The 21st Budapest Nephrology School

Nephrology, Hypertension, Dialysis, Transplantation

26 – 31 August, 2014

Renal denervation in patients with resistant hypertension – blood pressure reduction and beyond

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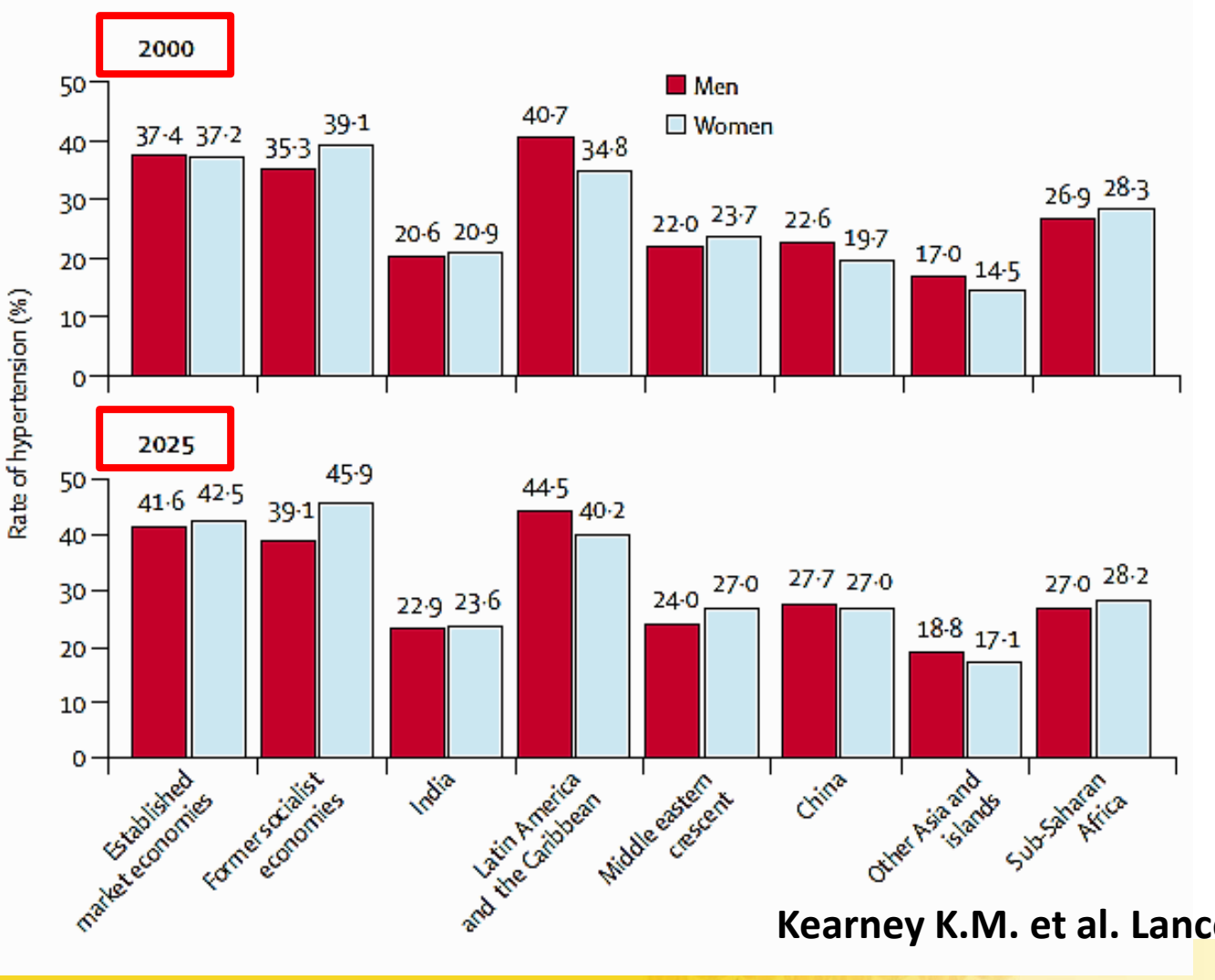
Frequency of hypertension in people aged 20 years and older by world region and gender in 2000 and 2025



Kearney K.M. et al. Lancet, 2005, 365, 217-223

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower SBP and DBP values to <140 and 90 mmHg, respectively. Depending on the population

Pathophysiology of resistant hypertension

- Inappropriate high sympathetic outflow
- Inappropriate high renin and/or aldosterone release or other neurohumoral mediators such as endothelin
- Inappropriate high cardiac output
- Relative or absolute volume expansion
- Abnormal sleep patterns, anxiety, depression, substances used and medication complience
- Incorrect medication combinations or doses

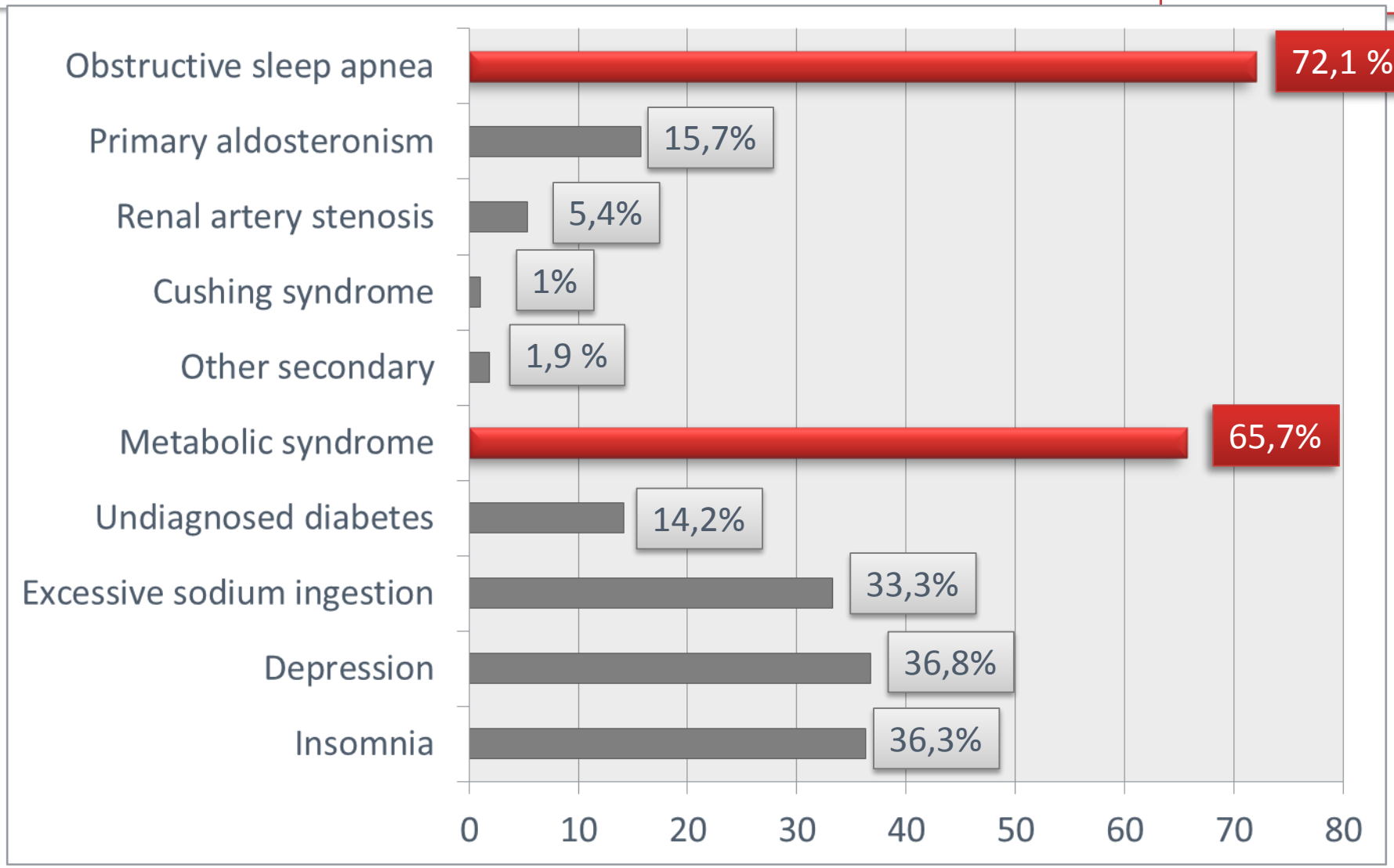
Resistant hypertension: Risk factors

- Hyperaldosteronism
- Pseudohypertension (mediasclerosis)
- Diabetes
- White coat hypertension
- Obesity
- Secondary hypertension (re-evaluation)
- Noncompliance (drugs)
- Discontinuation of nonpharmacological means
- Interaction with other drugs (nonsteroidal antirheumatics, glucocorticoids)

❖ **New conditions: ABPM, salt restriction, MCR blockers**

Frequency of OSA, secondary causes and associated conditions - in 204 patients with **true resistant hypertension**

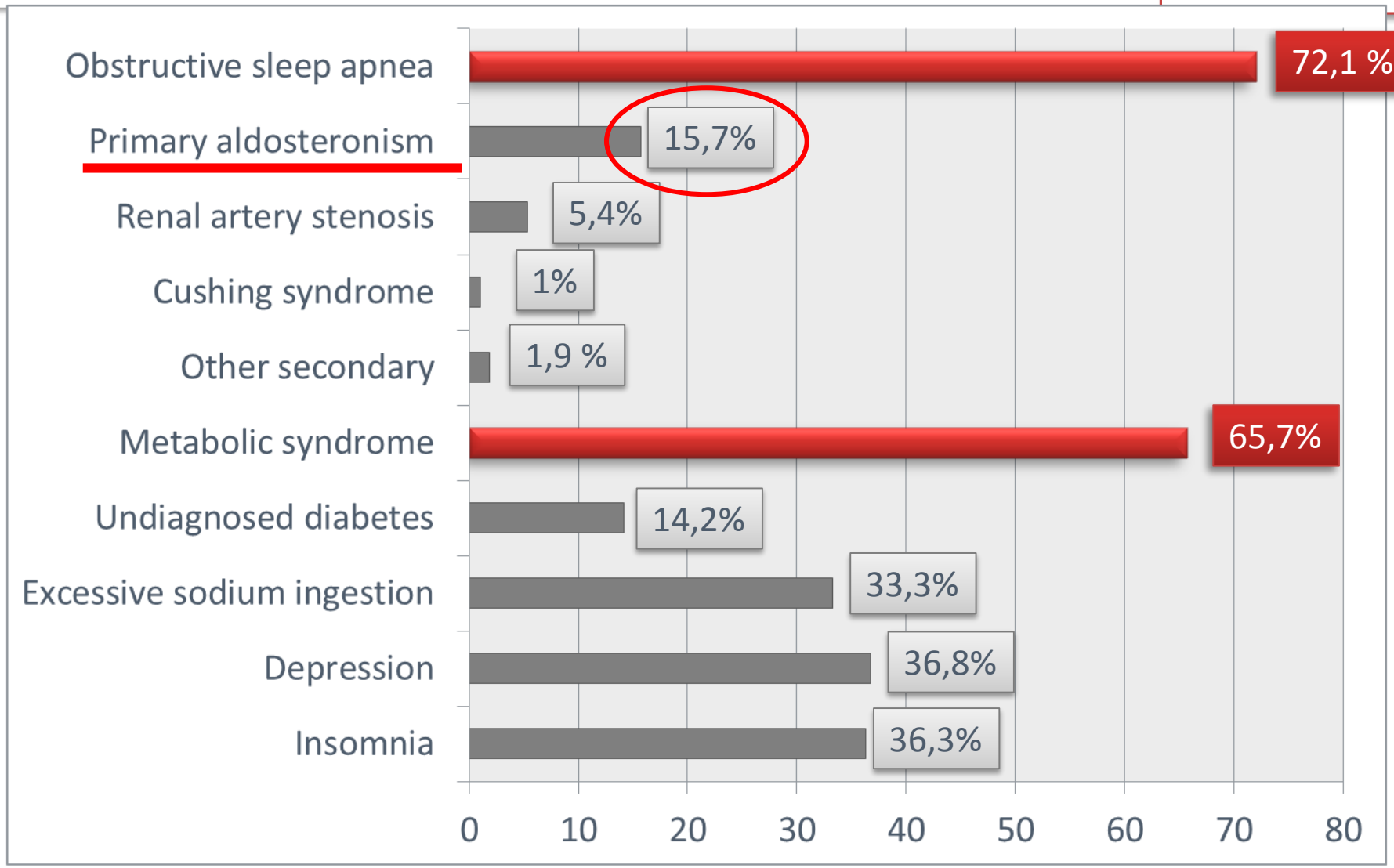
RESIST-POL STUDY



Florczak E….Wiecek A. et al. J. Human Hypertens., 2013, 27: 678-685

Frequency of OSA, secondary causes and associated conditions - in 204 patients with **true resistant hypertension**

RESIST-POL STUDY



Florczak E….Wiecek A. et al. J. Human Hypertens., 2013, 27: 678-685

High Prevalence of White-Coat Hypertension in Spanish Resistant Hypertensive Patients

William J. Elliott

Journal of Human Hypertension (2011) 25, 137–140
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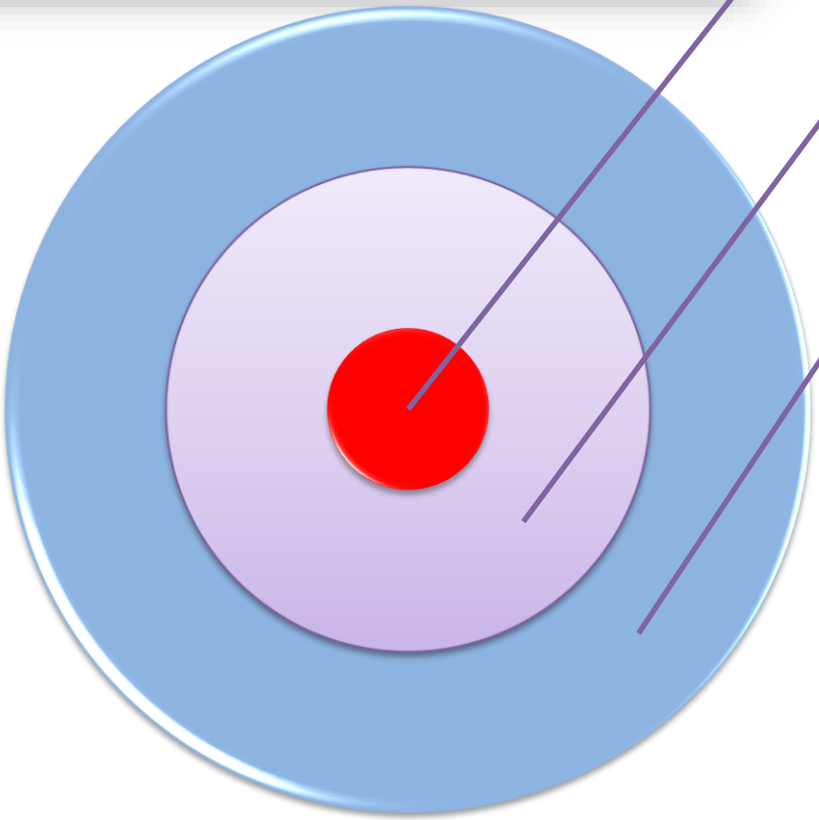
www.nature.com/jhh

RESEARCH LETTER

How common is true resistant hypertension?



True resistant hypertension - confirmed in ABPM –62,5% (7,6% of all treated pts)

Resistant HT (office readings) – 12,2%

68 045 patients with HT

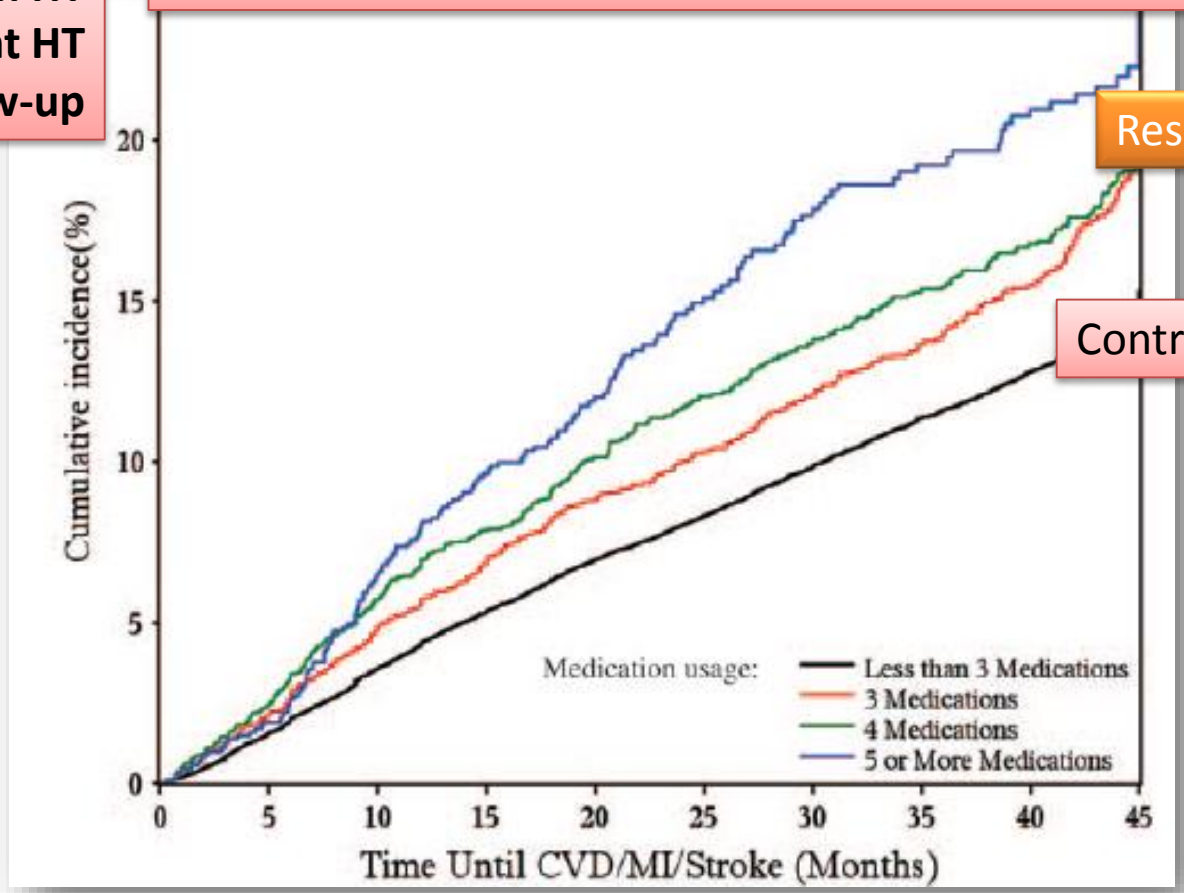
Persell SD, Hypertension 2011; de la Sierra, Hypertension 2011

Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis

Dharam J. Kumbhani[1], P. Gabriel Steg[2,3,4], Christopher P. Cannon[1,5], Kim A. Eagle[6], Sidney C. Smith Jr[7], Kevin Crowley[5], Shinya Goto[8], E. Magnus Ohman[9], George L. Bakris[10], Todd S. Perlstein[1], Scott Kinlay[1,11], and Deepak L. Bhatt[1,5,11]*, on Behalf of the REACH Registry Investigators[†]

53 530 patients with HT
12,7% - resistant HT
4-years follow-up

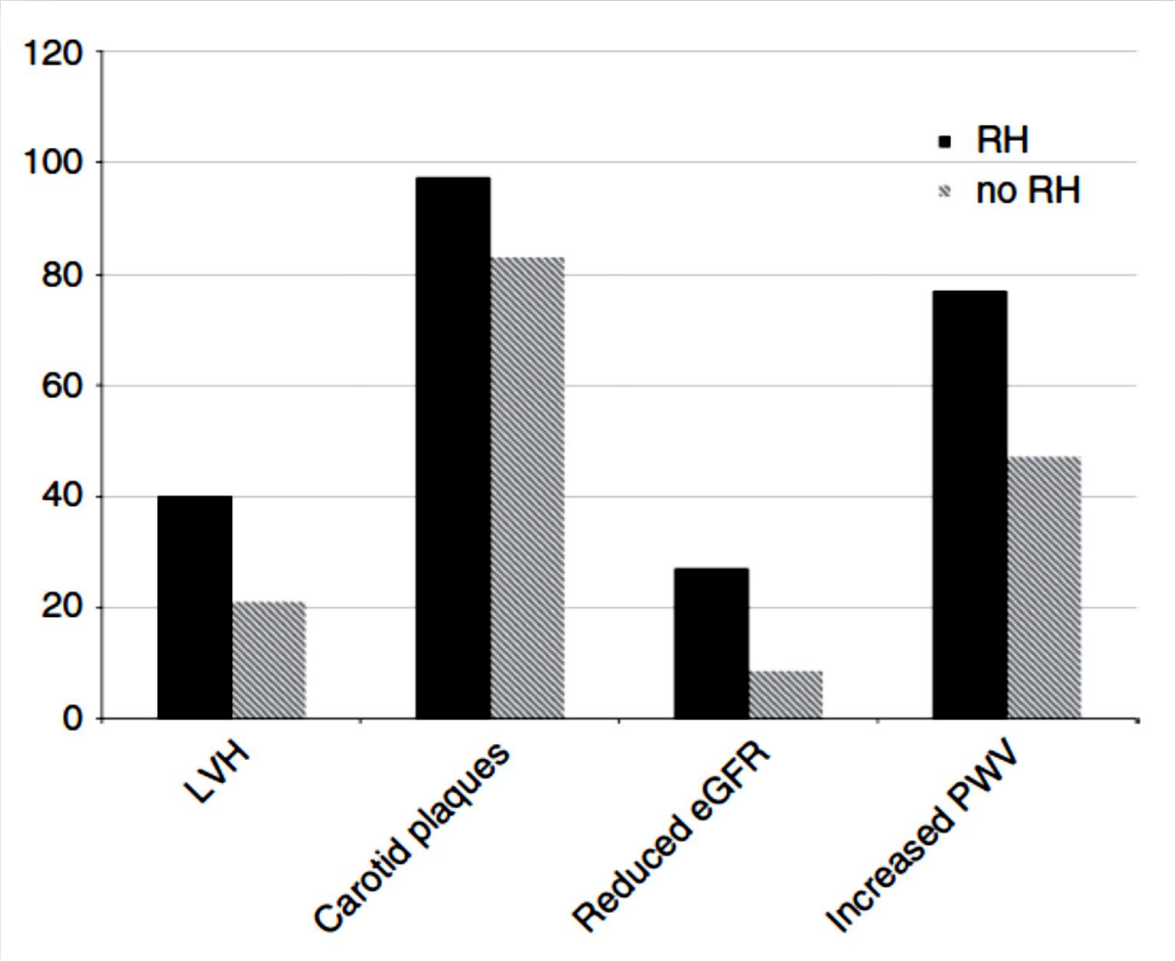
Risk of cardiovascular death, myocardial infraction, stroke



European Heart Journal, 2012

Resistant hypertension and target organ damage

Maria Lorenza Muiesan, Massimo Salvetti, Damiano Rizzoni, Anna Paini, Claudia Agabiti-Rosei, Carlo Aggiusti and Enrico Agabiti Rosei

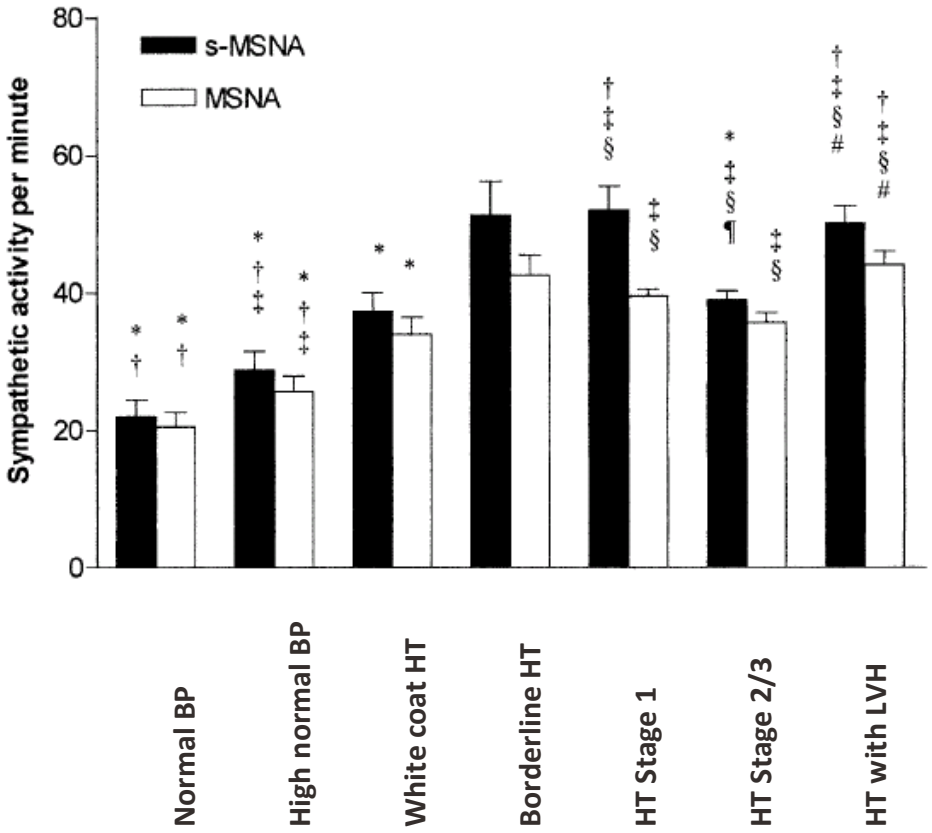


Hypertension Research, 2013

Sympathetic nervous system activity - assessed by microneurography

Increased sympathetic nervous system activity in patients with:

↑	High normal BP
↑	White coat HT
↑↑	Borderline HT
↑↑	HT – stage 1
↑↑	HT – stage 2-3
↑↑	HT with LVH



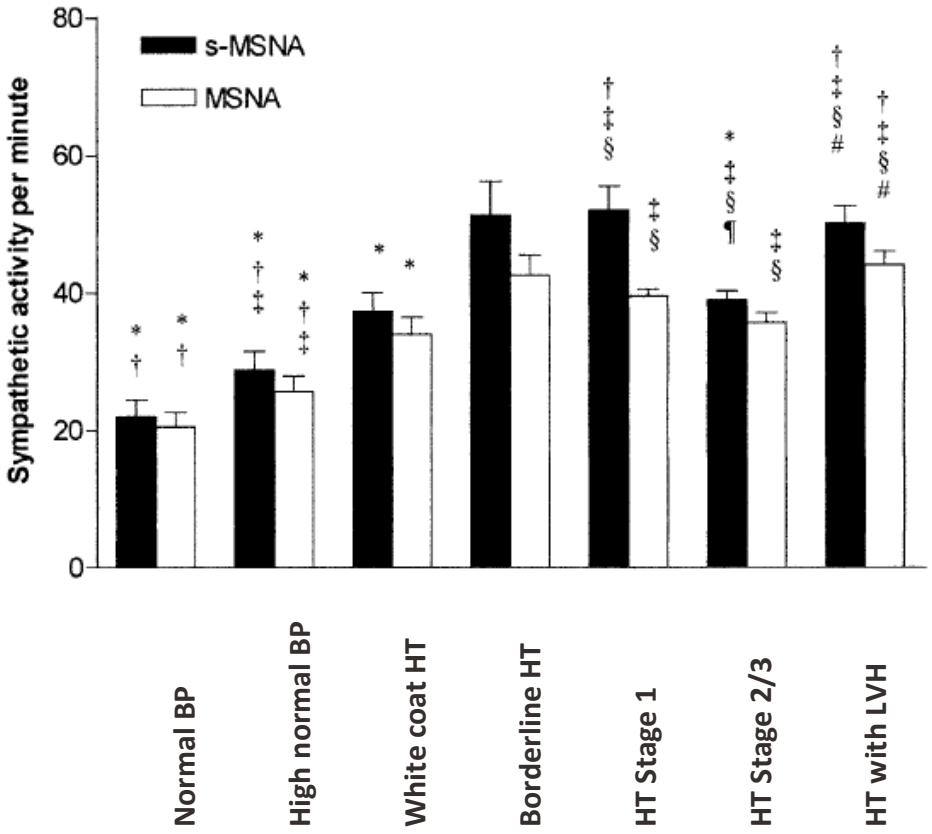
Smith et al. Am. J. Hypertens., 2004; 17217–222

Sympathetic nervous system activity - assessed by microneurography

Increased sympathetic nervous system activity in patients with:

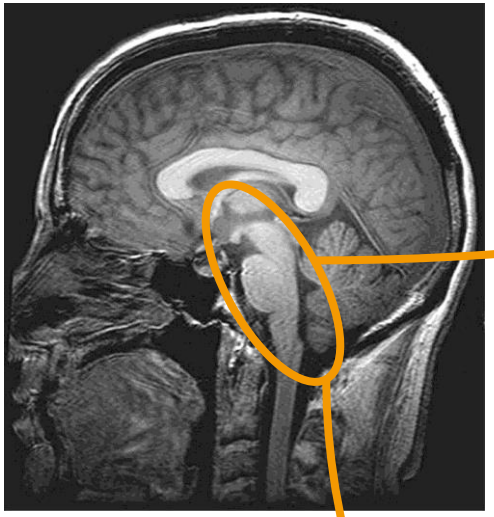
- ↑ High normal BP
- ↑ White coat HT
- ↑↑ Borderline HT
- ↑↑ HT – stage 1
- ↑↑ HT – stage 2-3
- ↑↑ HT with LVH

Hypertension, particulary resistant is characterized by marked sympathetic nervous system activation !

