
Denervaciòn Renal
ARTURO GARCIA TOUCHARD

AHA Scientific Statement

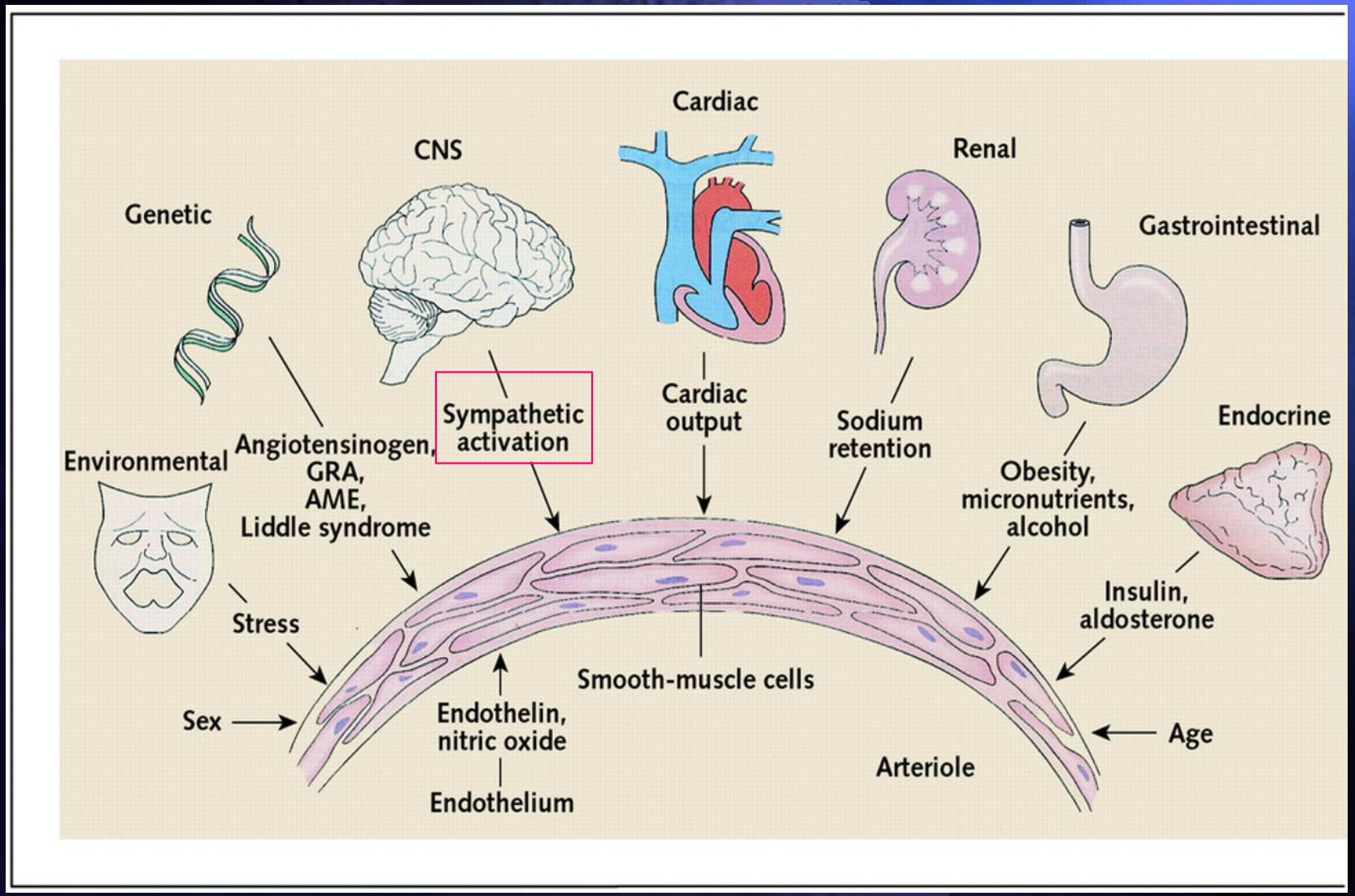
Resistant Hypertension: Diagnosis, Evaluation, and Treatment

A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research

David A. Calhoun, MD, FAHA, Chair; Daniel Jones, MD, FAHA; Stephen Textor, MD, FAHA; David C. Goff, MD, FAHA; Timothy P. Murphy, MD, FAHA; Robert D. Toto, MD, FAHA; Anthony White, PhD; William C. Cushman, MD, FAHA; William White, MD; Domenic Sica, MD, FAHA; Keith Ferdinand, MD; Thomas D. Giles, MD; Bonita Falkner, MD, FAHA; Robert M. Carey, MD, MACP, FAHA

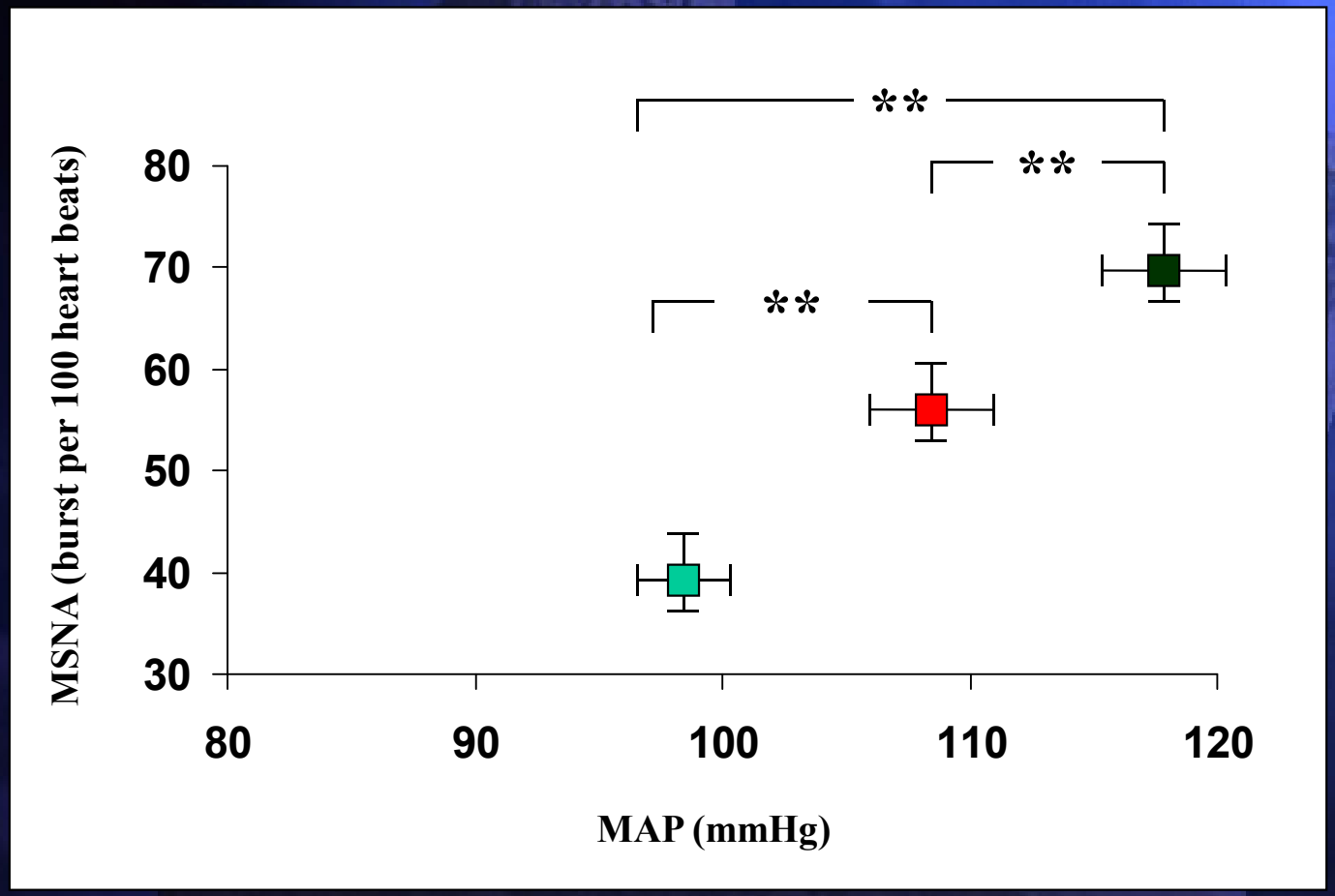
Abstract—Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants. As older age and obesity are 2 of the strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and heavier. The prognosis of resistant hypertension is unknown, but cardiovascular risk is undoubtedly increased as patients often have a history of long-standing, severe hypertension complicated by multiple other cardiovascular risk factors such as obesity, sleep apnea, diabetes, and chronic kidney disease. The diagnosis of resistant hypertension requires use of good blood pressure technique to confirm persistently elevated blood pressure levels. Pseudoresistance, including lack of blood pressure control secondary to poor medication adherence or white coat hypertension, must be excluded. Resistant hypertension is almost always multifactorial in etiology. Successful treatment requires identification and reversal of lifestyle factors contributing to treatment resistance; diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multidrug regimens. As a subgroup, patients with resistant hypertension have not been widely studied. Observational assessments have allowed for identification of demographic and lifestyle characteristics associated with resistant hypertension, and the role of secondary causes of hypertension in promoting treatment resistance is well documented; however, identification of broader mechanisms of treatment resistance is lacking. In particular, attempts to elucidate potential genetic causes of resistant hypertension have been limited. Recommendations for the pharmacological treatment of resistant hypertension remain largely empiric due to the lack of systematic assessments of 3 or 4 drug combinations. Studies of resistant hypertension are limited by the high cardiovascular risk of patients within this subgroup, which generally precludes safe withdrawal of medications; the presence of multiple disease processes (eg, sleep apnea, diabetes, chronic kidney disease, atherosclerotic disease) and their associated medical therapies, which confound interpretation of study results; and the difficulty in enrolling large numbers of study participants. Expanding our understanding of the causes of resistant hypertension and thereby potentially allowing for more effective prevention and/or treatment will be essential to improve the long-term clinical management of this disorder. (*Hypertension.* 2008;51:1403-1419.)

