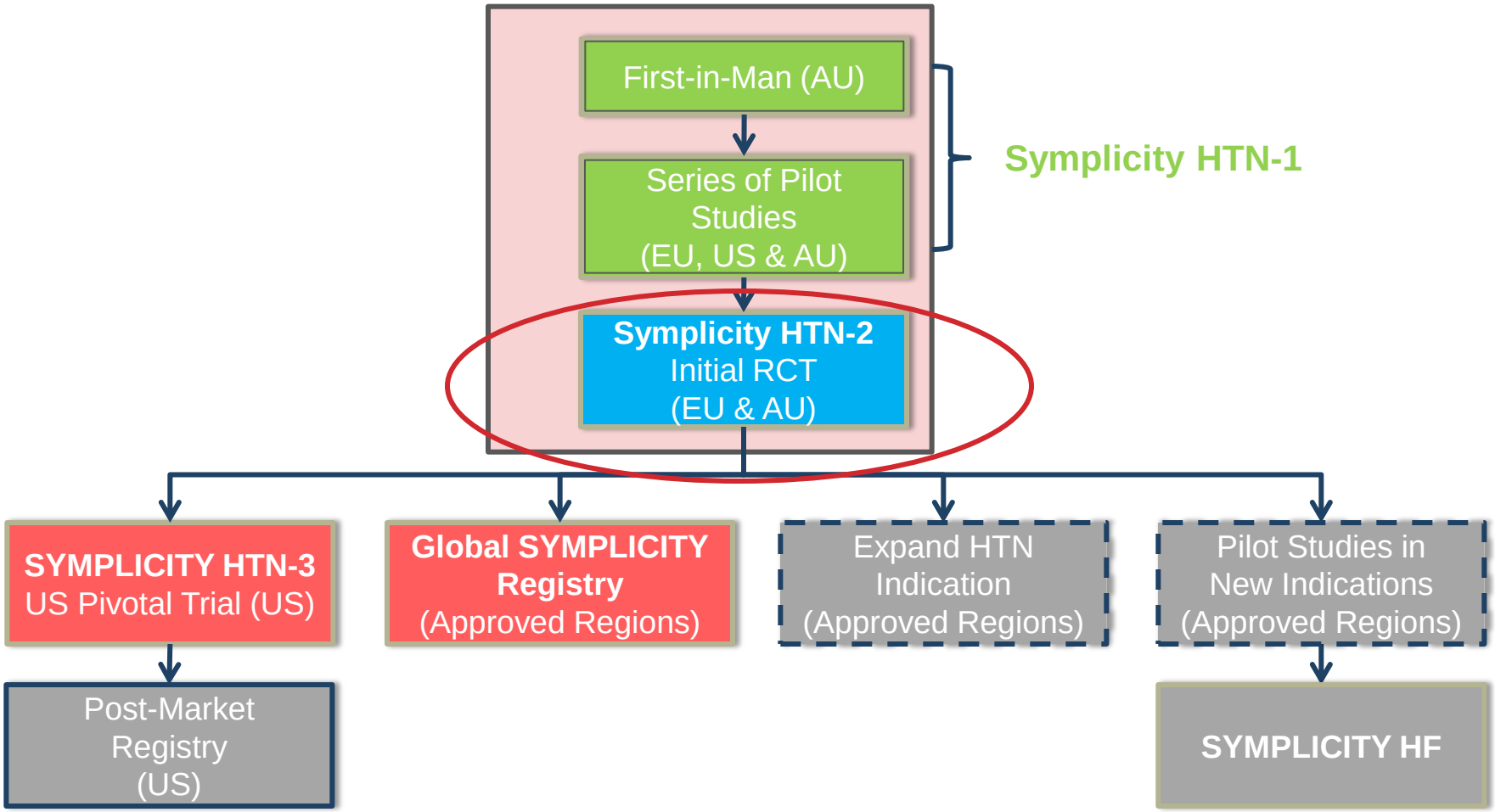
Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)

BRIEF PROCEDURE WITH A LOW COMPLICATION RATE

- **38-minute median time from first to last ablation**
  - Average of 4 ablations per artery
- **Intravenous narcotics and 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

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

SYMPLICITY Clinical Trial Programs:
over 5000 patients across multiple indications



SYMPLICITY HTN-2: RANDOMISED CONTROLLED TRIAL

THE LANCET
Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

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: 1903–09

SYMPLICITY HTN-2: RANDOMISED CONTROLLED TRIAL

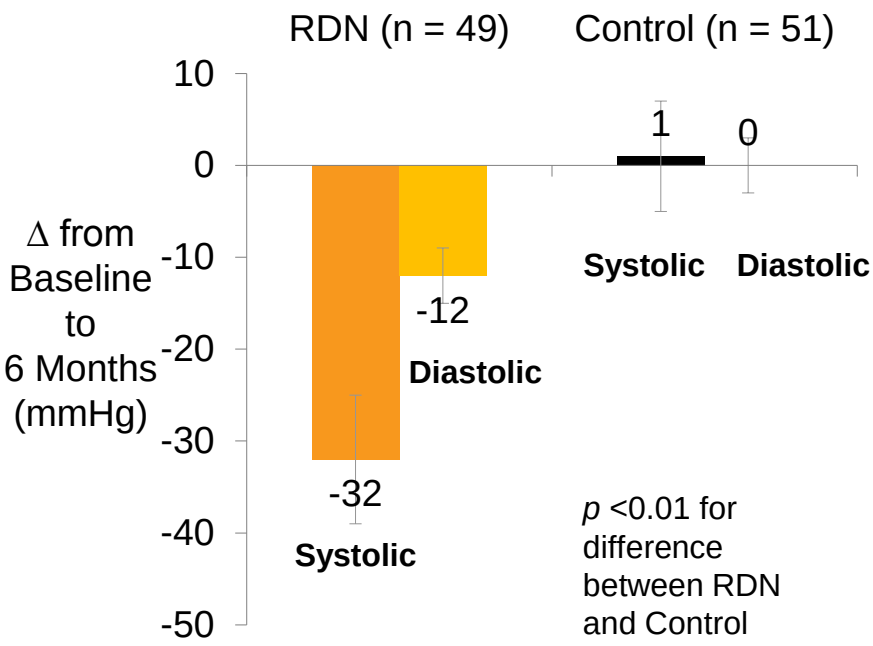
- **Patients: 106 patients randomised 1:1 to treatment with RDN vs. control**
- **Clinical sites: 24 centres in Europe, Australia and New Zealand**

Key Inclusion/Exclusion Criteria
• Inclusion: – Office SBP ≥160 mmHg (≥150 mmHg with type 2 diabetes mellitus) – Stable drug regimen of 3+ more anti-HTN medications – Age 18–85 years • Exclusion: – Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention – 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 past 6 months

Lancet 2010; 376: 1903–09; Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)

SYMPLICITY HTN-2: RDN SUPERIOR TO MEDICAL MANAGEMENT

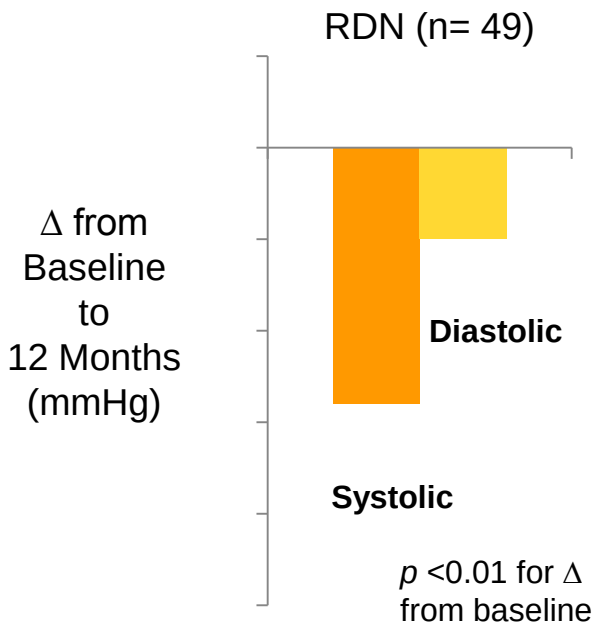
Primary Endpoint (6M post Randomisation)



Primary Endpoint:

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

Latest Follow-up (12M post Randomisation)



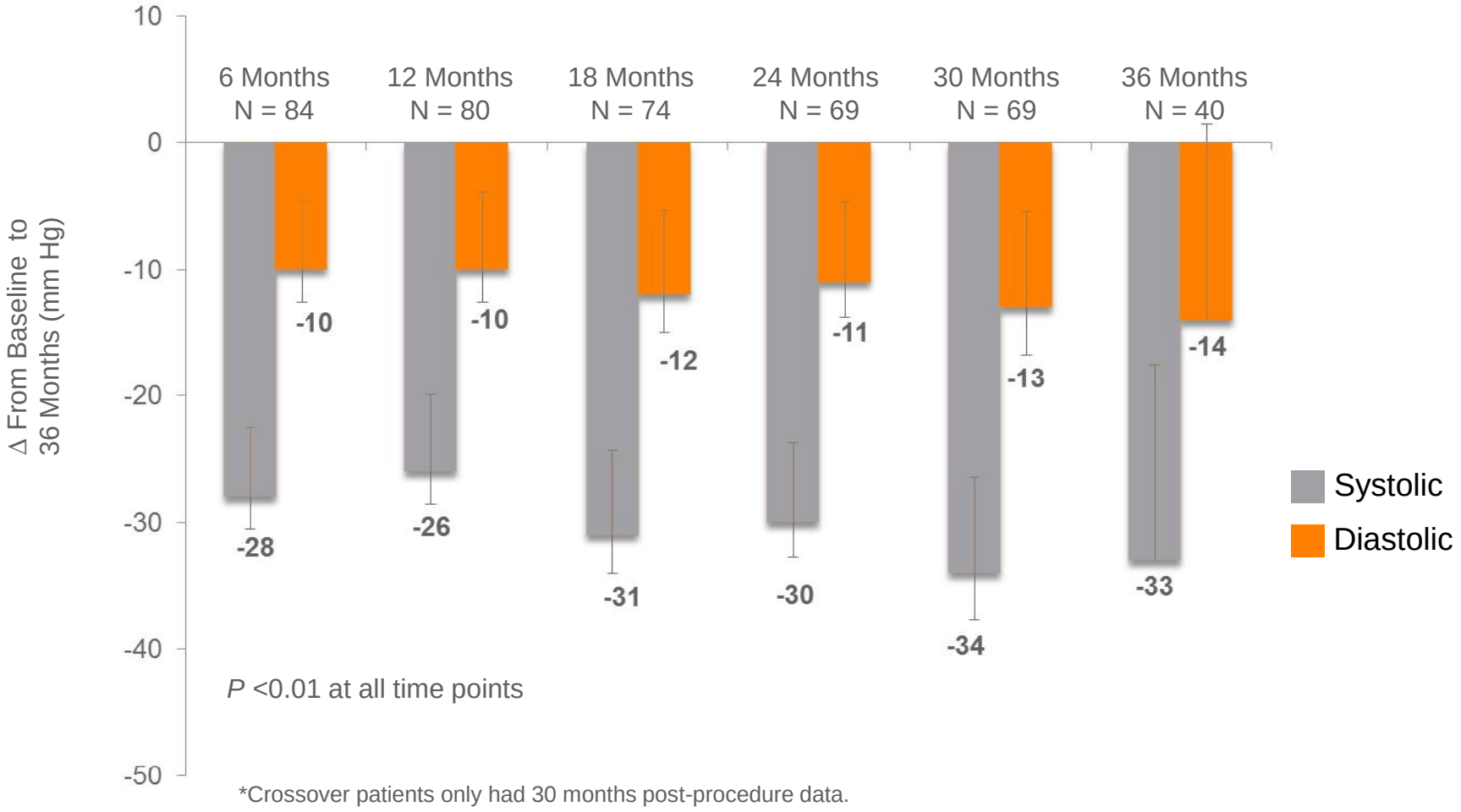
Latest Follow-up:

- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Lancet 2010; 376: 1903–09; Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)
Lancet 2010; 376: 1903–09; Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)

SYMPLICITY HTN-2: BP REDUCTIONS SUSTAINED TO 3 YEARS

Sustained Reductions in the Pooled (RDN and Crossover) Group*



*Crossover patients only had 30 months post-procedure data.

Whitbourn, TCT 2013

PROCEDURAL SAFETY (EXPANDED COHORT)

•One renal artery dissection from injection of contrast into renal artery wall during dye angiography. The lesion was stented without further consequences

•One hospitalization prolonged in a crossover patient due to hypotension following the RDN procedure. IV fluids administered, anti-hypertensive medications decreased and patient discharge without further incident

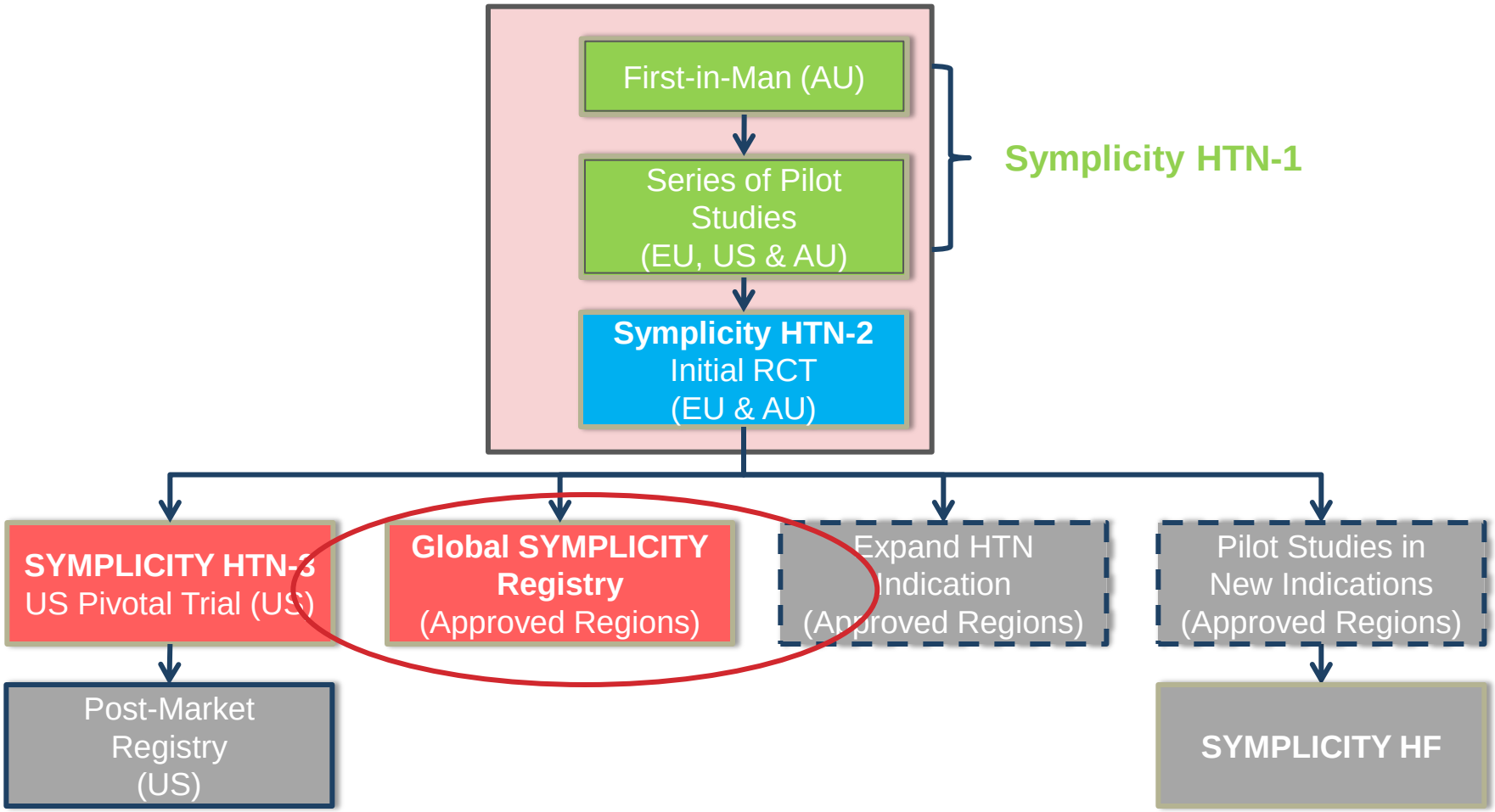
•No radiofrequency-related renal artery stenosis or aneurysm occurred in either Randomised group

•Minor adverse events (full cohort)

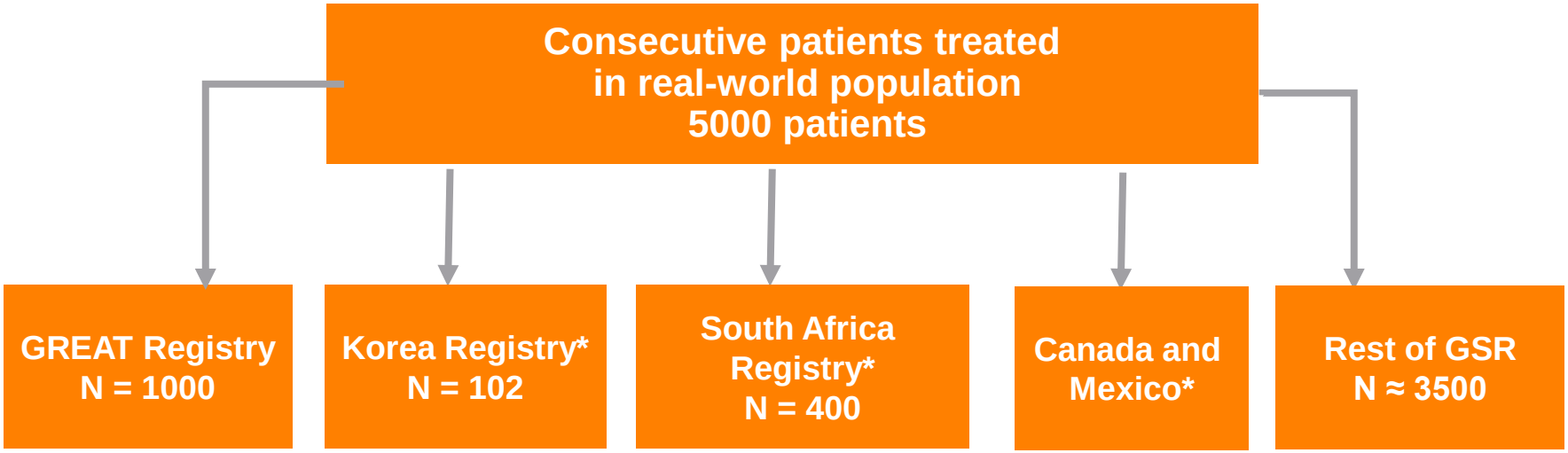
- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 postprocedural drop in BP resulting in a reduction in medication
- 1 urinary tract infection
- 1 prolonged hospitalisation for evaluation of paraesthesias
- 1 back pain treated with pain medications and resolved after 1 month

Lancet 2010; 376: 1903–09; Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)

SYMPLICITY Clinical Trial Programs:
over 5000 patients across multiple indications