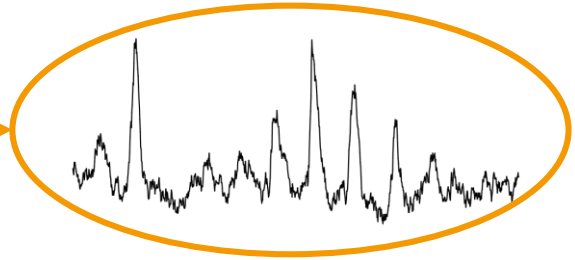


Smith et al. Am. J. Hypertens., 2004; 17217–222

Quantifying human SNS activity

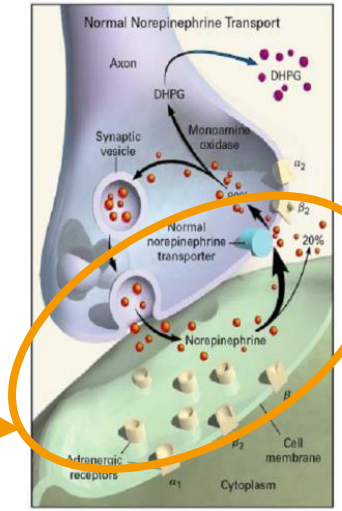


Central sympathetic nerve activity



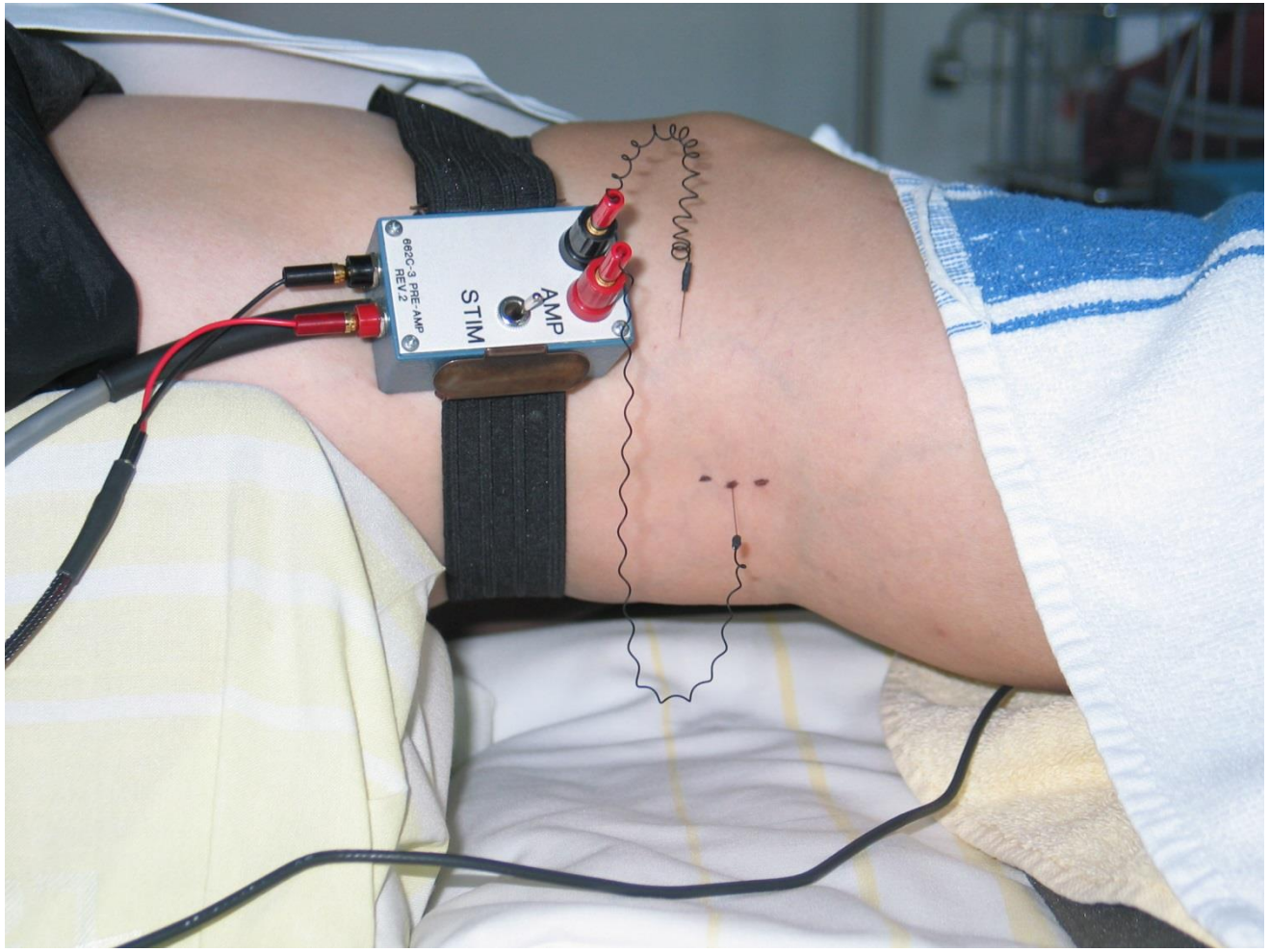
Muscle sympathetic nerve activity (MSNA)
recording postganglionic nerve traffic

Renal sympathetic nerve activity



Norepinephrine spillover
measuring transmitter release from sympathetic nerves to plasma

Microneurography - best method to measure sympathetic nerve activity in humans

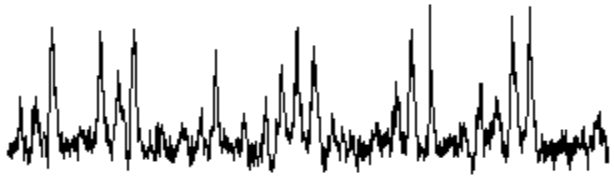


Proof of Principle

Direct measurement of reduced central sympathetic nerve activity

Denervation of patient with essential HTN

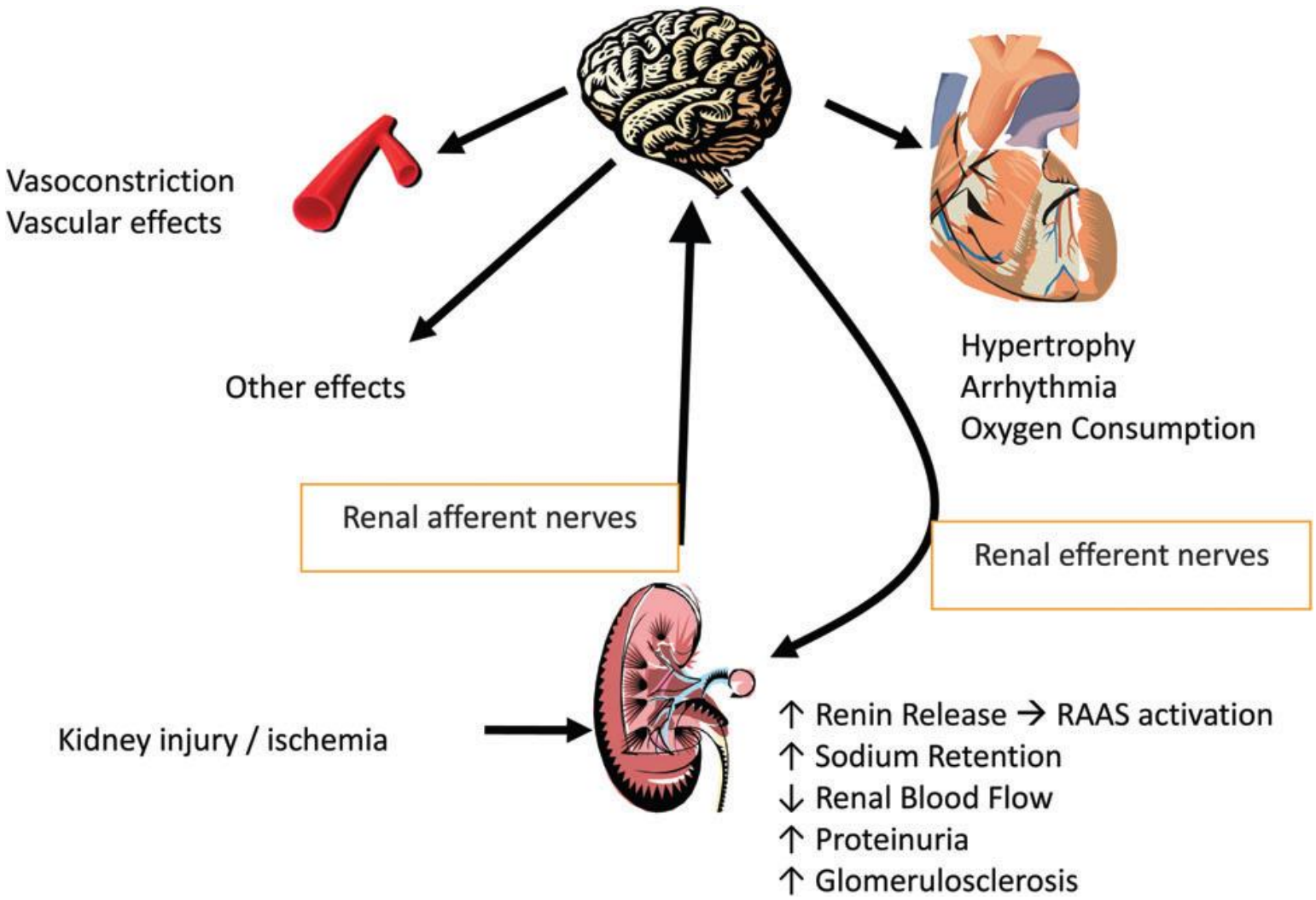
59-Year-Old Male on 7 HTN Meds

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

Improvement in cardiac baroreflex sensitivity after RDN (7.8 →11.7 msec/mmHg)

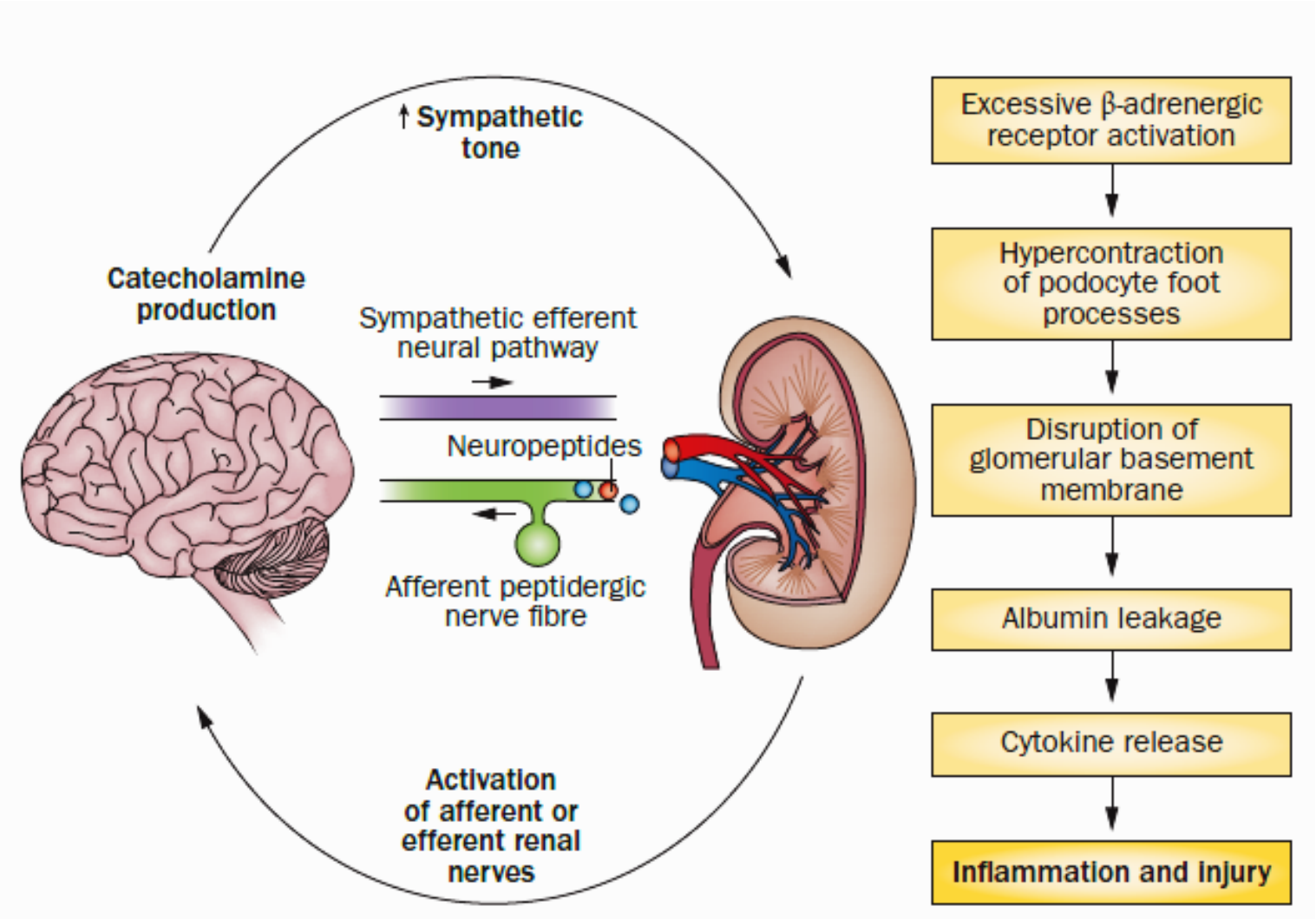
Schlaich M et al. N.Eng.J.Med., 2009; 36: 932-934

Kidney involvement on the function of renal afferent and efferent nerves



Blankestijn P.J. et al., Nephrol. Dial. Transplant., 2014, 29,1120-1123

Potential role of renal nerves in renal inflammation and injury

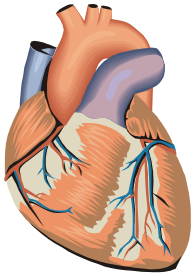


Veelken R., Schmieder R.E., Nat. Rev. Nephrol., 2014, 10, 305-313

Renal nerve and sympathetic activity

Kidney as origin and recipient of central sympathetic drive

Vasoconstriction
- Atherosclerosis



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

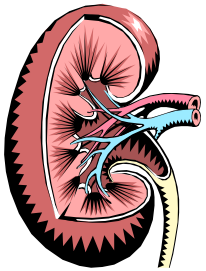
Efferent Nerves

-- Renal Denervation (RDN)--

Afferent Nerves

Blood Pressure

- Decrease co-morbidities
+ Increase co-morbidities



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

Blankestijn P.J. et al., Nephrol. Dial. Transplant., 2014, 29,1120-1123

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

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

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SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

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

Dr. Reginald H. Smithwick

Effective, but…

- **Significant morbidity**
- **Surgeries affected other nerves besides renal nerves**
- **Medical therapy improved significantly**

HYPERTENSION AND ITS SURGICAL TREATMENT BY BILATERAL SUPRADIAPHRAGMATIC SPLANCHNICECTOMY*

MAX MINOR PEET, M.D.
Ann Arbor, Michigan

Am. J. Surg., 1948

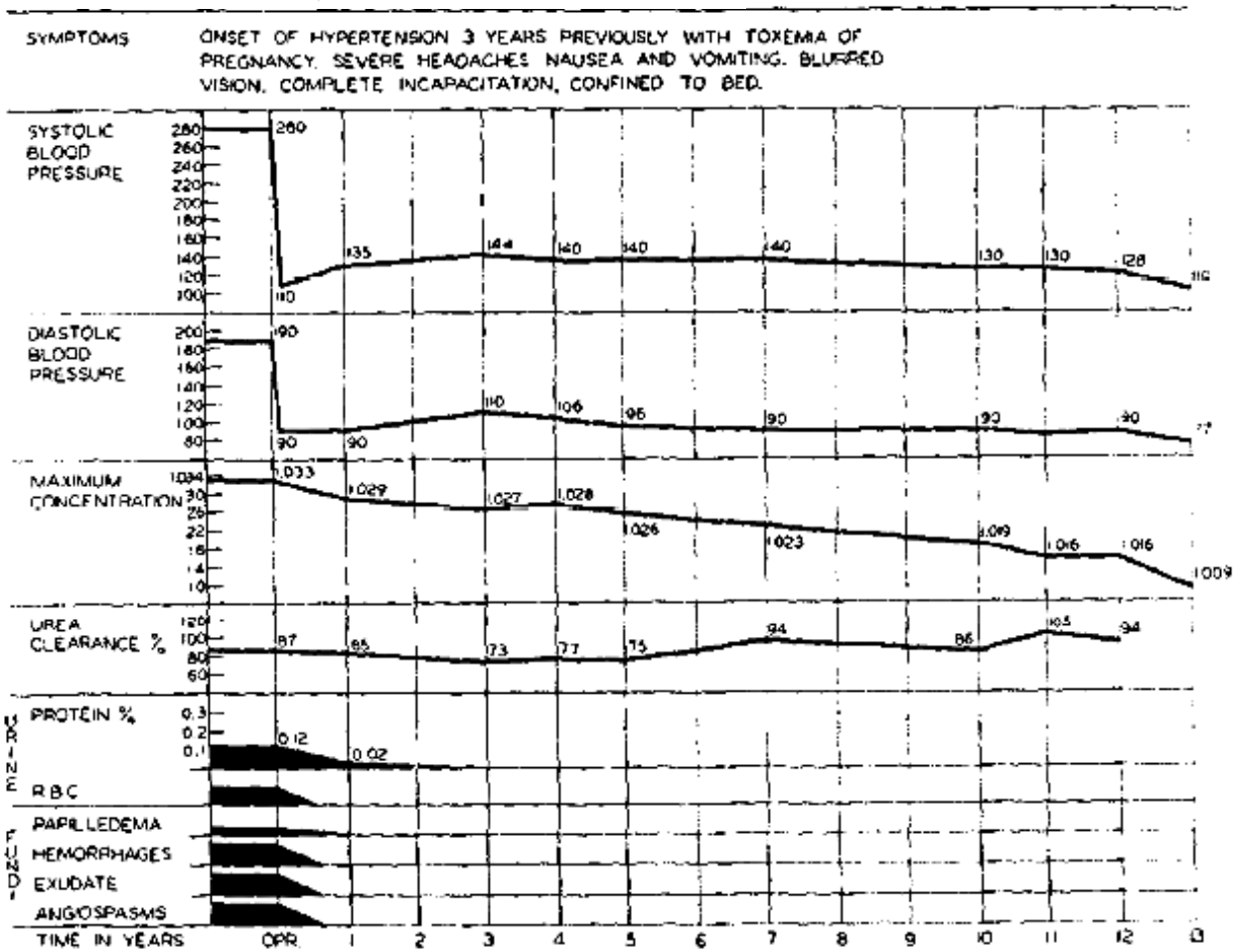
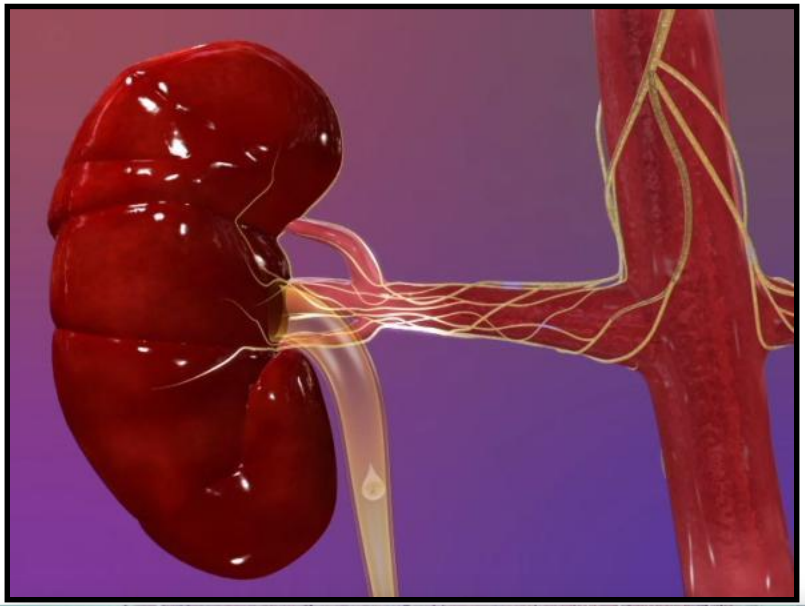
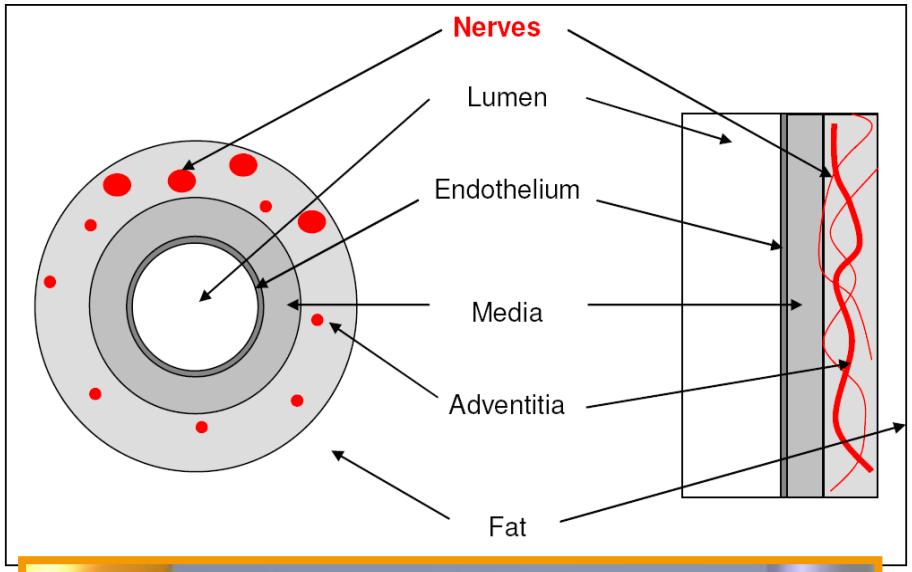
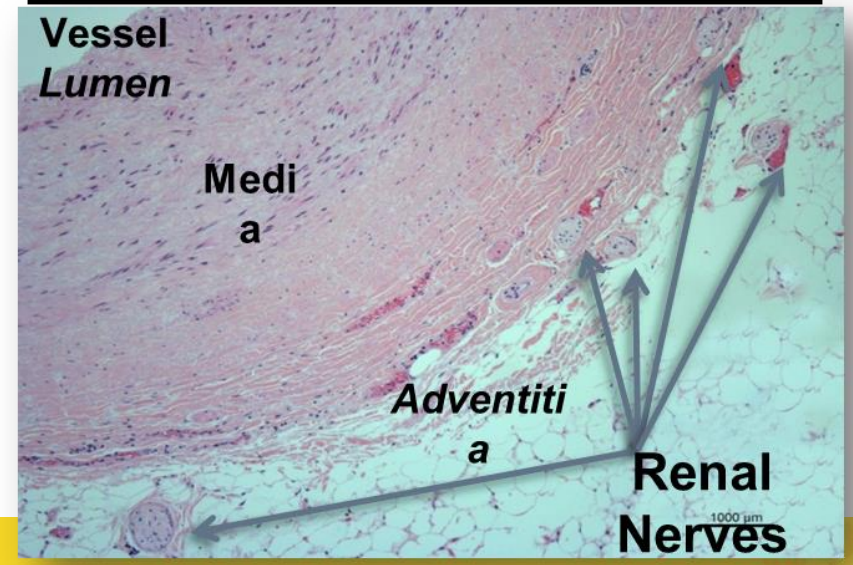


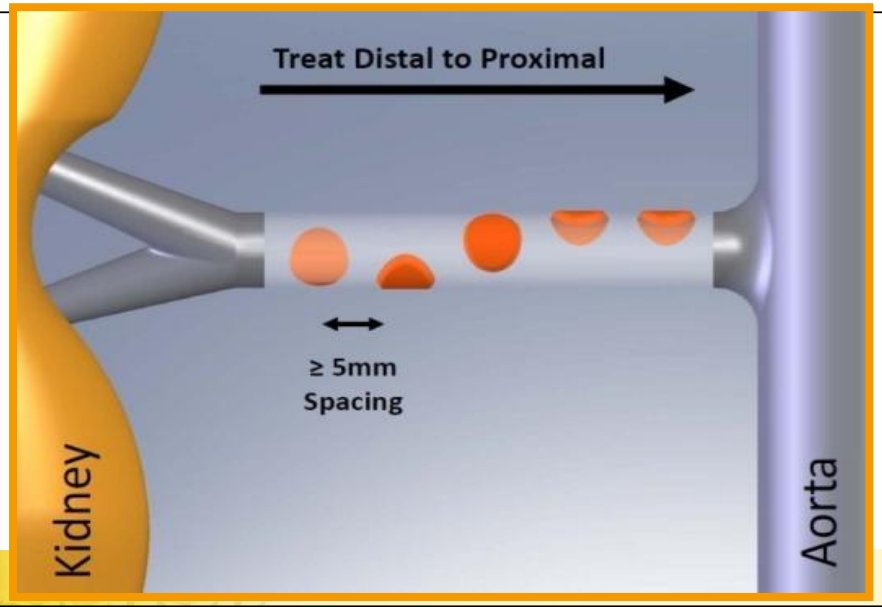
FIG. 1. Chart illustrating results of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy during a thirteen-year postoperative period. (Case 1.)