Pathophysiological Mechanism of Hypertention



Oparil S. et al.; Ann Intern Med 2003

Muscle Sympathetic Nerve Activity

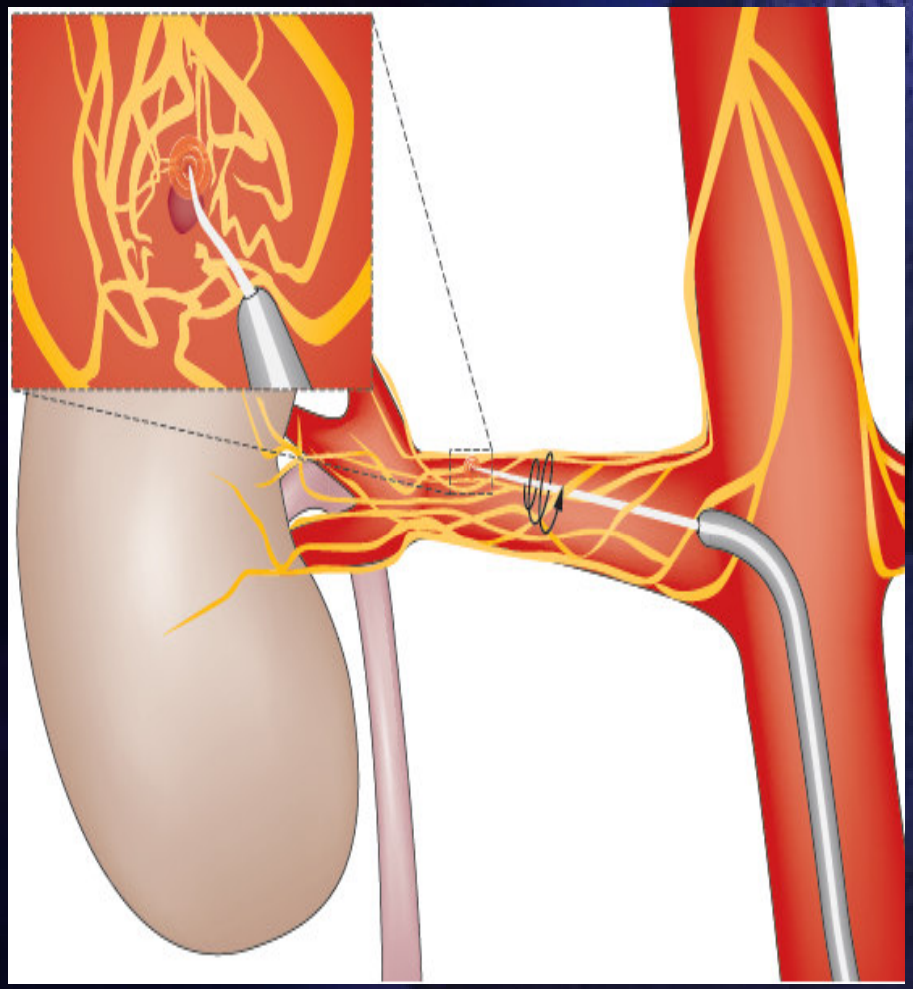


Progressive increase in muscle sympathetic nerve activity in normotensive control subjects (light green square), mild-to-moderate (red square) and more severe essential hypertensive patients (dark green square)

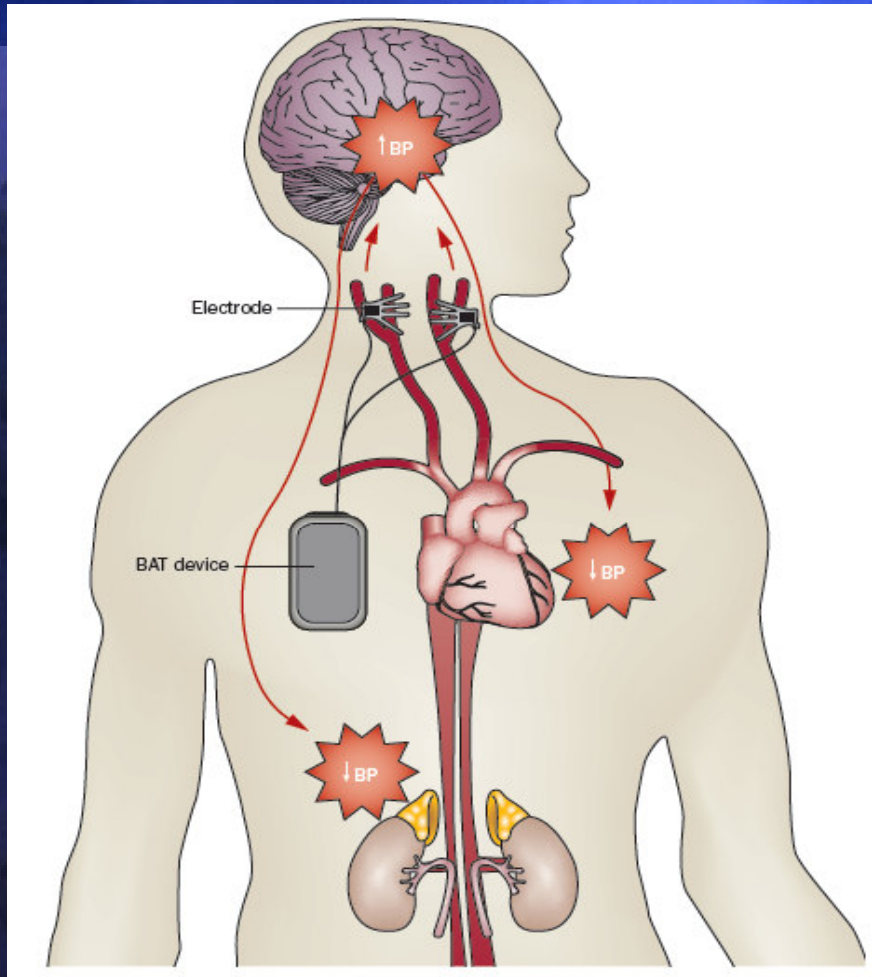
** $P < 0.01$ between groups.

Grassi G. et al.; Exp Physiol 2009

Device-based approaches to the treatment of Resistant Hypertension

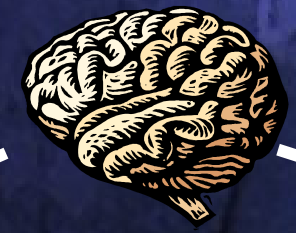


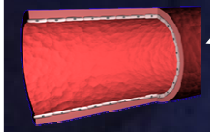
Renal Sympathetic Denervation



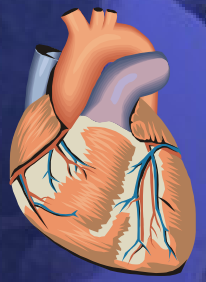
Baroreflex Activation Therapy
(Rheos carotid sinus stimulator)