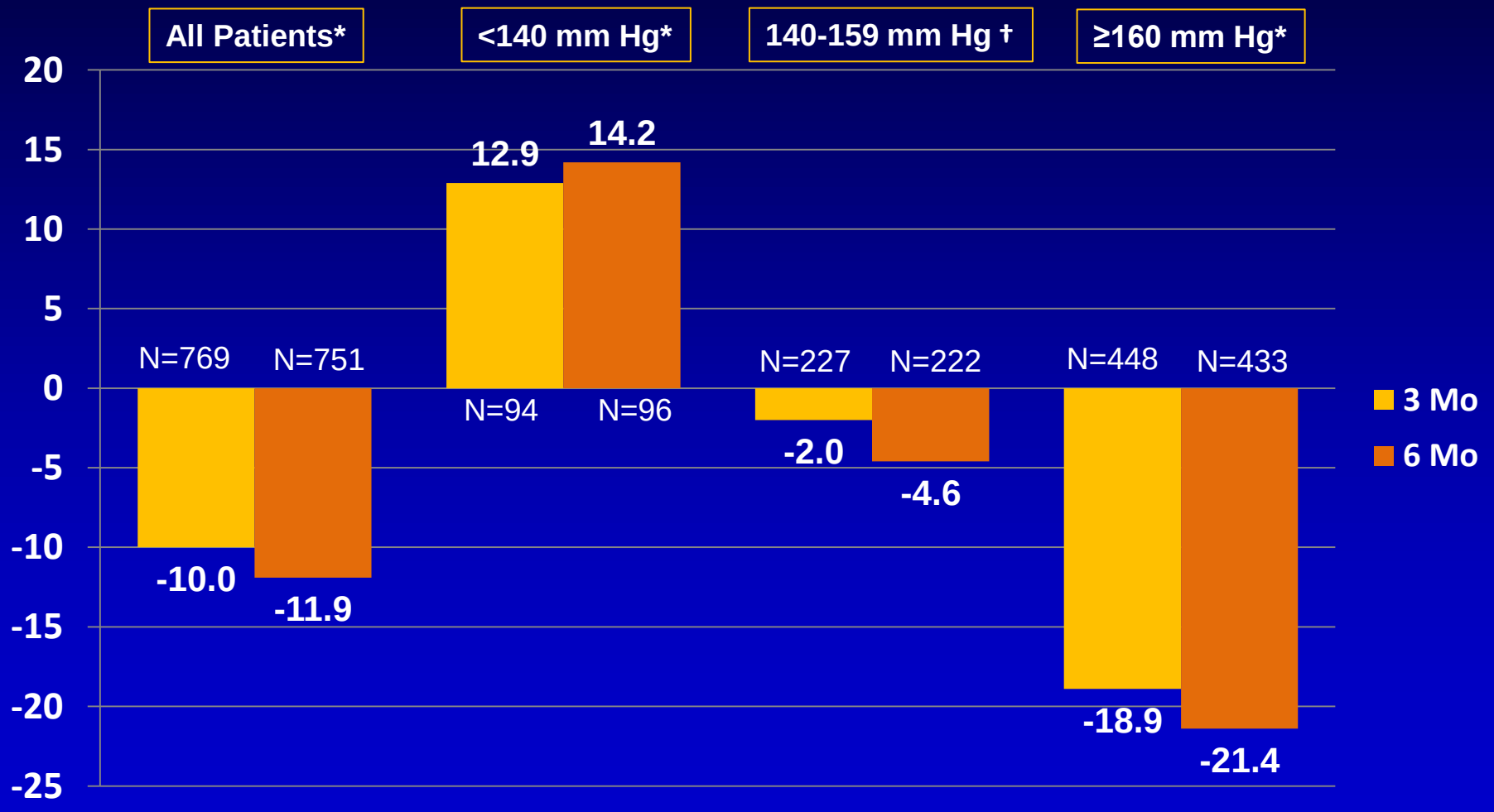


Global Symplicity Registry (GSR)



* Limited to resistant hypertension only

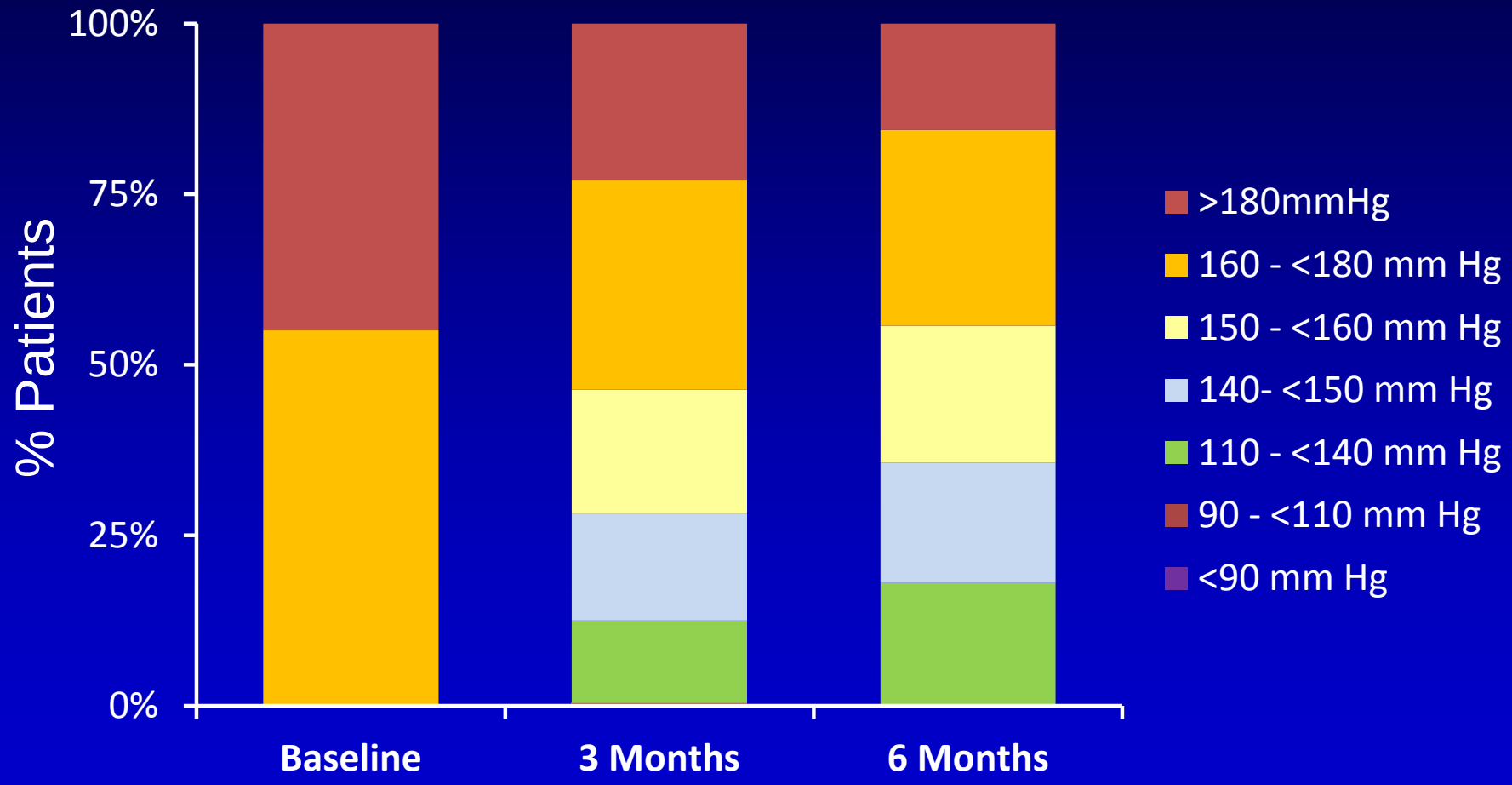
Change in Office Systolic BP for All Patients and Subgroups



*P<0.0001 for both 3 and 6 month change from baseline

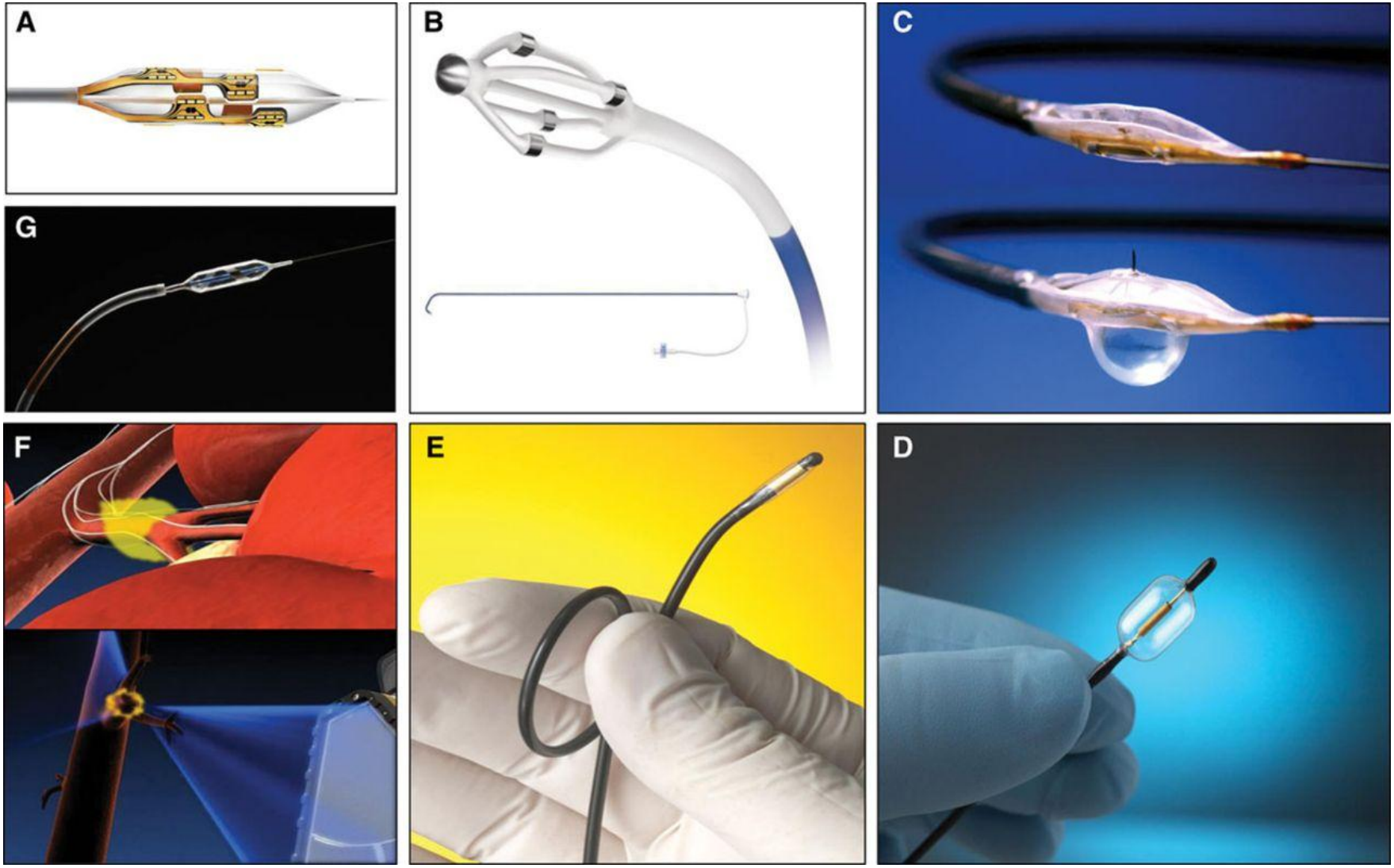
†P=0.14 at 3 months and P=0.0006 at 6 months

Distribution of SBP in Patients With Office SBP≥160 mm Hg and Ambulatory SBP ≥135 mm Hg* at Baseline