Renal nerves as a therapeutic target

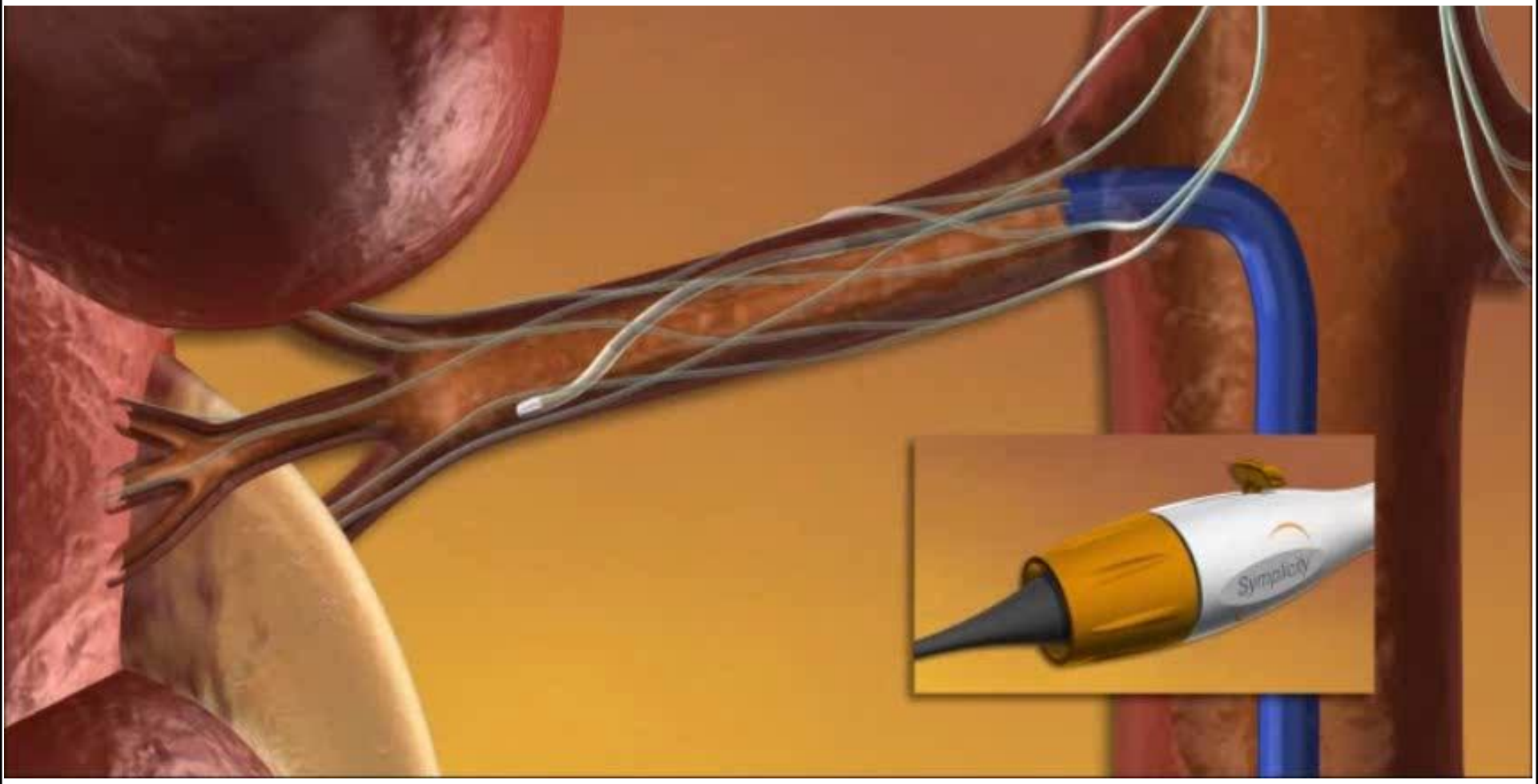




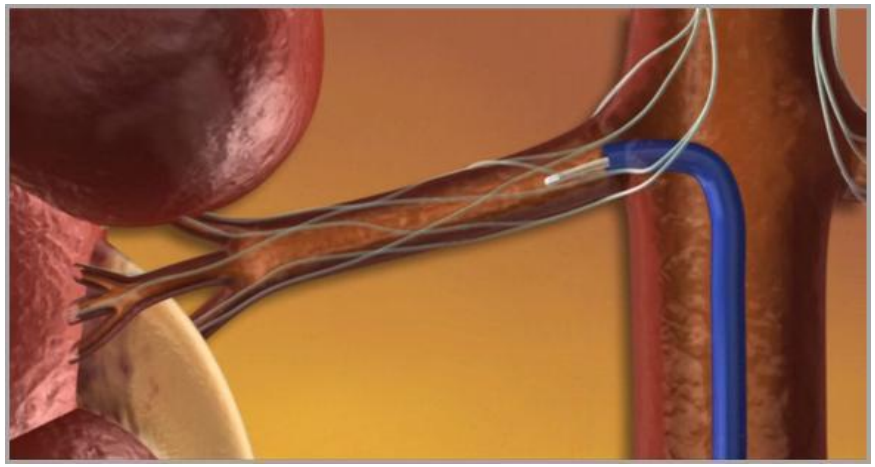


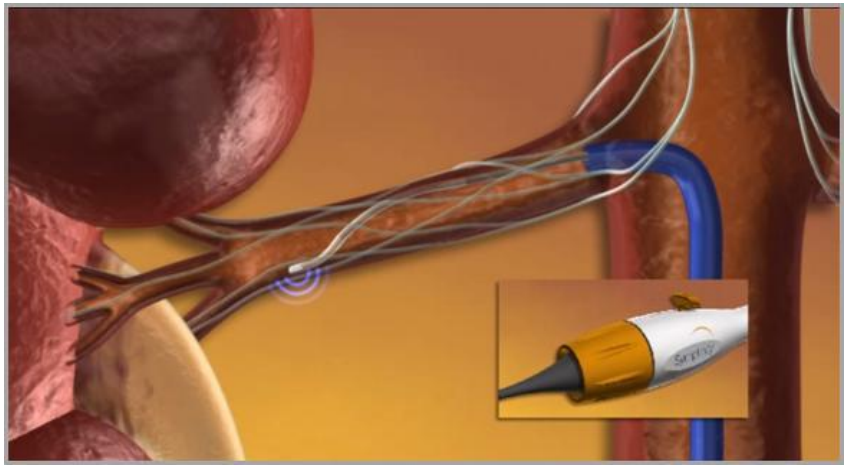


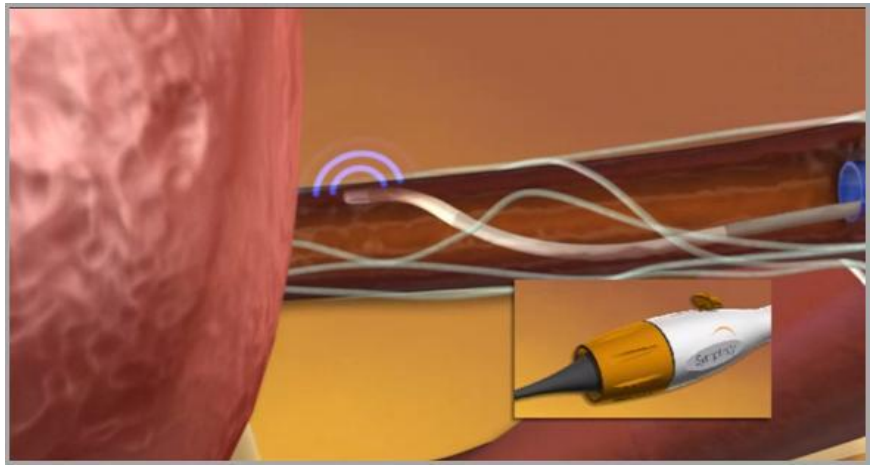
Procedure overview

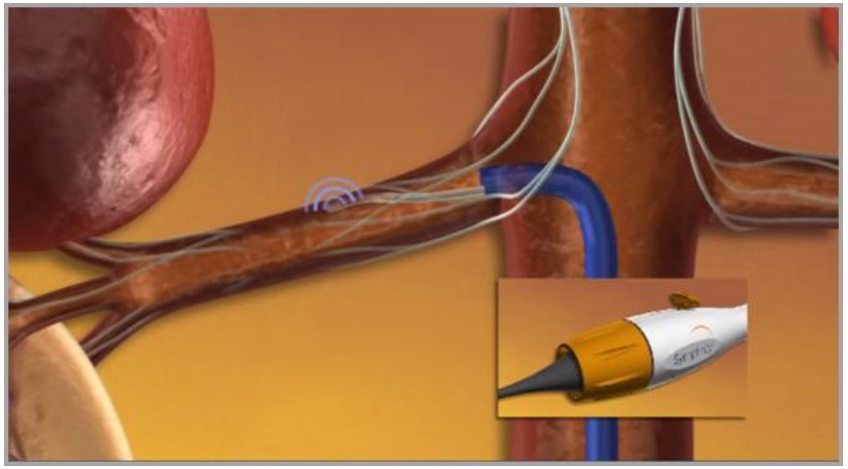


Procedure overview



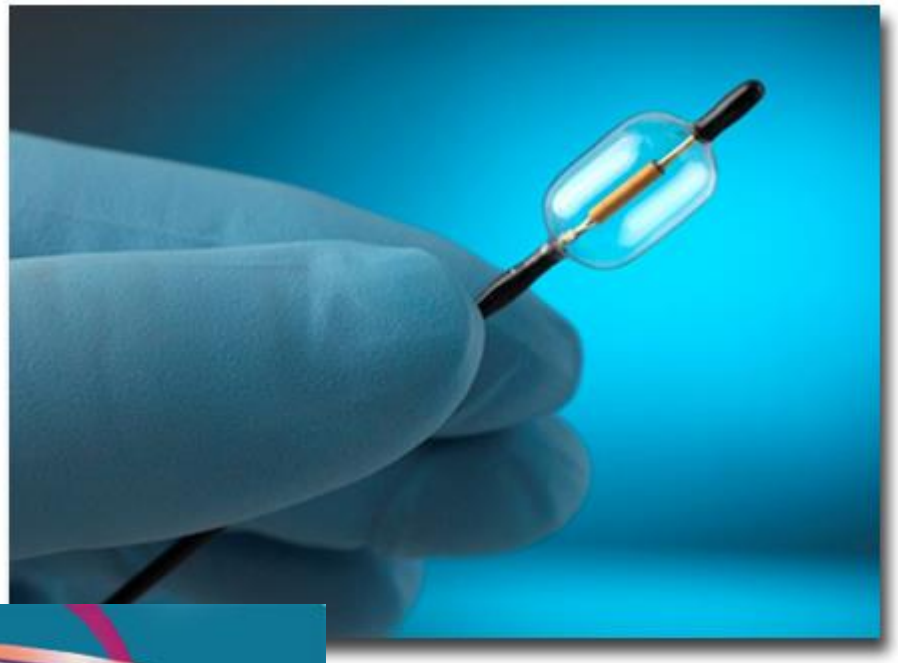


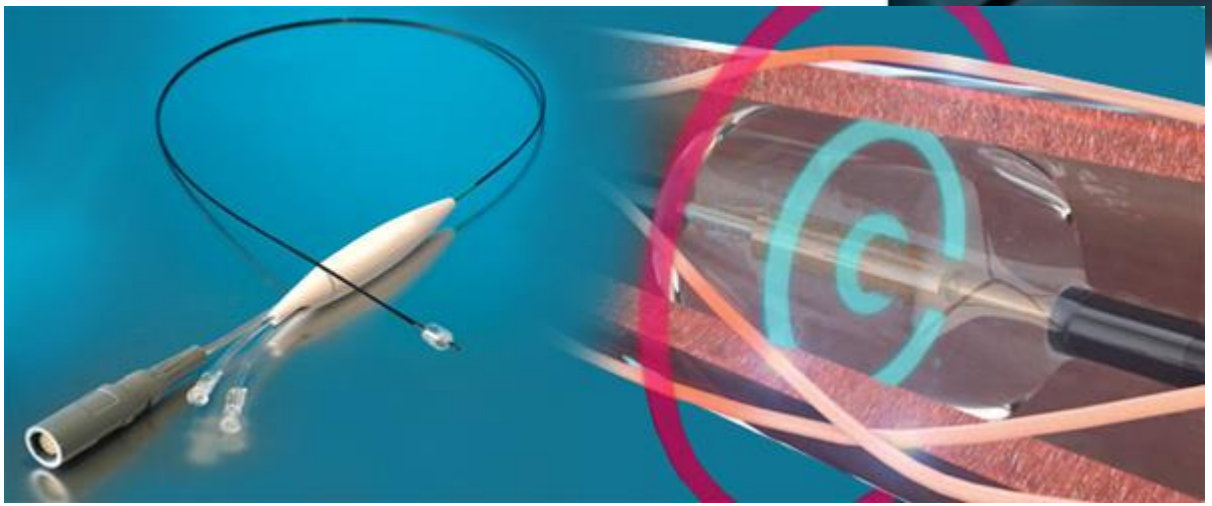




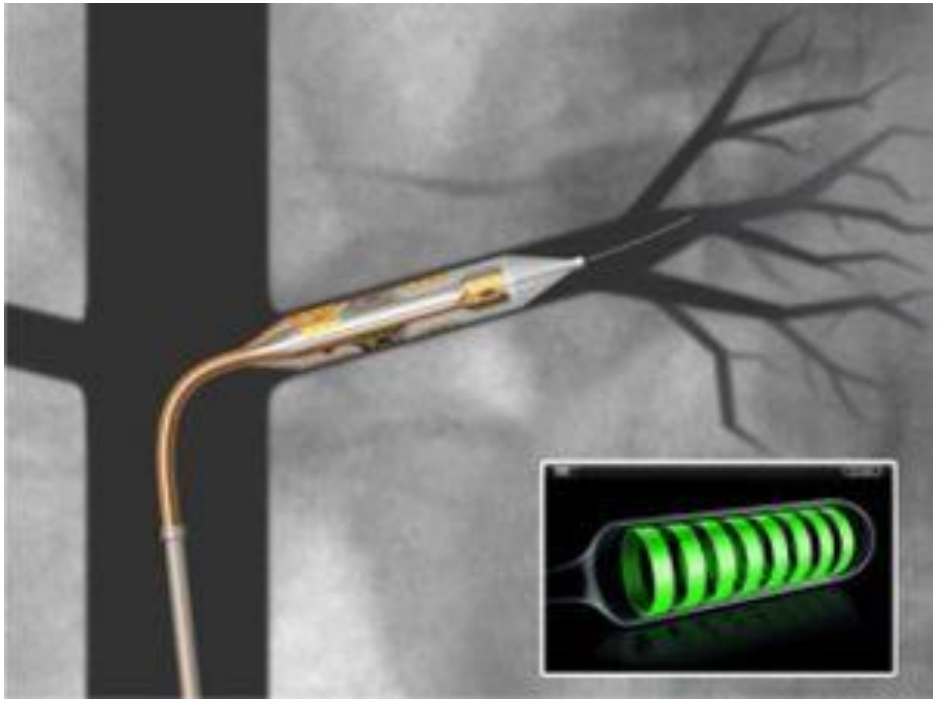
St. Jude Medical's renal denervarion

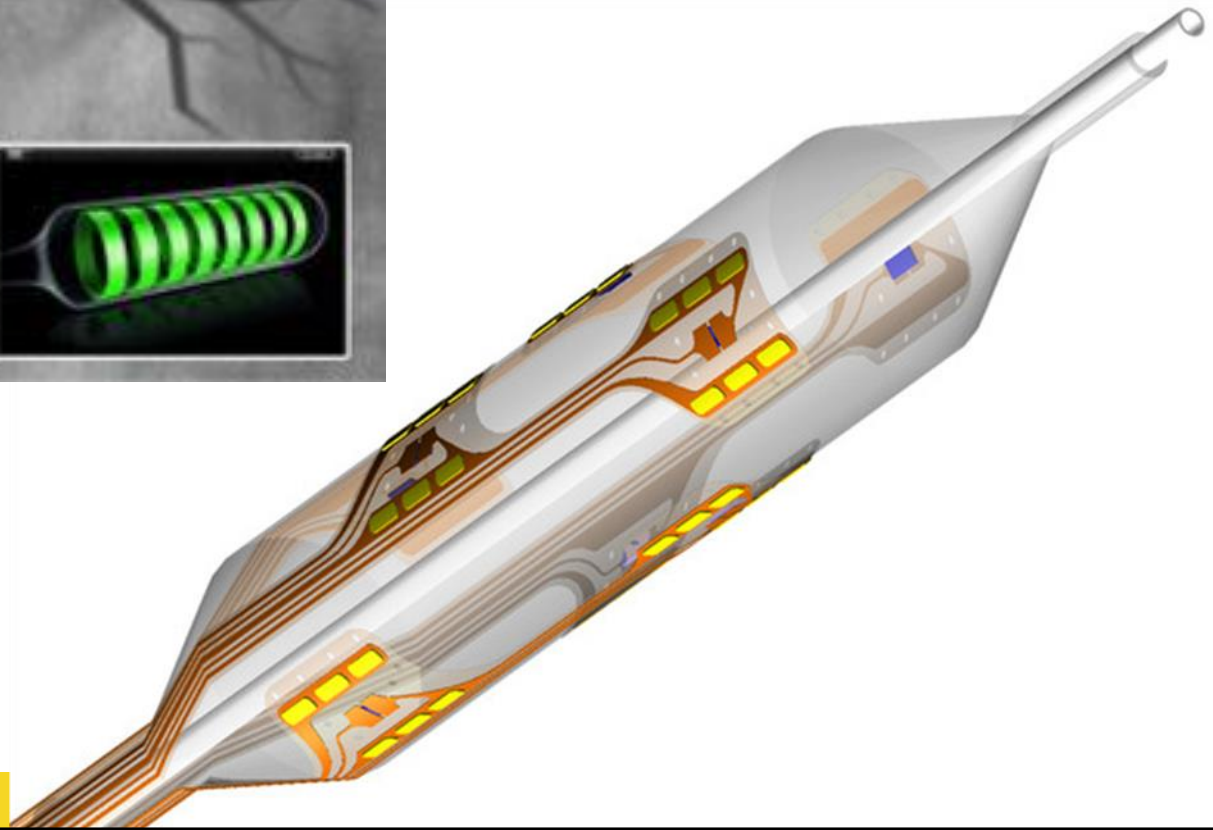
ReCor PARADISE Gen 2 renal denervarion system





Vessix V2 renal denervarion system





Novel bipolar radiofrequency delivery systems for renal denervation

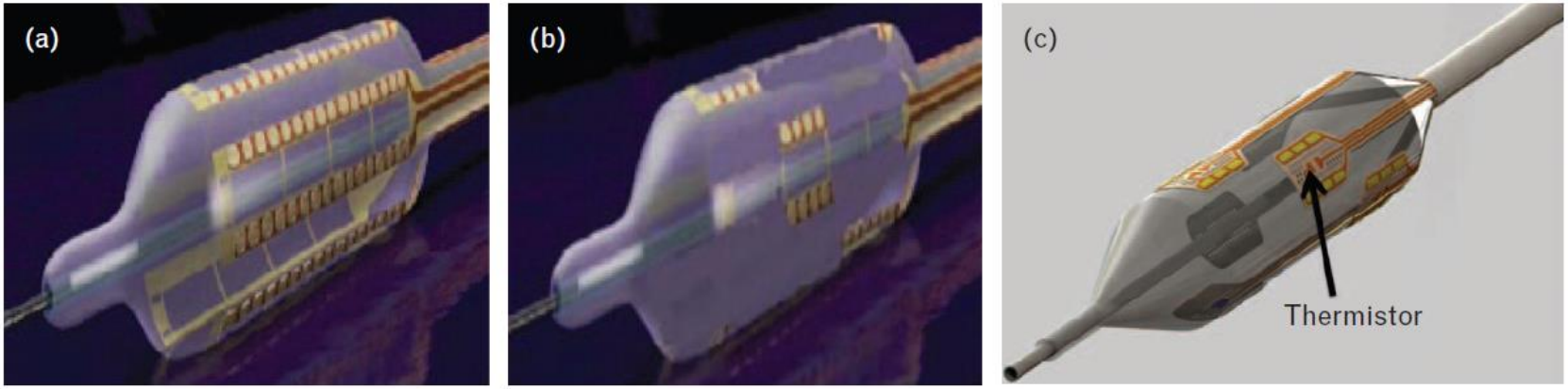
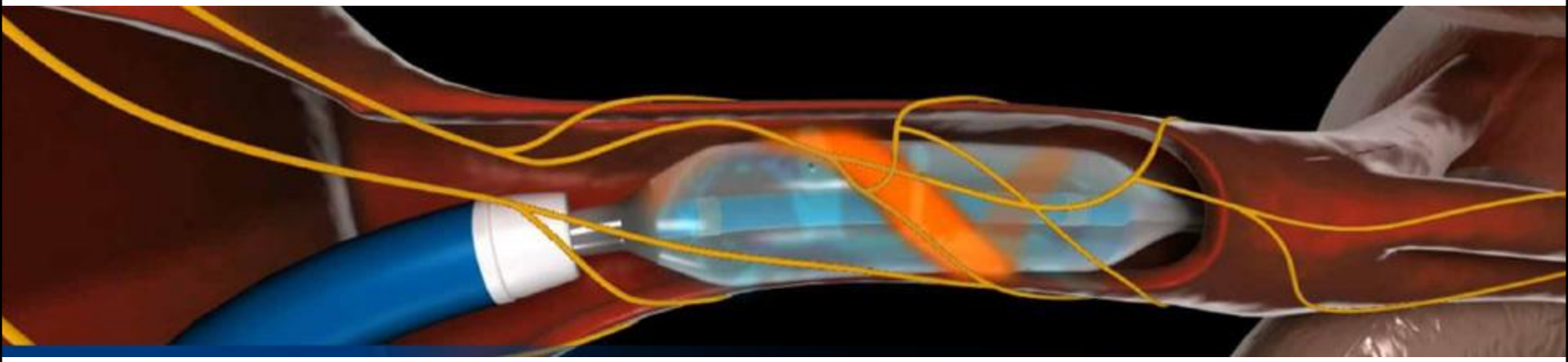


FIGURE 2 Bipolar electrode configurations used in the studies. (a) An illustration of the balloon catheter, with 16-mm long electrode pairs mounted on its surface. Eac electrode pair was activated one at a time in a sequential pattern. During treatment, the electrodes deliver a preset amount of radiofrequency energy (watts) titrated by measurement of impedance. (b) An illustration of the modified balloon catheter with 4-mm long gold electrodes mounted on its surface in an offset pattern. (c) Illustratio of the prototype balloon catheter with 4-mm long gold electrodes mounted on its surface. A thermistor was added at the center of each electrode pair to measure temperature during treatment. This allows the generator to control and titrate the amount of radiofrequency energy needed in order to reach a certain temperature for any duration specified.

Cohen-Mazor M. et al. J. Hypertens., 2014 , 32, 1678-1691

Covidien OneShot renal denervarion system



Technical features of available renal ablation radiofrequency devices

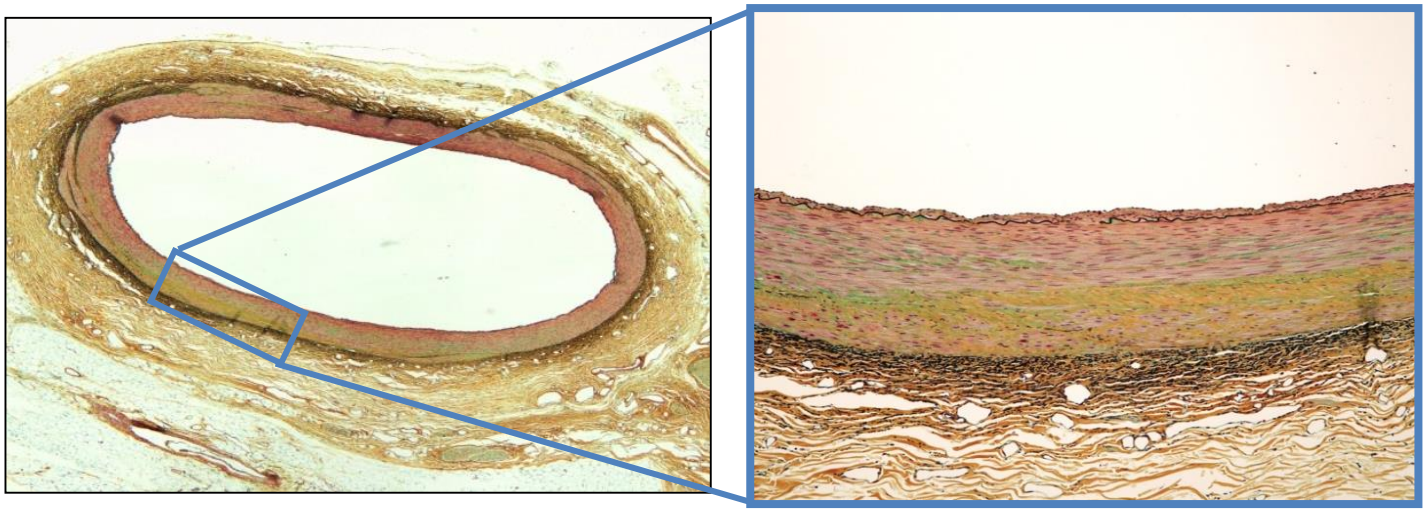
Table 1. Technical features of available renal ablation radiofrequency devices

	Medtronic Symplicity™	St. Jude Medical EnligHTN	Covidien OneShot™	Boston Scientific Vessix™
CE marking	2008/02	2011/12	2012/02	2012/04
Size	6 Fr, one size fits all	8 Fr, large and small baskets	7–8 Fr, balloon diameter 5, 6, 7 mm	8 Fr, balloon length 25 mm, balloon diameter 4, 5, 6, 7 mm
Renal artery treatment range	≥4 mm	4–8 mm	4–7 mm	3–7 mm
Treatment time	2 min/ablation, recommended minimum 4 ablations/artery	90 s/ablation, 8 ablations/artery	One single, 2 min ablations/artery	30 s/ablation, 1–2 ablations/artery
Over-the-wire system	no	no	yes	yes
Cooling features	no	no	yes	no
Total energy delivery	max. 8 W	max. 6 W	max. 25 W	max. 2 W
Maximum temperature	75° C	75° C	60° C	68° C
Catheter length	90 cm	115 cm	74 cm	90 cm

Ariyanon W. et al., Cardiorenal Med ., 2014; 4:22–33

Vascular safety in preclinical studies

- Research completed in swine
- Angiography and pathology at 7, 30, 60 and 180 days
- No stenosis or luminal reduction seen in treated arteries
- RF generator algorithm optimised to minimise vascular injury



Preclinical results may not be indicative of clinical performance.

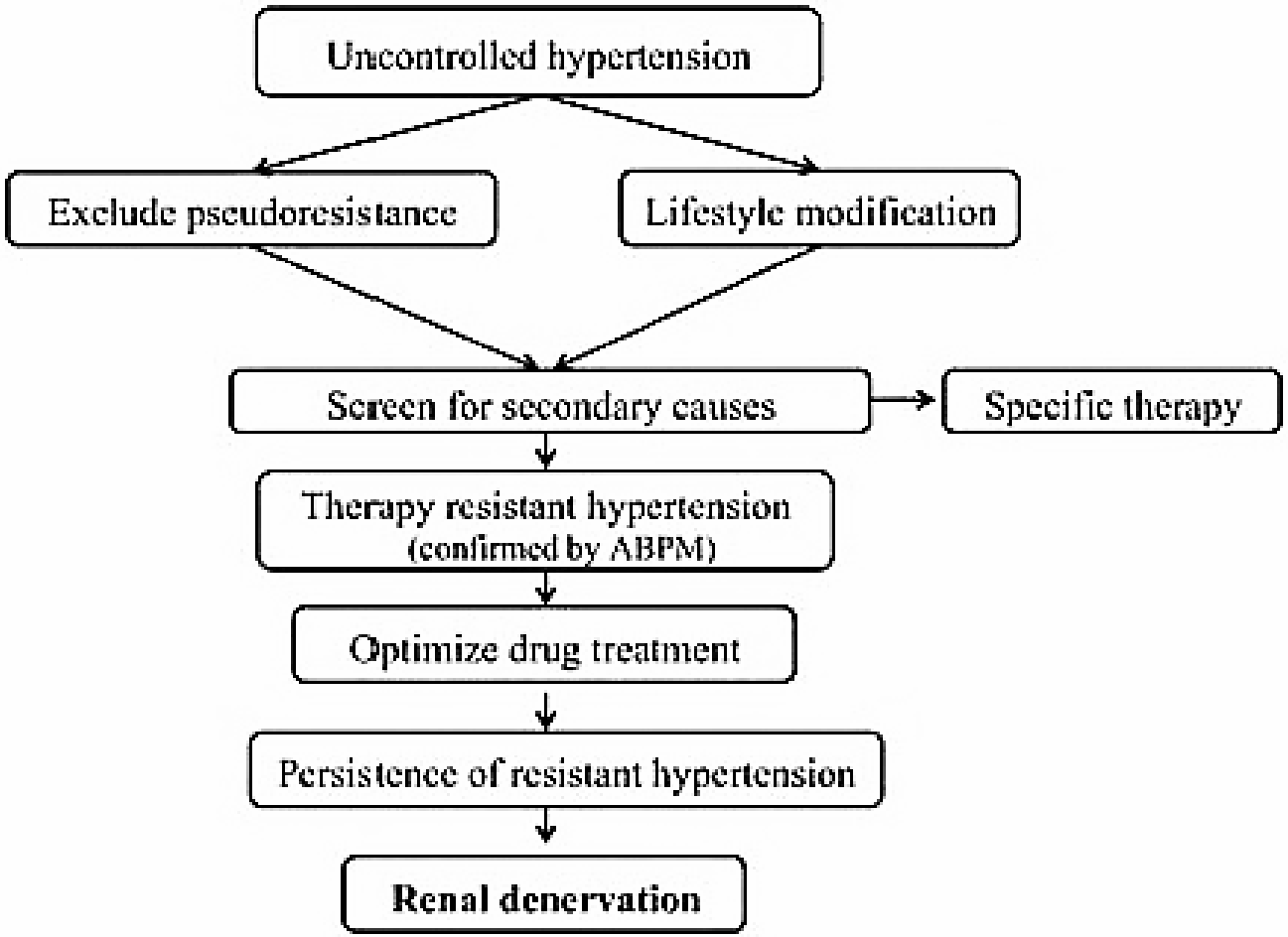
Rippy et al. Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. *Clin Res Cardiol*. 2011;100:1095-1101

Selection criteria for renal denervation

- Office-based systolic BP $\geq$ 160 mmHg ($\geq$150 mmHg diabetes type 2)
- $\geq$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 $\geq$45 ml/min/1.73 m^2)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

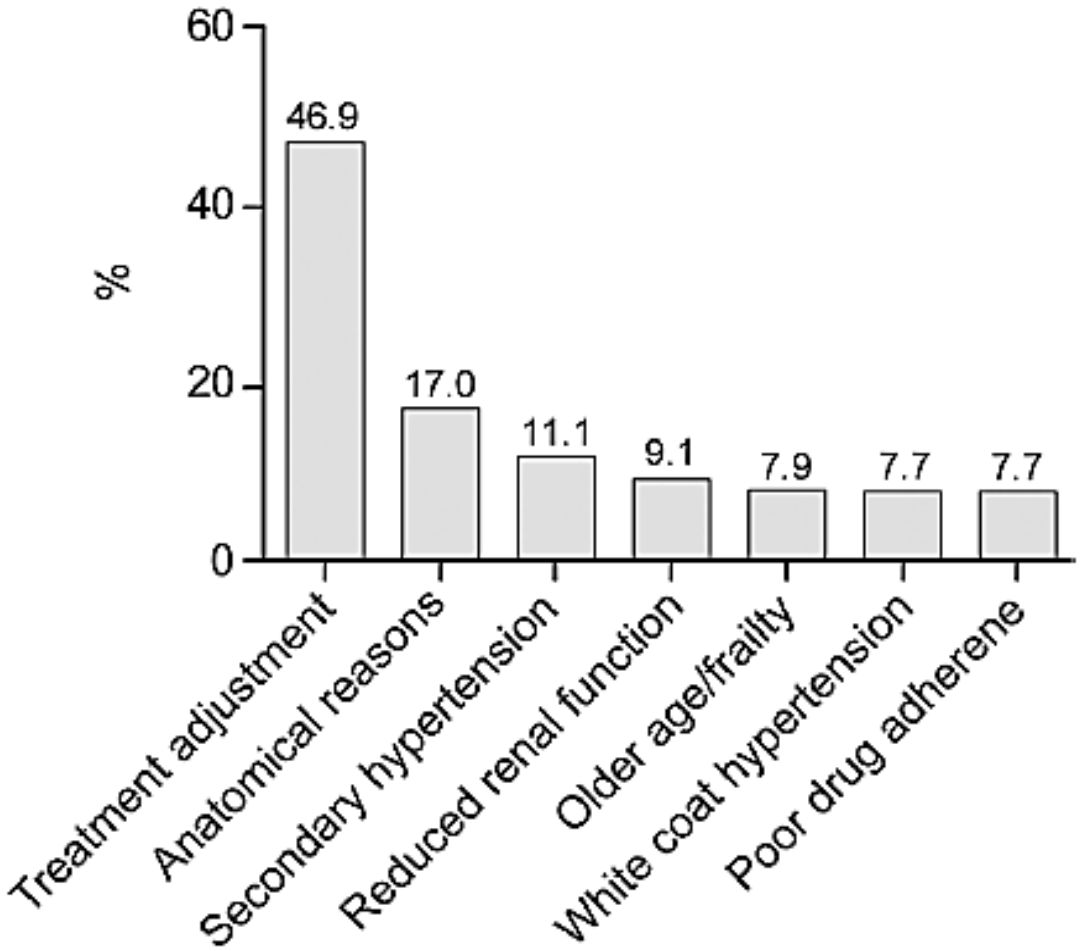
Mahfoud F. et al. Eur. Heart J., 2013, 34, 2149-2157

Appropriate screening to select the right patients



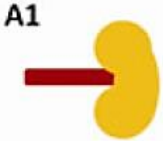
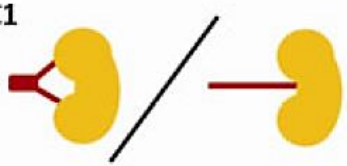
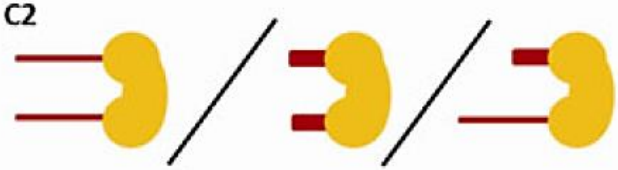
Mahfoud F. et al. Eur. Heart J., 2013, 34, 2149-2157

Reasons of noneligibility for renal denervation after thorough work-up and treatment optimization in 11 expert hypertension centers



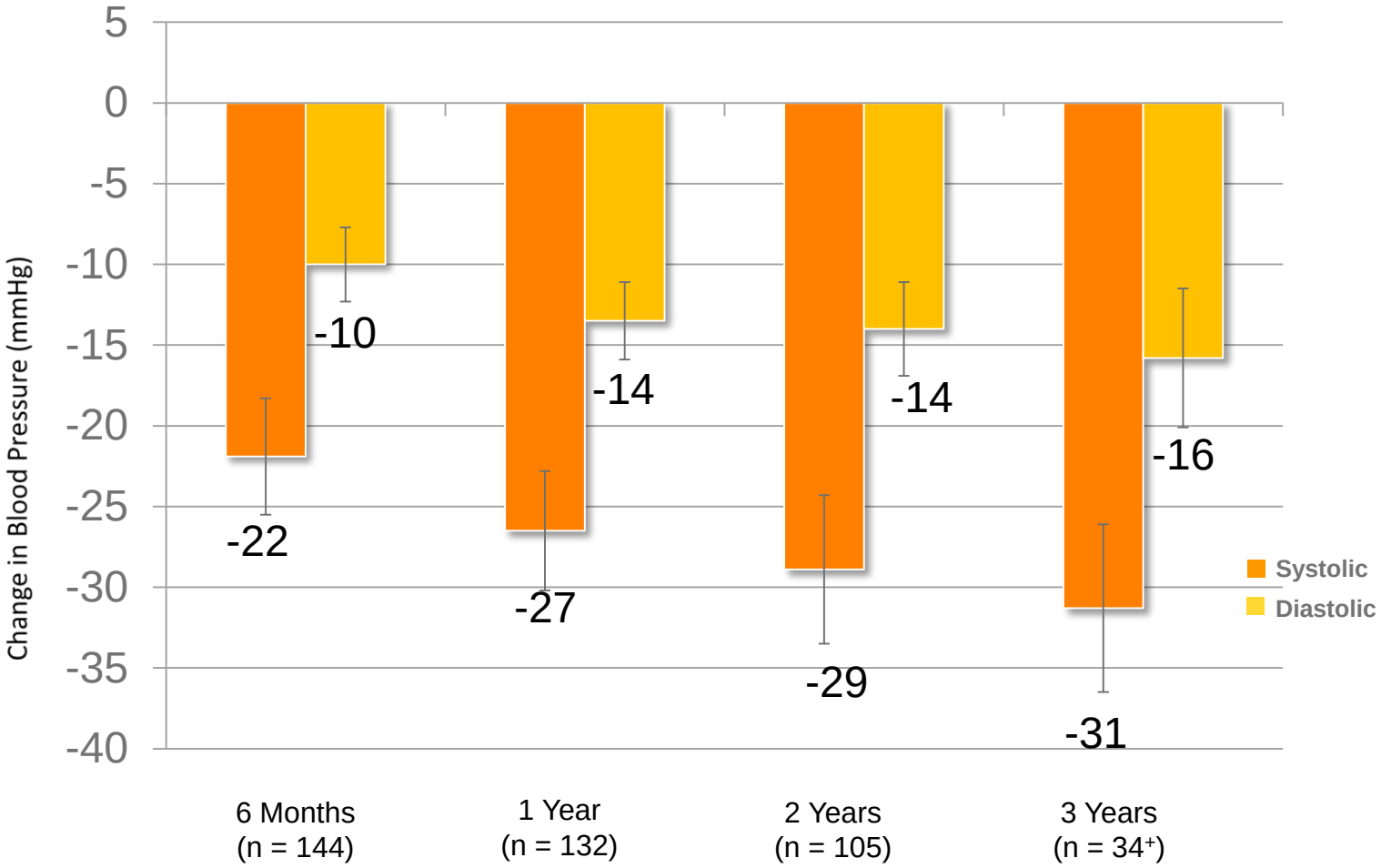
Persu A. et al., Hypertension., 2014; 63,1319-1325

Classification to identify anatomical eligibility for renal denervation

A: *Eligible anatomy: classical recommendations:* - Solitary renal artery with a length ≥20 mm and diameter ≥4 mm	**A1**  Artery without side branch / bifurcation	**A2** Artery with early* side branch (independent of diameter of the side branch)
B: *Eligible anatomy: "off label use"* - Multiple renal arteries	**B1** Multiple arteries, all arteries eligible (length ≥20mm & diameter 4mm)	**B2** Multiple arteries, at least 1 artery eligible (length ≥20mm & diameter ≥4mm)
C: *Ineligible anatomy:* - Solitary artery or multiple renal arteries	**C1**  Solitary artery: diameter <4mm or early* bifurcation and side branches diameter <4mm	**C2**  Multiple arteries, all arteries: length <20mm and/or diameter <4mm)

Verloop W. L. et al.,Eur. J. Clin. Invest., 2014, Jun 16., ahead of print

Symplicity HTN-1: significant, sustained BP reduction up to 3 years



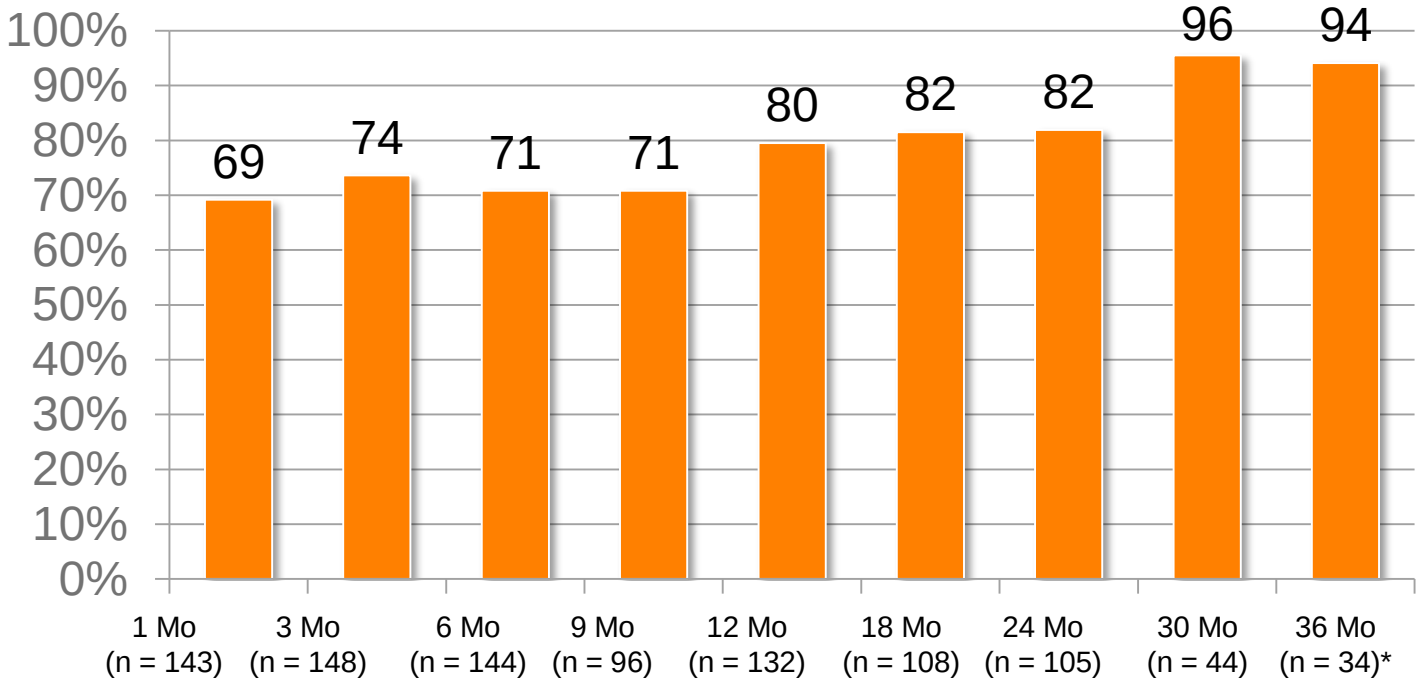
p <0.01 for Δ from baseline for all time points.
+ Number of patients represents data available at time of data-lock.