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





- Vasoconstriction
- Atherosclerosis
- Insulin resistance

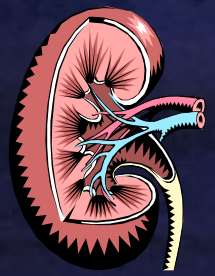


- ↑ Contractility
- ↑ Heart rate
- Hypertrophy
- Arrhythmia
- Heart Failure

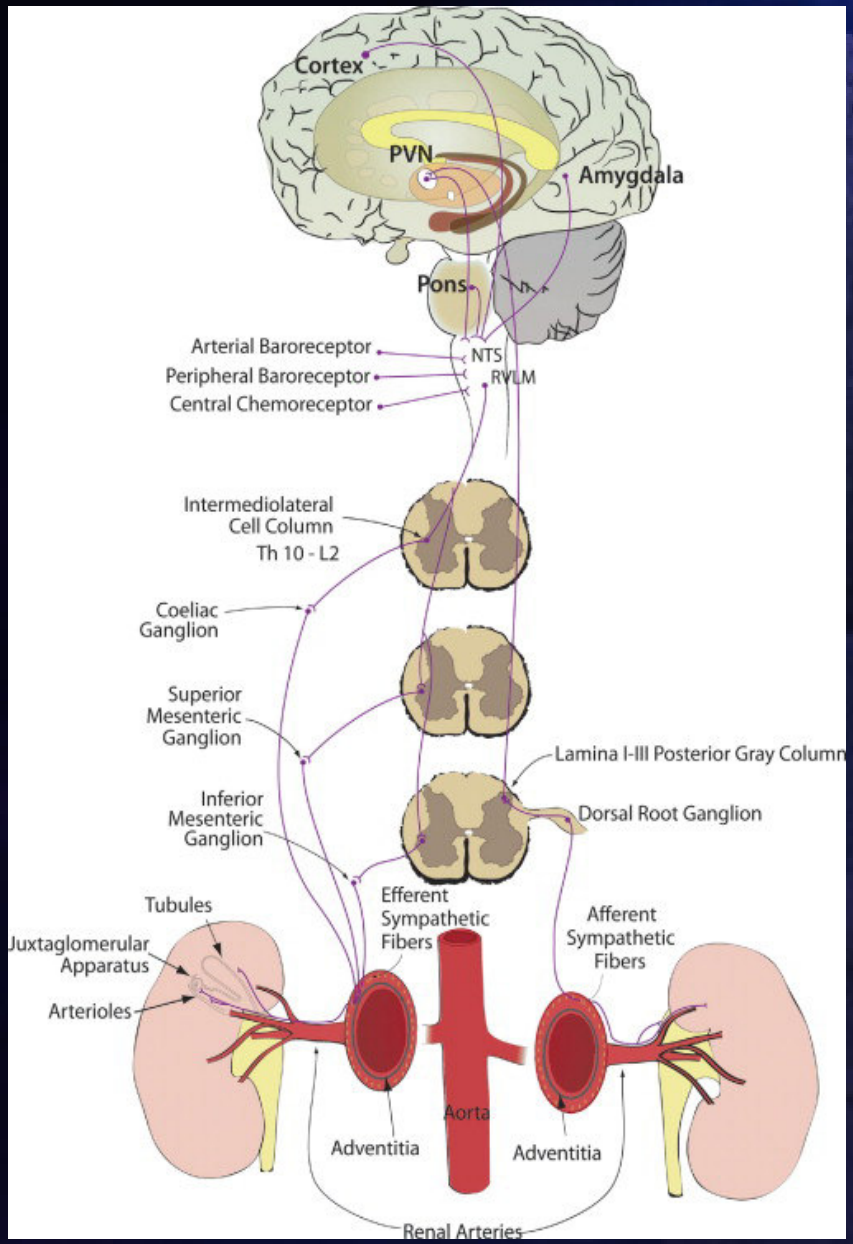
Efferent Nerves

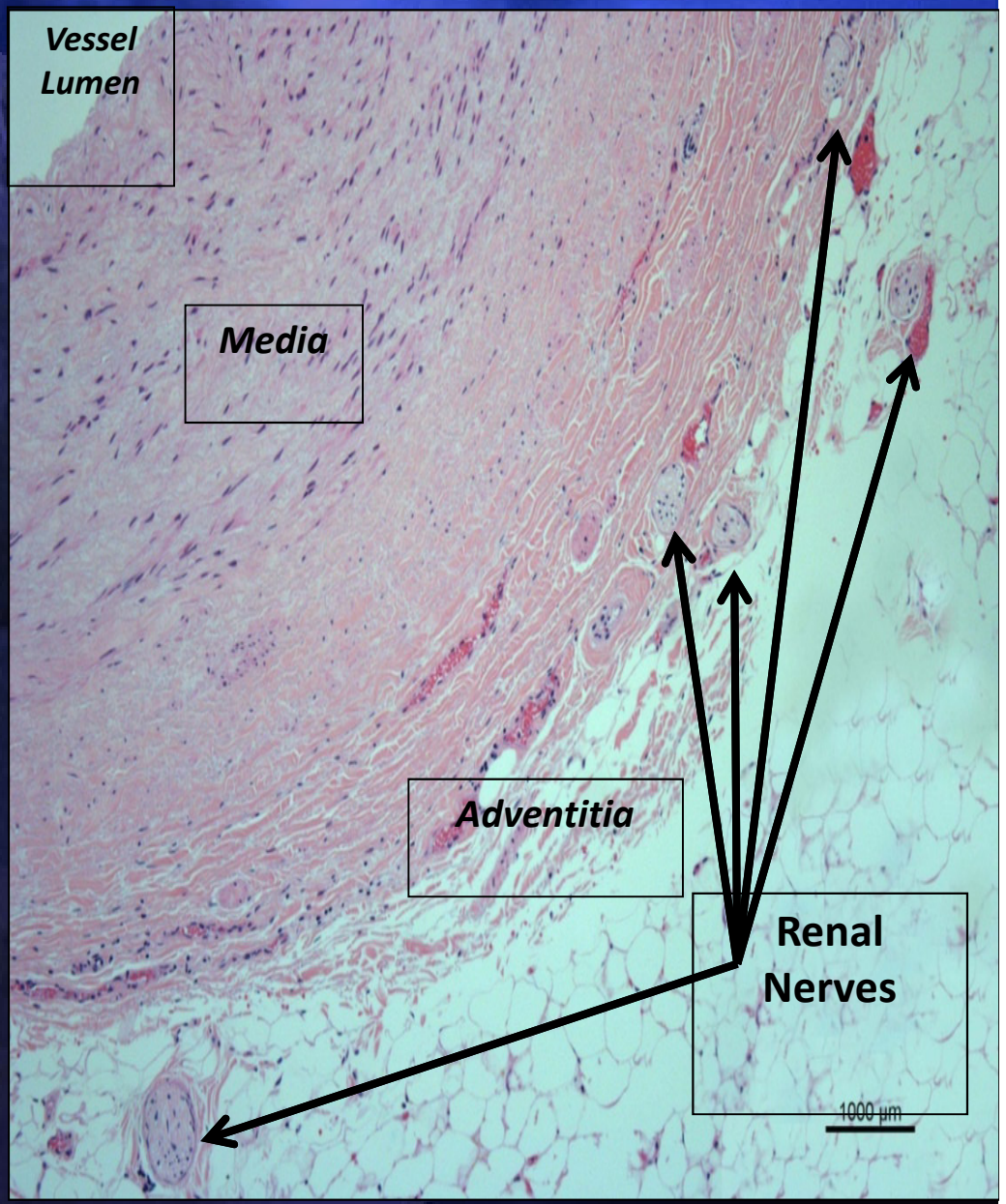
Afferent Nerves

Blood Pressure



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


Cortex
PVN
Amygdala
Pons
Arterial Baroreceptor
Peripheral Baroreceptor
Central Chemoreceptor
NTS
RVLM
Intermediolateral Cell Column
Th 10 - L2
Coeliac Ganglion
Superior Mesenteric Ganglion
Inferior Mesenteric Ganglion
Lamina I-III Posterior Gray Column
Dorsal Root Ganglion
Tubules
Juxtaglomerular Apparatus
Arterioles
Efferent Sympathetic Fibers
Afferent Sympathetic Fibers
Aorta
Adventitia
Adventitia
Renal Arteries


Vessel Lumen
Media
Adventitia
Renal Nerves
1000 µm

Renal Nerve Ablation Devices

Radiofrequency Ablation

- Medtronic Semplicity
- St. Jude EnligHTN
- Convidien One Shot system
- Vessix Vascular V2 system

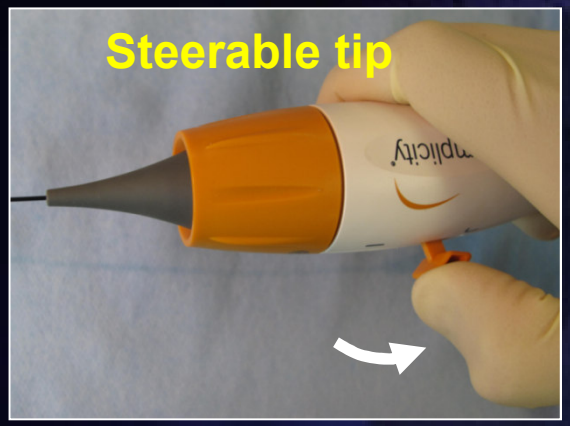
Ultrasound

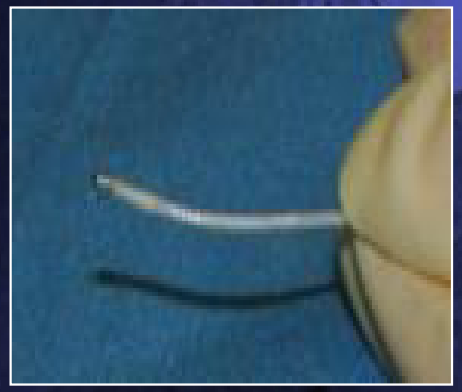
- ReCor Medical Paradise
- Kona Medical

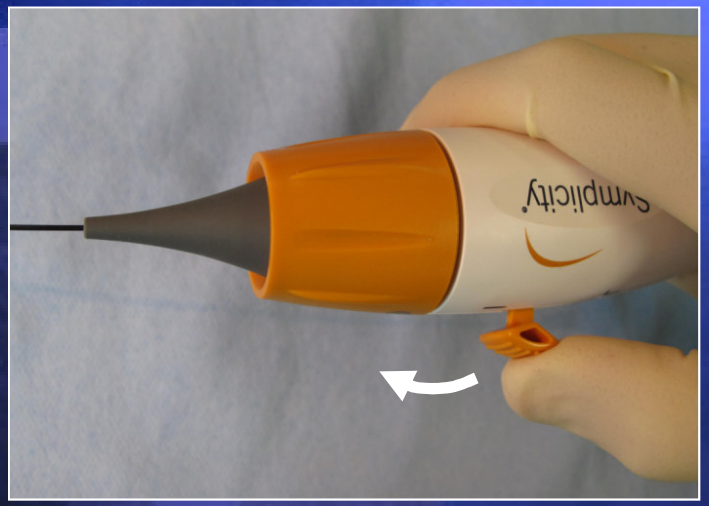
Chemical Ablation (Guanethedine,Ethanol, Botox B, Vincristine)

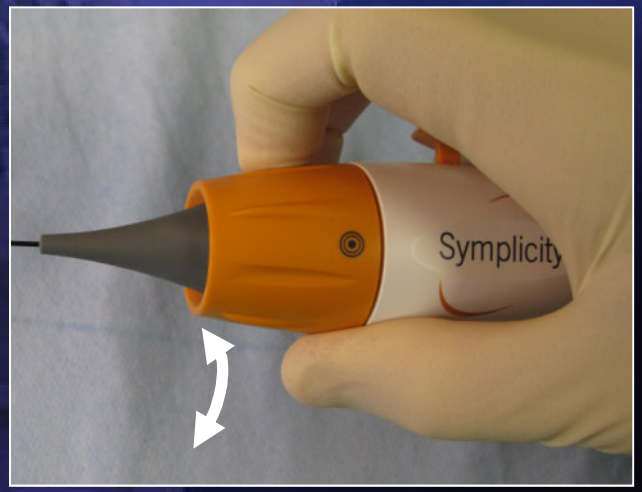
- Mercator MedSystems

Symplicity Catheter System (Medtronic)