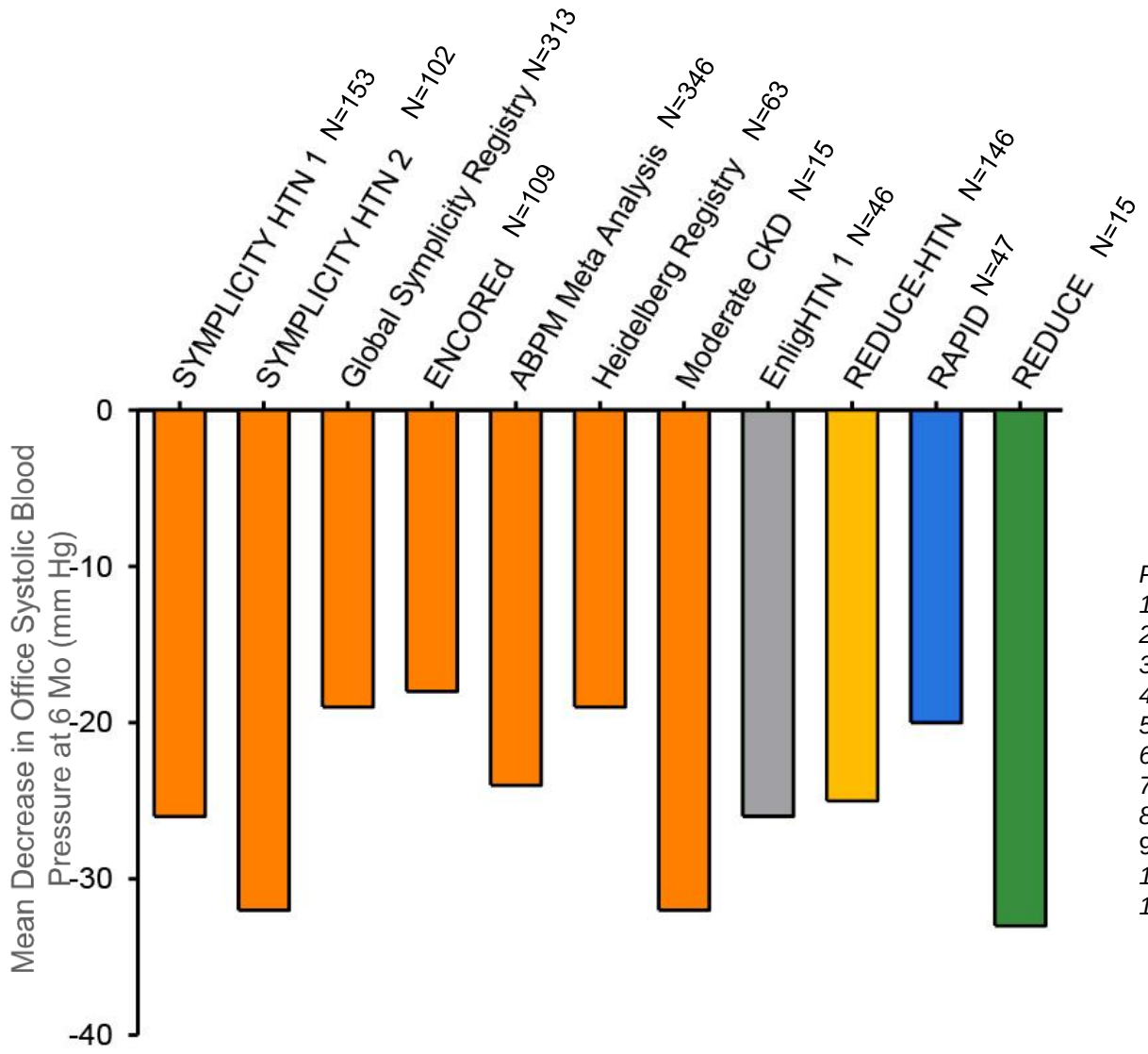


*with ≥3 antihypertensive medication classes

Multiple Devices Developed for Renal Denervation Therapy



MULTIPLE UNBLINDED TRIALS SHOW RDN LOWERS BLOOD PRESSURE



Medtronic
EnligHTN/St Jude
Vessix/Boston Sci.
Maya/Covidien
Recor

Published Sources:

1. *Lancet 2009*
2. *Lancet* 2010
3. *TCT 2013*
4. *Journal of Human Hypertension* 2013
5. *Circulation* 2013
6. *Clin Res Cardiol* 2013
7. *J Am Soc Nephrol* 2012
8. *Eur Heart J* 2013
9. TCT 2013
10. *Eurointervention* 2013
11. *EuroIntervention 2013*

European Heart Journal
doi:10.1093/eurheartj/eht154 (April 2013)

FASTTRACK CURRENT OPINION

Expert consensus document from the European Society of Cardiology on catheter-based renal denervation†

Felix Mahfoud[1]*, Thomas Felix Lüscher[2], Bert Andersson[3], Iris Baumgartner[4], Renata Cifkova[5], Carlo DiMario[6], Pieter Doevendans[7], Robert Fagard[8], Jean Fajadet[9], Michel Komajda[10], Thierry LeFèvre[11], Chaim Lotan[12], Horst Sievert[13], Massimo Volpe[14,15], Petr Widimsky[16], William Wijns[17], Bryan Williams[18], Stephan Windecker[19], Adam Witkowski[20], Thomas Zeller[21], and Michael Böhm[1]

- Office-based systolic BP ≥ 160 mmHg (≥150 mmHg diabetes type 2)
- ≥3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
- Lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ABPM (average BP > 130 mmHg or mean daytime BP > 135 mmHg)
- Preserved renal function (GFR ≥45 ml/min/1.73 m^2)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

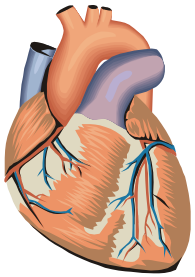
RENAL DENERVATION BEYOND HYPERTENSION

RENAL DENERVATION BEYOND HYPERTENSION

- **Vasoconstriction**
- **Atherosclerosis**

Efferent Nerves

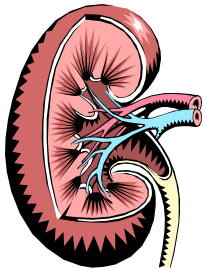
Afferent Nerves



- ↑ **Contractility**
- ↑ Heart rate
- **Hypertrophy**
- **Arrhythmia**
- **Heart Failure**

Blood Pressure

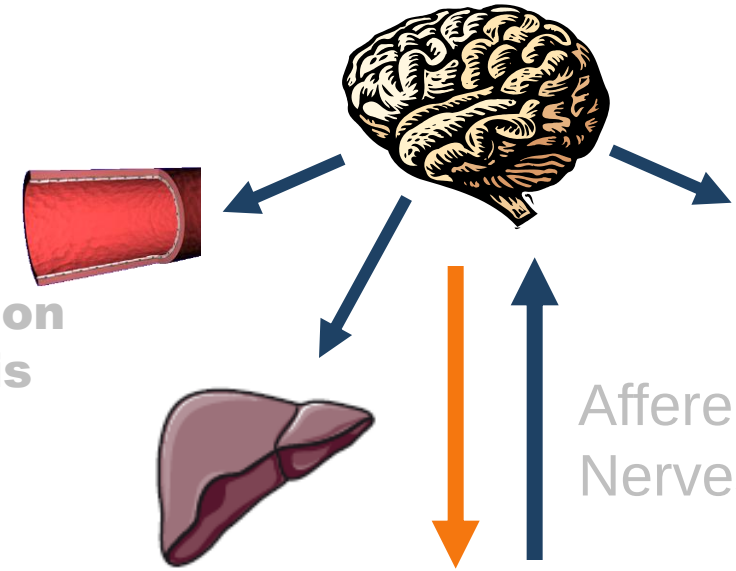
+ Increase co-morbidities



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

Schlaich et al. Hypertension. 2009;54(6):1195-120

RENAL DENERVATION BEYOND HYPERTENSION



- Vasoconstriction
- Atherosclerosis

- ↑ Contractility
- ↑ Heart rate
- **Hypertrophy**
- **Arrhythmia**
- **Heart Failure**