*

Krum H. et al. Lancet, 2014, 383, 622–29

Symplicity HTN-1: responder rate does not decrease over time

- **RDN responder rate sustained up to three years**



Responder was defined as an office SBP reduction ≥10 mmHg

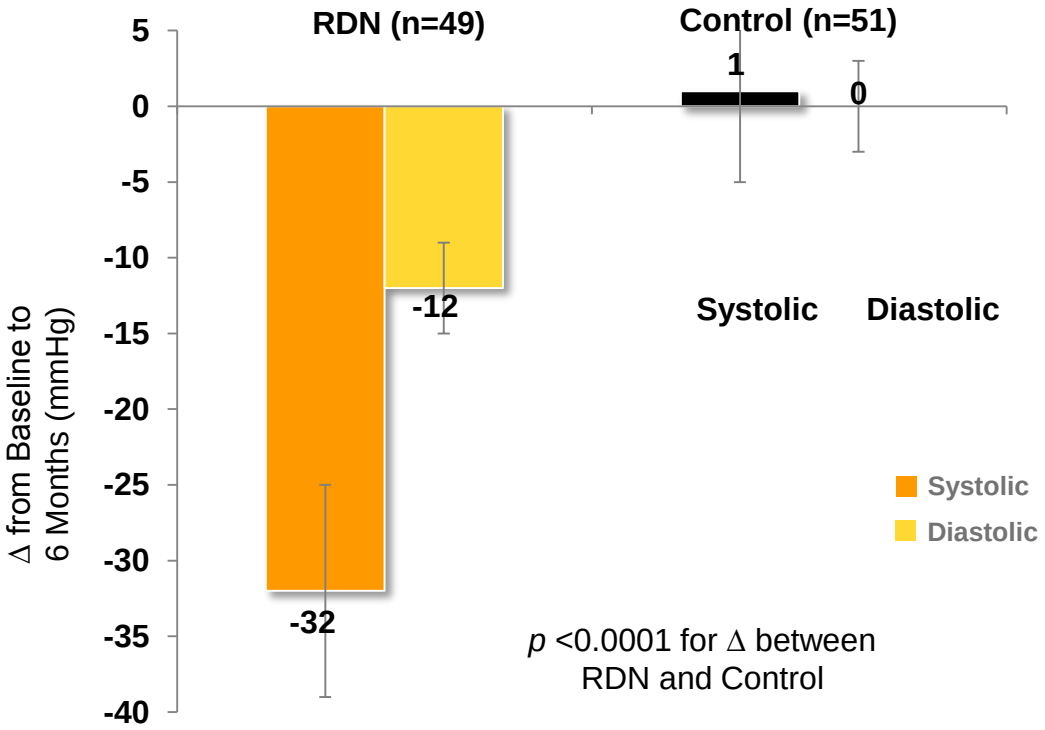
*Number of patients represents data available at time of data-lock

Krum H. et al. Lancet, 2014, 383, 622–29

Symplicity HTN-2:

Significant reductions in BP, RDN superior to medical management at 6M

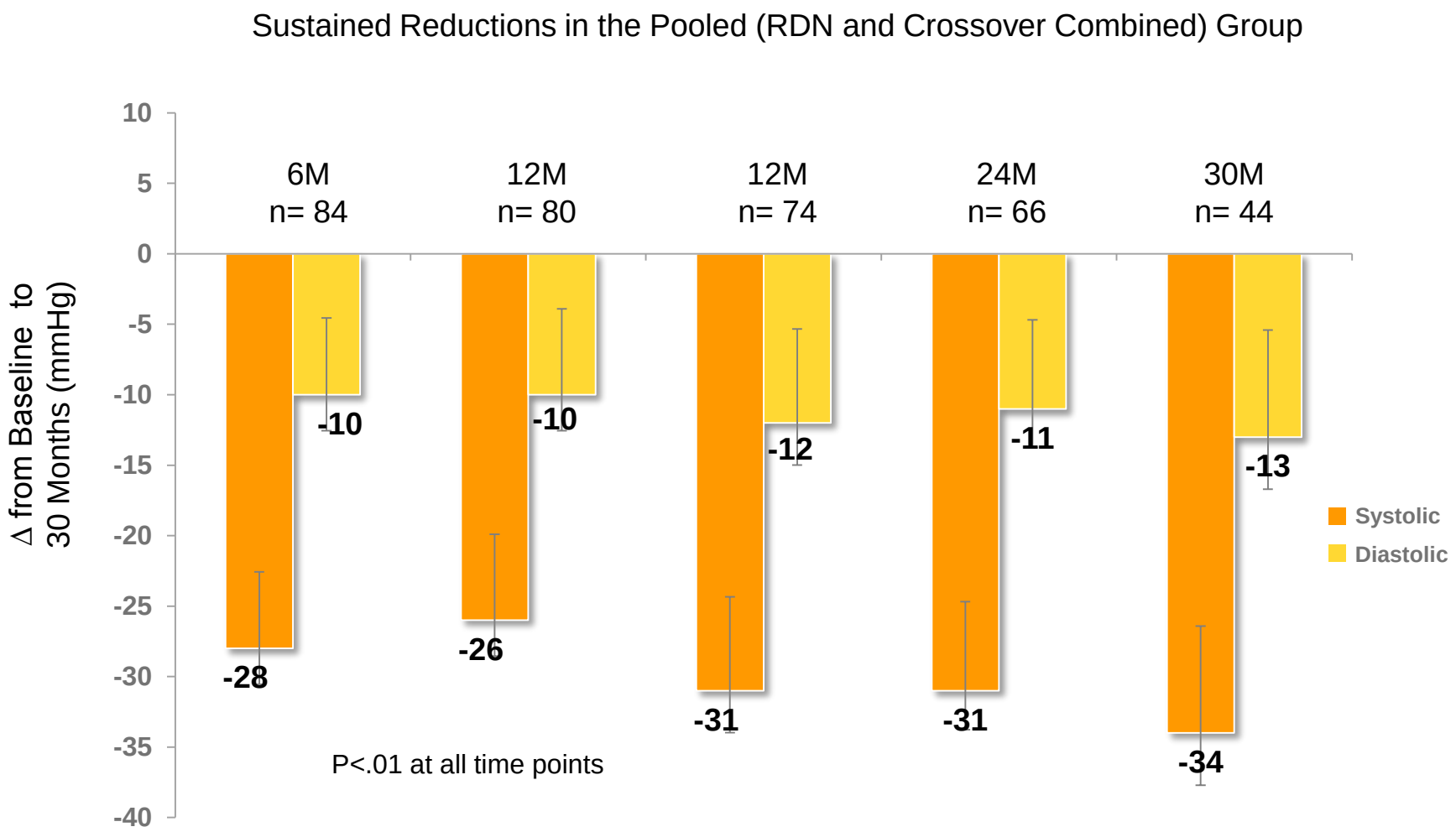
Primary Endpoint (6M post randomization)



>80% of RDN patients had ≥10 mmHg reduction in SBP

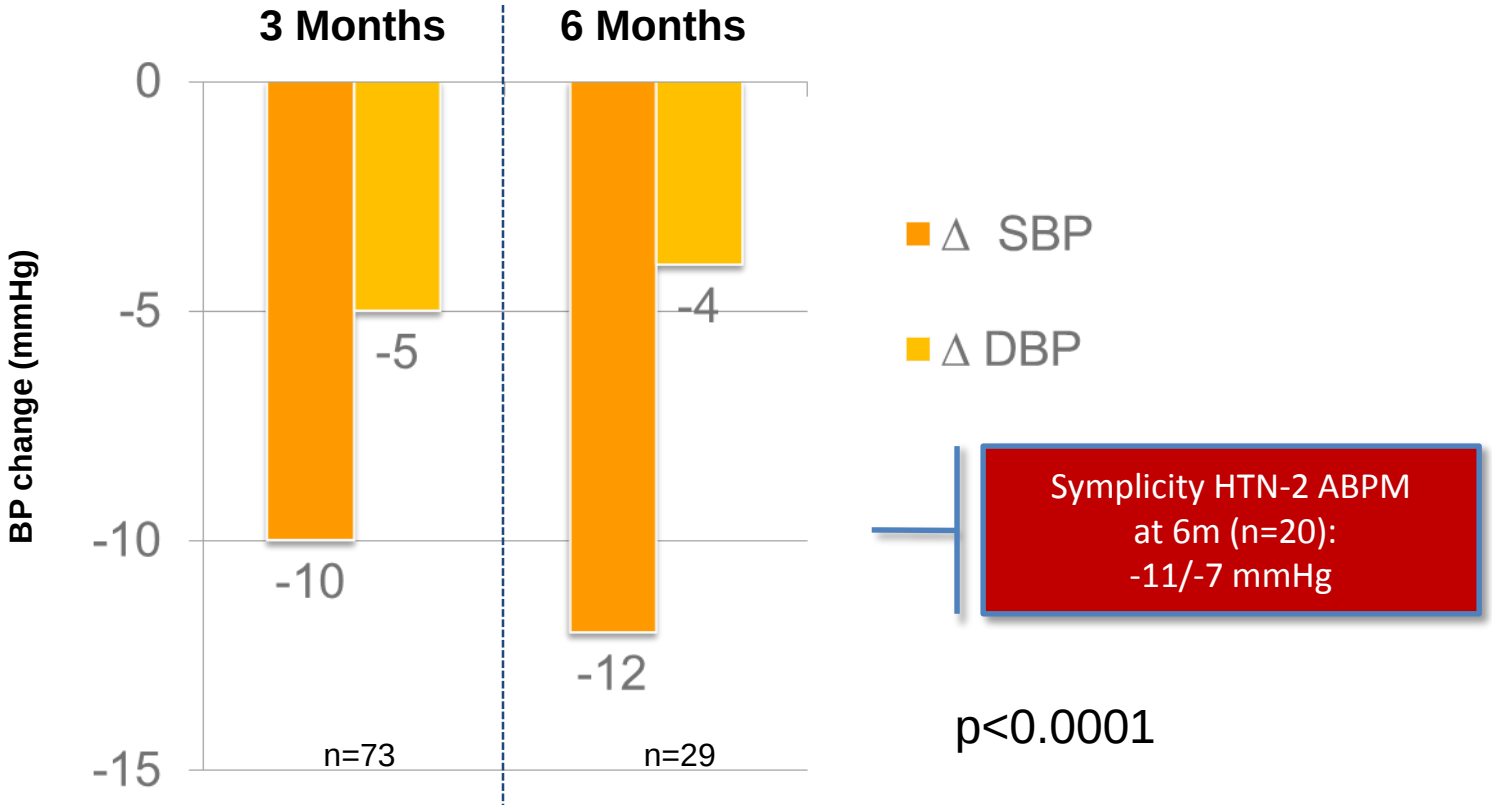
*Symplicity HTN-2 Investigators. The Lancet. 2010

Symplicity HTN-2:
BP reductions sustained to 30 months



***Expanded results presented at the American Society of Hypertension annual meeting 2013**

Significant reductions in ambulatory BP for patients that match current consensus criteria



***Baseline office SBP ≥160 (SBP ≥ 150 T2DM), and baseline 24 hour ABPM ≥130 or daytime ABPM ≥135**

Results Presented at EuroPCR 2013 annual meeting

Original Article

Catheter-Based Renal Denervation for Resistant Hypertension

12-Month Results of the EnligHTN I First-in-Human Study Using a Multielectrode Ablation System

Vasilios Papademetriou, Costas P. Tsioufis, Ajay Sinhal, Derek P. Chew, Ian T. Meredith, Yuvi Malaiapan, Matthew I. Worthley, Stephen G. Worthley

Abstract—Renal denervation has emerged as a novel approach for the treatment of patients with drug-resistant hypertension. To date, only limited data have been published using multielectrode radiofrequency ablation systems. In this article, we present the 12-month data of EnligHTN I, a first-in-human study using a multielectrode ablation catheter. EnligHTN I enrolled 46 patients (average age, 60±10 years; on average 4.7±1.0 medications) with drug-resistant hypertension. Eligible patients were on ≥3 antihypertensive medications and had a systolic blood pressure (BP) ≥160 mm Hg (≥150 mm Hg for diabetics). Bilateral renal artery ablation was performed using a percutaneous femoral approach and standardized techniques. The average baseline office BP was 176/96 mm Hg, average 24-hour ambulatory BP was 150/83 mm Hg, and average home BP was 158/90 mm Hg. The average reductions (mm Hg) at 1, 3, 6, and 12 months were as follows: office: −28/−10, −27/−10, −26/−10, and −27/−11 mm Hg ($P<0.001$ for all); 24-hour ambulatory: −10/−5, −10/−5, −10/−6 ($P<0.001$ for all), and −7/−4 for 12 months ($P<0.0094$). Reductions in home measurements (based on 2-week average) were −9/−4, −8/−5,−10/−7, and −11/−6 mm Hg ($P<0.001$ at 12 months). At 12 months, there were no signals of worsening renal function and no new serious or life-threatening adverse events. One patient with baseline nonocclusive renal artery stenosis progressed to 75% diameter stenosis, requiring renal artery stenting. The 12-month data continue to demonstrate safety and efficacy of the EnligHTN ablation system in patients with drug-resistant hypertension. Home BP measurements parallel measurements obtained with 24-hour ambulatory monitoring. (*Hypertension*. 2014;64:00-00.) • Online Data Supplement

Key Words: ambulatory blood pressure ■ home blood pressure ■ multielectrode ■ renal denervation ■ resistant hypertension

The EnligHTN I First-in-Human Study Using a Multielectrode Ablation System

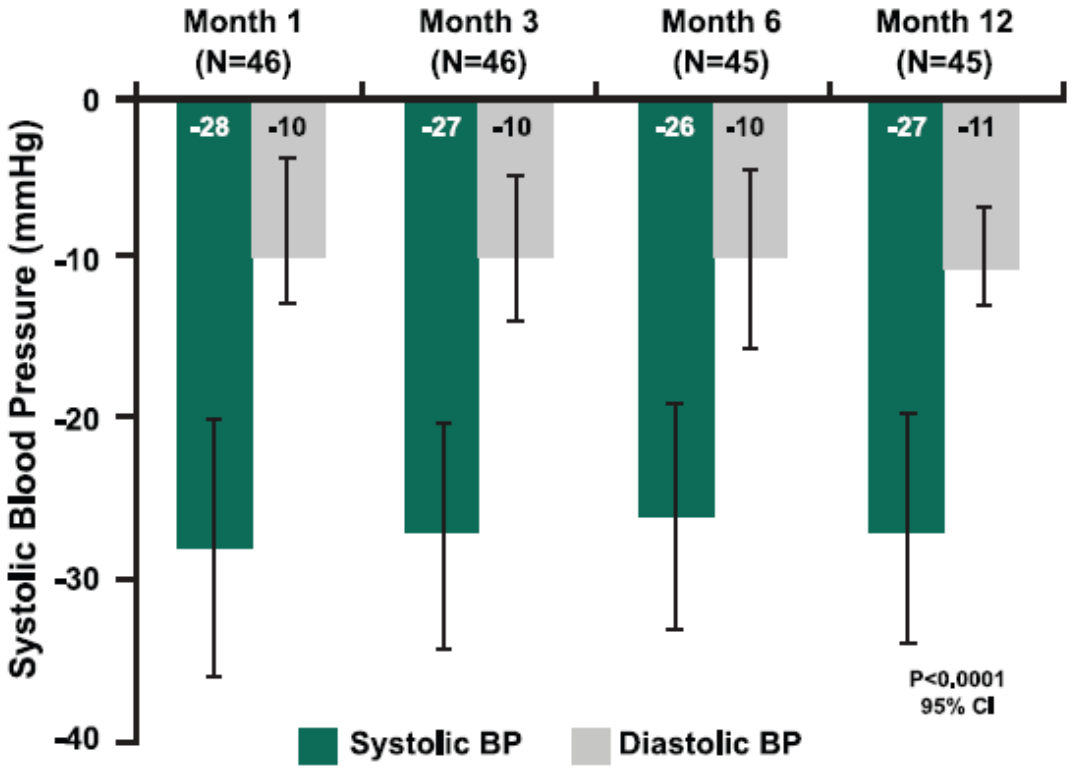


Figure 1. Office systolic and diastolic blood pressure (BP) reduction from baseline.

Papademetriou V. et al., Hypertension., 2014; in press

The EnligHTN I First-in-Human Study Using a Multielectrode Ablation System

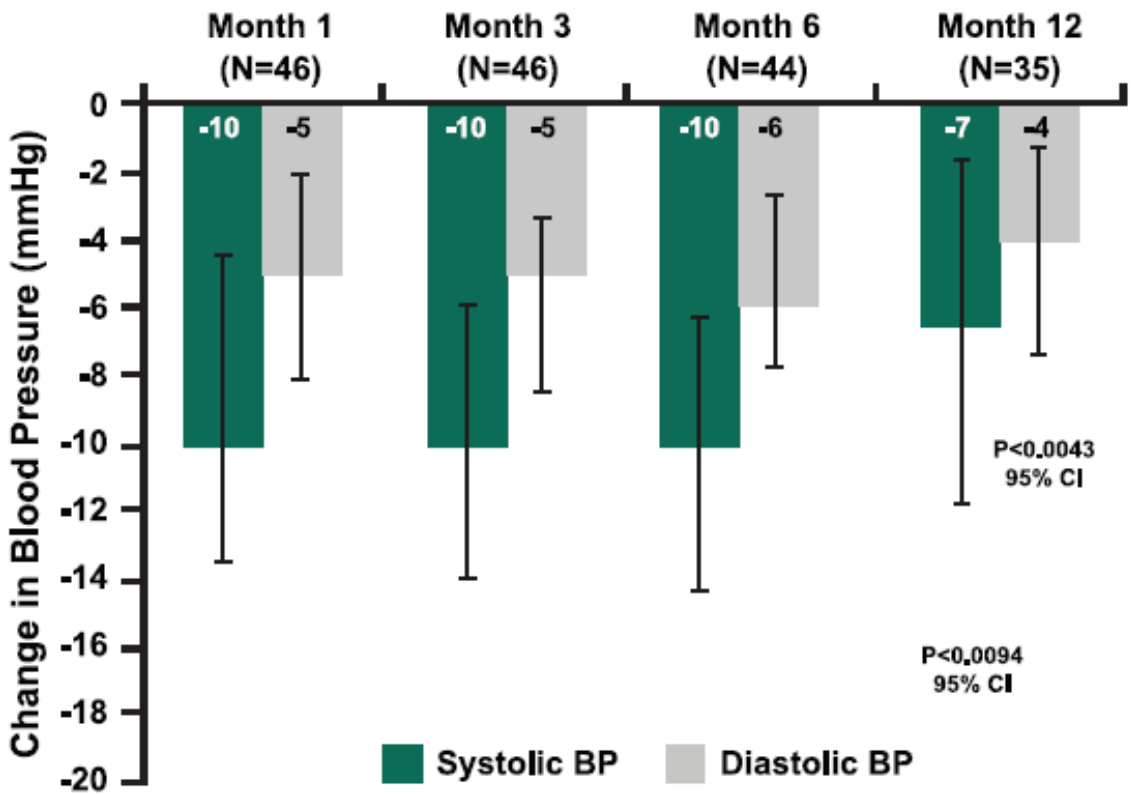


Figure 2. Twenty-four–hour ambulatory systolic and diastolic blood pressure (BP) reduction from baseline.

Papademetriou V. et al., Hypertension., 2014; in press

Blood pressure reduction effect – drug treatment vs. renal denervation

Original Article

Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients With True Treatment-Resistant Hypertension

Fadl Elmula M. Fadl Elmula, Pavel Hoffmann, Anne C. Larstorp, Eigil Fossum, Magne Brekke, Sverre E. Kjeldsen, Eyvind Gjønnæss, Ulla Hjørnholm, Vibeke N. Kjær, Morten Rostrup, Ingrid Os, Aud Stenehjem, Aud Høieggen

Abstract—We aimed to investigate for the first time the blood pressure (BP)–lowering effect of renal sympathetic denervation (RDN) versus clinically adjusted drug treatment in true treatment-resistant hypertension (TRH) after excluding patients with confounding poor drug adherence. Patients with apparent TRH (n=65) were referred for RDN, and those with secondary and spurious hypertension (n=26) were excluded. TRH was defined as office systolic BP (SBP) >140 mm Hg, despite maximally tolerated doses of ≥3 antihypertensive drugs including a diuretic. In addition, ambulatory daytime SBP >135 mm Hg after witnessed intake of antihypertensive drugs was required, after which 20 patients had normalized BP and were excluded. Patients with true TRH were randomized and underwent RDN (n=9) performed with Symplicity Catheter System versus clinically adjusted drug treatment (n=10). The study was stopped early for ethical reasons because RDN had uncertain BP-lowering effect. Office SBP and diastolic BP in the drug-adjusted group changed from 160±14/88±13 mm Hg (±SD) at baseline to 132±10/77±8 mm Hg at 6 months ($P<0.0005$ and $P=0.02$, SBP and diastolic BP, respectively) and in the RDN group from 156±13/91±15 to 148±7/89±8 mm Hg ($P=0.42$ and $P=0.48$, SBP and diastolic BP, respectively). SBP and diastolic BP were significantly lower in the drug-adjusted group at 6 months ($P=0.002$ and $P=0.004$, respectively), and absolute changes in SBP were larger in the drug-adjusted group ($P=0.008$). Ambulatory BPs changed in parallel to office BPs. Our data suggest that adjusted drug treatment has superior BP lowering effects compared with RDN in patients with true TRH.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01673516

(***Hypertension*. 2014;63:00-00.**) • **Online Data Supplement**

Key Words: blood pressure ■ drug therapy ■ hypertension

Hypertension

Blood pressure reduction effect – drug treatment vs. renal denervation

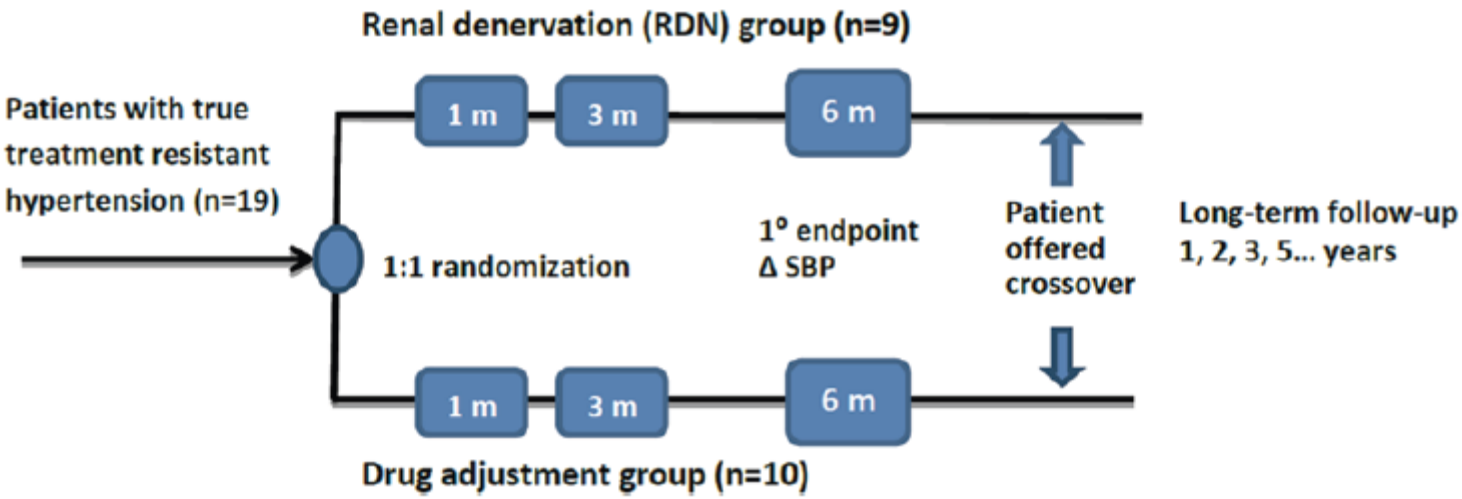


Figure 1. Illustration shows the study design. Primary (1°) end point was change (Δ) in office systolic blood pressure (SBP) from randomization to 6 months when patients could be offered alternative treatment (crossover) and long-term follow-up. RDN indicates renal sympathetic denervation.

Elmula F. et al., Hypertension, 2014, 63, 991-999

Changes in office systolic blood pressure (SBP) and diastolic blood pressure (DPP) at 3 and 6 month follow up for renal denervation (RDN) and drug-adjusted groups

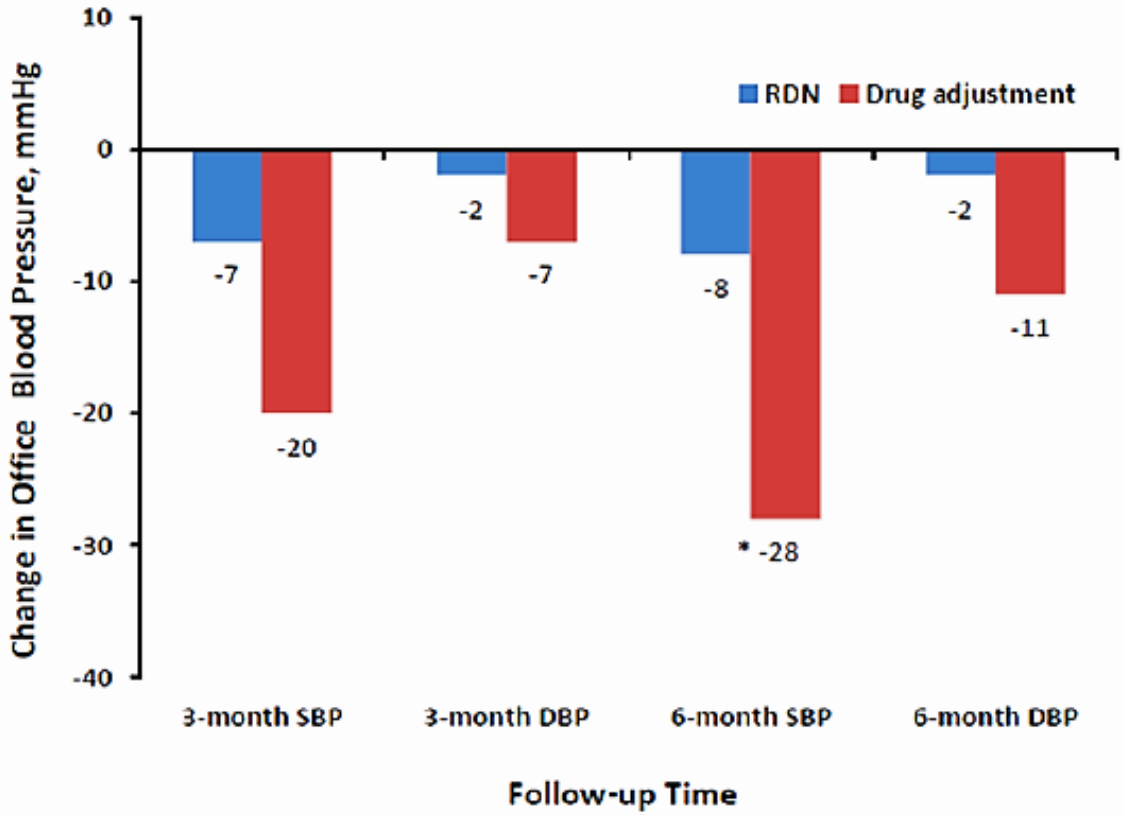


Figure 5. Graph shows paired changes in office systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3-month and 6-month follow-up for renal sympathetic denervation (RDN) and drug-adjusted groups (*P=0.008 for changes between groups).

Elmula F. et al., Hypertension, 2014 63, 991-999

Paired changes in ambularory daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3 and 6 month follow up for renal denervation (RDN) and drug-adjusted groups

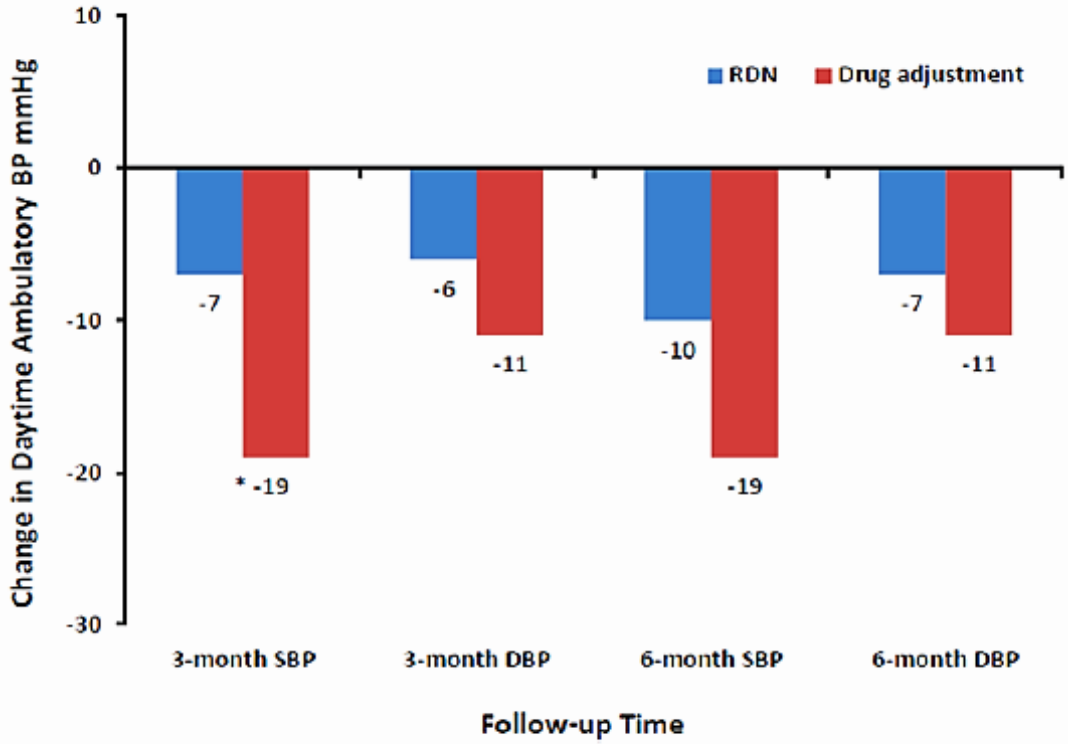


Figure 8. Graph shows paired changes in ambulatory daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3-month and 6-month follow-up for renal sympathetic denervation (RDN) and drug-adjusted groups (*P=0.03 for changes between groups).

Elmula F. et al., Hypertension, 2014, 63, 991-999

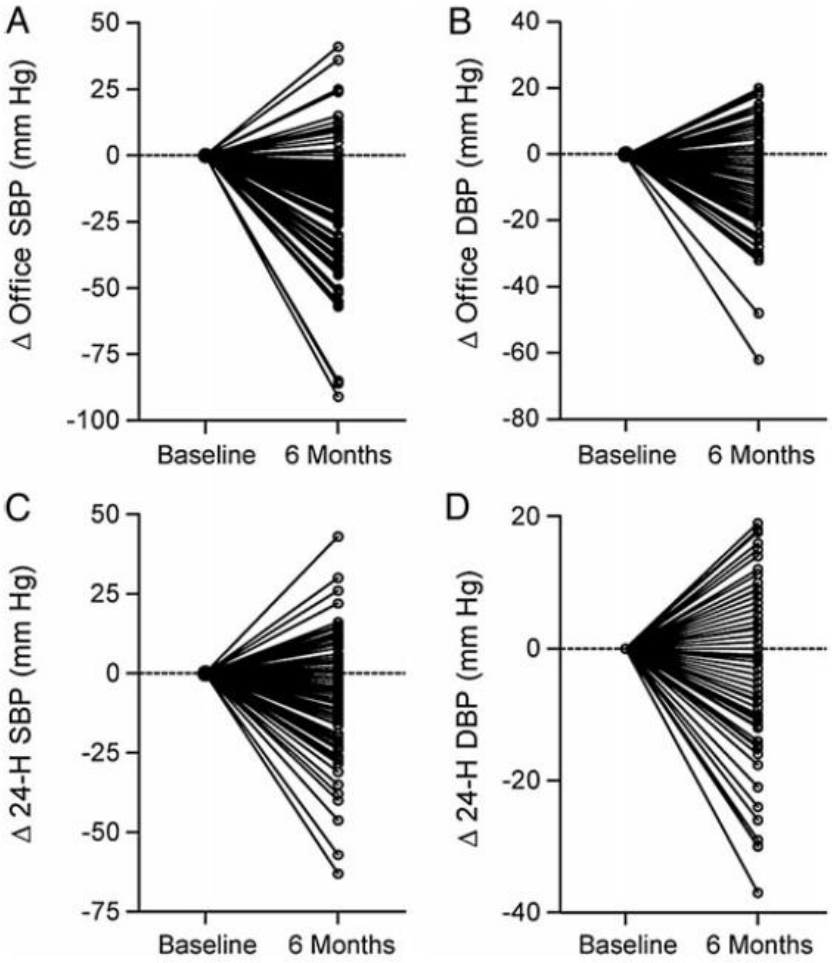
Kjeldsen S.E. Oslo, Norway

Perspectives

We did the first ever prospective and randomized comparison of RDN versus clinical drug adjustment in patients with true TRH who qualified by having elevated ambulatory BP after witnessed intake of BP medication. BP control through 6 months was superior by drug adjustment compared with renal denervation. RDN did not cause a meaningful decrease of BP in patients with true TRH and it is in our opinion currently not indicated in routine clinical use.

Elmula F. et al., Hypertension, 2014, 63, 991-999

Individual responses of systolic (A, C) and diastolic (B, D) blood pressure on office (A, B) and 24-h ambulatory (C, D) measurement after renal denervation in 109 patients from the ENCOReD network.



Persu A. et al. Nephrol . Dial . Transplant ., 2014, 29: 1116–1119

SYMPLICITY HTN-3 Study

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*

ABSTRACT

N.Engl. J. Med. 2014 Apr 10;370: 1393 - 1400

SYMPLICITY HTN-3 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.