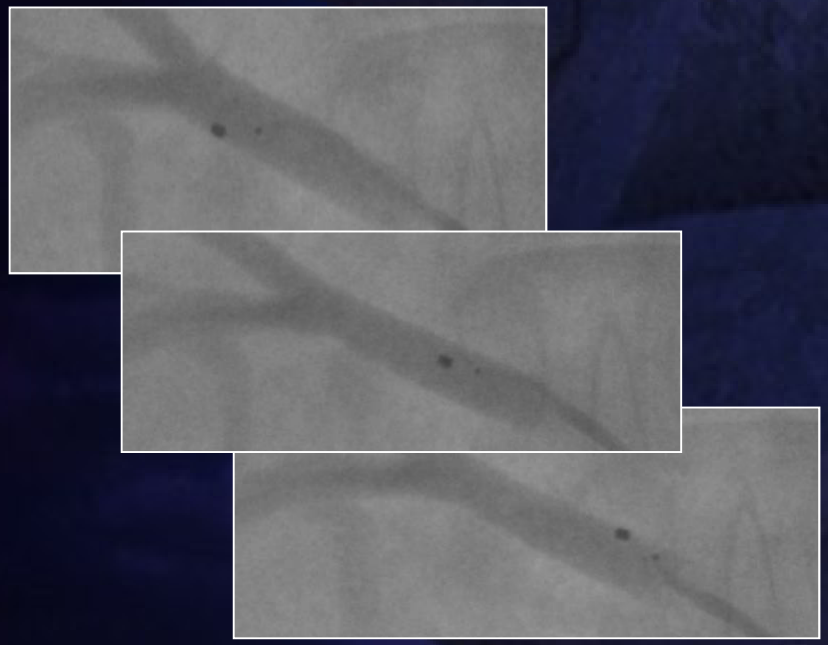


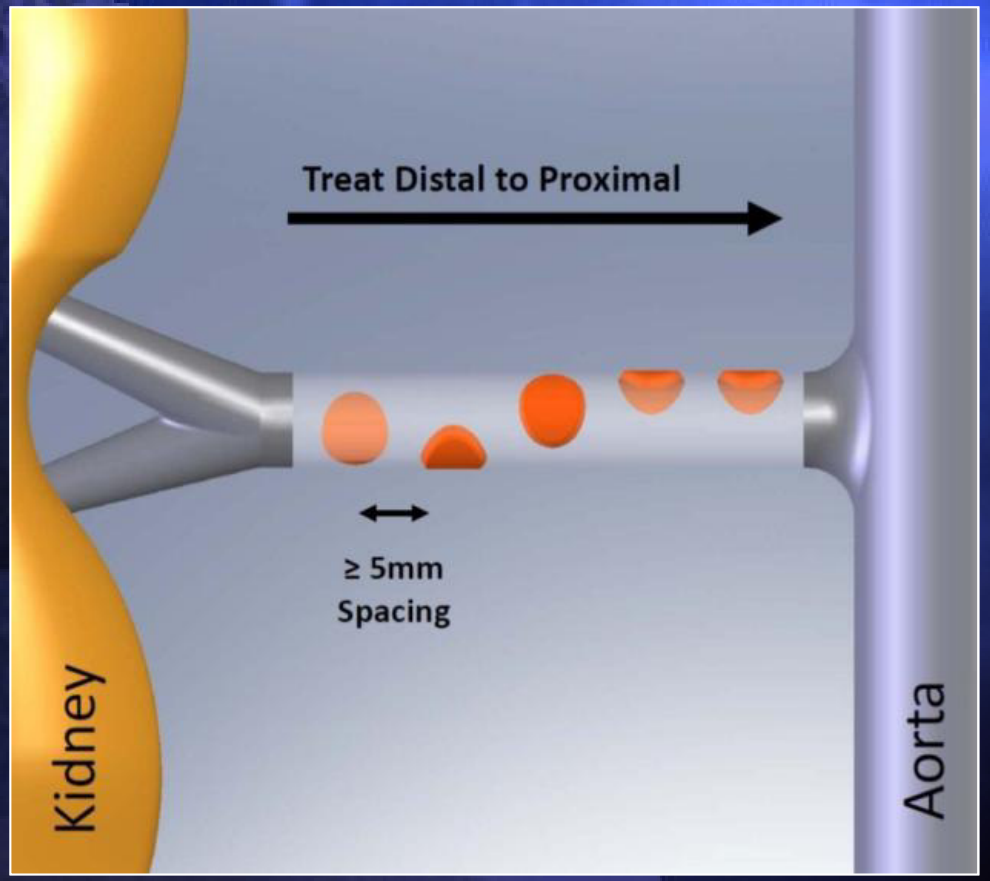


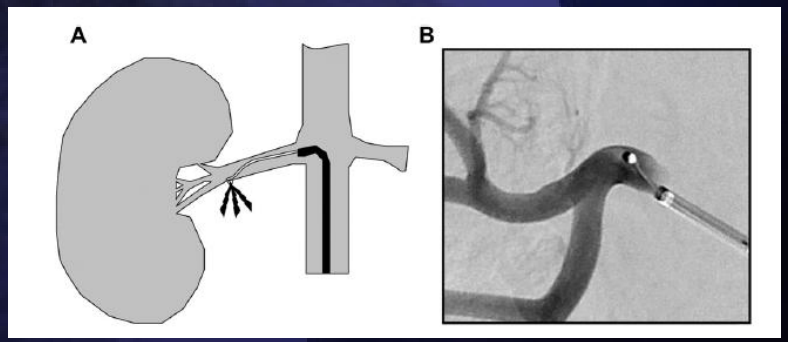


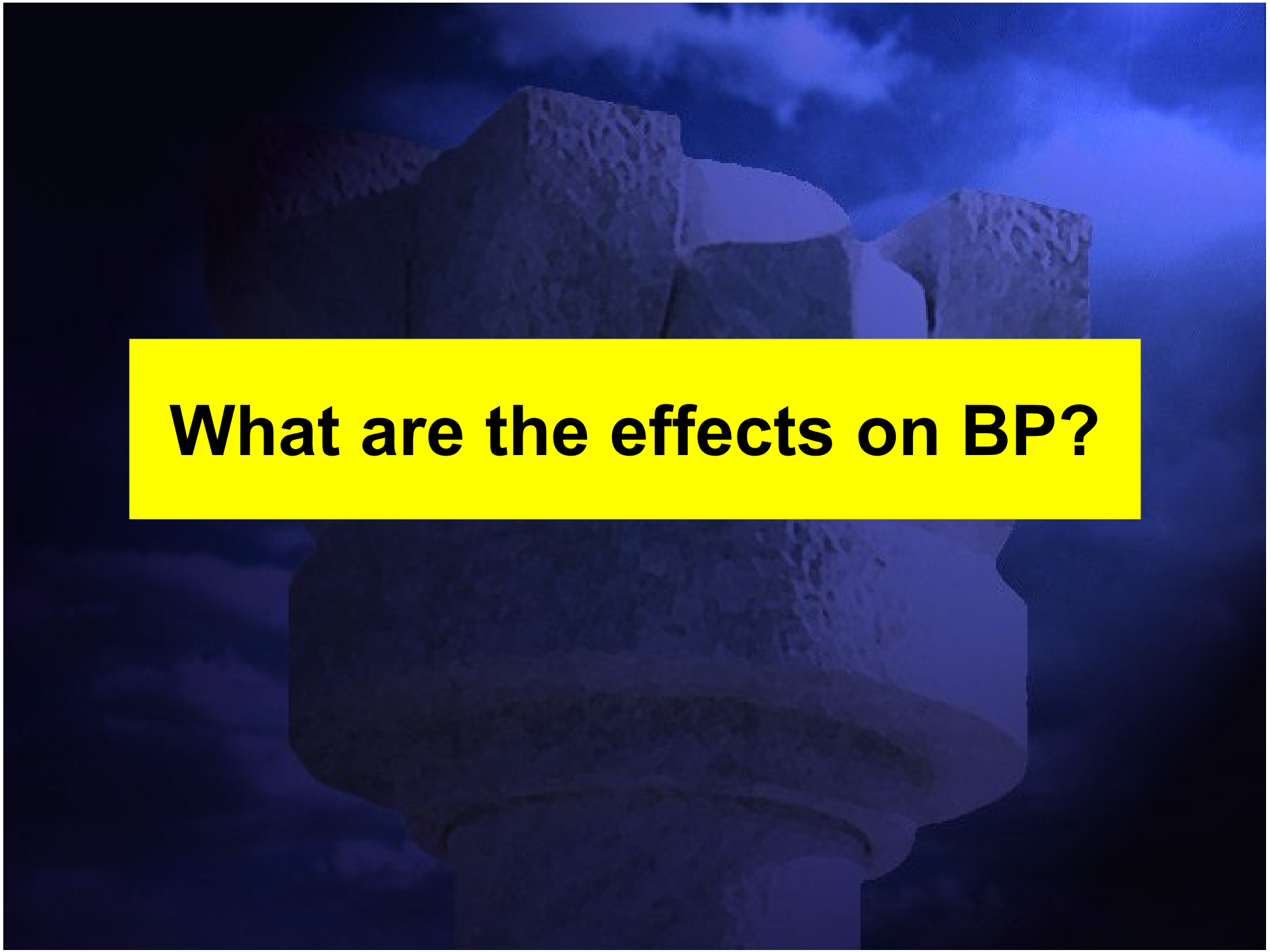
Technique of treatment

- From distal to proximal
- 4-6 ablation spots
  - 2 min for each spot
  - ≥ 5 mm of distance








What are the effects on BP?

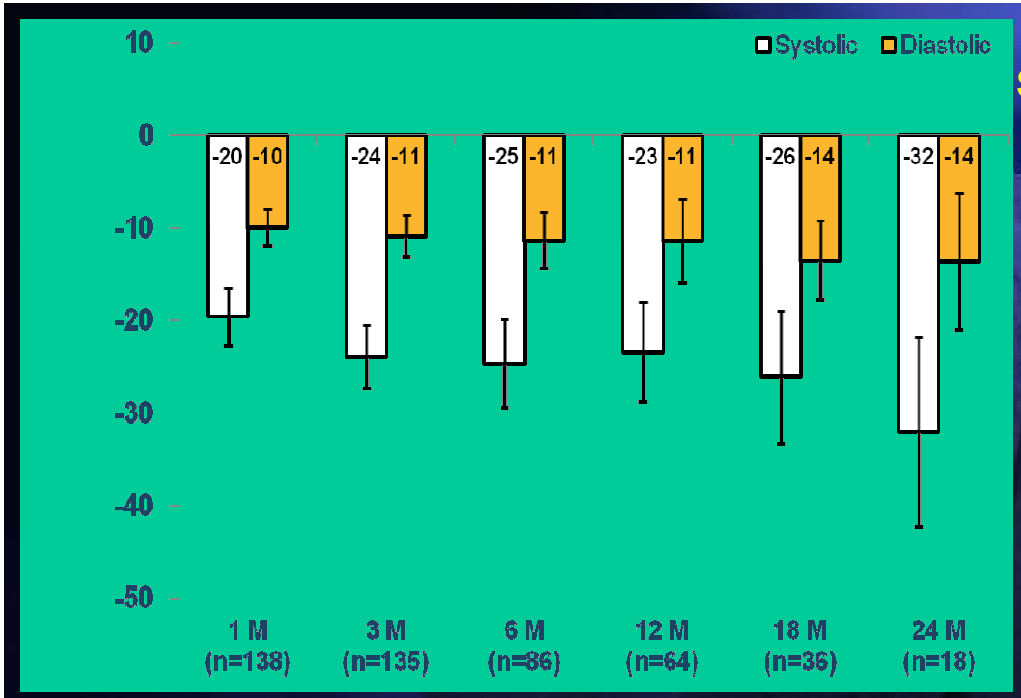
Details of the five CE-marked renal denervation devices

Catheter system	French	Energy	Electrodes/ polarity	Design	Patients[a]	Longest follow-up[a]	BP changes at 6 months (mmHg)[a]	BP changes at longest follow-up (index a)
Symplicity	6F	RF	1 unipolar	Single-tip	235	36 months ($n = 34$)	$-32/-12$ ($n = 49$)	$-33/-16$ ($n = 34$)
EnligHTN	8F	RF	4 unipolar	Basket	46	6 months ($n = 45$)	$-26/-10$ ($n = 45$)	$-26/-10$ ($n = 45$)
Vessix V2	8F	RF	4–8 bipolar	Over-the-wire balloon	10	1 month ($n = 10$)		$-30/-10$ ($n = 10$)
OneShot	7/8F	RF	1 unipolar	helical, irrigated balloon	9	1 month ($n = 9$)		$-31/-6$ ($n = 9$)
Paradise	7/8F	Ultrasound	1 transducer	fluid-filled balloon	15	12 months ($n = 3$)	$-32/-17$ ($n = 11$)	$-25/-13$ ($n = 3$)

F, French; BP, blood pressure; RF, radiofrequency.
[a]Data are referring to manuscript published or orally presented.
[b]Hoppe UC, oral presentation during EuroPCR 2012, Paris, France.