Afferent Nerves

- ↑ **Gluconeogenesis**
- **Insulin resistance**

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

Schlaich et al. Hypertension. 2009;54(6):1195-120

RDN REDUCES LV HYPERTROPHY & INCREASES CARDIAC FUNCTION IN RHTN PATIENTS

LEFT VENTRICULAR MASS

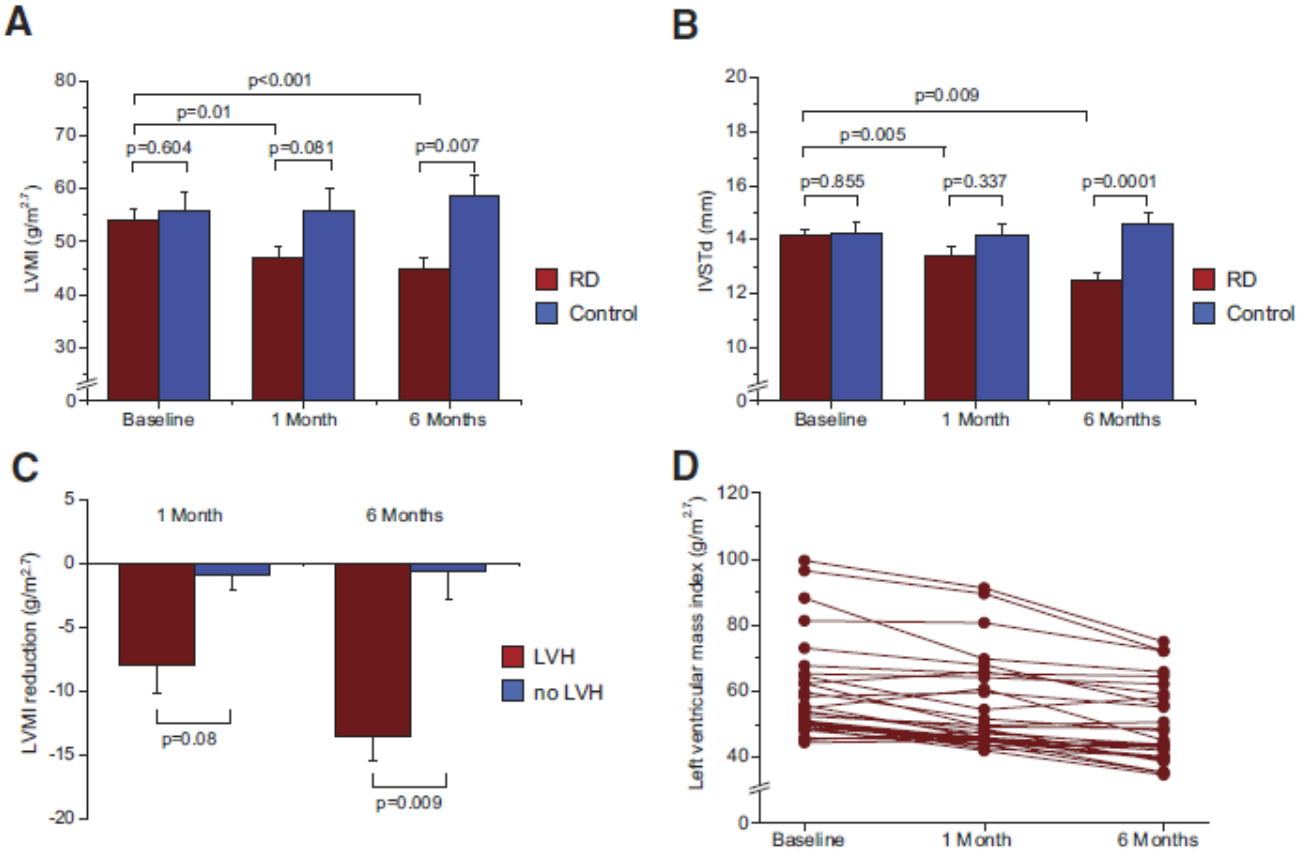


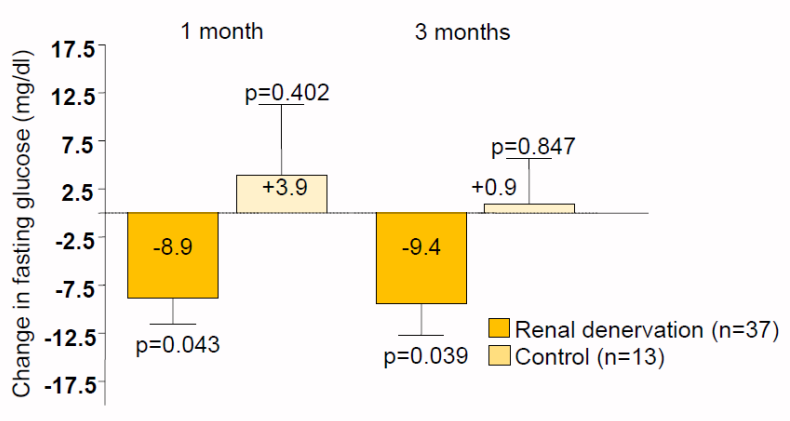
Figure 2 **Impact of RD on LV Mass**

(A) Left ventricular (LV) mass/height$^{2.7}$ and **(B)** end-diastolic interventricular septum thickness (IVSTd) measured in renal sympathetic denervation (RD) and control patients at baseline, 1 month, and 6 months. While there was a steady decrease in the average left ventricular (LV) mass and IVSTd after RD, these parameters slightly increased in control patients. In the treatment group, p for statistical trend was p = 0.004 for LV mass/height$^{2.7}$ **(A)**, p = 0.007 for IVSTd **(B)**. **(C)** Differential effect of RD on LV mass regression depends on the degree of left ventricular hypertrophy (LVH) at baseline. LV mass/height$^{2.7}$ regression by RD was significantly greater in those patients with LVH at baseline. Values are presented as mean ± standard error. **(D)** Regression of LV mass after RD in individual patients with a LVH at baseline (n = 29). LVMI = left ventricular mass index.

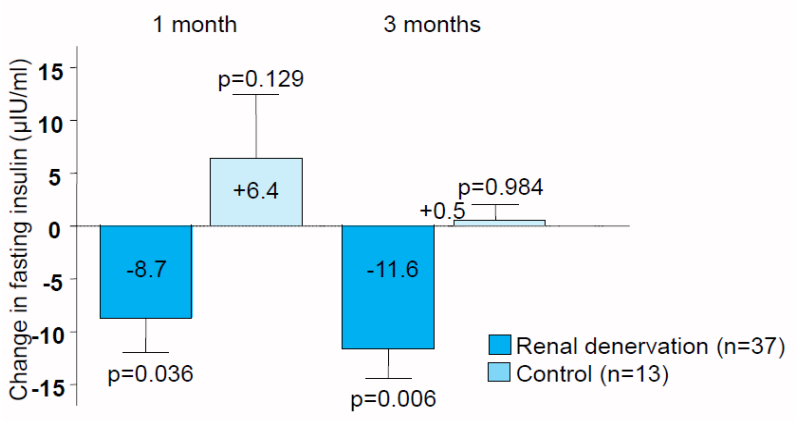
Brandt MC, JACC 2012

RDN IMPROVES GLUCOSE METABOLISM

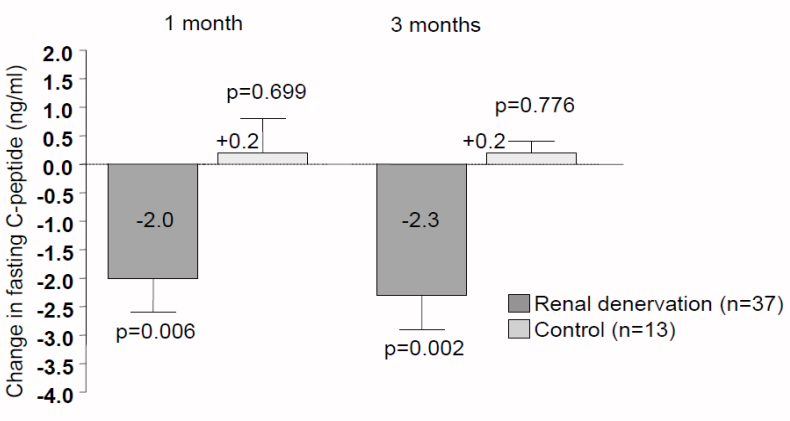
Fasting Glucose



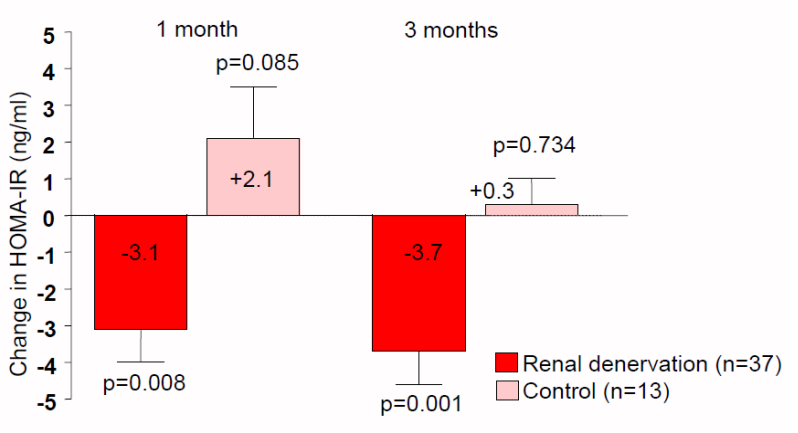
Fasting Insulin



Fasting C-Peptide



Insulin Sensitivity



Mahfoud et al. Circulation 2011;123:1940-1946

RENAL DENERVATION THERAPY FOR RESISTANT HYPERTENSION IN TYPE 2 DIABETES MELLITUS (HTN2DM STUDY)

ClinicalTrials.gov Identifier: NCT01887067

PI: Dr. Tsui Kin Lam (Pamela Youde Nethersole Eastern Hospital)

Renal Denervation Therapy for Resistant Hypertension in Type 2 Diabetes Mellitus

HTN2DM Study Design

Office systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mmHg
Stable regimen of 3 or more anti-hypertensive medications of different classes at fully tolerated dosage, including a diuretic
Type 2 diabetes mellitus

Symplicity Catheter

15 patients

1 site (Pamela Youde Nethersole Eastern Hospital)

Office Systolic & Diastolic BP

Primary endpoint:

- Change in office systolic & diastolic blood pressure from baseline to 6 months

Secondary endpoints:

- Change in office systolic and diastolic blood pressure up to 3 years
- Fasting glucose, HbA1c level, OGTT and spot urine albumin to creatinine ratio before and after renal denervation at 3-month, 12-month, and 36-month; HOMA-IR index before and after renal denervation at 3-month and 12-month

RENAL DENERVATION:

RENAL DENERVATION:
THE ROAD TURNS BUMPY

Press Release

View printer-friendly version

Download PDF

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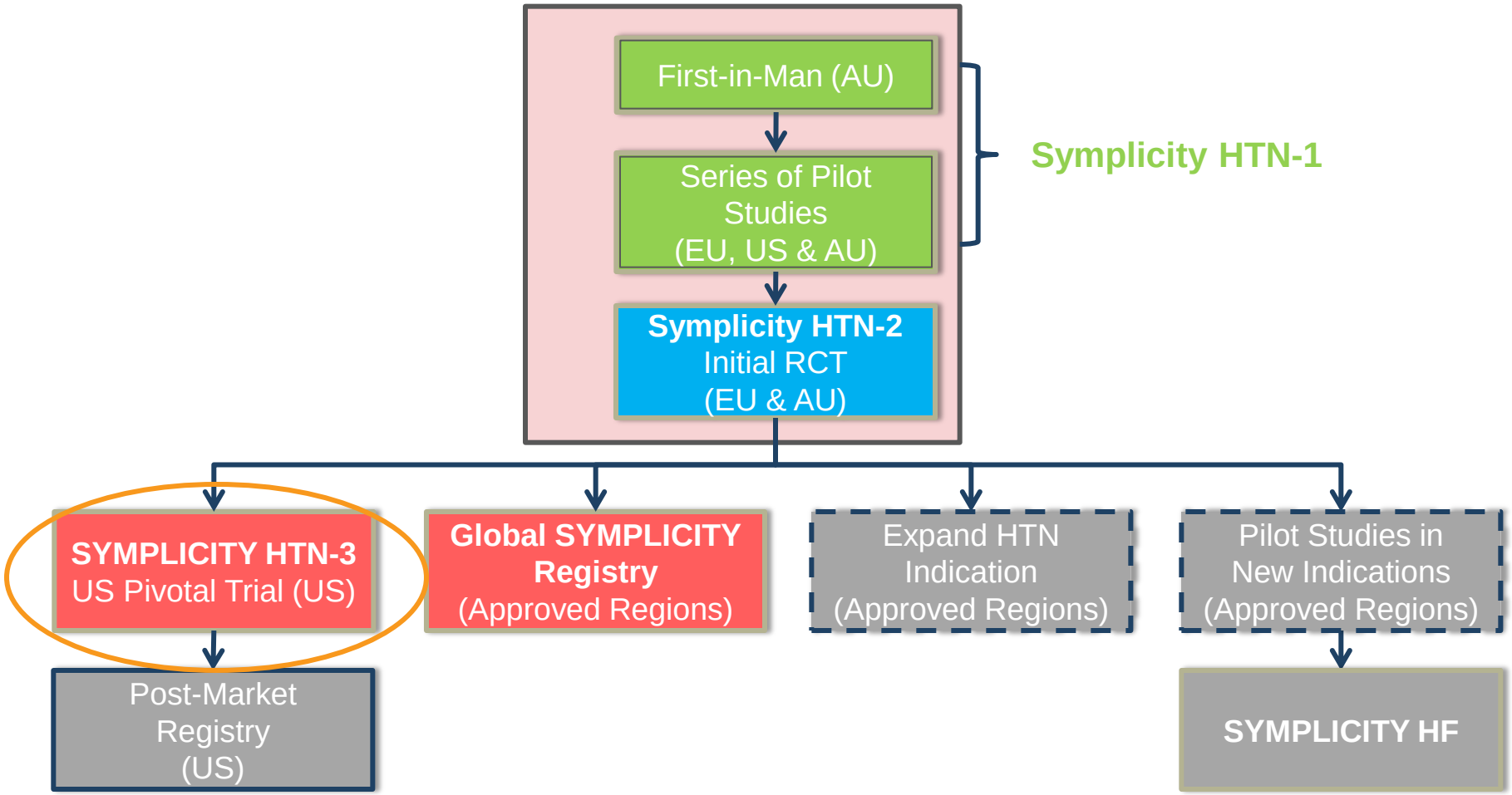
Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint

MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

"SYMPLICITY HTN-3 met its primary safety endpoint related to the incidence of major adverse events one month following randomization and renal artery stenosis to six months," said Deepak L. Bhatt, M.D., M.P.H., executive director, Interventional Cardiovascular Programs, Brigham and Women's Hospital Heart and Vascular Center, professor of medicine, Harvard Medical School, and co-principal investigator of SYMPLICITY HTN-3. "Importantly, however, the trial did not meet its primary efficacy endpoint."