Key Inclusion/Exclusion Criteria

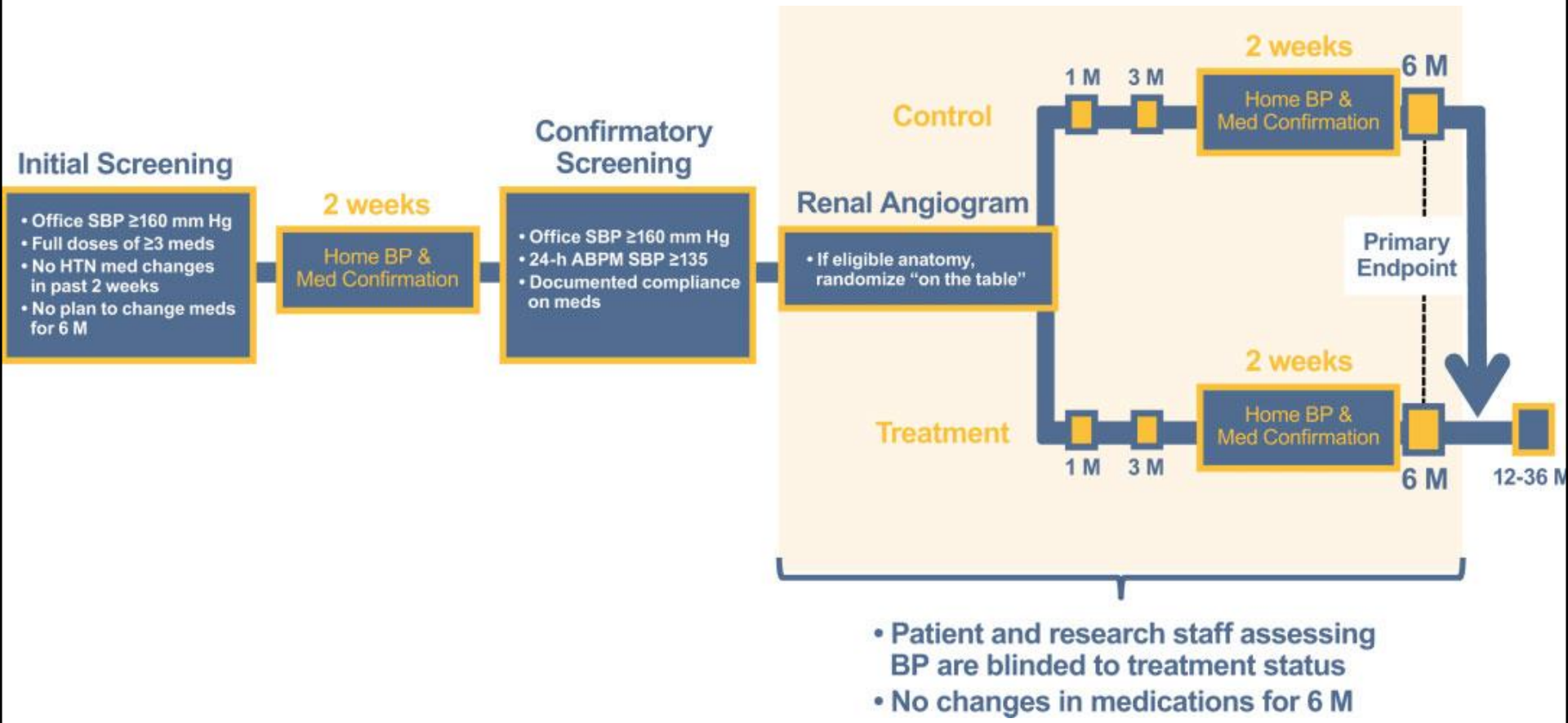
Key Inclusion:

- 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:

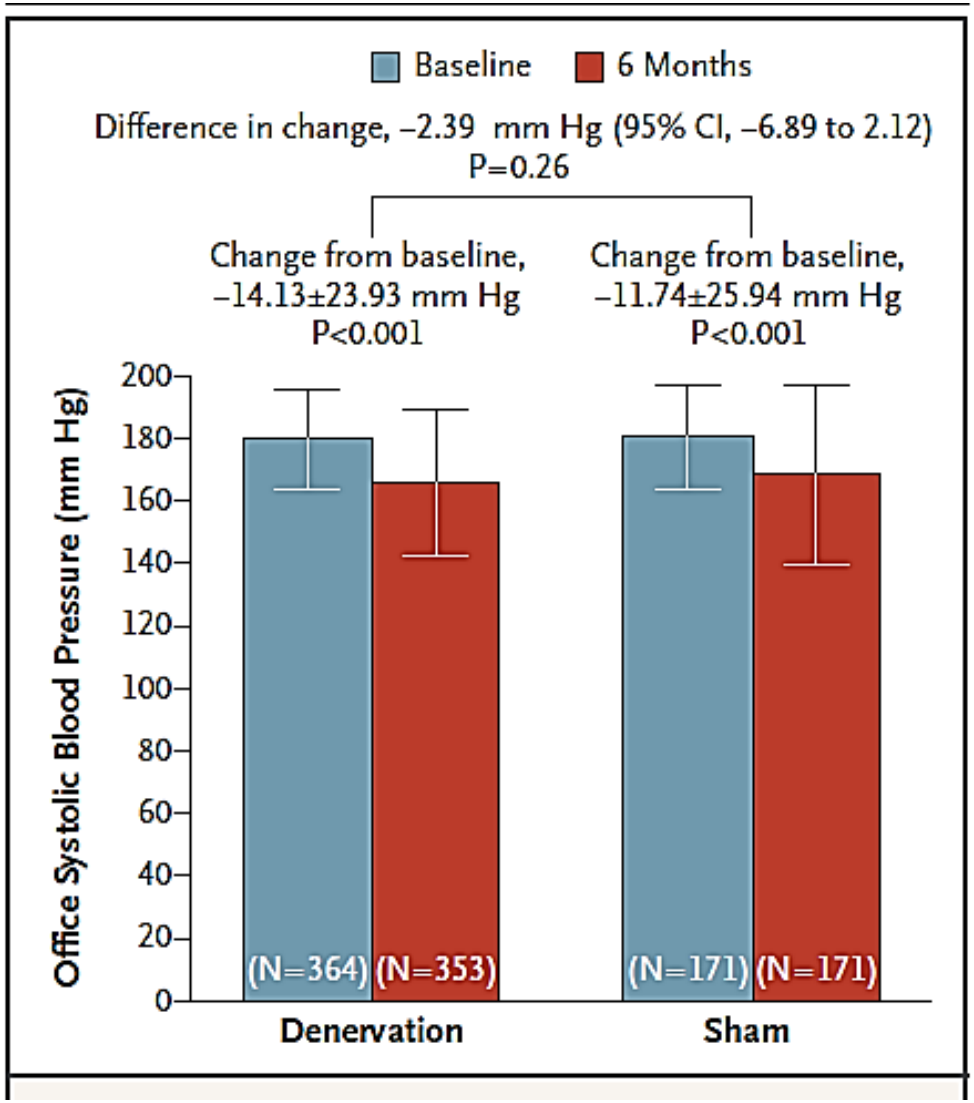
- ABPM 24 hour average SBP <135 mm Hg
- eGFR of <45 mL/min/1.73 m^2
- Main renal arteries <4 mm diameter or <20 mm treatable length

Trial design for the randomized SYMPLICITY HTN-3



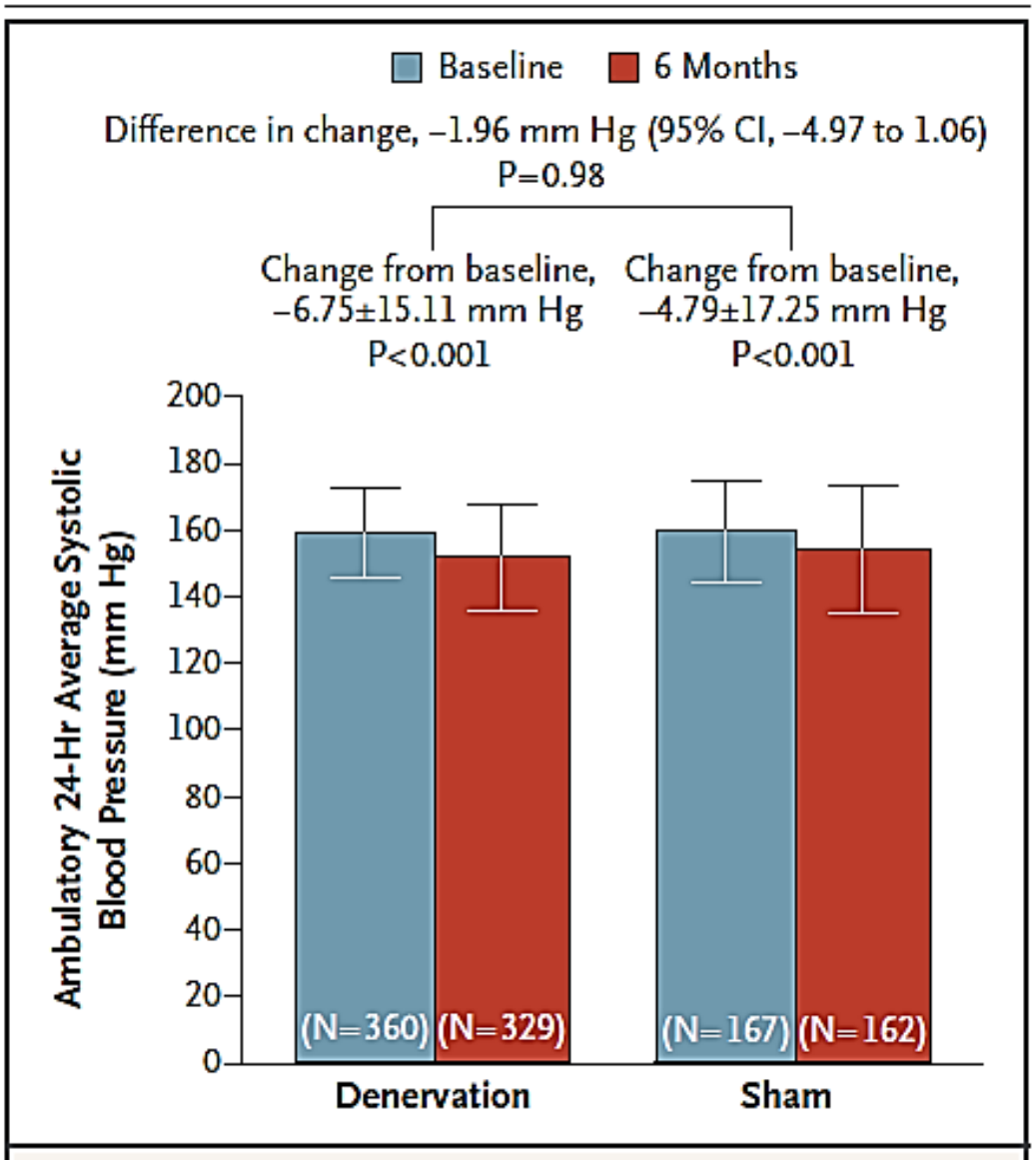
D.E. Kandzari et al., Clin. Cardiol. 2012, 35, 9, 528–535

SYMPLICITY HTN-3 Study Primary Efficacy End Point



Bhatt D.J. et al., N.Engl. J. Med. 2014 Apr 10;370(15):1393-1400

SYMPLICITY HTN-3 Study Secondary Efficacy End Point



Bhatt D.J. et al., N.Engl. J. Med. 2014 Apr 10;370(15):1393-1400

Causes of non response to renal denervation

- Inappropriate patients selection (e.g. secondary forms of hypertension)
- Minor contribution of the sympathetic nervous system to the expresion of hypertension
- Changes of antihypertensive medication and non-adherence after the procedure
- Ineffective renal denervation procedure

Nephrol Dial Transplant (2014) 0: 1–3
doi: 10.1093/ndt/gfu192

ndt
Nephrology Dialysis Transplantation

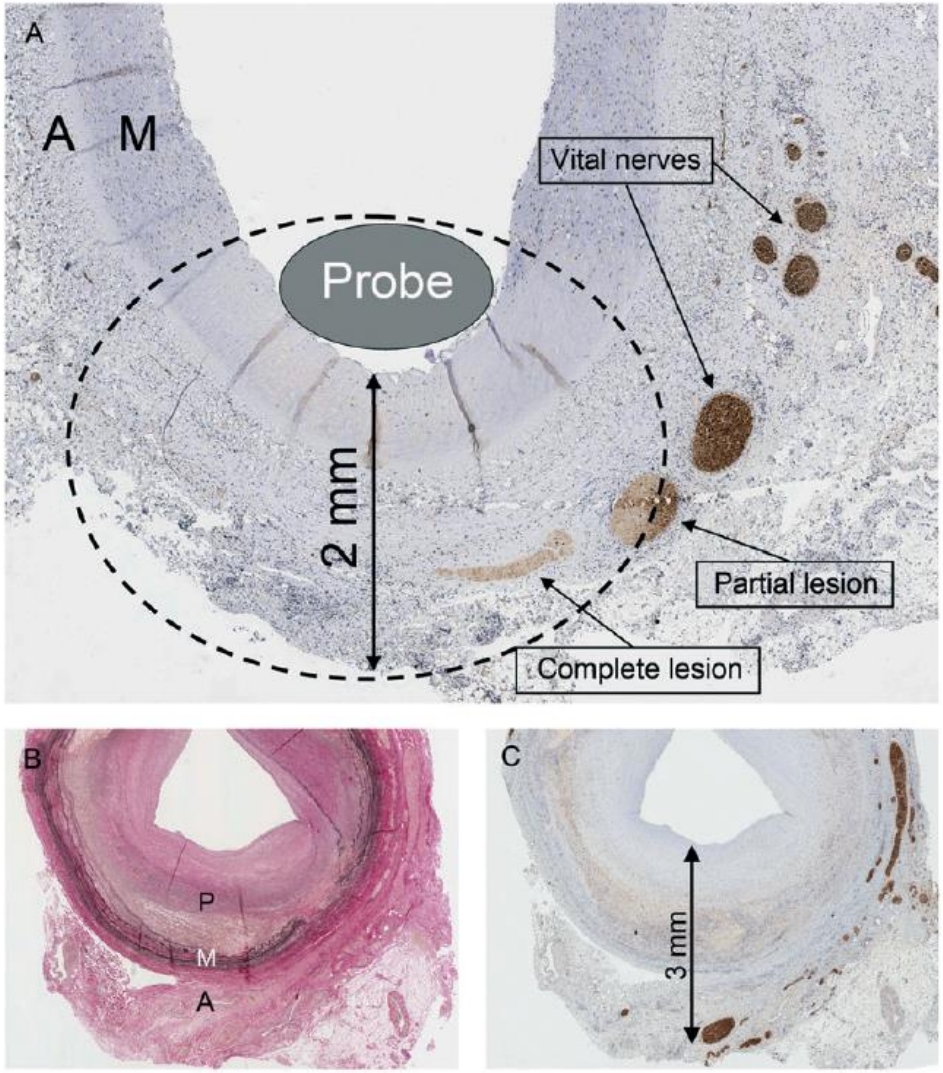
The Bench-to-Bedside Transition

Limited destruction of renal nerves after catheter-based renal denervation: results of a human case study

Eva E. Vink[1], Roel Goldschmeding[2], Aryan Vink[2], Callista Weggemans[3], Ronald L.A.W. Bleijs[4] and Peter J. Blankestijn[1]

[1]Department of Nephrology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Department of Pathology, Bethesda Hospital Hoogeveen, Hoogeveen, Netherlands and [4]Department of Anatomy, University Medical Center Utrecht, Utrecht, Netherlands

Histology of a human renal artery after renal denervation (RDN)

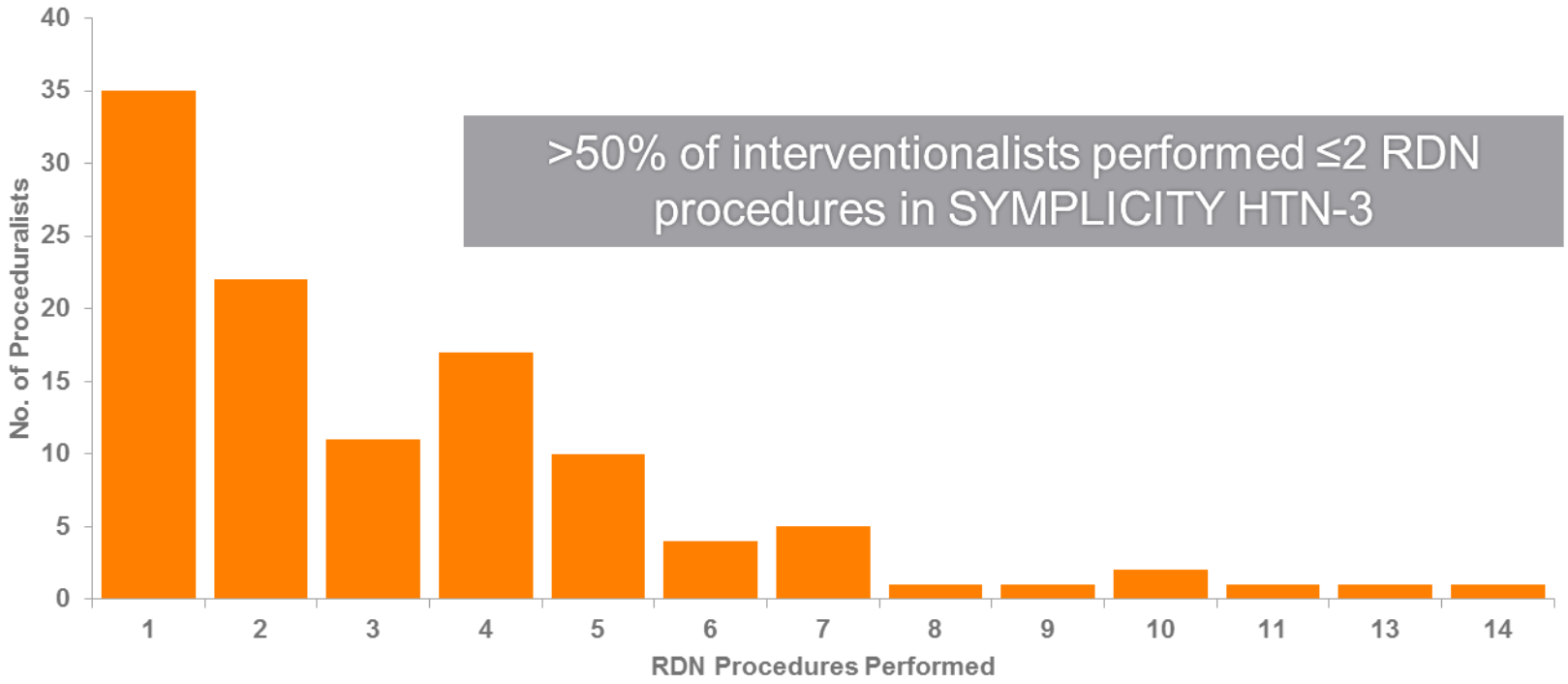


Vink E.E. et al., Nephrol. Dial. Transplnat., 2014, 29, 1608-1610

HTN-3: Procedural Experience

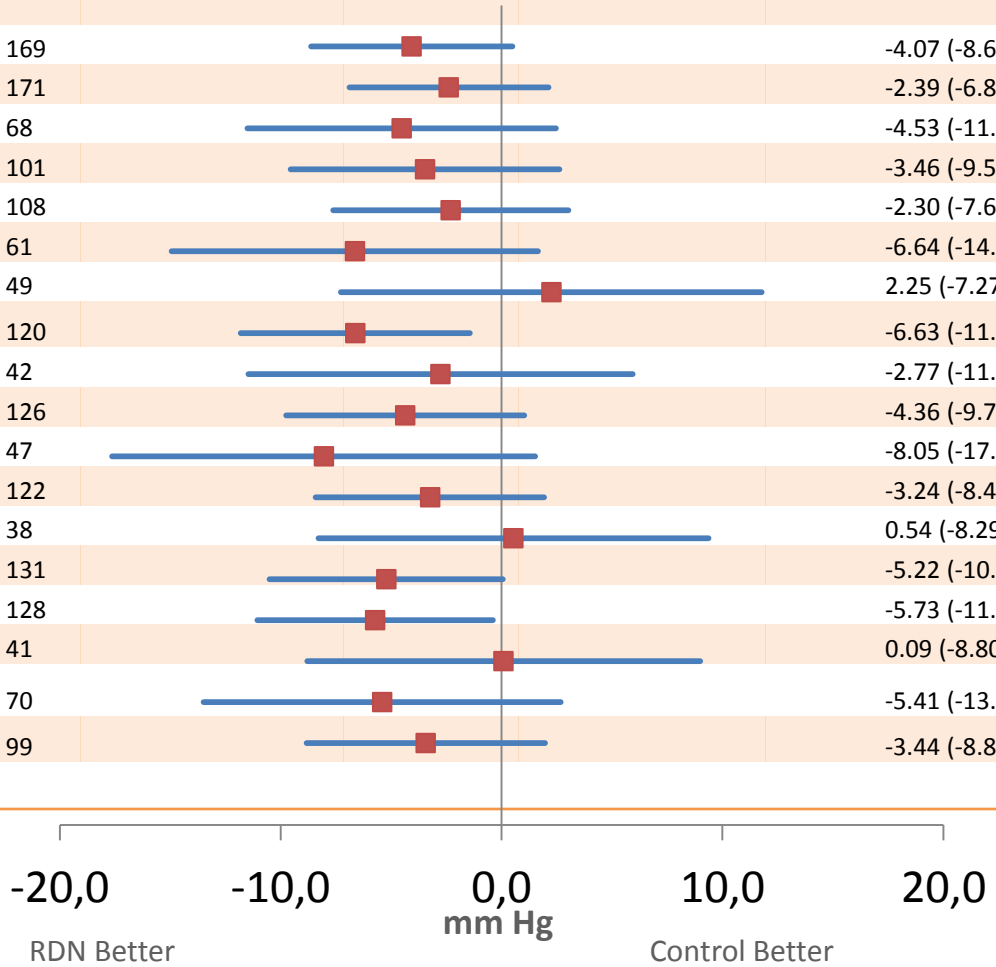
	HTN-1	HTN-3
No. of operators	20	112
No. of procedures per operator	6.0	3.3
No. of procedures per site	8.6	4.7

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



SYMPLICITY HTN-3 StudyPre-Specified Subgroup Analysis

	RDN	Sham	Difference (95% CI)	P value	Interaction P value
All patients	350	169	-4.07 (-8.63, 0.49)	0.080	
All patients*	353	171	-2.39 (-6.89, 2.12)	0.255	
Diabetics	169	68	-4.53 (-11.51, 2.46)	0.203	0.821
Non-diabetics	181	101	-3.46 (-9.55, 2.62)	0.264	
Male	208	108	-2.30 (-7.63, 3.03)	0.396	0.365
Female	142	61	-6.64 (-14.94, 1.65)	0.116	
African American	85	49	2.25 (-7.27, 11.78)	0.641	0.089
Non-African American	264	120	-6.63 (-11.81, -1.44)	0.012	
BMI <30	91	42	-2.77 (-11.47, 5.93)	0.53	0.766
BMI ≥30	259	126	-4.36 (-9.76, 1.03)	0.112	
On AA at BL	76	47	-8.05 (-17.63, 1.52)	0.098	0.364
Not on AA at BL	274	122	-3.24 (-8.42, 1.93)	0.219	
eGFR <60	68	38	0.54 (-8.29, 9.37)	0.904	0.309
eGFR ≥60	282	131	-5.22 (-10.51, 0.06)	0.053	
Age <65	246	128	-5.73 (-11.06, -0.40)	0.035	0.273
Age ≥65	104	41	0.09 (-8.80, 8.99)	0.985	
Any med change	132	70	-5.41 (-13.49, 2.67)	0.188	0.677
No med change	218	99	-3.44 (-8.83, 1.96)	0.211	



* ITT population, 5 mm Hg superiority margin test .

Bhatt D.J. et al., N.Engl. J. Med. 2014 Apr 10, 370: 1393-1400

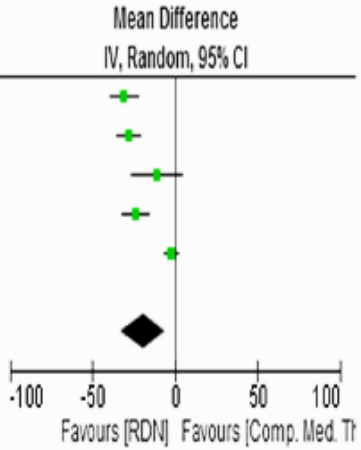
Systolic (A) and diastolic (B) change at 6 months, RD versus MMT

A

Study or Subgroup	RDN Mean	RDN SD	RDN Total	MMT Mean	MMT SD	MMT Total	Weight	Mean Difference IV, Random, 95% CI
Esler 2010	-32	23	52	-1	21	54	20.3%	-31.00 [-39.39, -22.61]
Ewen 2014	-26	12.36	50	2	10.4	10	20.7%	-28.00 [-35.30, -20.70]
Mahfoud 2014	-22	27.5	55	-11	28.4	17	17.1%	-11.00 [-26.33, 4.33]
Pokushalov 2012	-28	12.2	13	-4	9.1	14	20.4%	-24.00 [-32.17, -15.83]
Simplicity 3	-14.1	28.9	364	-11.8	23.2	171	21.5%	-2.30 [-6.87, 2.27]
Total (95% CI)			534			266	100.0%	-19.36 [-32.80, -5.92]

Heterogeneity: Tau² = 213.25; Chi² = 60.69, df = 4 (P < 0.00001); I² = 93%

Test for overall effect: Z = 2.82 (P = 0.005)

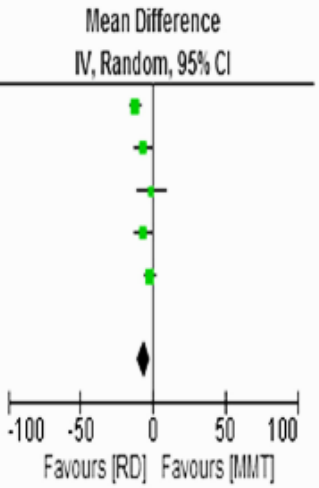


B

Study or Subgroup	RD Mean	RD SD	RD Total	MMT Mean	MMT SD	MMT Total	Weight	Mean Difference IV, Random, 95% CI
Esler 2010	-12	11	52	0	10	54	24.8%	-12.00 [-16.01, -7.99]
Ewen 2014	-7	8.9	50	0	9.24	10	19.1%	-7.00 [-13.24, -0.76]
Mahfoud 2014	-8	19.9	55	-7	18.5	17	11.4%	-1.00 [-11.25, 9.25]
Pokushalov 2012	-10	7.8	13	-3	6.9	14	20.7%	-7.00 [-12.57, -1.43]
Simplicity 3	-6.9	23.9	364	-4.8	23.8	171	24.0%	-2.10 [-6.43, 2.23]
Total (95% CI)			534			266	100.0%	-6.38 [-10.73, -2.03]

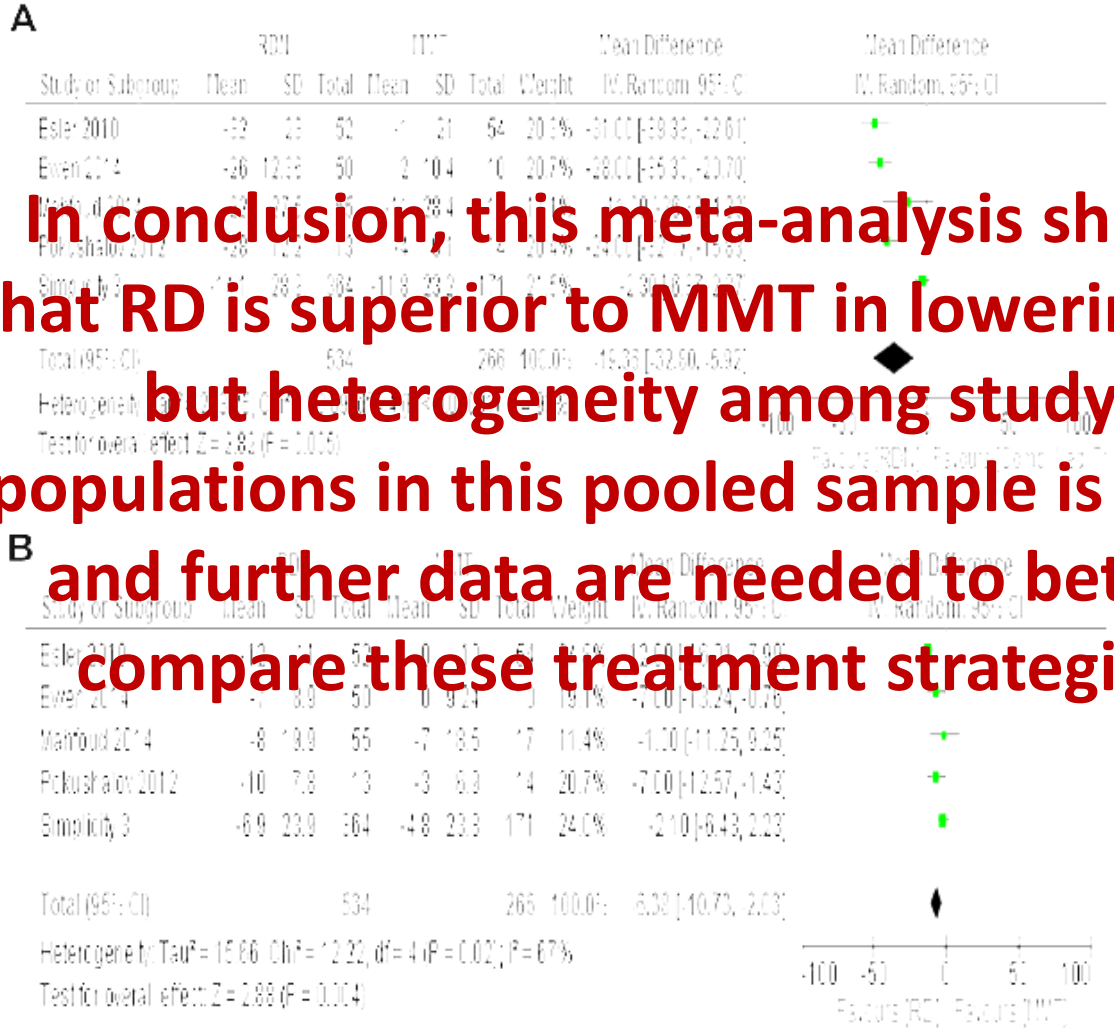
Heterogeneity: Tau² = 15.66; Chi² = 12.22, df = 4 (P = 0.02); I² = 67%

Test for overall effect: Z = 2.88 (P = 0.004)



Pancholy S.B. et al. Am.J. Cardiol., in press

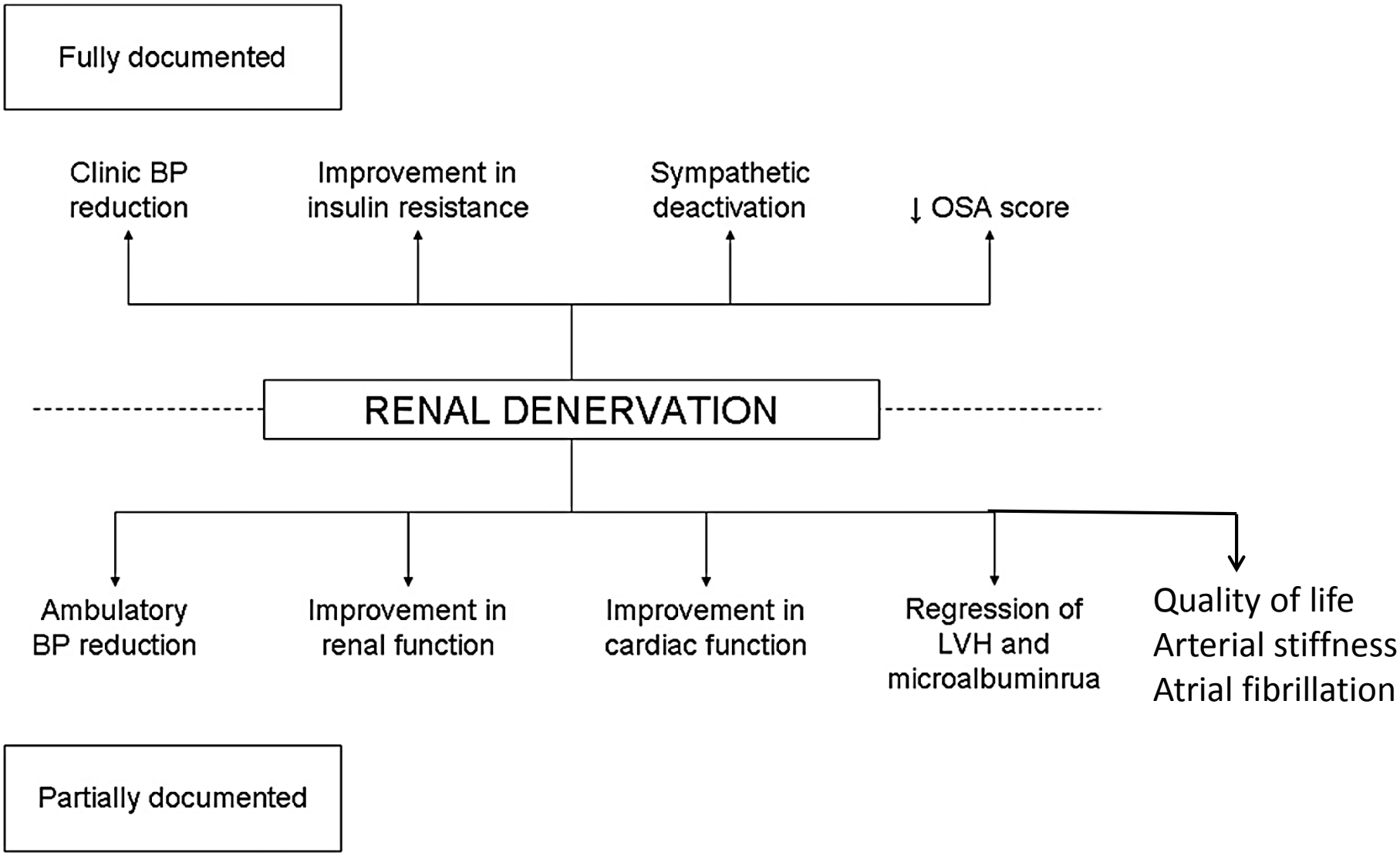
Systolic (A) and diastolic (B) change at 6 months, RD versus MMT