Average BP reduction : -29/-11 mmHg

ESC Expert Consensus:European Heart Journal 2013



Symplicity HTN-1 Investigators: Hypertension 2011

Reduction PAS ≥ 10 mmHg:

(Mean baseline BP: 176/98±17/14 mmHg)

Responders: 92%

Non-responders: 8%

Reduction PAS ≥ 10 mmHg:

(Mean baseline BP: 178/97±18/16 mmHg)

Responders: 84%

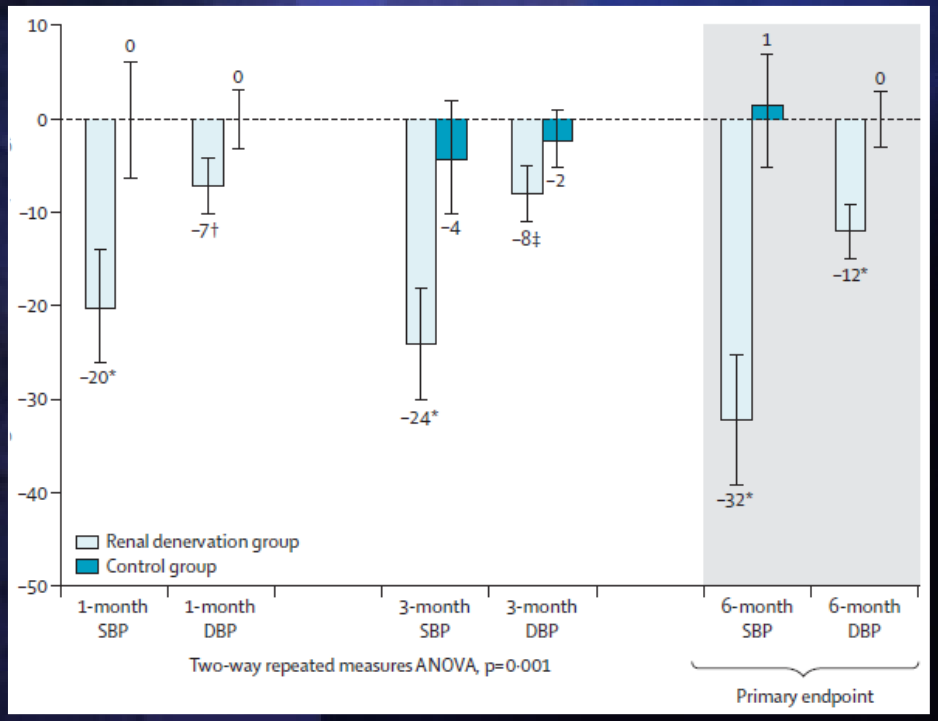
Non-responders: 16%

THE LANCET

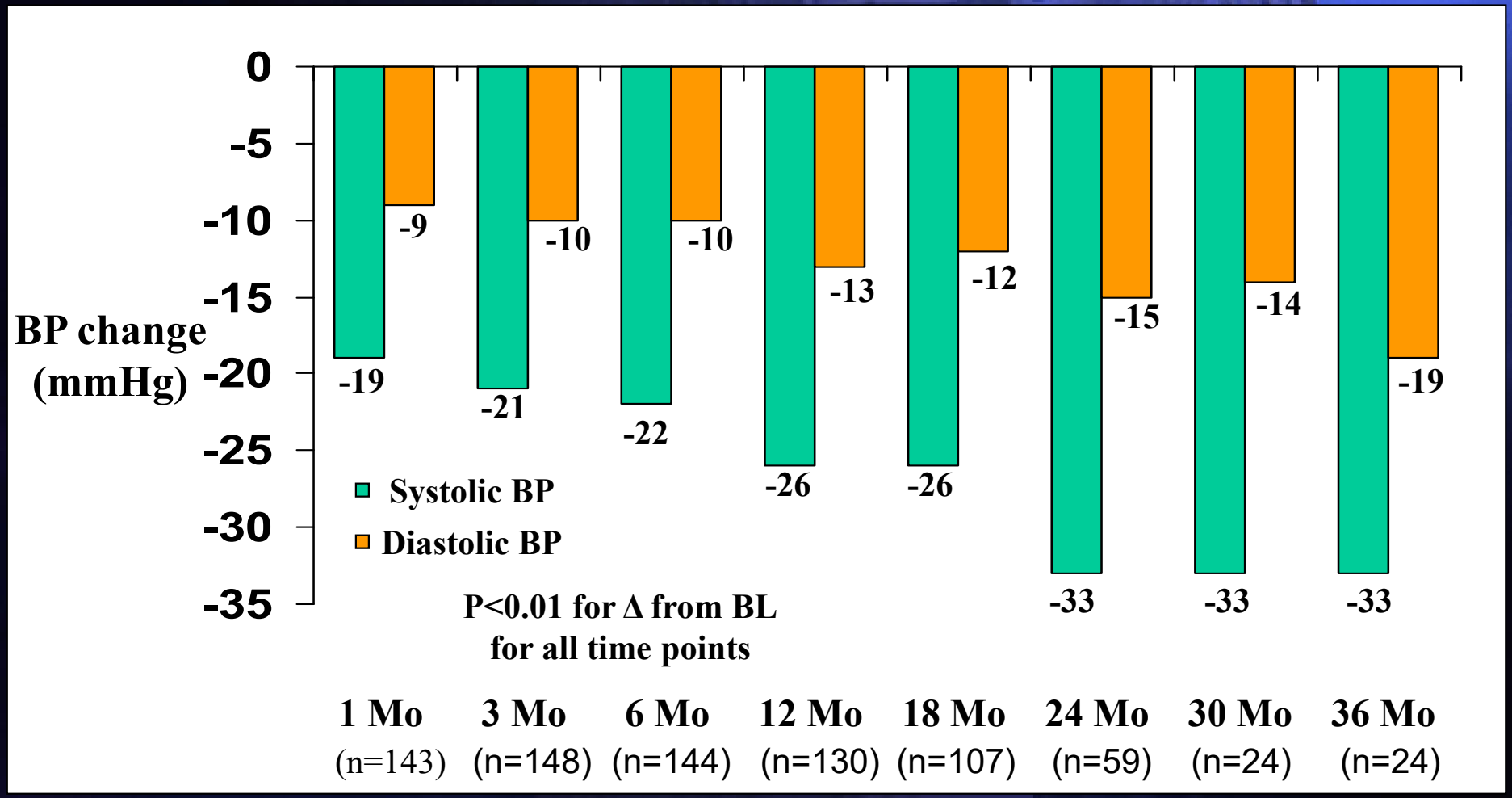
Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators*

Lancet. 2010. published electronically on November 17, 2010



Symplicity HTN-1: Reduction through 3 years



Krum H. : American College of Cardiology Annual Meeting 2012

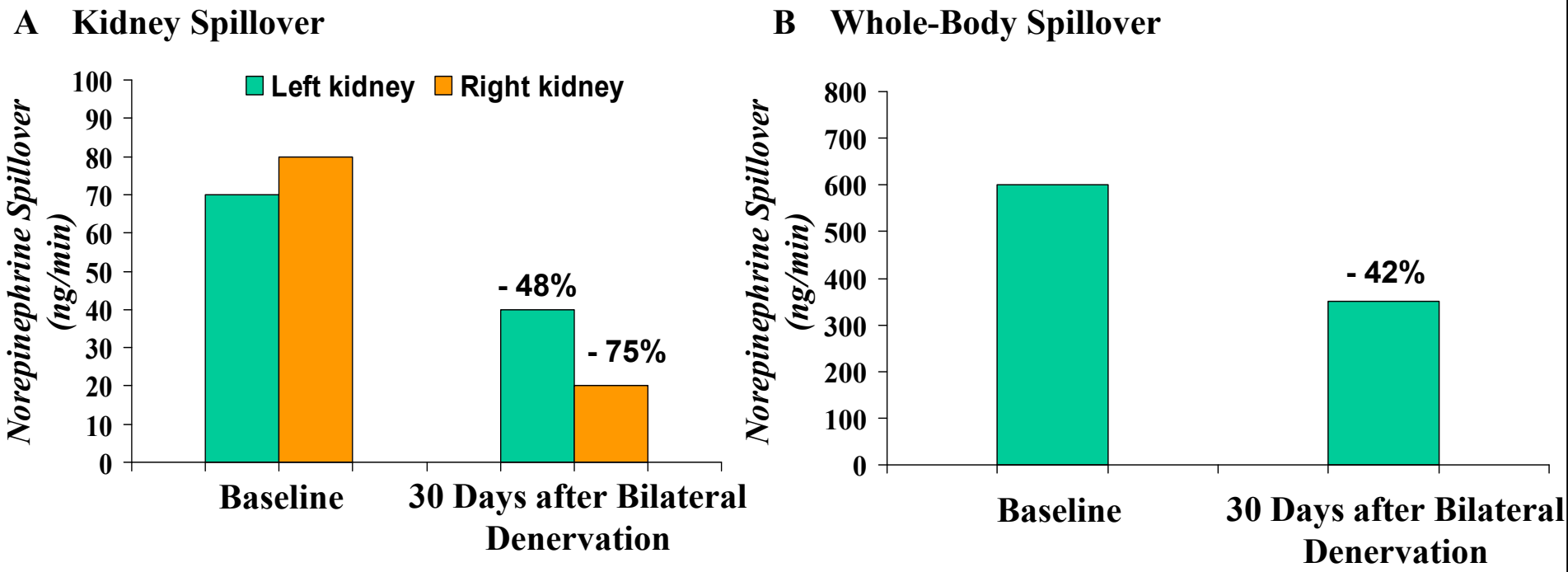
The Symplicity HTN-2 Trial: MEDICATION CHANGES

	RDN (n=49)	Control (n=51)	P-value
Med Dose Decrease (%)	10 (20%)	3 (6%)	0.04
Med Dose Increase (%)	4 (8%)	6 (12%)	0.74

Symplicity HTN-2 Investigators: Lancet 2010


Does RDN reduce Sympathetic tone?