SYMPLICITY Clinical Trial Programs:
over 5000 patients across multiple indications



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

N Engl J Med 2014; 370:1393-1401, 10 April 2014

Key Inclusion/Exclusion Criteria

Key Inclusion:

•Stable medication regimen including full tolerated doses of 3+ anti hypertensive medications of different classes, including a diuretic

•Office SBP ≥160 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit

Key Exclusion:

- ABPM 24 hour average SBP <135 mm Hg
- eGFR of <45 mL/min/1.73 m^2
- Main renal arteries <4 mm diameter or <20 mm treatable length

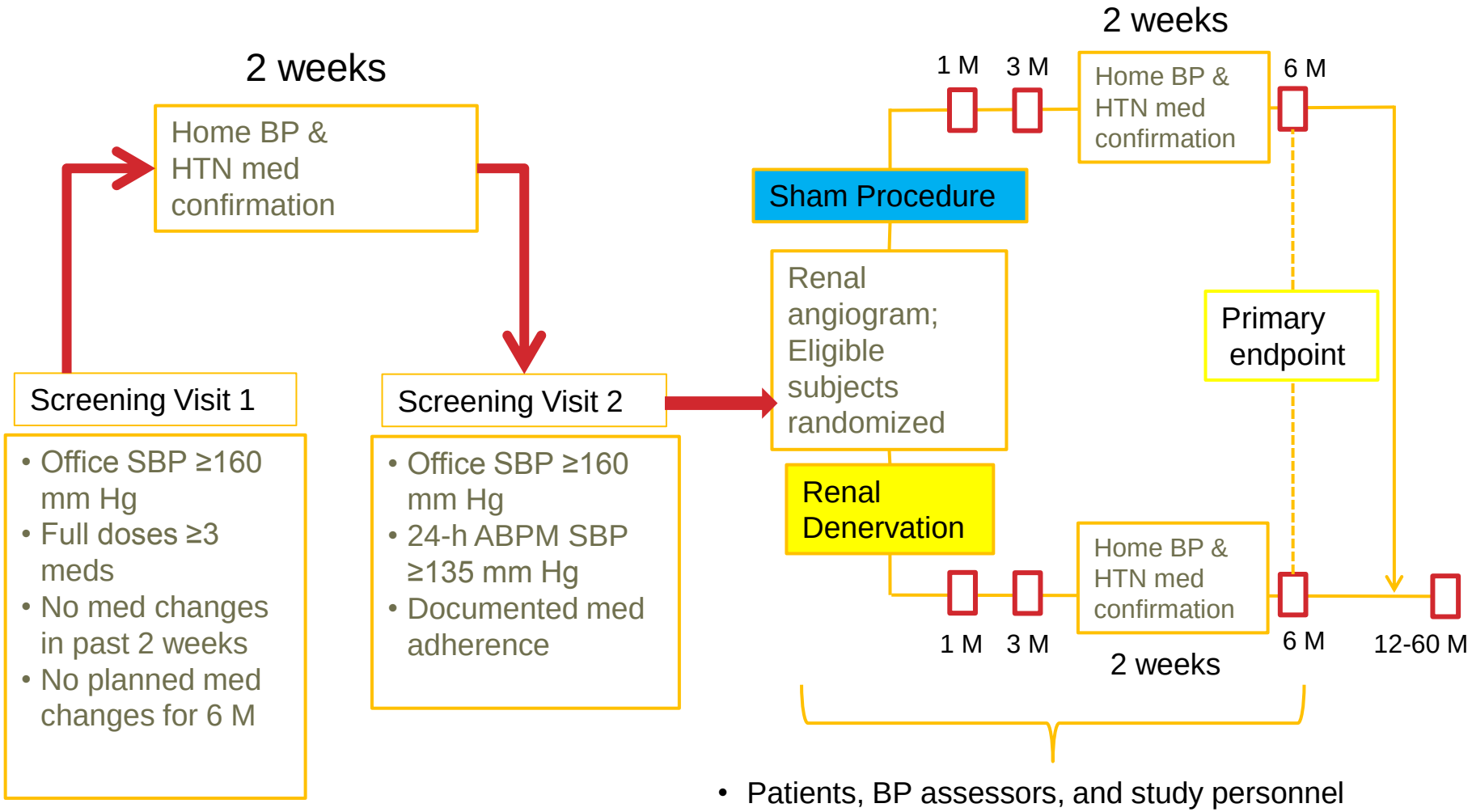
TRIAL OBJECTIVES

•SYMPLICITY HTN-3 is the first prospective, multi-center, randomized, blinded, sham controlled study to evaluate both the safety and efficacy of percutaneous renal artery denervation in patients with severe treatment-resistant hypertension.

•The trial included 535 patients enrolled by 88 participating US centers.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

SYMPLICITY HTN-3 TRIAL DESIGN



- Patients, BP assessors, and study personnel all blinded to treatment status
- No changes in medications for 6 M

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

EFFICACY ENDPOINTS

Primary Effectiveness Endpoint:

•Comparison of office SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

$$\text{Endpoint} = (SBP_{RDN\ 6\ month} - SBP_{RDN\ Baseline}) - (SBP_{CTL\ 6\ month} - SBP_{CTL\ Baseline})$$

•*Superiority margin of 5 mm Hg*

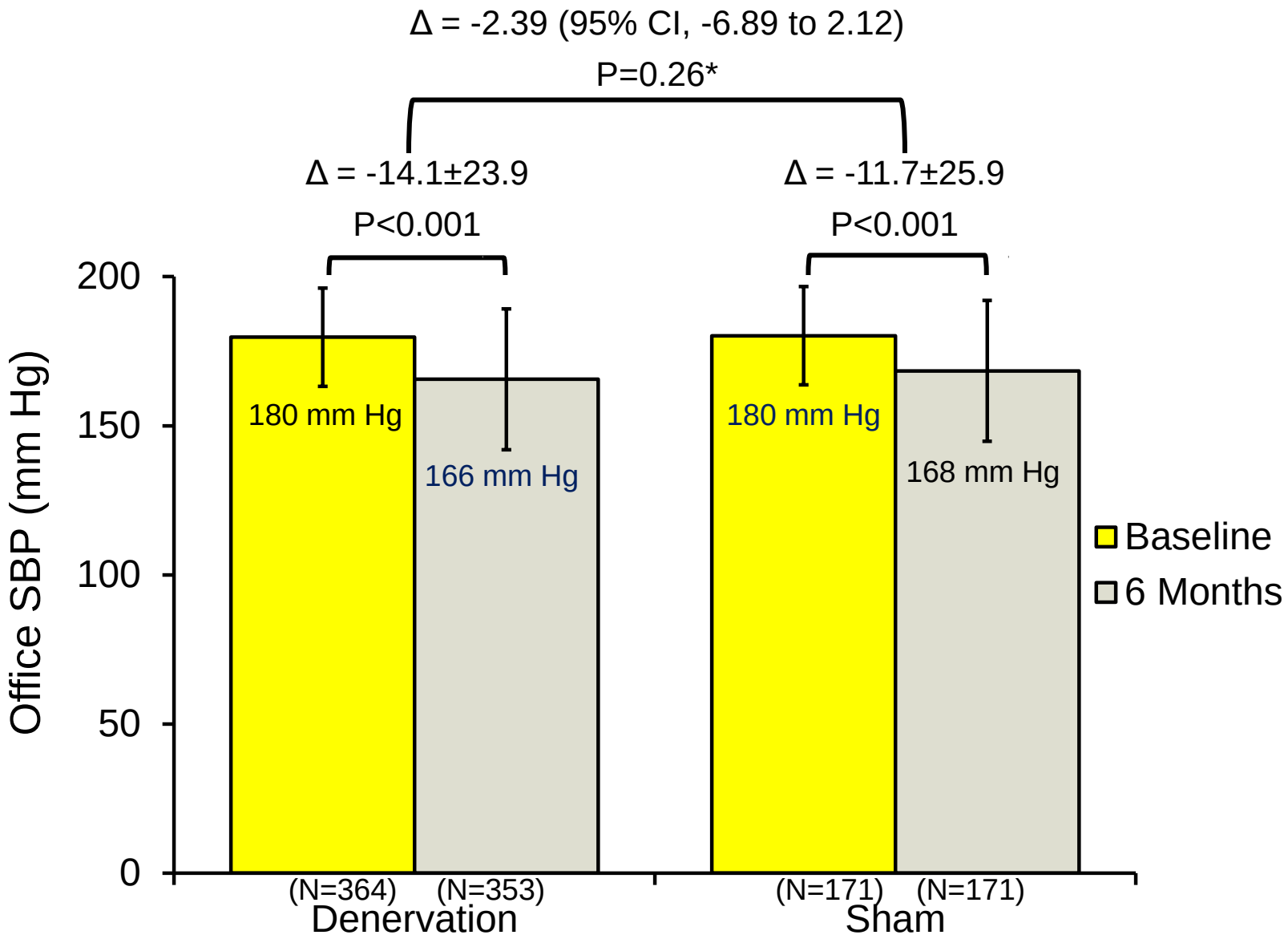
Powered Secondary Effectiveness Endpoint:

•Comparison of mean 24-hour ambulatory (ABPM) SBP change from baseline to 6 months in RDN arm compared with change from baseline to 6 months in control arm