In conclusion, this meta-analysis shows that RD is superior to MMT in lowering BP, but heterogeneity among study populations in this pooled sample is high, and further data are needed to better compare these treatment strategies

Pancholy S.B. et al. Am.J. Cardiol., in press

Effects of renal denervation



Grassi et al., Can. J.Cardiol., 2012, 28, 311–317

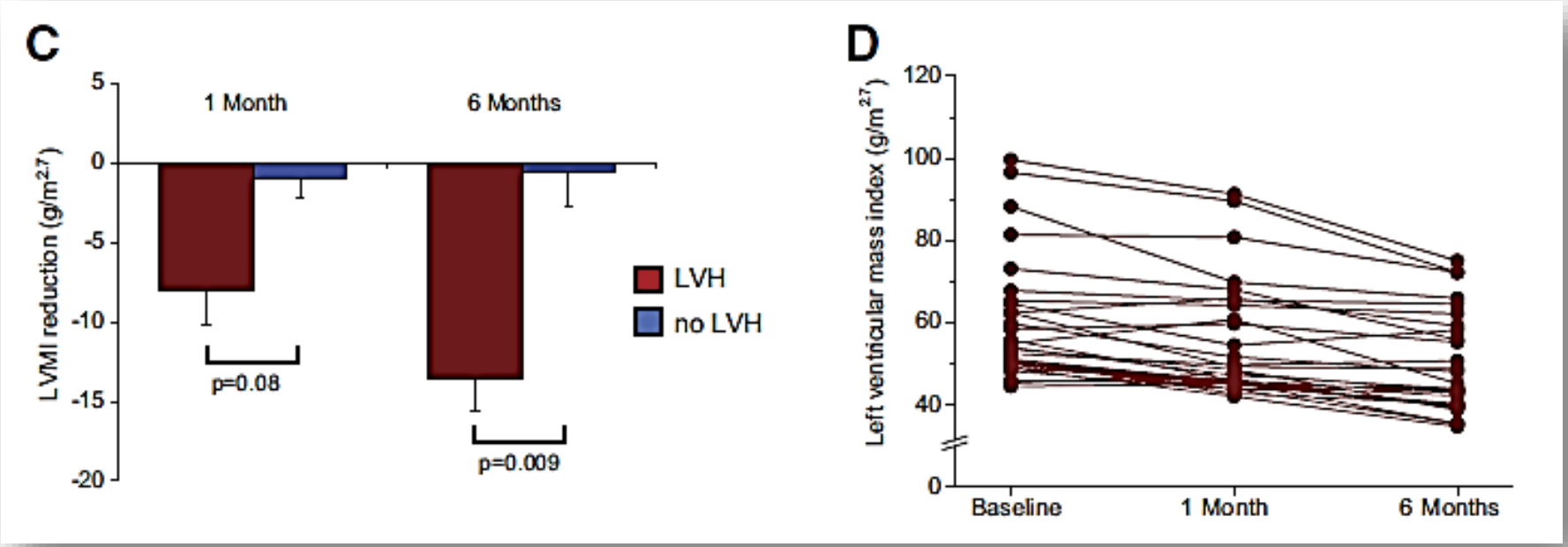
Potential patient groups likely to benefit of renal denervation

- Chronic kidney disease, not on dialysis
- Chronic kidney disease, on dialysis
- Native kidneys of patients with kidney transplant
- Kidney pain syndromes, including PKD and loin pain hematuria
- Heart failure
- Obesity/metabolic syndrome/Type 2 diabetes
- Patients with sleep apnoe syndrome

Blankestijn P.J. et al., Nephrol. Dial. Transplant., 2014, 29, 1120-1123

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*†‡

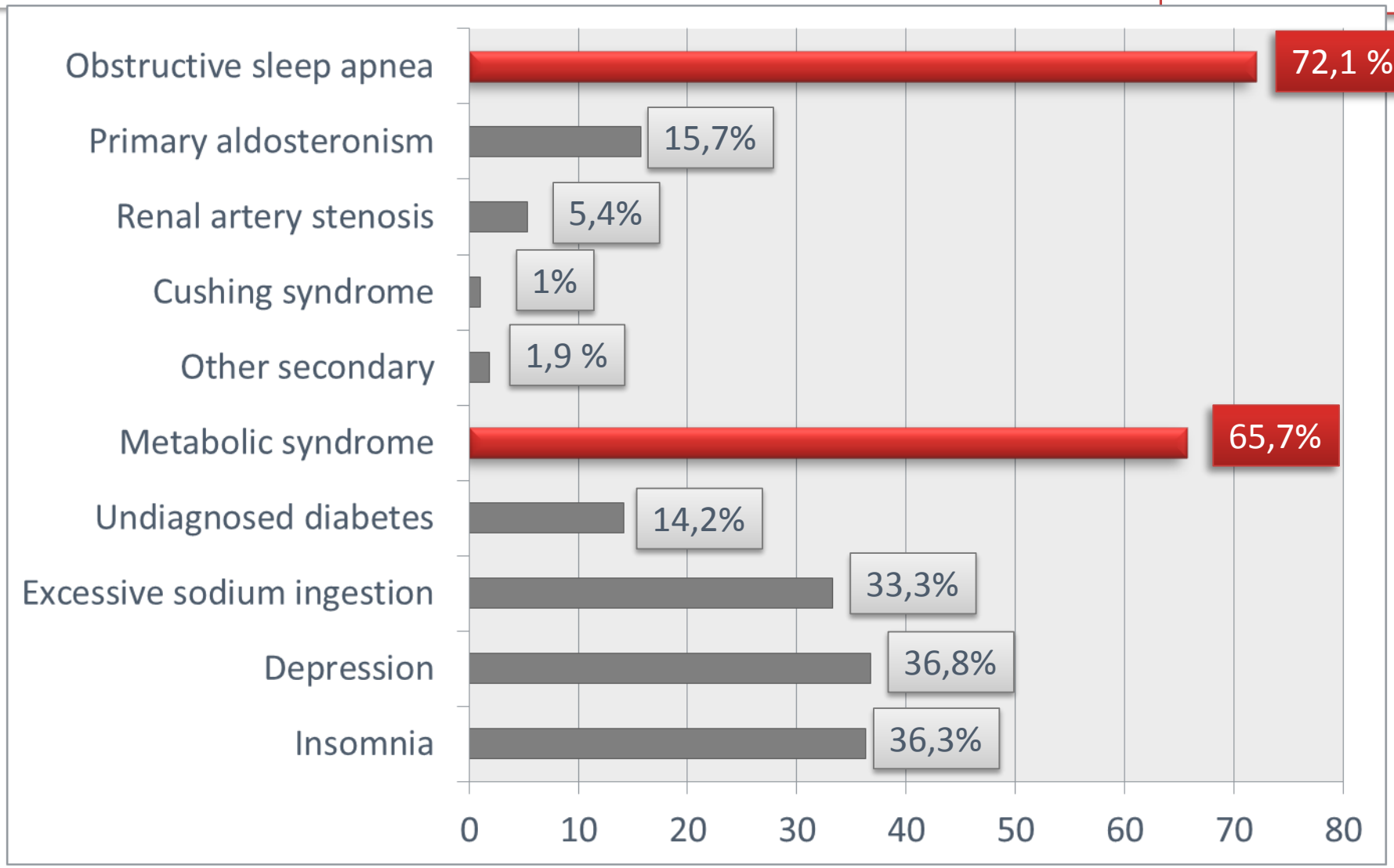


RD significantly reduces LV mass and improves diastolic function, which might have important prognostic implications in patients with resistant hypertension

JACC 2012

Frequency of OSA, secondary causes and associated conditions - in 204 patients with **true resistant hypertension**

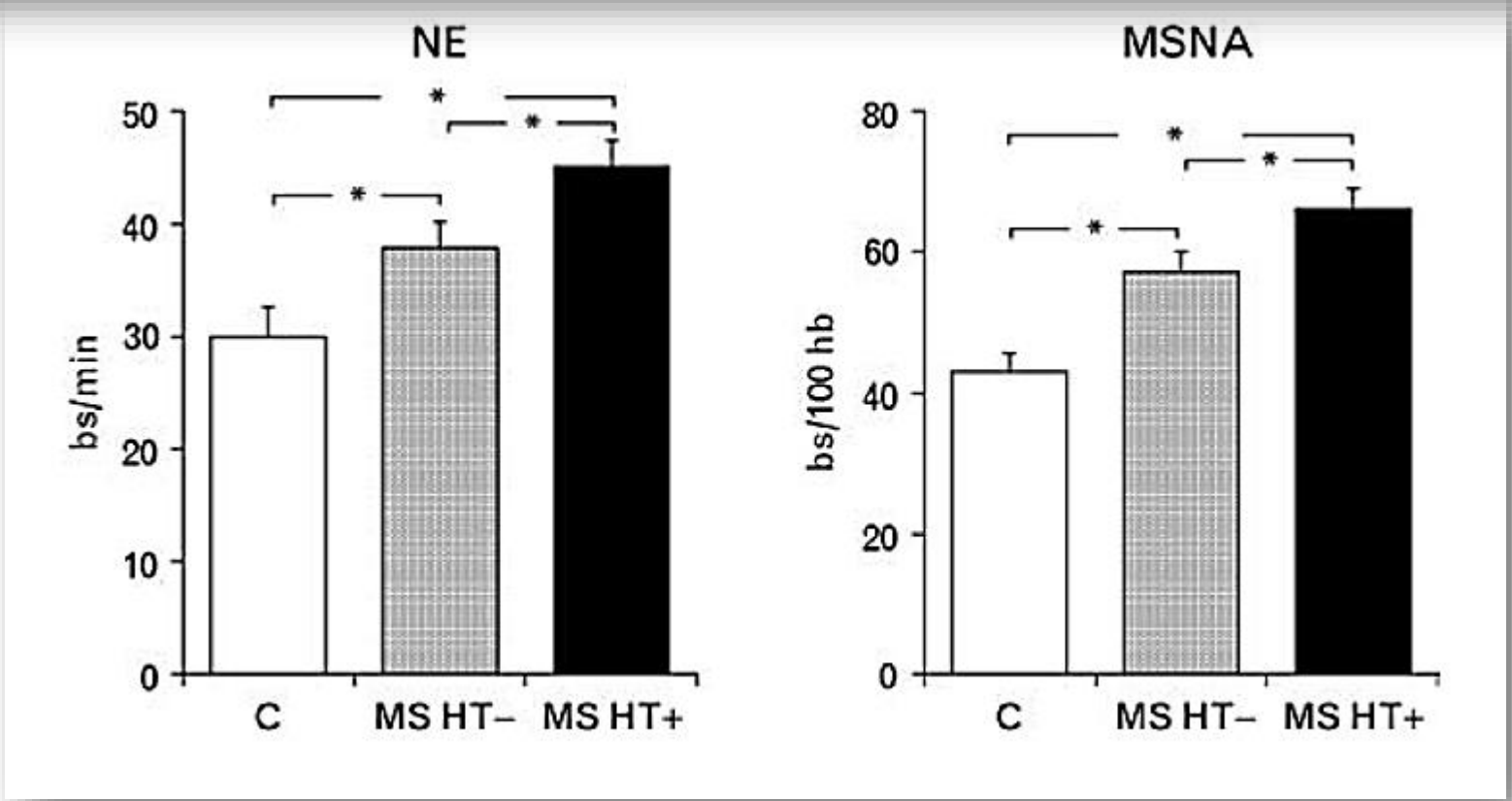
RESIST-POL STUDY



Florczak E….Wiecek A. et al. J. Human Hypertens., 2013, 27: 678-685

The sympathetic nervous system and the metabolic syndrome

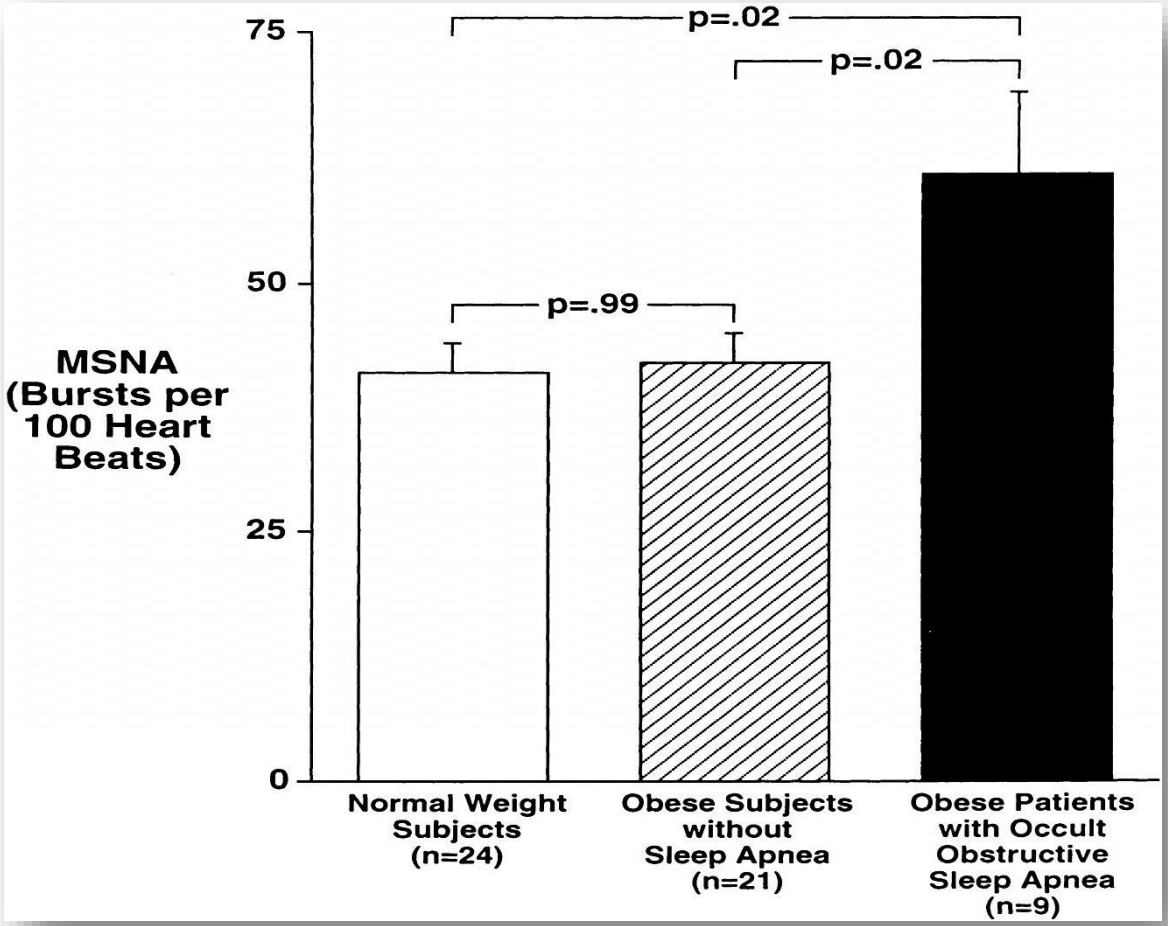
Giuseppe Mancia[a], Pascal Bousquet[b], Jean Luc Elghozi[c], Murray Esler[d], Guido Grassi[a], Stevo Julius[e], John Reid[f] and Peter A. Van Zwieten[g]



Components of the metabolic syndrome
- including obesity and insulin resistance -
associated with markers of adrenergic overdrive

J. Hypertens. 2008

Increased sympathetic nervous system activity in patient with obstructive sleep apnea



Basner RC i wsp. NEJM 2007; Narkiewicz, K. et al. Circulation 1998; Narkiewicz, K. et al. Circulation 1999;

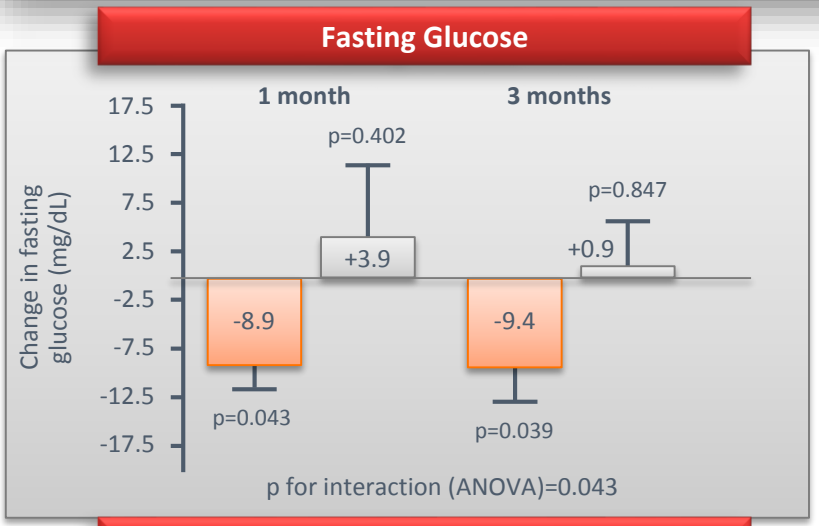
Hypertension

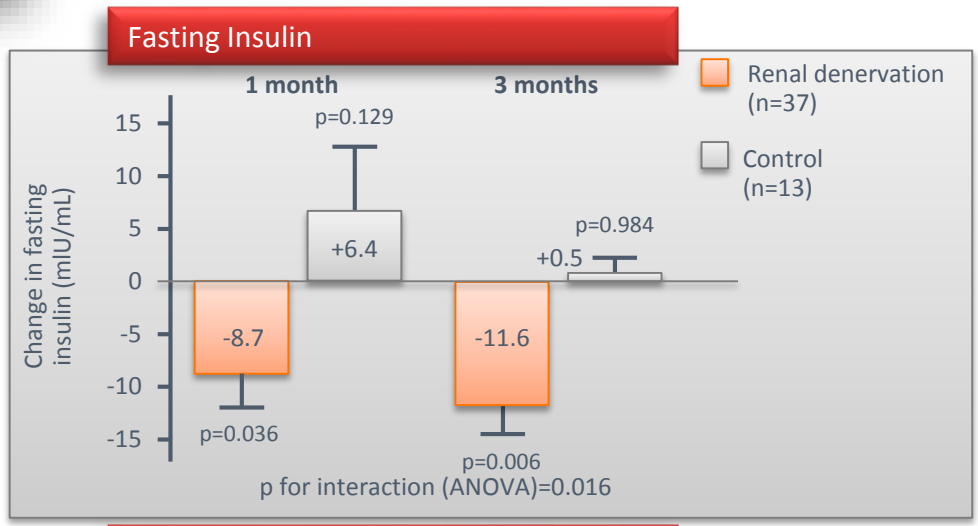
Effect of Renal Sympathetic Denervation on Glucose Metabolism in Patients With Resistant Hypertension

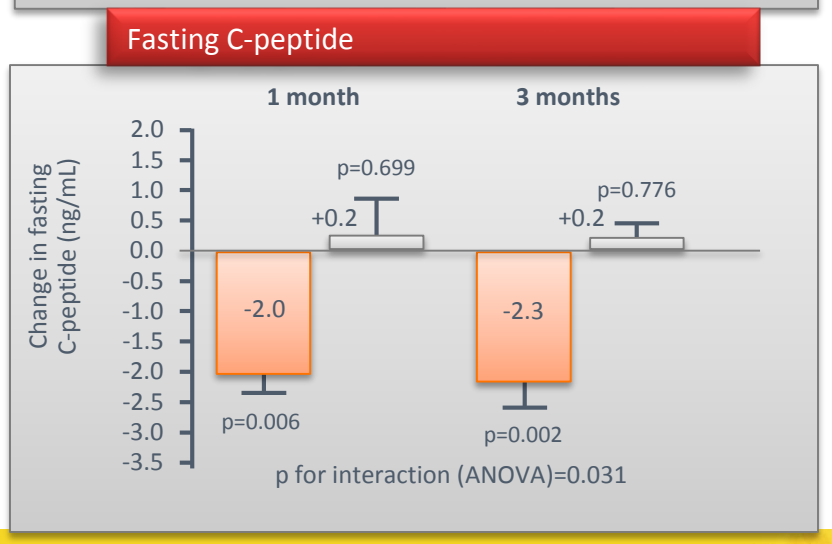
A Pilot Study

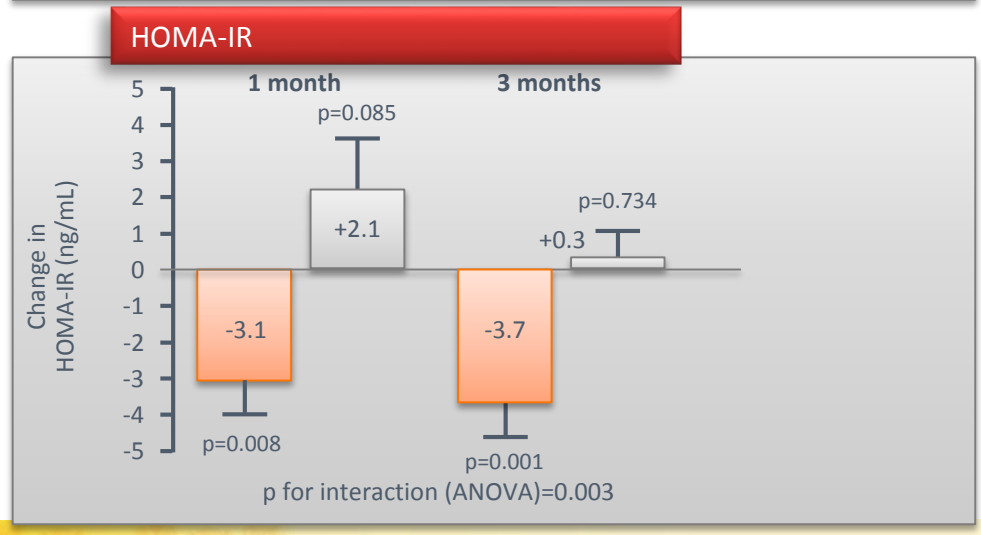
Felix Mahfoud, MD; Markus Schlaich, MD; Ingrid Kindermann, MD; Christian Ukena, MD; Bodo Cremers, MD; Mathias C. Brandt, MD; Uta C. Hoppe, MD; Oliver Vonend, MD; Lars C. Rump, MD; Paul A. Sobotka, MD; Henry Krum, MBBS, PhD; Murray Esler, MBBS, PhD, FRACP; Michael Böhm, MD

RDN showed improvements in several key insulin resistance markers



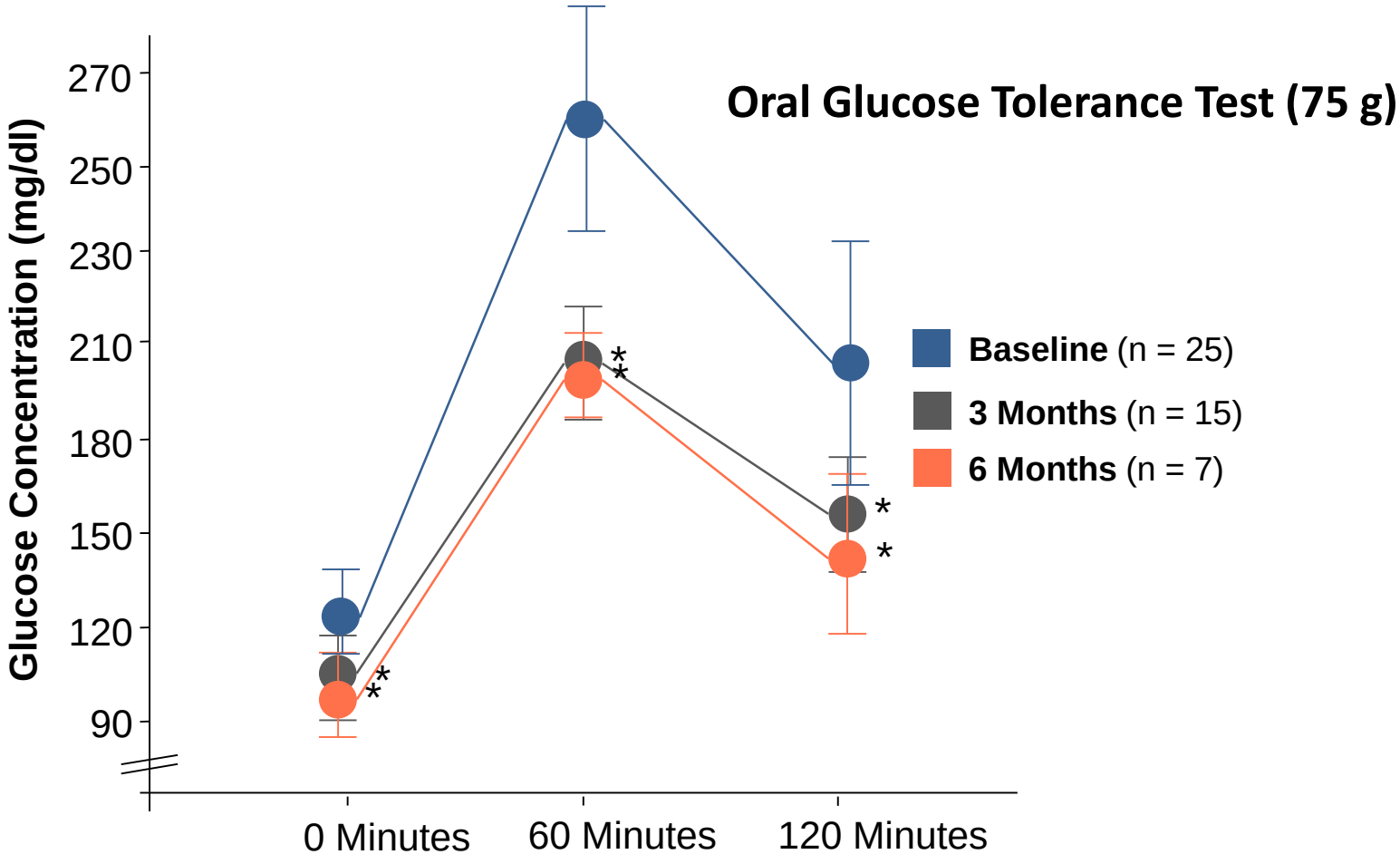






Mahfoud F. et al. Circulation. 2011;123:1940-1946

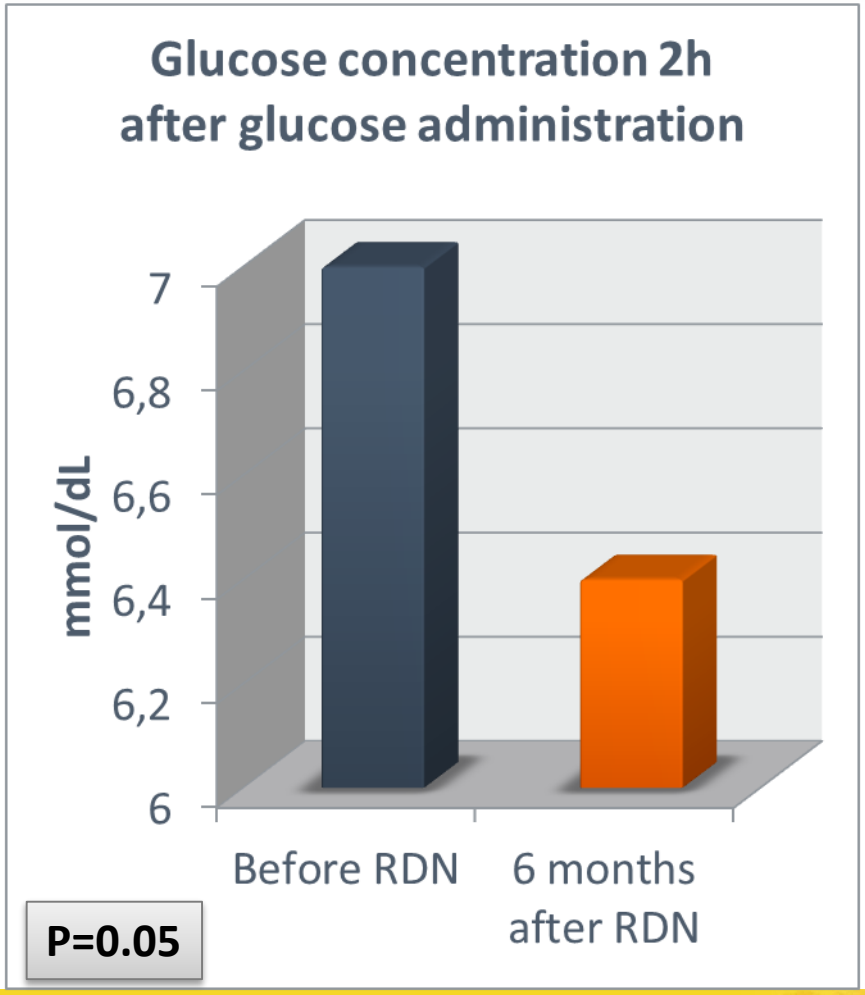
Glucose metabolism improved following RDN in subset of Symplicity HTN-2 patient population



*Significant reduction (p <0.05) compared with baseline.