Direct Measurement of Reduced Sympathetic Nerve Activity

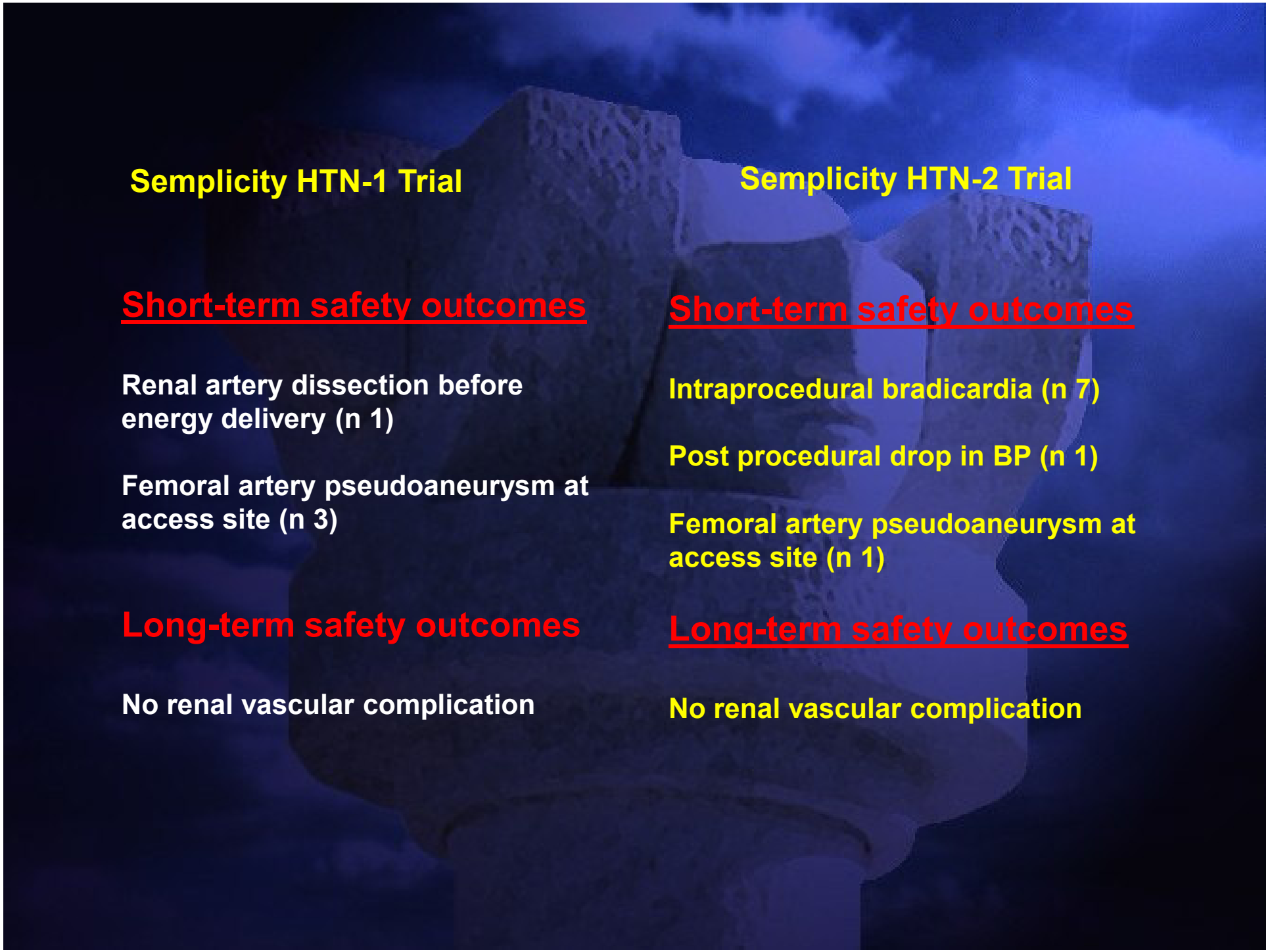


161/107 mmHg (baseline) 141/90 mmHg (30 days after RDN)

Mean Systolic/Diastolic Office BP

Schlaich MP et al.; NEJM 2009


What are the risks?


Semplicity HTN-1 Trial
Short-term safety outcomes
Renal artery dissection before energy delivery (n 1)
Femoral artery pseudoaneurysm at access site (n 3)
Long-term safety outcomes
No renal vascular complication
Semplicity HTN-2 Trial
Short-term safety outcomes
Intraprocedural bradicardia (n 7)
Post procedural drop in BP (n 1)
Femoral artery pseudoaneurysm at access site (n 1)
Long-term safety outcomes
No renal vascular complication

Research Correspondence

Renal Artery Stenosis After Renal Sympathetic Denervation

After 5 months, due to recurrent hypertension, renal angiography was performed demonstrating an 80% ostial and 70% mid-segment right main renal artery stenosis and a mid 50% stenosis in the right upper pole accessory renal artery

Kaltenbach B. et al.: JACC 2012

Case Report

Secondary rise in blood pressure after renal denervation

Oliver Vonend, Gerald Antoch, Lars Christian Rump, Dirk Blondin

After six months increse of BP . Renal Angiography showed a 75% stenosis near the ostium of the right renal artery

Lancet 2012

Morphological assessment of renal arteries after radiofrequency catheter-based sympathetic denervation in a porcine model

Kristin Steigerwald[a], Anna Titova[a], Caroline Malle[a], Elisabeth Kennerknecht[a], Clemens Jilek[a], Jörg Hausleiter[a], Jörg M. Nährig[b], Karl-Ludwig Laugwitz[a], and Michael JONER[a]

- Local loss of the endotelial monolayer as acute phase
- Acute edematous cellular swelling and connective tissue coagulation within the medial and adventitial layer
- Subacute reduction in nerve fascicle quantity and size
- Tickening of perinerium and reduced neurofilament of nerve

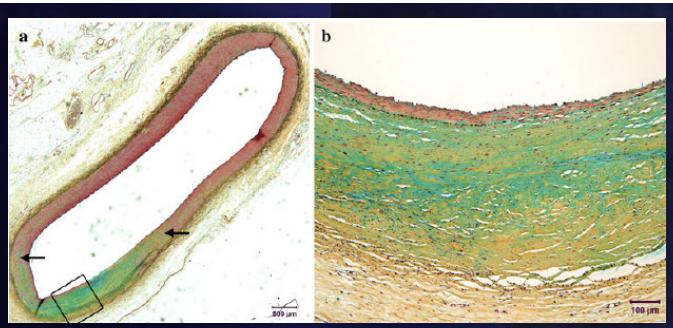
J Hypertens 2012

Clin Res Cardiol
DOI 10.1007/s00392-011-0346-8

ORIGINAL PAPER

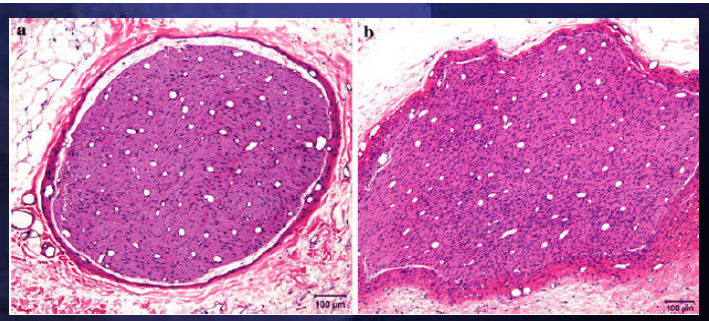
Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety

Marian K. Rippy · Denise Zarins · Neil C. Barman · Andrew Wu · Keith L. Duncan · Christopher K. Zarins



Fibrosis of 10%-25% of total media and underlying adventitia with mild disruption of the external elastic lamina

6 months



Nerve fibrosis, replacement of nerve fascicles with fibrous cennective tissue and thickening of the perineurium

Clin Res Cardiol 2011

European Heart Journal Advance Access published April 25, 2013

European Heart Journal
doi:10.1093/eurheartj/eht141

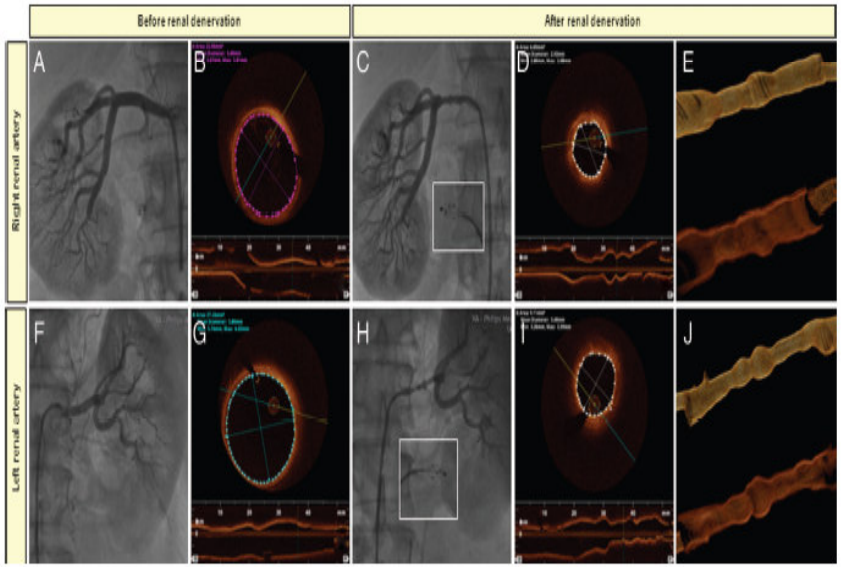
FASTTRACK CLINICAL RESEARCH

Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicityw catheter system and the EnligHTN™ multi-electrode renal denervation catheter