•*Superiority margin of 2 mm Hg*

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

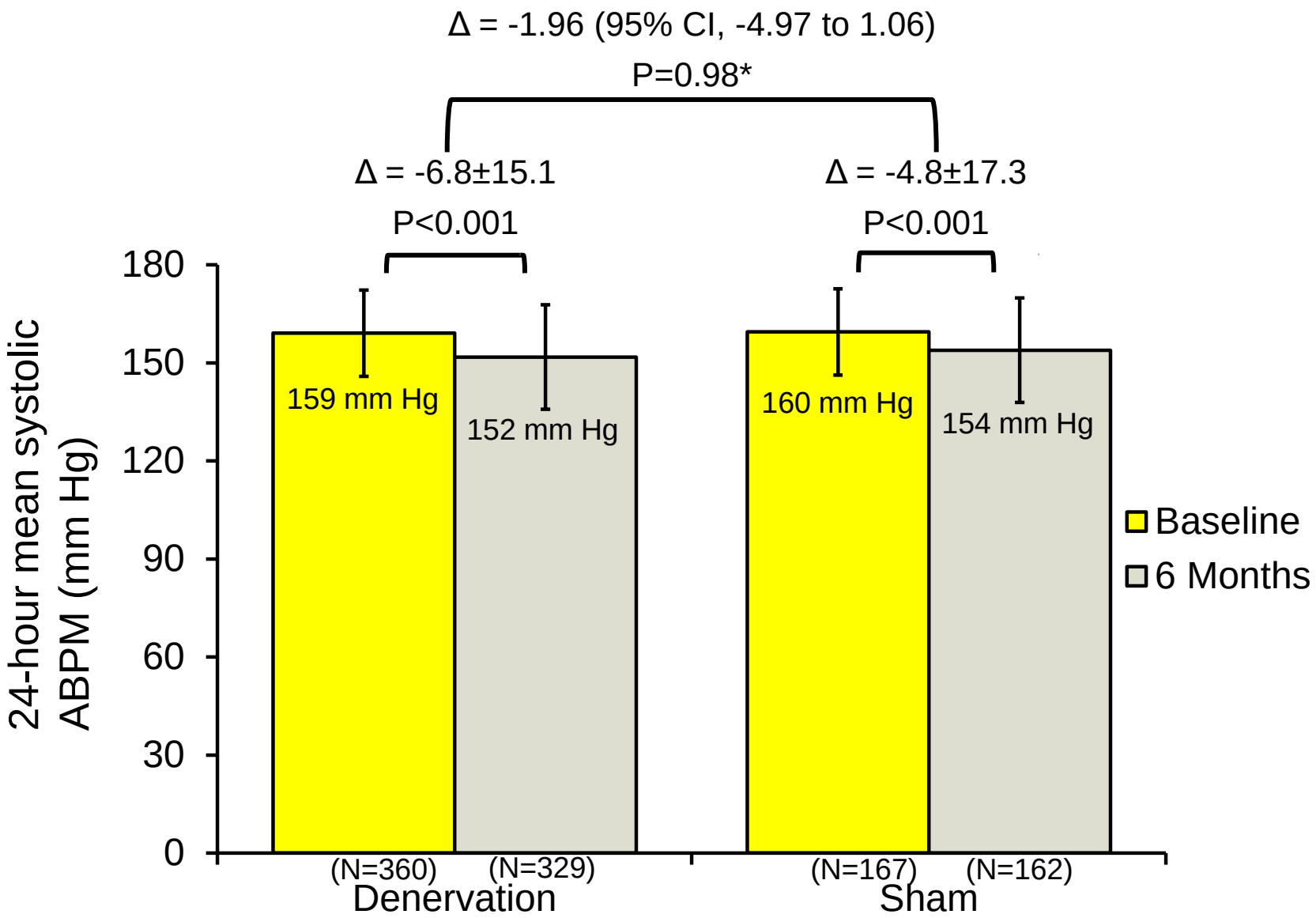
PRIMARY EFFICACY ENDPOINT



*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

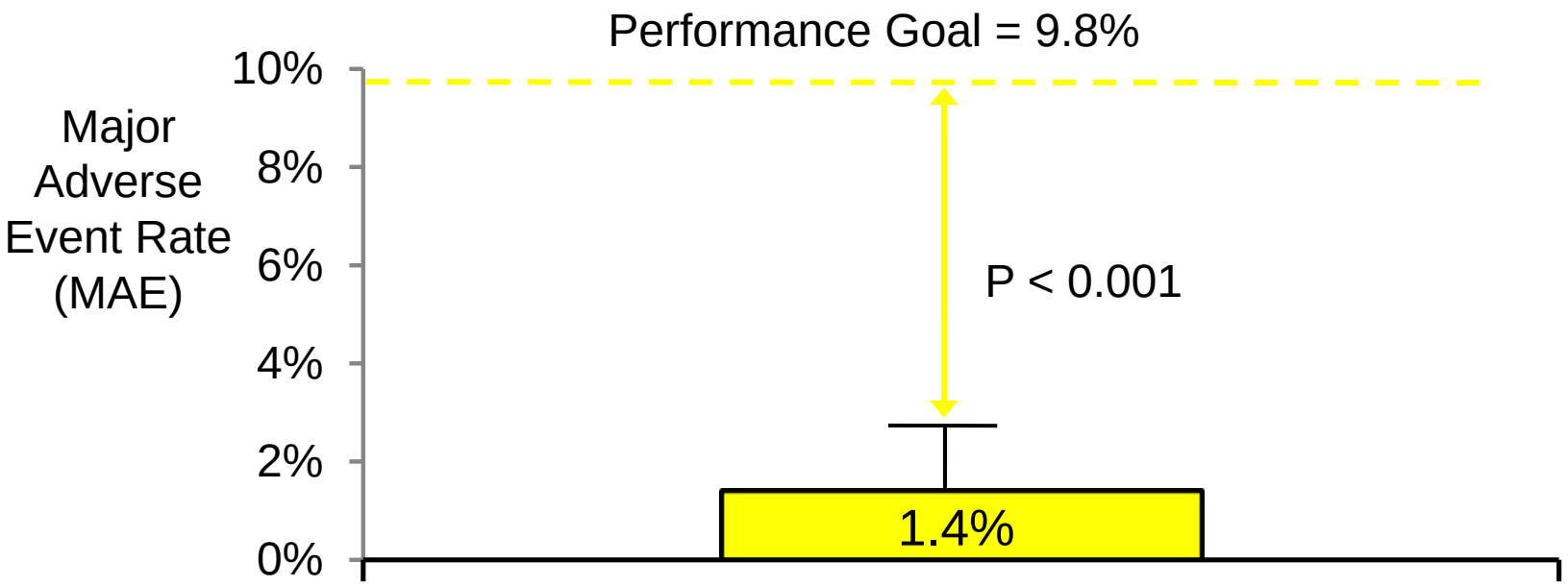
POWERED SECONDARY EFFICACY ENDPOINT



*P value for superiority with a 2 mm Hg margin; bars denote standard deviations

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

PRIMARY SAFETY ENDPOINT



	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference [95% CI]	P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% [-0.9%, 2.5%]	0.67

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

HTN-3 RESULTS: POTENTIAL FACTORS

The Patient

- **Patient behavior** (improved or modified lifestyle and drug adherence) may change due to being enrolled and closely monitored in a clinical trial (“Hawthrone effect”)

The Trial

- **Patient demographics**
- **Medication adherence and medication change**
- **Duration of primary endpoint may have been too short**

The Doctor

- **Greater variation in procedural experience**

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RESULTS: POPULATION DEMOGRAPHICS

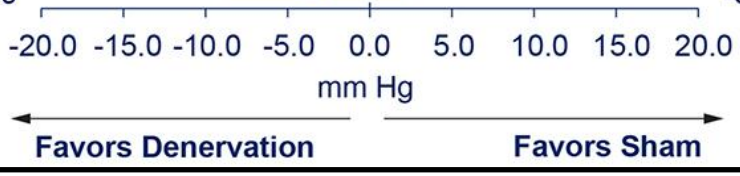
	Renal Denervation (N=364)	Sham Procedure (N=171)	P
Age (years)	57.9 ± 10.4	56.2 ± 11.2	0.09
Male sex (%)	59.1	64.3	0.26
Office systolic blood pressure (mm Hg)	180±16	180±17	0.77
24 hour mean systolic ABPM (mm Hg)	159±13	160±15	0.83
BMI (kg/m^2)	34.2 ± 6.5	33.9 ±6.4	0.56
Race* (%)			0.57
African American	24.8	29.2	
White	73.0	69.6	
Medical history (%)			
Renal insufficiency (eGFR<60 ml/min/1.73m^2)	9.3	9.9	0.88
Renal artery stenosis	1.4	2.3	0.48
Obstructive sleep apnea	25.8	31.6	0.18
Stroke	8.0	11.1	0.26
Type 2 diabetes	47.0	40.9	0.19
Hospitalization for hypertensive crisis	22.8	22.2	0.91
Hyperlipidemia	69.2	64.9	0.32
Current smoking	9.9	12.3	0.45

*Race also includes Asian, Native American, or other

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

RESULTS: PRESPECIFIED SUBGROUP ANALYSES

	No. of Patients		Difference (95% CI) mm Hg	P Value	Interaction P Value
	Denervation	Sham			
All patients	353	171	-2.39 (-6.89 – 2.12)	0.26 *	
Diabetes mellitus					0.82
Yes	169	68	-4.53 (-11.51 – 2.46)	0.20	
No	181	101	-3.46 (-9.55 – 2.62)	0.26	
Sex					0.37
Male	208	108	-2.30 (-7.63 – 3.03)	0.40	
Female	142	61	-6.64 (-14.94 – 1.65)	0.12	
African American					0.09
Yes	85	49	2.25 (-7.27 – 11.78)	0.64	
No	264	120	-6.63 (-11.81 – -1.44)	0.01	
BMI					0.77
<30 kg/m²	91	42	-2.77 (-11.47 – 5.93)	0.53	
≥30 kg/m²	259	126	-4.36 (-9.76 – 1.03)	0.11	
On AA at baseline					0.36
Yes	76	47	-8.05 (-17.63 – 1.52)	0.10	
No	274	122	-3.24 (-8.42 – 1.93)	0.22	
eGFR					0.31
<60 mL/min/1.73 m²	68	38	0.54 (-8.29 – 9.37)	0.90	
≥60 mL/min/1.73 m²	282	131	-5.22 (-10.51 – 0.06)	0.05	
Age					0.27
<65 yr	246	128	-5.73 (-11.06 – -0.40)	0.04	
≥65 yr	104	41	0.09 (-8.80 – 8.99)	0.99	
Any medication change					0.68
Yes	132	70	-5.41 (-13.49 – 2.67)	0.19	
No	218	99	-3.44 (-8.83 – 1.96)	0.21	



* P value for superiority with margin of 5 mm Hg

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Medication Adherence and Medication Change