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

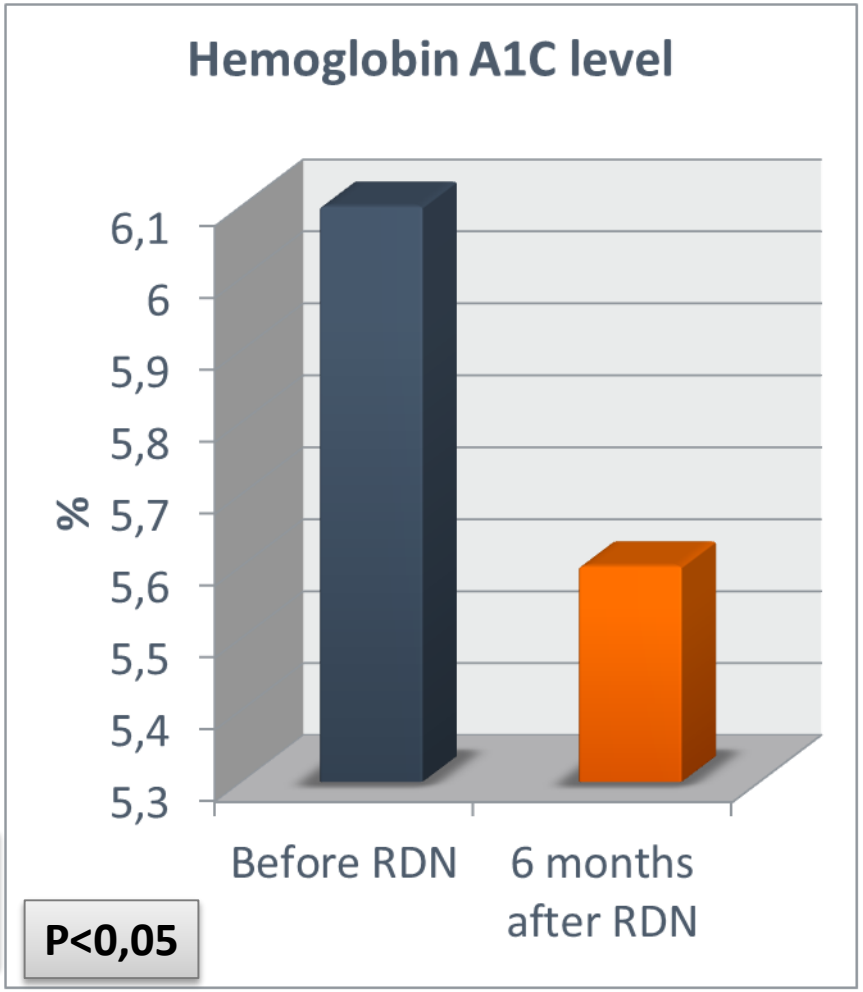


At 6 months significant decrease in plasma glucose concentration 2 hours after glucose challenge was observed

Hypertension, 2011

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



At 6 months significant decrease in HgbA1C level was observed

Hypertension 2011

Potential mechanisms by which renal denervation favorably affects insulin metabolism

- **Decrease in vascular alpha adrenergic tone, leading to skeletal muscle vasodilatation**
- **An inhibition of the renin-angiotensin system**
- **An improved glucose transport to skeletal muscle**
- **An increased sensitivity to the nonesterified fatty acid-lowering effects of insulin**
- **A change in glucose transporters and in glucagon secretion**

Grassi G. Nut Met Cardiovasc Dis 2012

Renal sympathetic denervation in patients with resistant HT

Safety of the procedure

SYMPLICITY – HTN 1

Lancet 2009

Periprocedural safety:
2 complications (4,4%)

- 1 - Artery dissection (treated with stent)
- 1 - Pseudoaneursym

No change in renal function

SYMPLICITY – HTN 2

Lancet 2010

No serious complications related to the device or procedure

Minor periprocedural events, including:
- femoral artery pseudoaneurysm
- Intraprocedural bradycardia requiring atropine

	Renal denervation group		Control group		Difference in mean change (95% CI)	p value
	Patients (n)	Mean change (SD)	Patients (n)	Mean change (SD)		
eGFR* (mL/min per 1·73 m²)	49	0·2 (11)	51	0·9 (12)	−0·7 (−5·4 to 3·9)	0·76
Serum creatinine (μmol/L)	49	0·2 (17·6)	51	−1·1 (10·3)	1·3 (−4·5 to 7·0)	0·67
Cystatin C (mg/L)	37	0·1 (0·2)	40	0·0 (0·1)	0·0 (0·0 to 0·1)	0·31

eGFR=estimated glomerular filtration rate. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[12]

No change in renal function

Lancet 2009, Lancet 2010

No influence of bilateral renal denervation on eGFR in patients with CKD

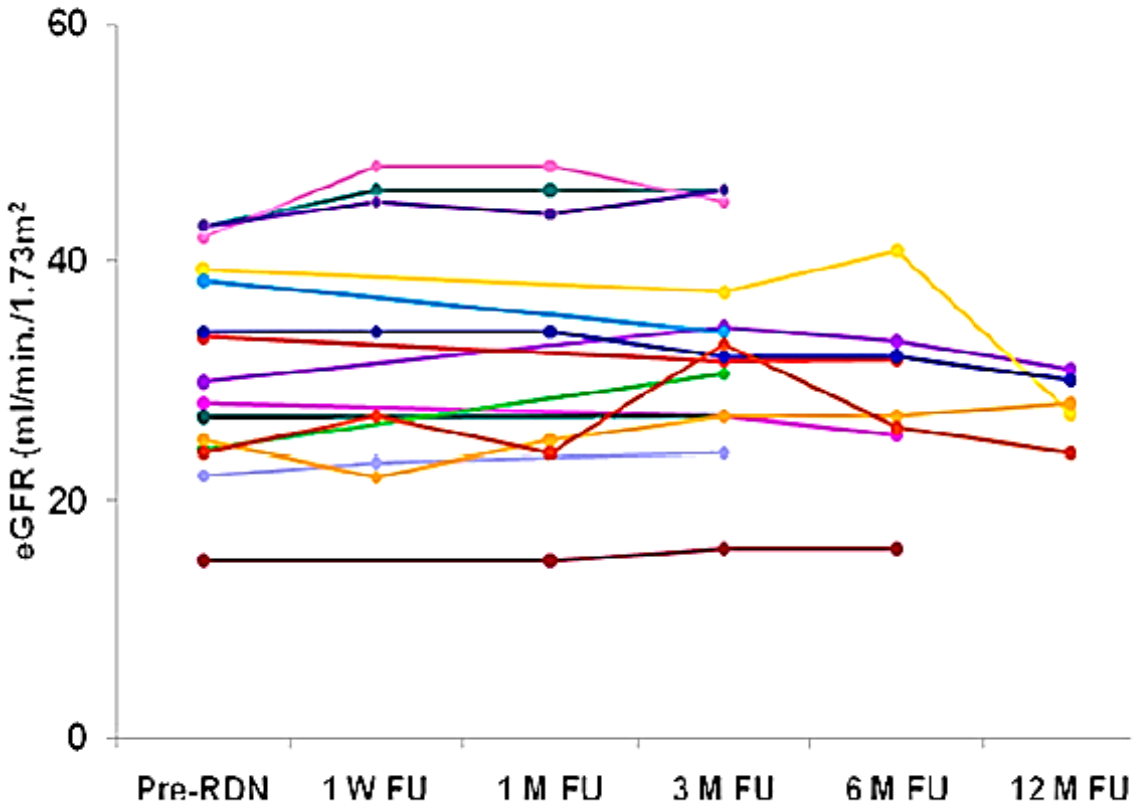
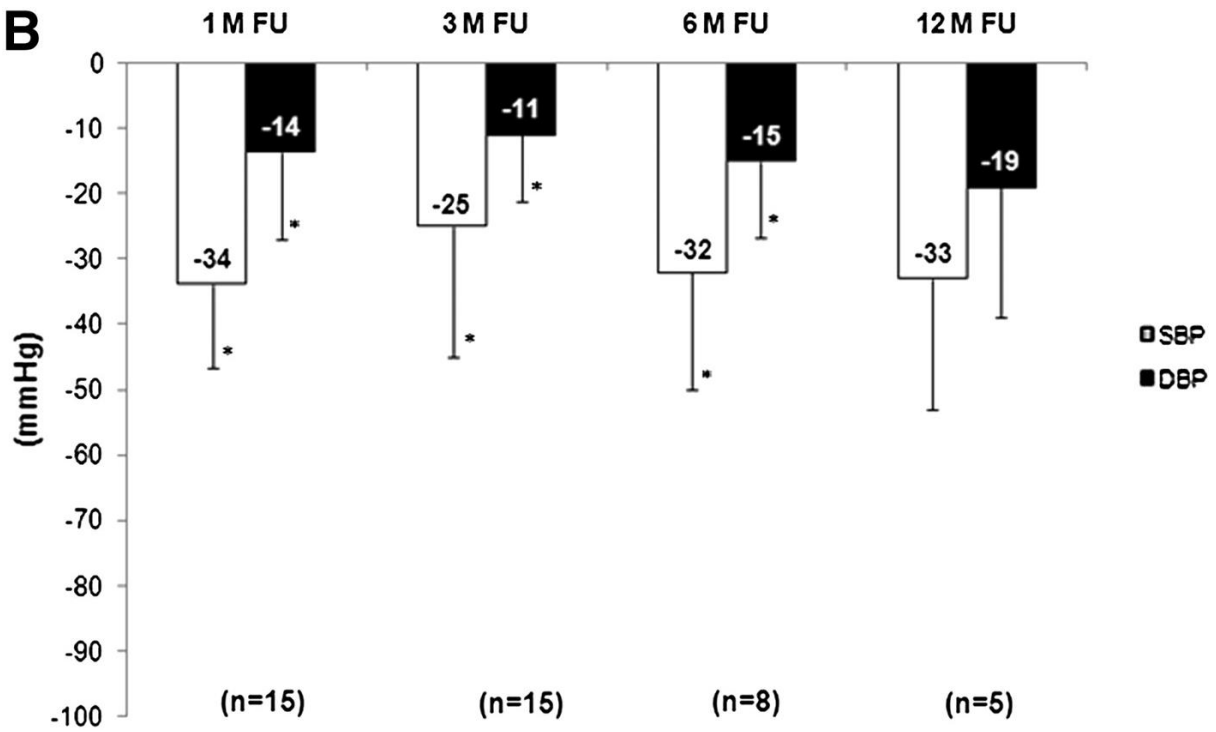


Figure 1. Individual changes in creatinine-based estimated GFR before renal denervation (pre-RDN); at 1 week (W); and at 1-, 3-, 6-, and 12-month (M) follow-up (FU).

Hering D. et al., J. Am. Soc. Nephrol., 2012, 23: 1250–1257

RDN in patients with CKD 3-4

- Baseline BP 174 ± 22/91 ± 16 mmHg
- 5.6 ± 1.3 antihypertensive drugs
- GFR 31 ± 9 ml/min 1.73 m2



Hering D. et al., J. Am. Soc. Nephrol., 2012, 23: 1250–1257

Improvement of albuminuria after renal denervation

C.Ott[1], F. Mahfoud[2], A. Schmid[3], T. Ditting[1], R. Veelken[1], S. Ewen[2], C. Ukena[2], M. Uder[3], M. Böhm[2], R.E. Schmieder[1]

[1]Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Germany
[2] Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany
[3]Department of Radiology, University of Erlangen-Nuremberg, Germany

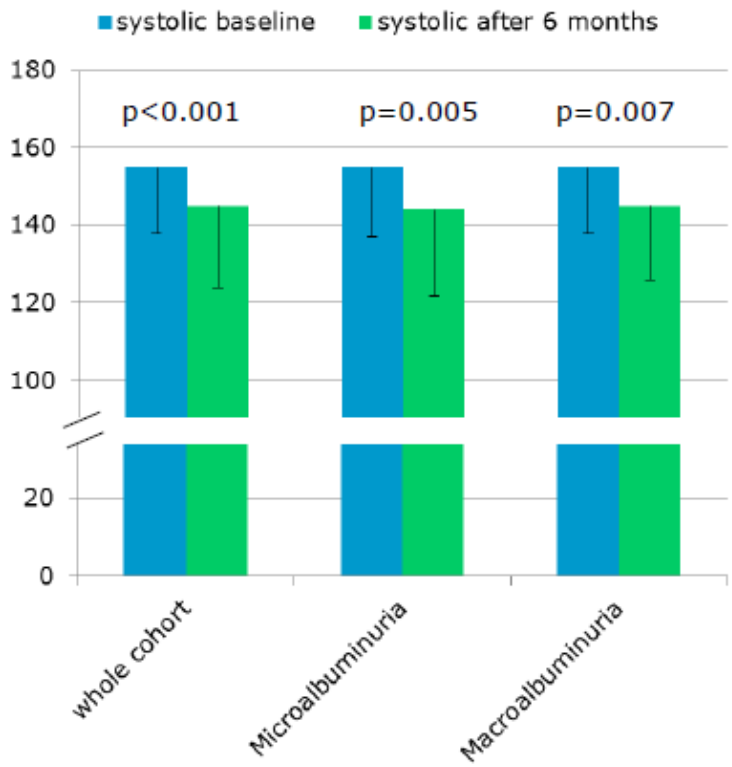
EDTA, Amsterdam June 1st, 2013

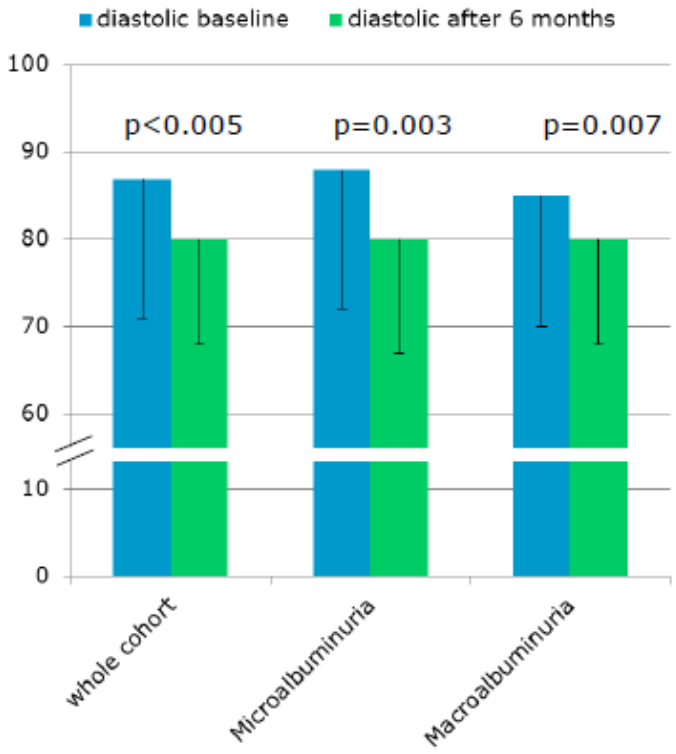
Changes of clinical characteristics

N=59		prior to RDN	6 months after RDN	p-Value
office BP (mmHg)	systolic	169 ± 23	151 ± 26	p<0.001
	diastolic	91 ± 17	81 ± 14	p<0.001
24-h ABP (mmHg)	systolic	156 ± 18	145 ± 21	p<0.001
	diastolic	87 ± 15	80 ± 12	p<0.001
heart rate (bpm)		72 ± 13	66 ± 12	p<0.001
eGFR (ml/min/1.73 m^2) (CKD-EPI equation)		67.2 ± 22	65 ± 24	p=0.157
Doubling of serum creatinine		N=0	N=0	
Number of antihypertensive medication (93 % on RAS blockers)		5.5 ± 2.6	5.3 ± 1.6	

Schmieder RE ACC 2014

SBP between baseline and 6 months after RDN

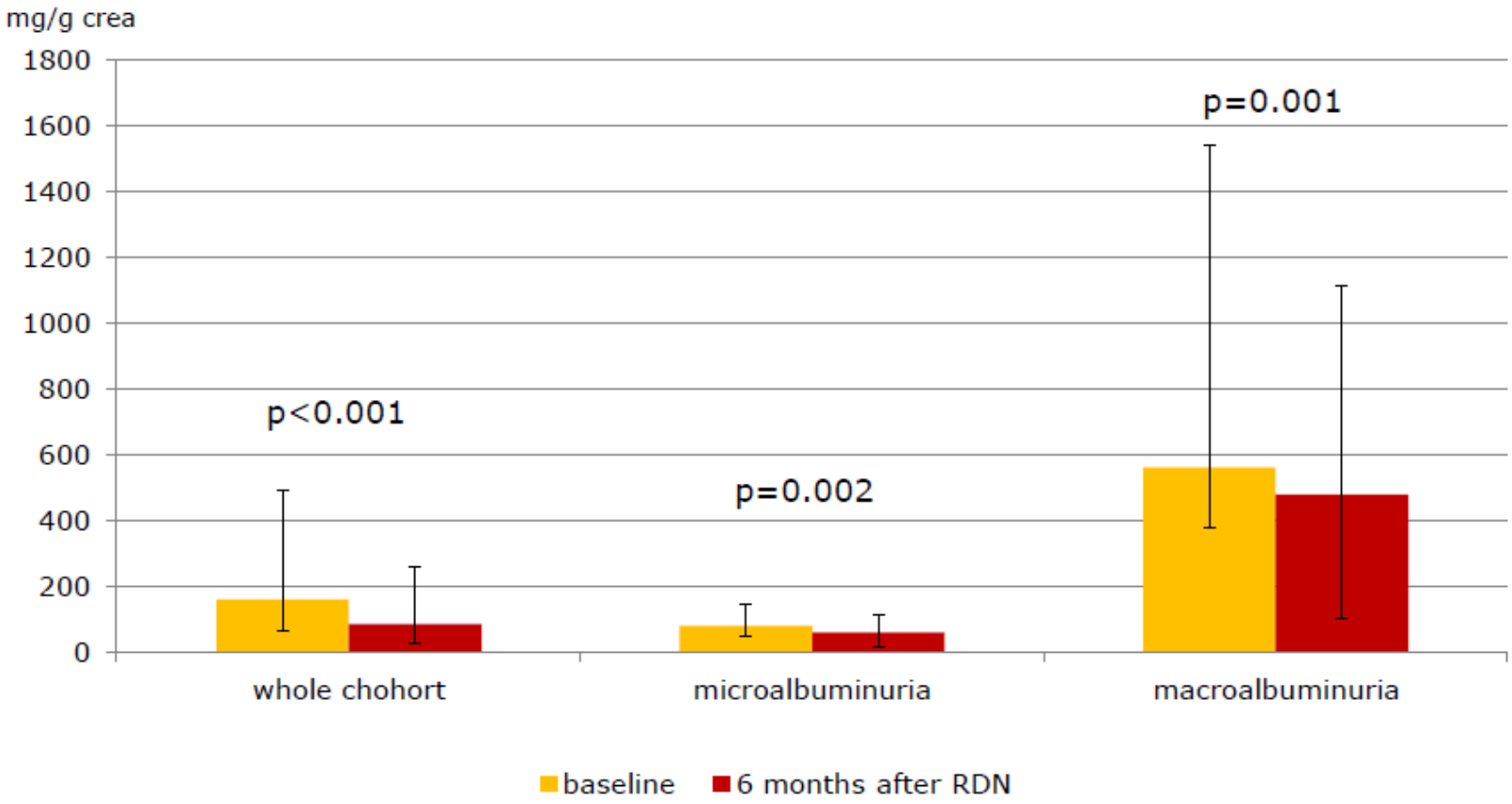




x±SD

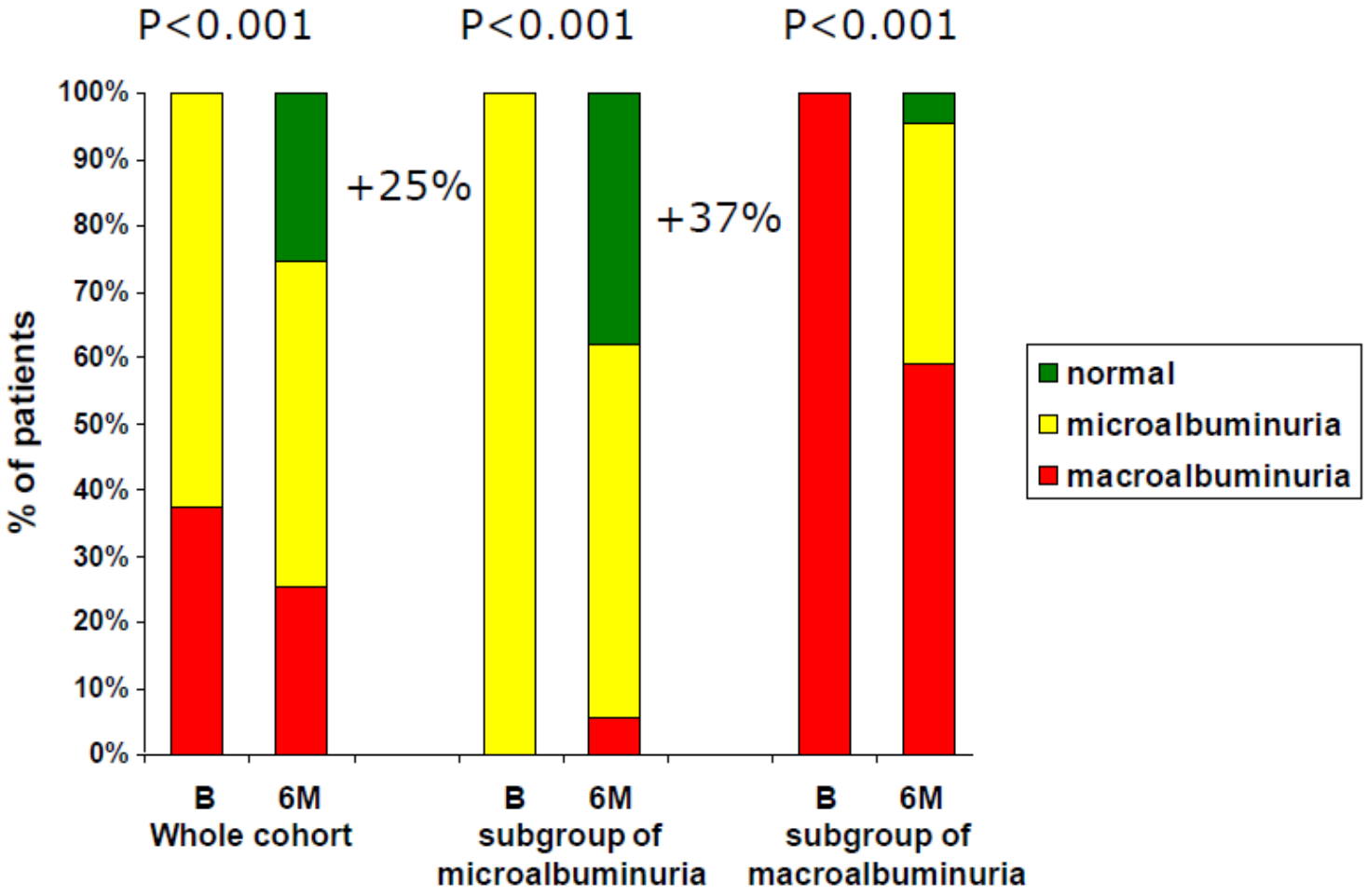
Schmieder RE ACC 2014

Albuminuria (UACR) between baseline and 6 months after RDN



Schmieder RE ACC 2014

Change in categories of albuminuria



Schmieder RE ACC 2014

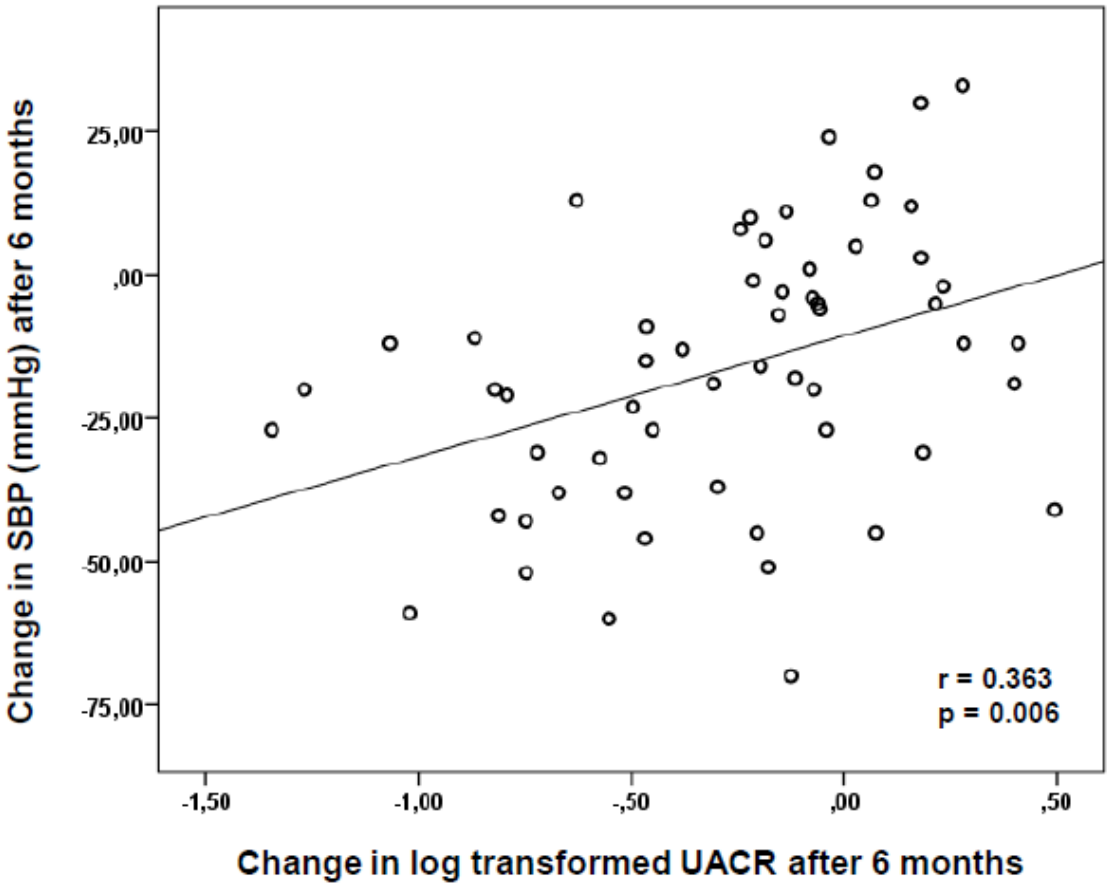
Change of albuminuria: Stratification of the study cohort into patients without and **with type 2 diabetes** (N=31)

Change in UACR (mg/g crea)		Baseline	6 months after RDN	p-Value
Whole group	without diab.	86 (60-204)	78 (24-164)	0.003
	with diab.	**313 (90-553)**	**113 (45-551)**	**0.001**
Microalbuminuria	without diab.	78 (57-122)	48 (17-106)	0.012
	with diab.	**83 (45-150)**	**68 (18-113)**	**0.056**
Macroalbuminuria	without diab.	672 (430-1203)	410 (94-1195)	0.045
	with diab.	**536 (384-1541)**	**478 (113-963)**	**0.003**

median (interquartile range)

Schmieder RE ACC 2014

Correlation between decrease in systolic BP and decrease in albuminuria



Schmieder RE ACC 2014

Conclusion

1) Renal denervation reduced elevated albuminuria in treatment-resistant hypertensive patients:

   in mico- and macroalbuminuric patients

   in diabetic and non diabetic patients

2) The antiproteinuric effect appeared to be in part related to the decrease in blood pressure, and

3) decreased sympathetic activity to the kidneys may have played a role as well,
   but this cannot delineated from our trial

Renal Denervation stops the Decline of Renal Function in Patients with Chronic Kidney Disease and Resistent Hypertension

Prof. Roland E. Schmieder
FESC, FACC, FACP, FASN

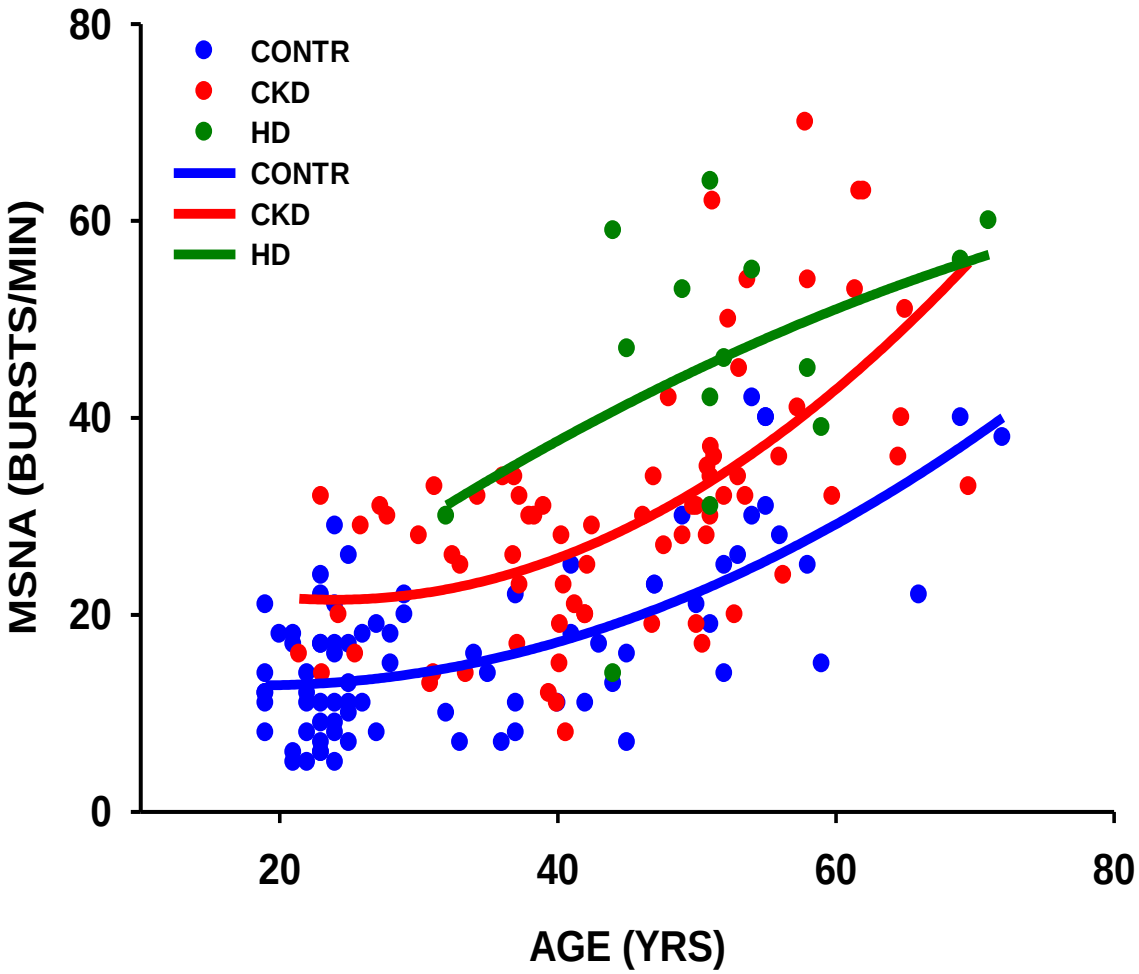
University Hospital
University Erlangen/Nürnberg
Germany

EDTA,
Amsterdam June 1st ,2014

Microneurographic Evidence of Increased Sympathetic Activity in Chronic Renal Disease

- **Hemodialysis** — Converse RL et al. New Engl J Med.1992;327:1912.
- **CRF (Stage 3)** — Ligtenberg et al. *New Engl J Med*. 1999;340:1321.
- **Ischemic Nephropathy** — Johansson et al. *Circulation.* 1999;99:2537.
- **Renal Transplantation** — Hausberg et al. *Circulation.* 2002;106:1974.
- **Polycystic Kidney Disease** — Klein et al. *J Am Soc Nephrol.*2001;12:2427.

Sympathetic hyperactivity in patients with CKD



Controls n=80

CKD n=74

HD n=17

Hypertension, 2009

Pathophysiology of sympathetic activation in patients with chronic kidney disease (CKD)

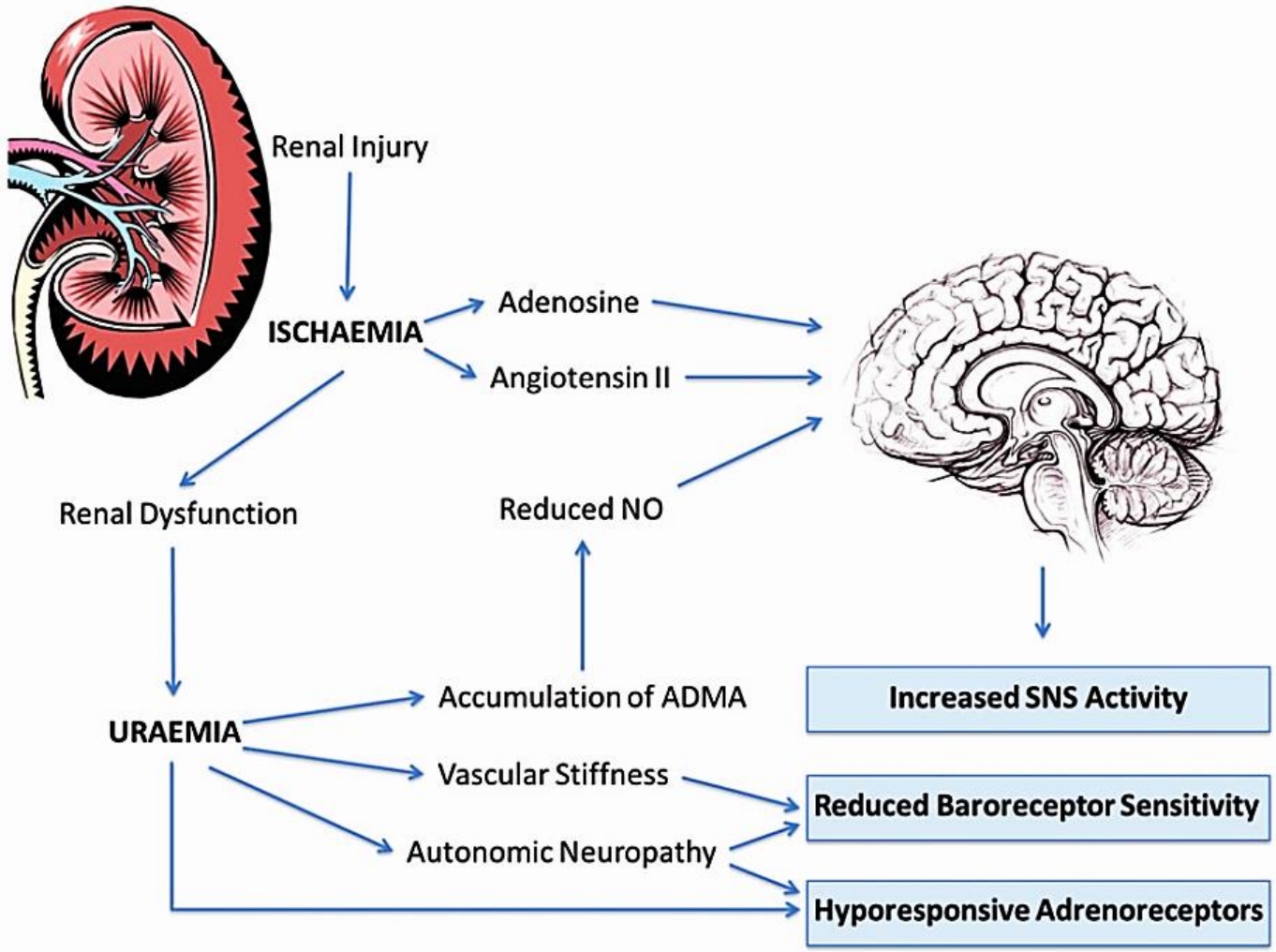
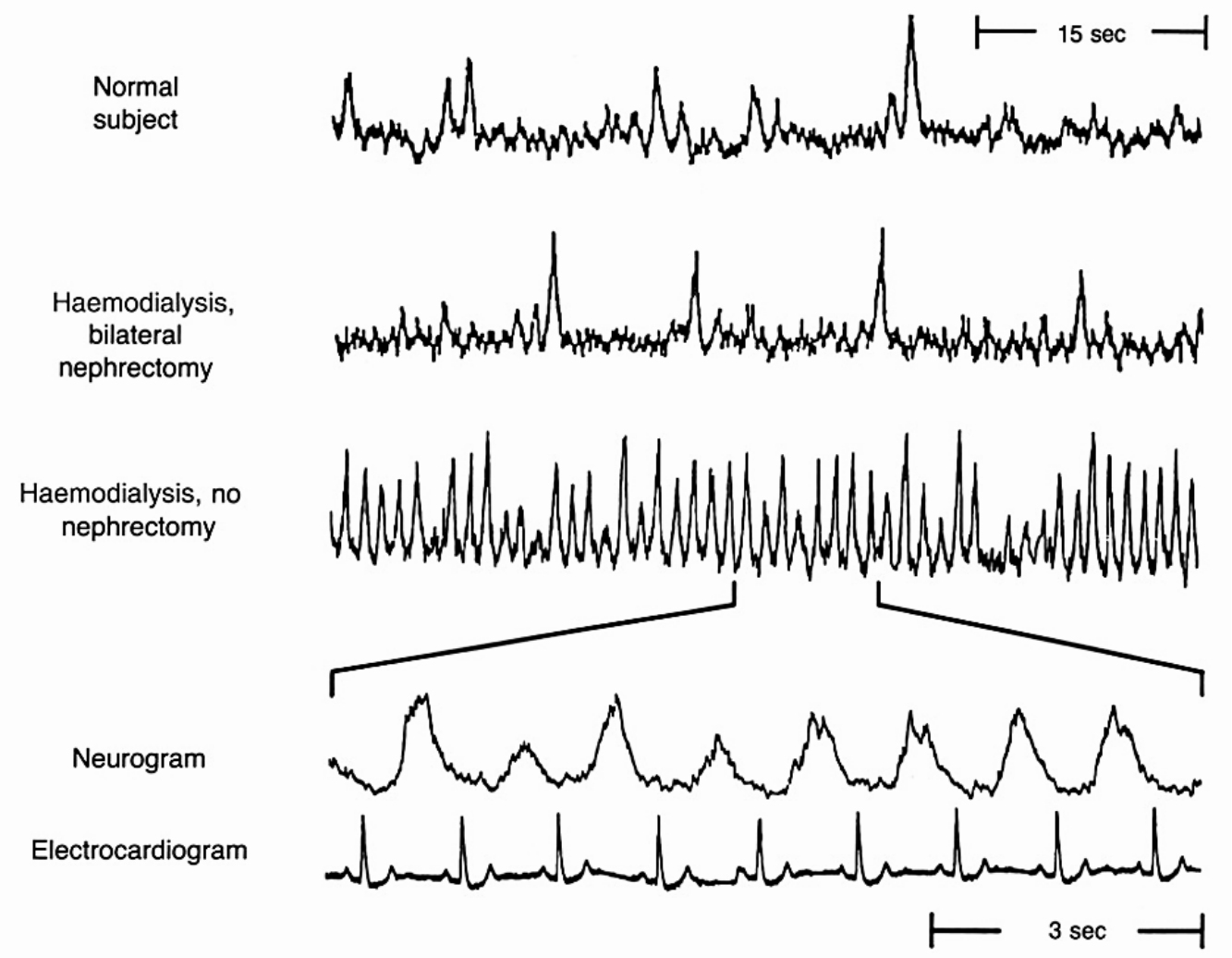


Fig. 2. The pathophysiology of sympathoexcitation in CKD.