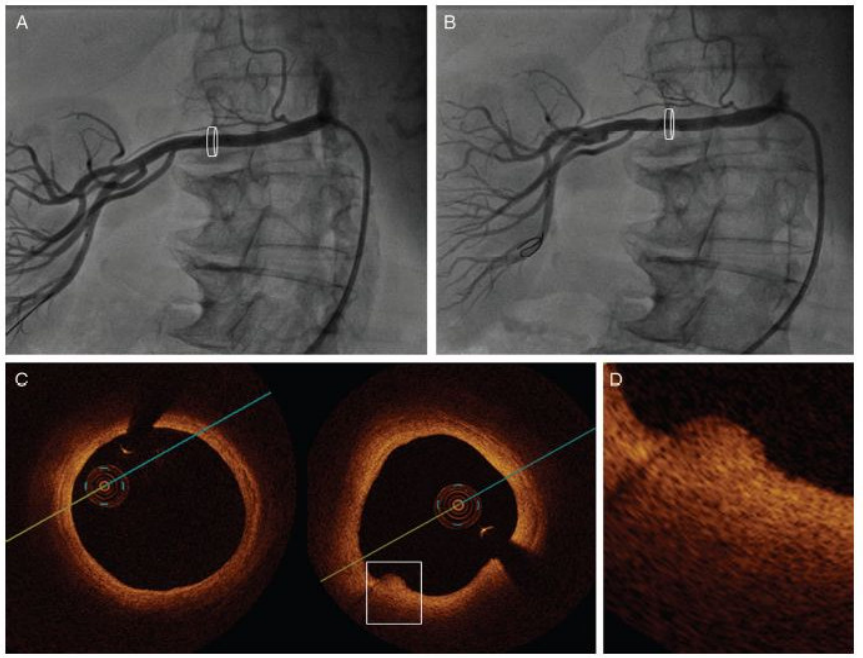
Christian Templin[1†], Milosz Jaguszewski[1†], Jelena R. Ghadri[1], Isabella Sudano[1], Roman Gaehwiler[1], Jens P. Hellermann[2], Renate Schoenenberger-Berzins[3], Ulf Landmesser[1], Paul Erne[3], Georg Noll[1], and Thomas F. Lüscher[1*]

[1]Department of Cardiology, Cardiovascular Center, University Hospital Zurich, Raemistrasse 100, Zurich CH-8091, Switzerland; [2]Division of Cardiology, Altstätten Hospital, Altstätten, Switzerland; and [3]Department of Cardiology, Luzerner Kantonsspital, Luzerner, Switzerland

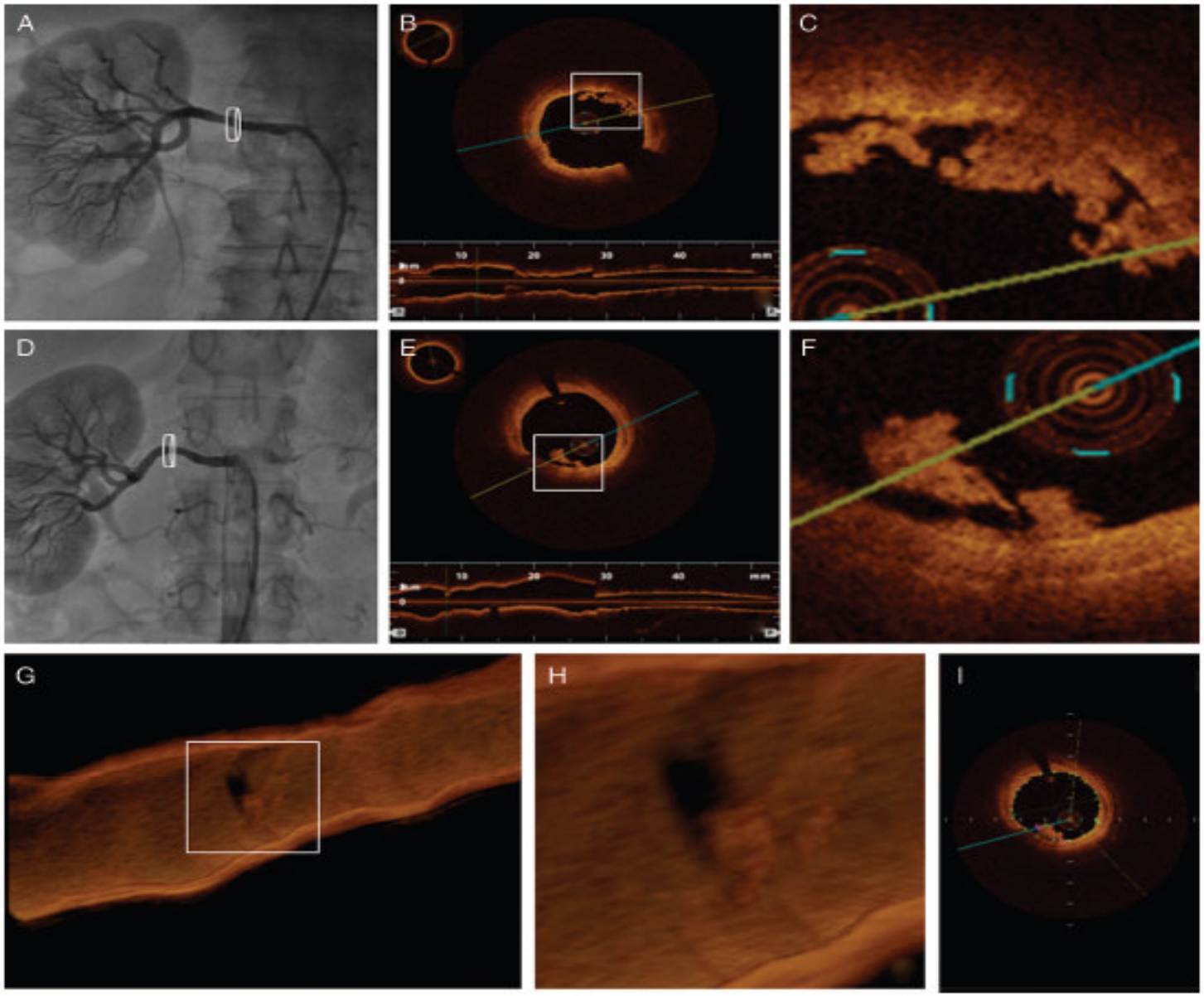
Received 3 February 2013; revised 27 March 2013; accepted 7 April 2013



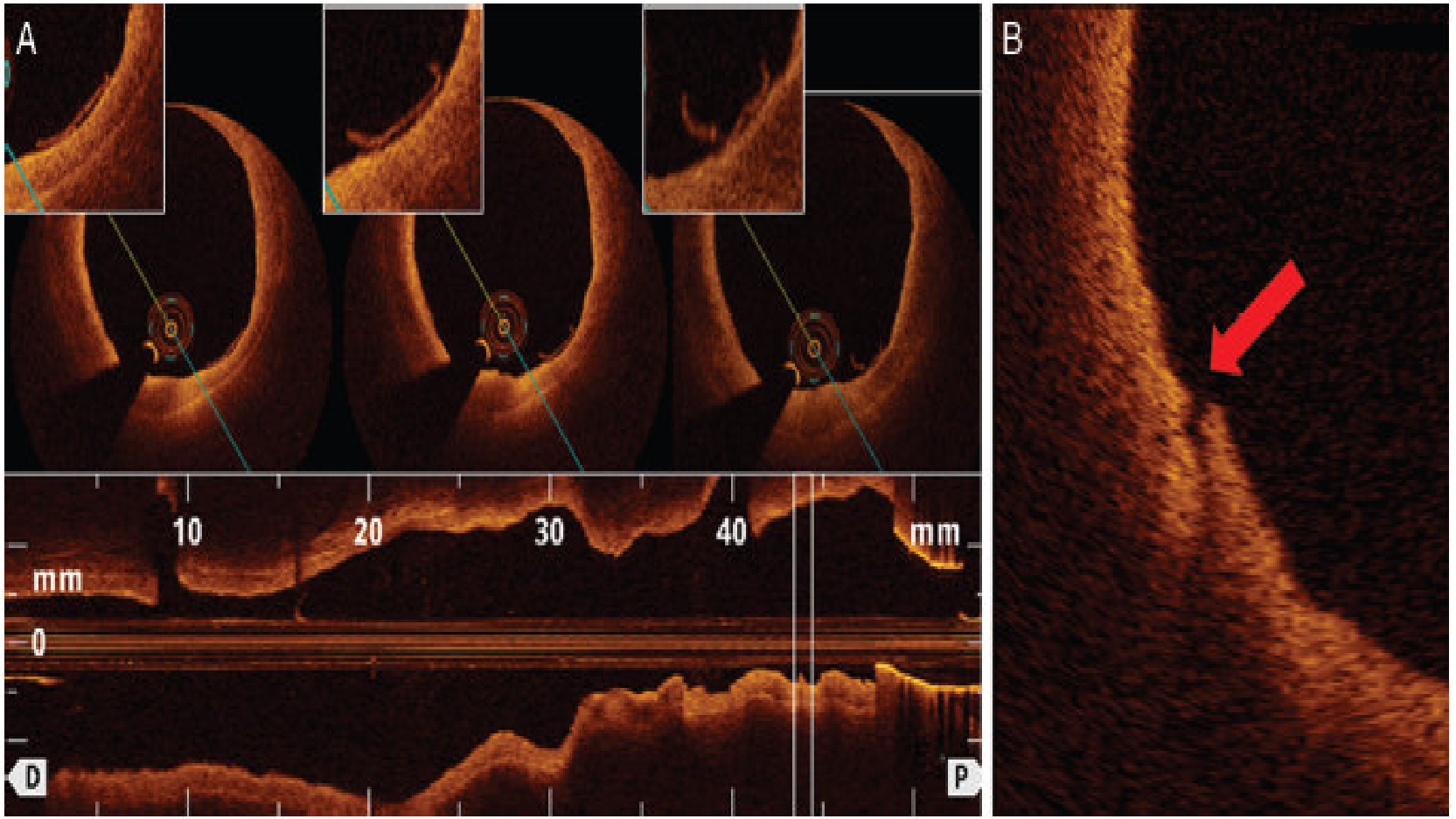
Vasospasm of renal arteries after renal nerve ablation. Right renal artery (*A*–*E*) and left renal artery (*F*–*J*). Baseline angiography (*A* and *F*) and OCT imaging (*B* and *G*) before renal artery ablation with the EnligHTN™ catheter. Vasospasm observed after radiofrequency therapy with both angiography (*C* and *H*) and OCT (*D* and *I*). Three-dimensional OCT reconstruction of right and left renal artery after renal denervation (*E* and *J*).