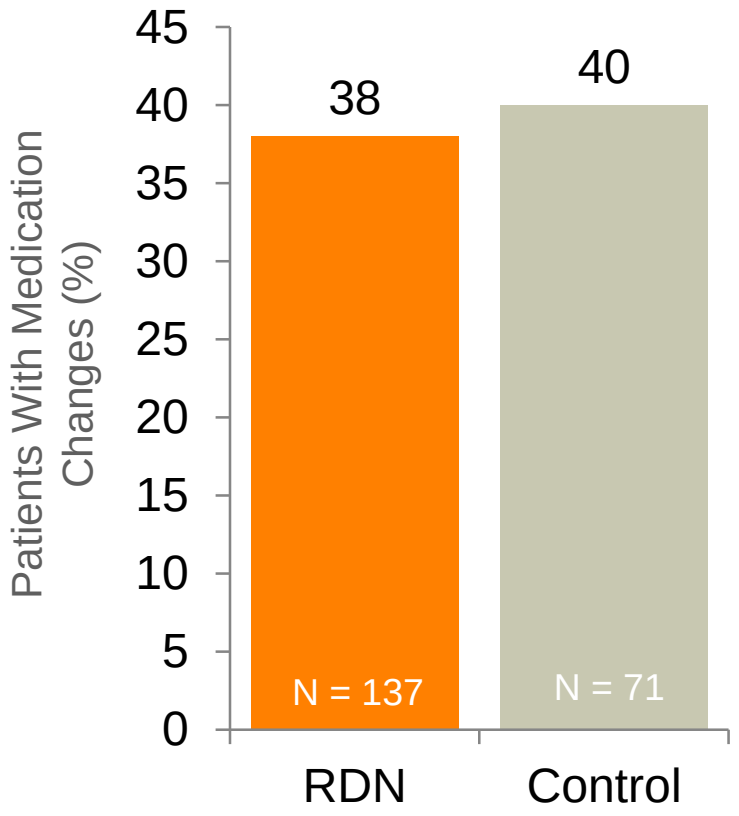
- Drug adherence not measured by blood levels, but adherence was measured by patient diaries at baseline and 6 months.

Medication Change

Protocol mandated maximum doses and *no* medication changes

~40% of patients(n = 211) in the trial required medication changes

- **69%** of first medication changes were medically necessary



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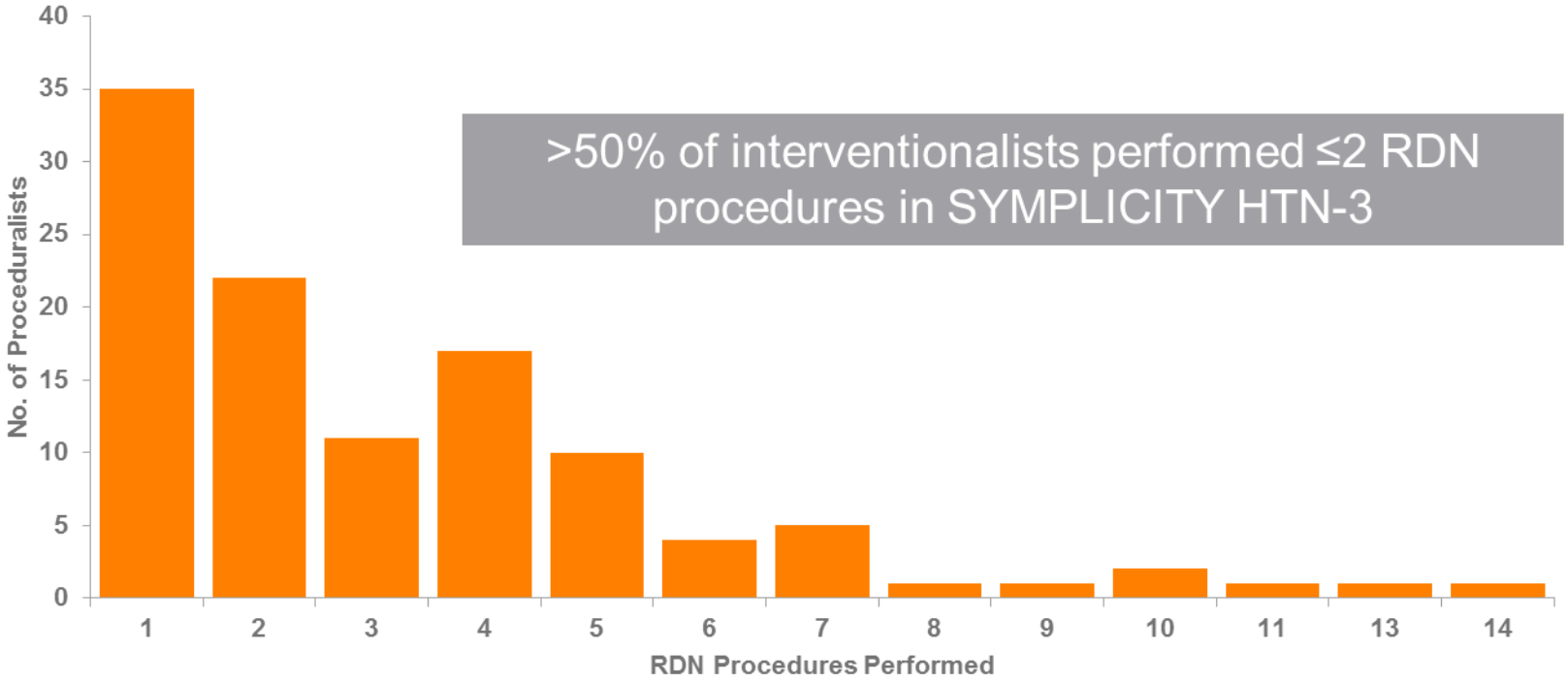
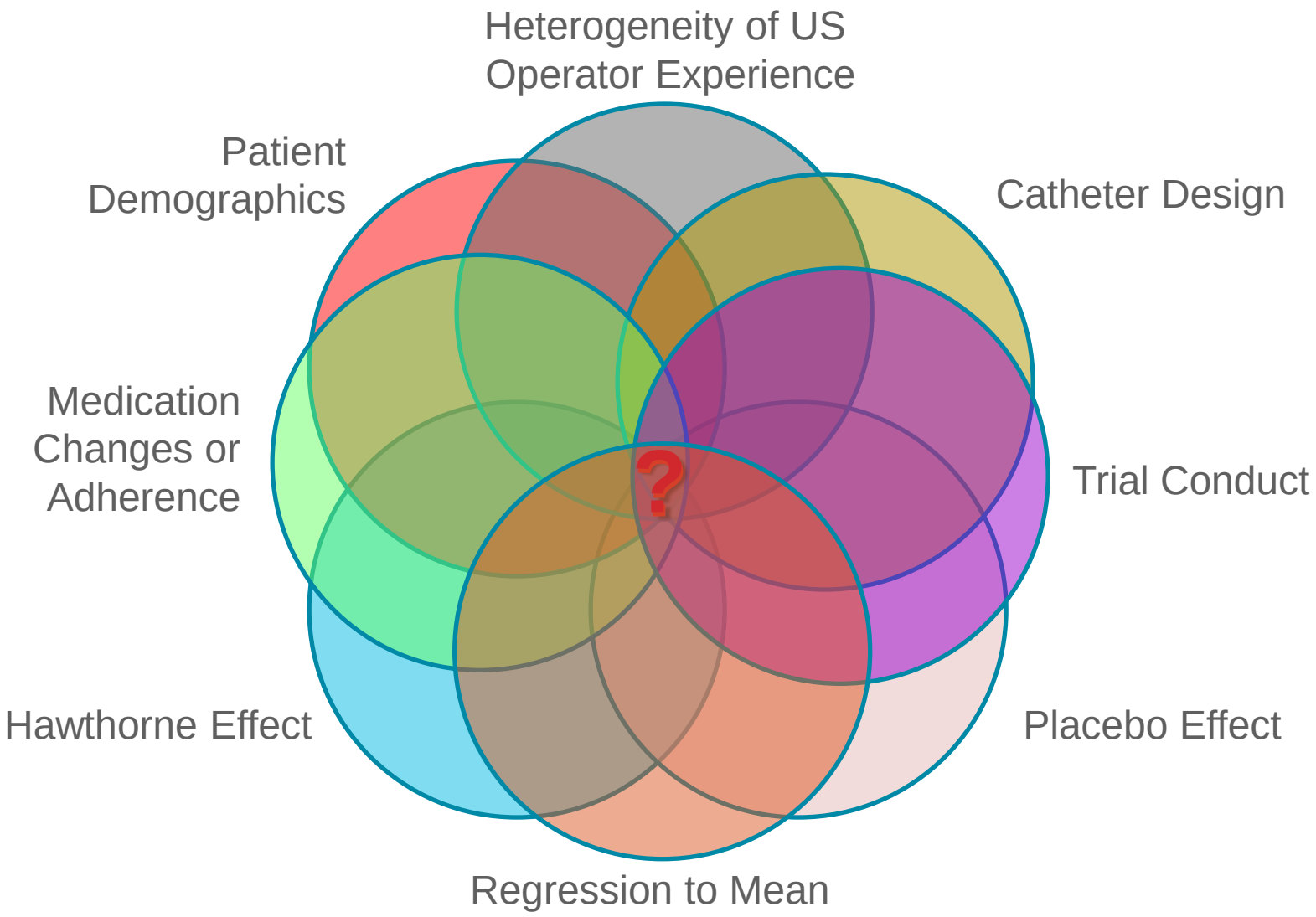
HTN-3: PROCEDURAL EXPERIENCE

	HTN-1	HTN-3
No. of operators	20	112
No. of procedures per operator	6.0	3.3
No. of procedures per site	8.6	4.7

a) 5X more operators vs HTN-1
b) Greater heterogeneity of operator experience vs. HTN-1 and HTN-2
c) Case proctoring was different and not comparable



HTN-3: CONTINUING AREAS OF INVESTIGATION



FUTURE DIRECTION

Further study / data

- Longer term follow-up
- Effects of medication change
- Any means to predict response

Define appropriate treatment populations

- Key subgroups

Reinforce medication adherence

- Before and after procedure

Operator experience

- Optimal training and proctoring

SUMMARY

- **Resistant hypertension is associated with high rates of cardiovascular complications**
- **Sympathetic nervous system appears to play an important role in resistant hypertension**
- **Renal denervation therapy (RDN) has emerged as a potential therapy for resistant hypertension**
- **Effectiveness of RDN was shown in non-randomized studies and randomized, unblinded trials**
- **However, the latest blinded, randomized, sham-controlled trial confirmed the safety of RDN but not the efficacy**
- **The optimal clinical use of RDN needs to be defined**