Hoye N.A. et al., Clin. Kidney J., 2014, 7, 3-10

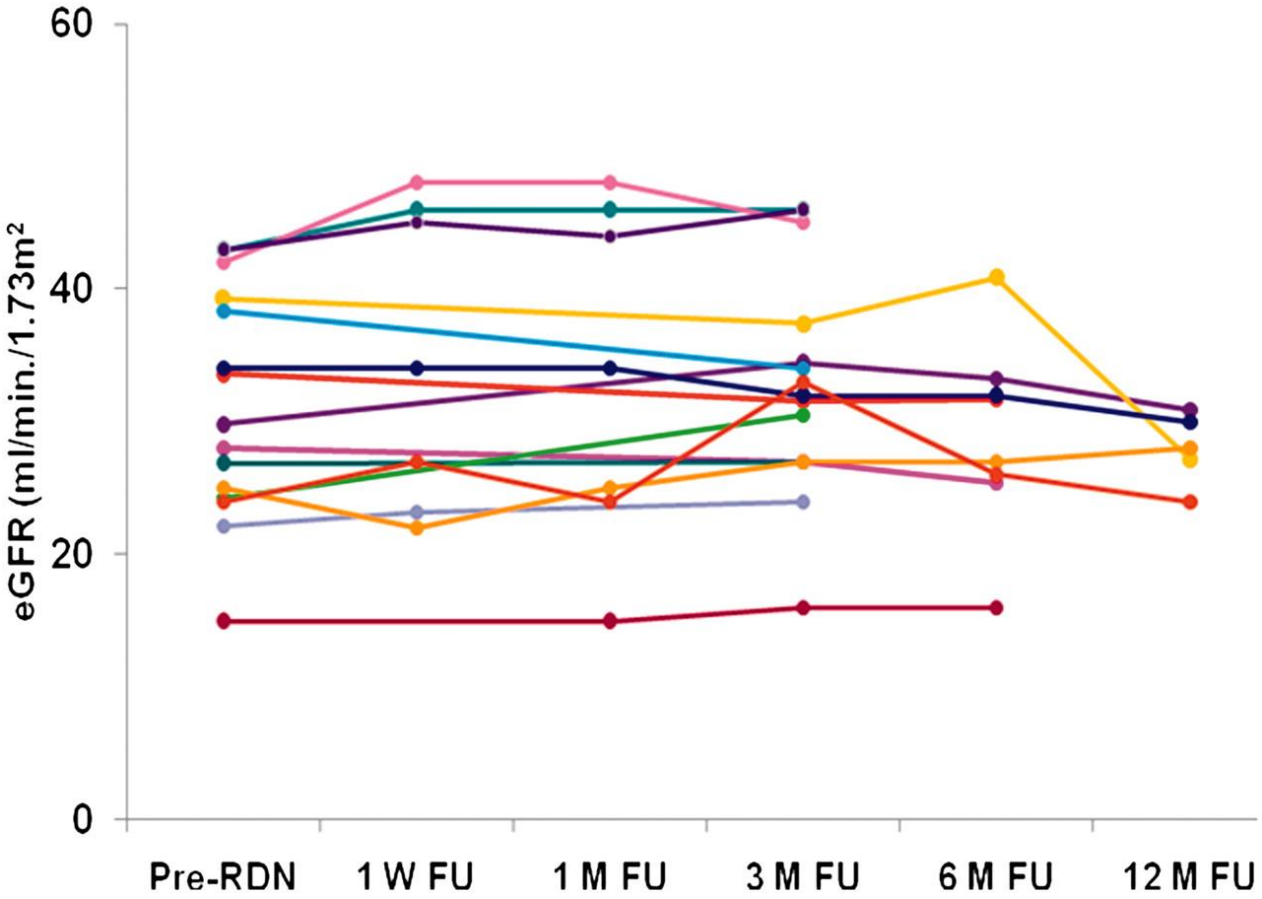
Recordings of sympathetic nerve discharge to the vasulature of the leg muscles in a normal subject and in two hemodialysis patients one with and one without bilateral nephrectomy



Hoye N.A. et al., Clin. Kidney J., 2014, 7, 3-10

RDN in patients with CKD 3-4 – a pilot study

- 15 patients, baseline: mean GFR 31 ± 9 ml/min/1.73 m^2



Hering D. et al., J. Am. Soc. Nephrol., 2012, 23, 1250-1257

RDN in patients with CKD 3-4 – a pilot study

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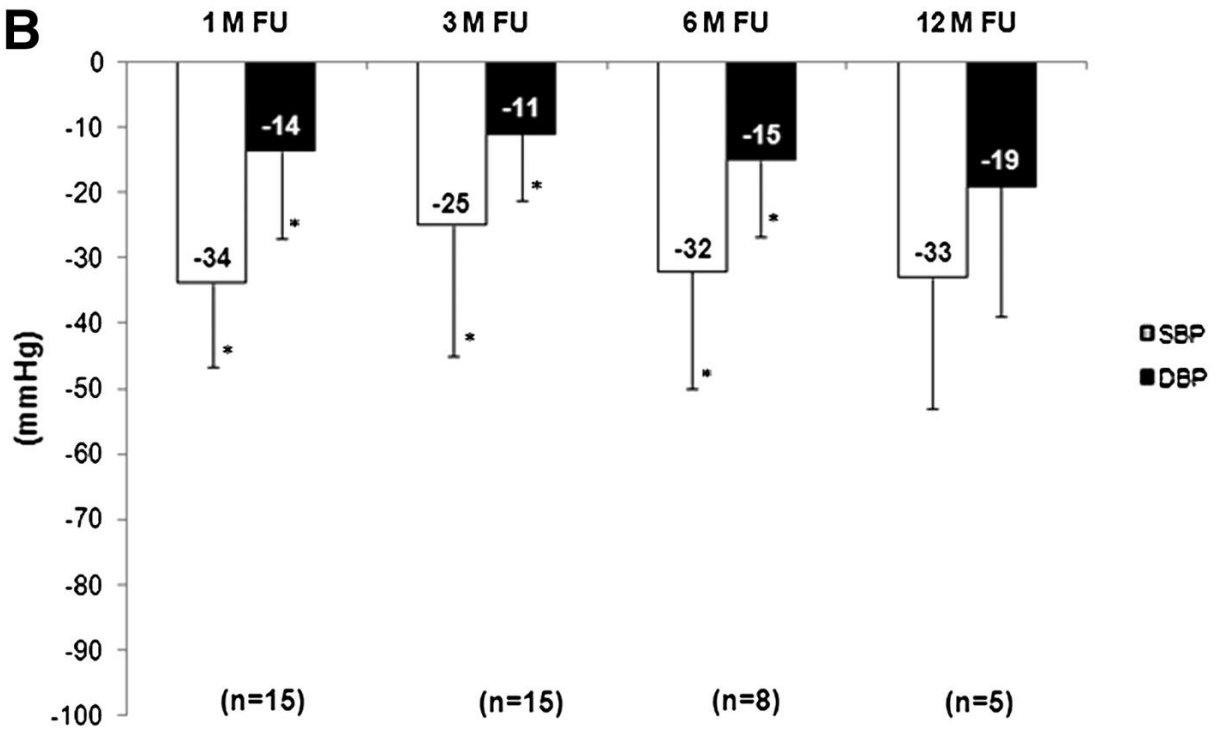
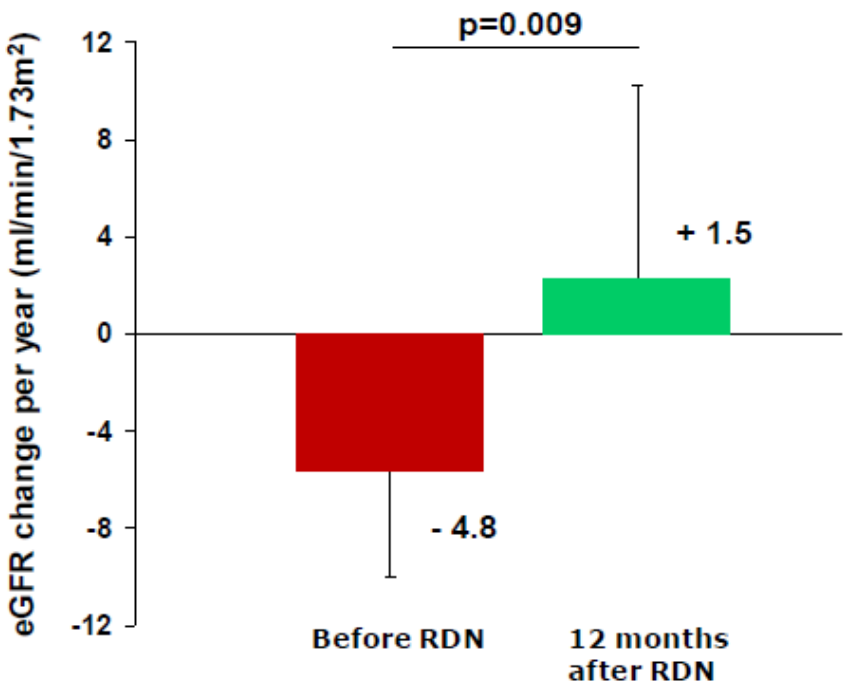


Hering D. et al., J. Am. Soc. Nephrol., 2012, 23, 1250-1257

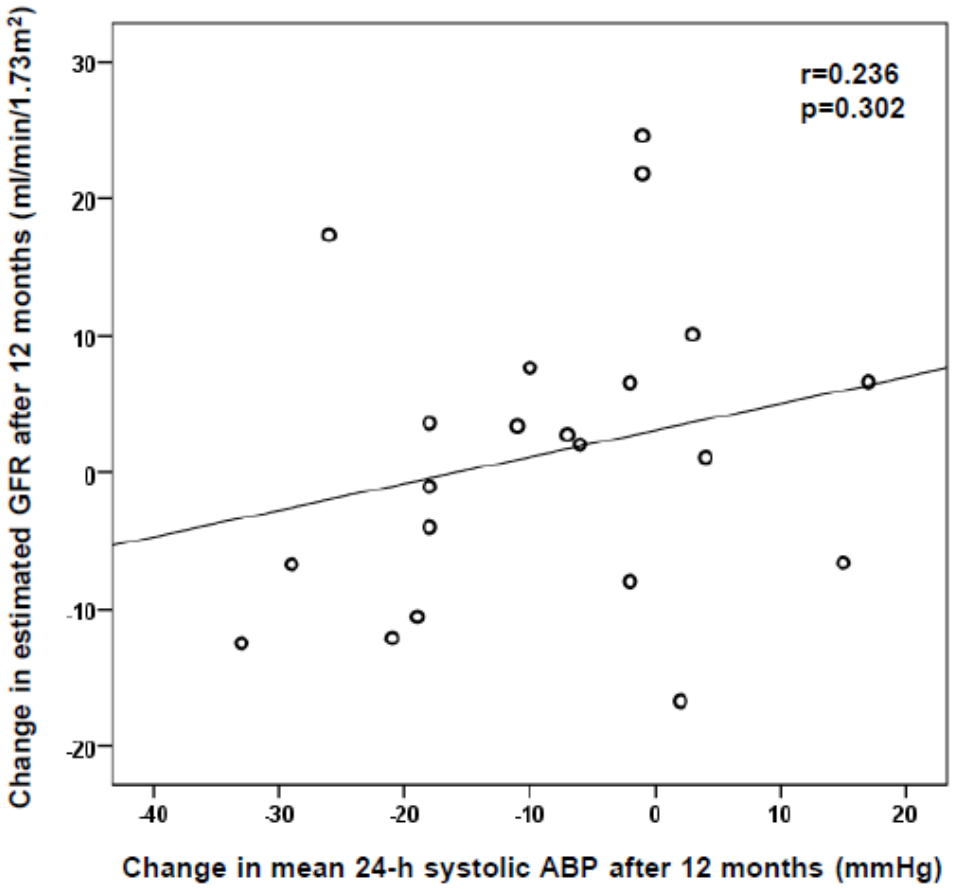
Renal Denervation: Response as judged by eGFR change per year



- On average mean eGFR decline before RDN was −4.8 ml/min/1.73 m^2 per year, which fits with the postulated decline of renal function (about −5 ml/min per year at MAP of 105 mmHg) based on a metaanalysis of long-term clinical trials (Bakris et al, Am J Kidney Dis 2000; 36:646-61).
- In contrast, eGFR remained stable (baseline: 48.5 12 vs. 1 year: 49.6 15 ml/min/1.73m^2), with a significance between eGFR change per year before vs. after RDN.
- **None of the patients developed a doubling of serum creatinine or required dialysis after RDN at any point of time.**

Schmieder RE, Ott C., EDA 2014

Change in eGFR per year after RDN is not clearly related to change in 24 h ABP



Schmieder RE, Ott C., EDTA 2014

Conclusion

1) Renal denervation reduced elevated the decline of renal function in treatment-resistant hypertensive patients with CKD stage 3 and4

2) The reduction of eGFR decline appeared to be related to
   # the decrease in blood pressure
   # Hawthorne effect (procedural effect)
   # improved adherence to medication

3) Decreased sympathetic activity to the kidneys may have played a role as well, but this cannot delineated from our trial

Schmieder RE, Ott C., EDTA 2014

ORIGINAL ARTICLE

Renal Denervation in a Hypertensive Patient With End-Stage Renal Disease and Small Arteries: A Direction for Future Research

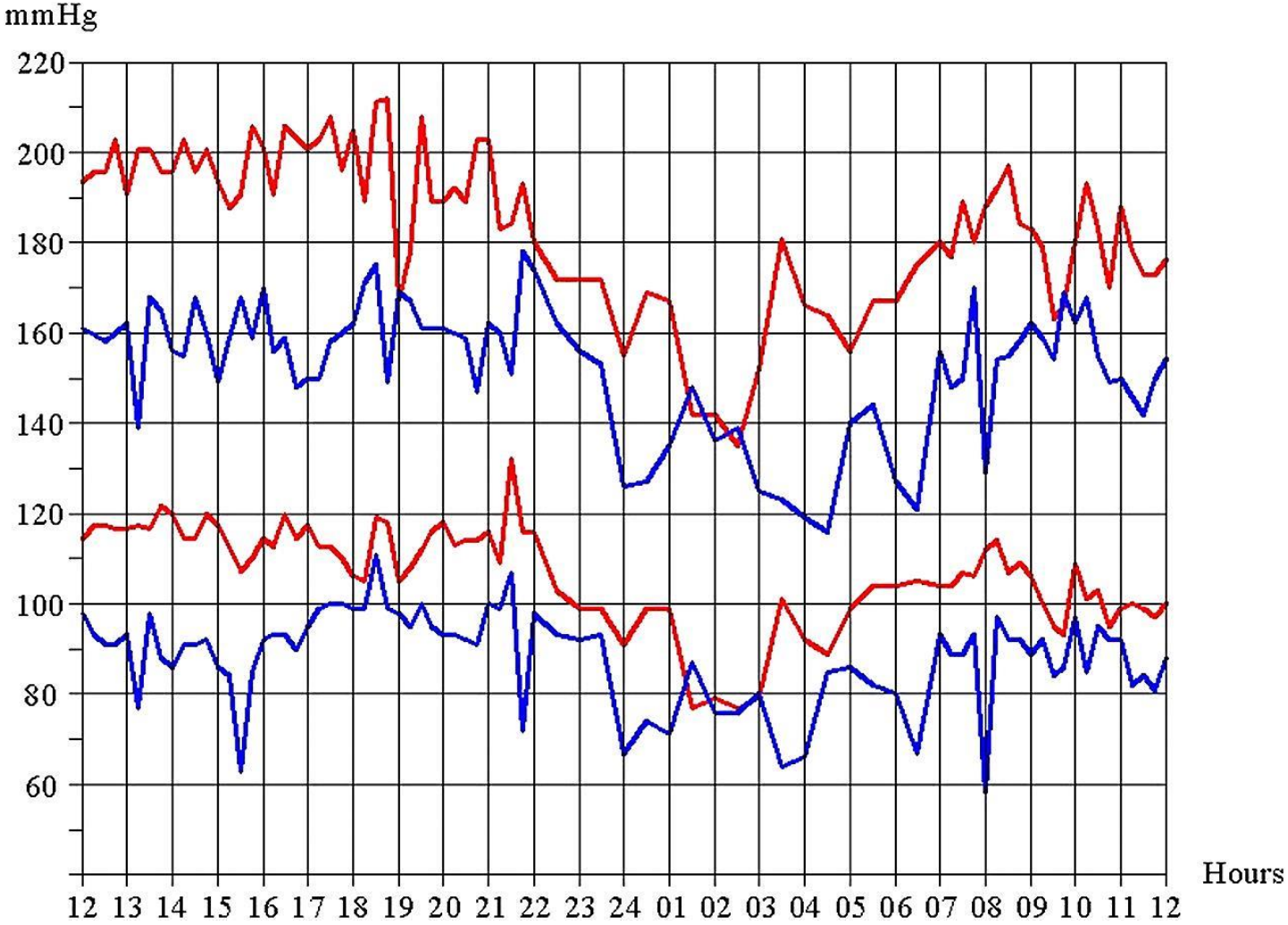
Christian Ott, MD;[1] Axel Schmid, MD;[2] Tilmann Ditting, MD;[1] Paul A. Sobotka, MD;[3,4] Roland Veelken, MD;[1] Michael Uder, MD;[2] and Roland E. Schmieder, MD[1]

From the Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany;[1] the Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany;[2] The Ohio State University, Columbus, OH;[3] and Coridea-NC1, New York, NY[4]

Sympathetic overactivity plays a crucial pathogenetic role in the maintenance and aggravation of arterial hypertension in patients with end-stage renal disease (ESRD). Renal denervation has been shown to be effective and safe in reducing blood pressure (BP) in patients with treatment-resistant hypertension; however, there are only case reports in hypertensive patients with ESRD and data are lacking about possibility of renal denervation in small renal arteries. A woman with uncontrolled treatment-resistant hypertension on chronic hemodialysis underwent bilateral native kidney, catheter-based renal denervation. Both native renal arteries were <4 mm. After 6 months without any change of antihypertensive medication or hemodialysis parameters, the authors observed a remarkable BP reduction of 38/30 mm Hg (from baseline 172/100 mm Hg to 134/70 mm Hg) as evaluated by 24-hour ambulatory BP monitoring. The authors report that renal denervation seems to be effective in controlling hypertension in patients with ESRD, even in cases of small renal arteries.
J Clin Hypertens (Greenwich). 2012;14:799–801. ©2012 Wiley Periodicals, Inc.

Ott. Chr. et al., J. Clin. Hypertens., 2012, 14, 799-801

Twenty-four-hour ambulatory blood pressure monitoring before and 1 month after the procedure in a hemodialysis patient



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Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease

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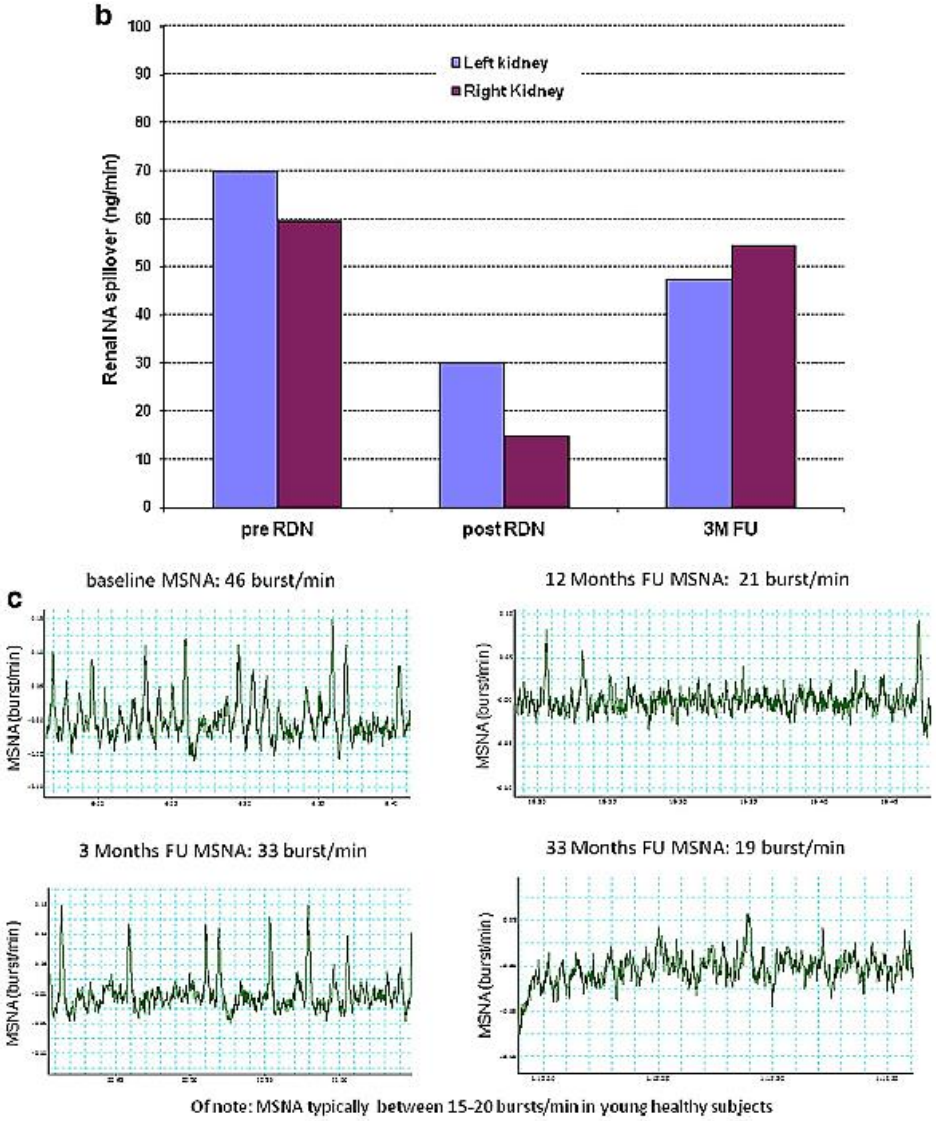
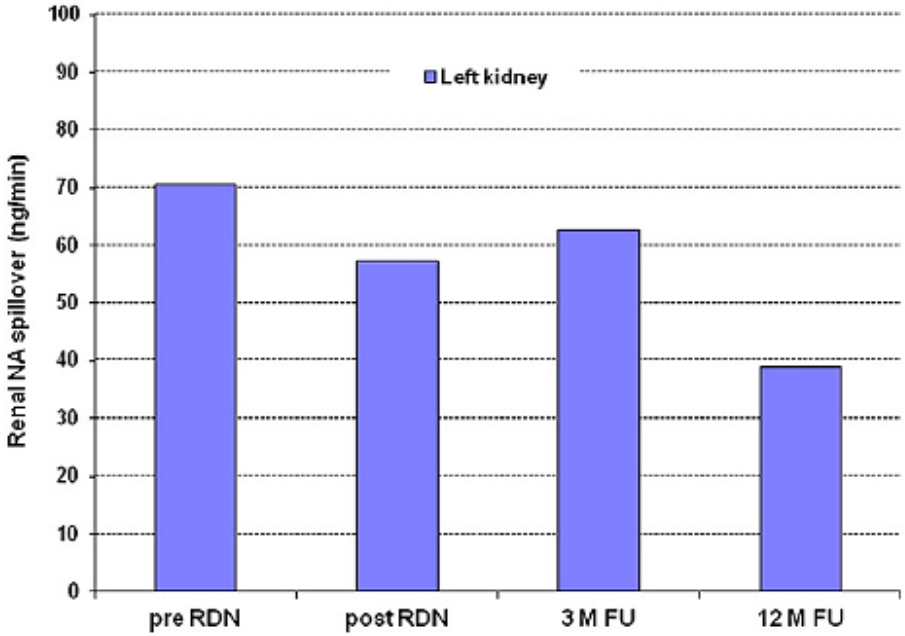
Feasibility of cathether –based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in 12 patients with ESDR





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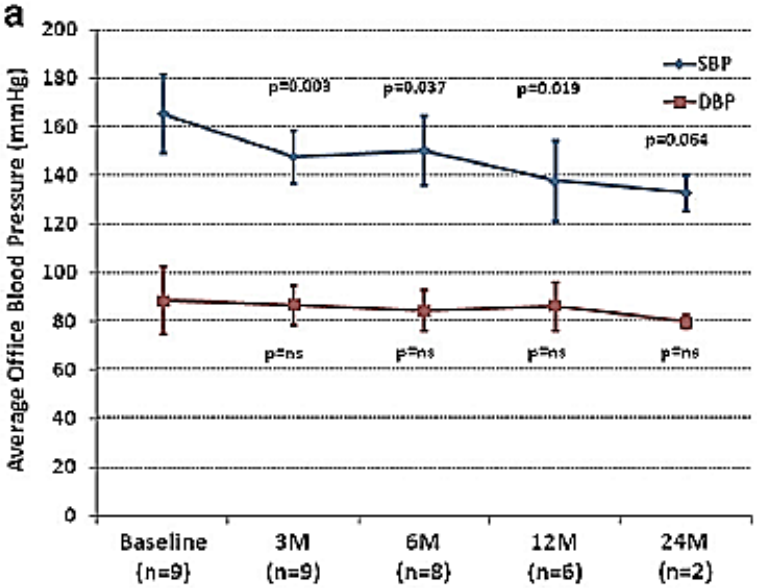
Feasibility of cathether - based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in 12 patients with ESDR



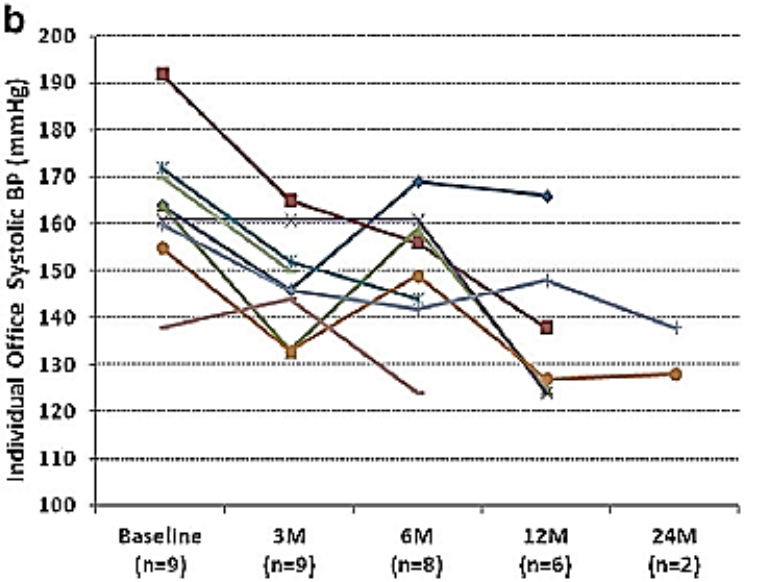


Table 2
Baseline clinical and biochemical parameters, indices of sympathetic activation, and antihypertensive medication of 5 patients who underwent assessment of sympathetic nervous system activation (mean ± SD); MSNA: muscle sympathetic nerve activity; NA: noradrenaline.

Age (years)	52.8 ± 10.5
Weight (kg)	66.0 ± 13.6
Height (cm)	163.0 ± 12.5
Office systolic BP (mm Hg)	174.6 ± 17.1
Office diastolic BP (mm Hg)	90.4 ± 4.3
ABPM 24 h (mm Hg) (n = 3)	163.7/88.7 ± 11.9/8.4
ABPM day (mm Hg) (n = 3)	160.7/89.3 ± 16.7/9.1
ABPM night (mm Hg) (n = 3)	170.3/87.3 ± 5.0/7.4
Heart rate (beats/min)	78.4 ± 10.8
Sodium (mmol/L)	140.2 ± 2.9
Potassium (mmol/L)	4.9 ± 0.6
Creatinine (μmol/L)	740.2 ± 117.5
Urea (mmol/L)	21.4 ± 4.4
Plasma glucose (mmol/L)	5.5 ± 1.4
MSNA (bursts/min)	50.8 ± 12.8
MSNA (burst/100 heatbeats)	69.4 ± 7.8
Whole body NA spillover (ng/min)	767.0 ± 199.8
Renal NA spillover (ng/min)	105.5 ± 20.9

Schlaich M. et al., Int.J. Cardiol. 2013

Renal denervation in kidney transplant patient

Successful Renal Artery Denervation in a Renal Transplant Recipient With Refractory Hypertension

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Keywords: blood pressure; hypertension; renal denervation; transplant recipient.

doi:10.1093/ajh/hpt291

Arterial hypertension in renal transplant recipients is the main risk factor of cardiovascular diseases, which remain the primary cause of death in patients with a functioning renal graft.[1,2] The risk of cardiovascular death is four times higher in patients with kidney transplants compared with the general population.[3] In renal transplant recipients, a 10-mm Hg rise in systolic blood pressure increases the risks of death by 18% and increases the risk of graft failure by 17%.[4] The existing literature indicates that 70%–90% to smooth muscle contraction and a subsequent rise in sodium tubular absorption.

Excessive adrenergic activity in renal transplant recipients is a primary pathogenic mechanism in the development of arterial hypertension and organ complications. Therefore, we performed percutaneous denervation of native kidney arteries to treat resistant arterial hypertension in a renal transplant patient. To the best of our knowledge, this treatment has not been previously performed in this type of patient.

Protasiewicz M. et al. Am. J. Hypertens, 2014, advanced access

Renal denervation in transplant patient with resistant hypertension

In summary, we described the case of a renal transplant recipient who underwent safe denervation of the native renal arteries. The procedure successfully lowered arterial blood pressure. However, the procedure's efficacy in such a specific and diverse group of patients requires further study. The assessment of native renal artery morphology and illness duration and etiology are of great importance prior to renal denervation in transplant patients.

Protasiewicz M. et al. Am. J. Hypertens, 2014, advanced access

Conclusions (1)

- Sympathetic denervation is safe and effective in the treatment of resistant hypertension (up to 36 moths)
- New RCT did not confirm the spectacular clinical benefit in terms of BP reduction as was observed in the previous studies
- Sympathetic denervation may improve cardiac function, glucose metabolism and improve symptoms of sleep apnea syndrome, exercise capacity in heart failure, atrial fibrilation

Conclusions (2)

- Sympathetic denervation seems to preserve the decline of renal function in patients with CKD and the results in experimental models of CKD are very promissing

- Longer observation and larger cohorts of patients are still needed - especially for assessment of the effect of RDN on morbidity (e.g. kidney function) and mortality

Personal vision for the future of renal denervation

- Better patients selection - based on the knowledge of pathophysiology of RH, including patients with:
  - CKD (inc. ESKD and transplant patients)
  - heart failure
  - obesity/metabolic syndrome, diabetes mellitus t.2
  - kidney pain syndrome: PKD/ loin pain hematuria
  - atrial fibrilation

- Better device technology (more effective denervation procedure)

- Variable to quatify the intervention itself are mandatory

Thank you very much for your attention !

Andrzej Wiecek

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Poland