Vessel wall oedemas after renal nerve ablation. Renal artery before (*A*) and after (*B*) Simplicityw catheter-based renal denervation. Direct after ablation vessel notches are inapparent in angiography (*B*) and discernible at the lesion site by OCT imaging (*C*, frame and *D*).



Thrombus formation after renal nerve ablation. Significant intraluminal thrombus formation after renal nerve denervation are inapparent in angiography (*A* and *D*), however displayed in different OCT cross-sections (*B*, *C*, *E*, *F* and *I*) and in three-dimensional reconstructed renal artery (*G* and *H*).



Dissections after renal nerve ablation. Endothelial detachments (*A*, white box) and vessel wall dissections (*B*, red arrow) detected in treated renal arteries with the EnligHTN™ catheter.

The Symplicity HTN-2 Trial: Renal Function Changes

	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 m^2)	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

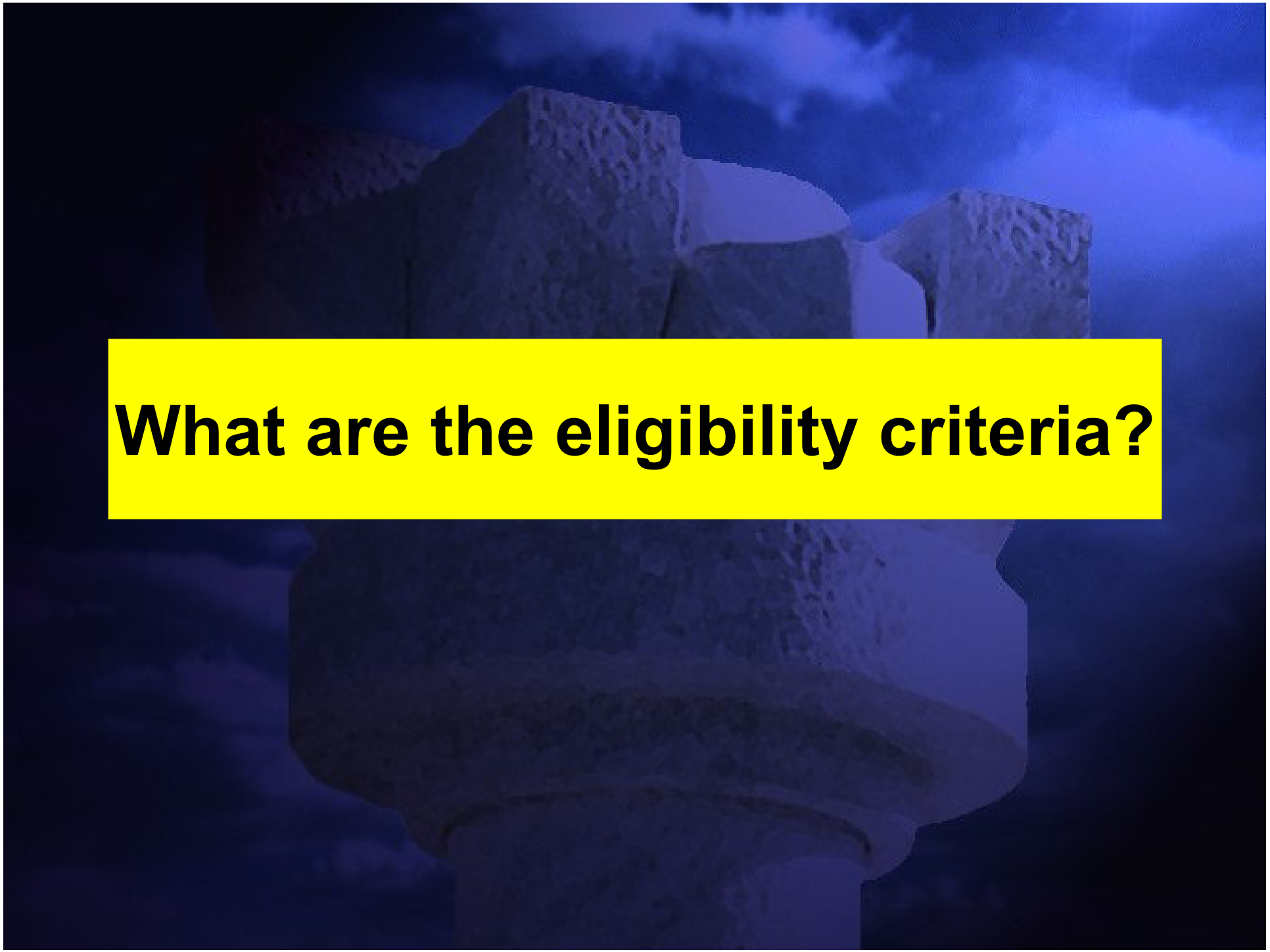
eGFR= Calculated on the basis of MDRD

Symplicity HTN-2 Investigators: Lancet 2010

The Symplicity HTN-1 Trial: RENAL FUNCTION

months	1	3	6	12	24
eGFR (mL/min per 1,73 m^2)	+ 0.1	- 1.6	- 0.1	- 2.9	- 16.0
n° pts	112	102	87	64	10

Symplicity HTN-1 Investigators: Hypertension 2011


What are the eligibility criteria?

European Heart Journal Advance Access published April 25, 2013

European Heart Journal
doi:10.1093/eurheartj/eht154

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 SBP ≥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
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, main renal arteries of < 4 mm in diameter or < 20 mm in lenght, no prior revas-scularization (stenting/PTA)
- Preserved renal function (eGFR ≥ 45 ml/min/1.73m2)
- Pts should be referred to Hypertension Excellence Centers

European Heart Journal Advance Access published April 25, 2013

European Heart Journal
doi:10.1093/eurheartj/eht154

FASTTRACK CURRENT OPINION

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

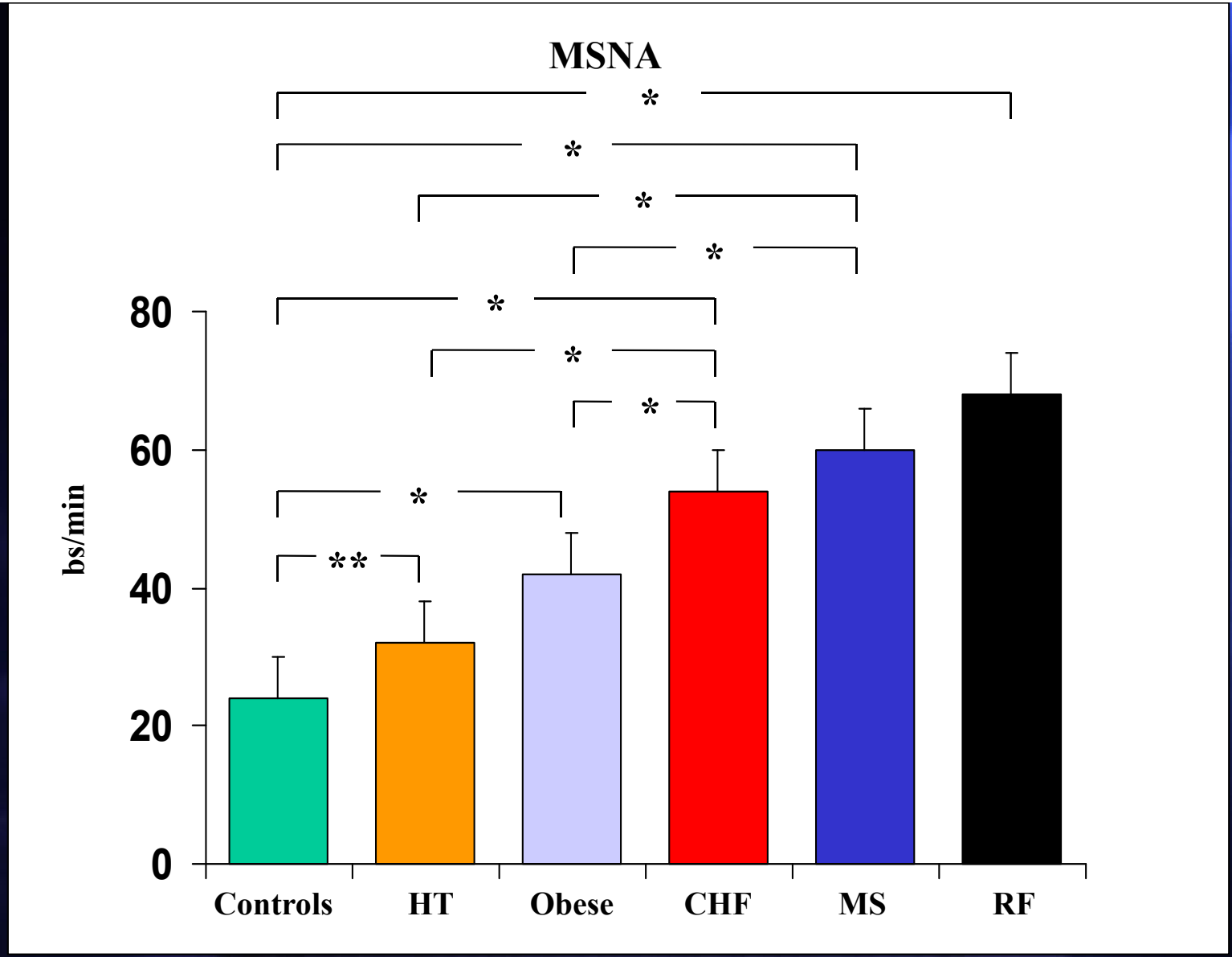
Felix Mahfoud[1]*, Thomas Felix Lüscher[2], Bert Andersson[3], Iris Baumgartner[4], Renata Cifkova[5], Carlo DiMario[6], Pieter Doevendans[7], Robert Fagard[8], Jean Fajadet[9], Michel Komajda[10], Thierry LeFèvre[11], Chaim Lotan[12], Horst Sievert[13], Massimo Volpe[14,15], Petr Widimsky[16], William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

Table 3 Suggested follow-up examinations after renal denervation

	Baseline	3 months	6 months	12 months	24 months	36 months	48 months	60 months
Office BP	×	×	×	×	×	×	×	×
ABPM	×	×	×	×	×	×	×	×
Heart rate	×	×	×	×	×	×	×	×
Body weight	×	×	×	×	×	×	×	×
Review medications	×	×	×	×	×	×	×	×
Blood tests, including GFR determination	×	×	×	×	×	×	×	×
ECG	×		×	×	×	×	×	×
Renal artery imaging (duplex ultrasound, MRI/CT with contrast or angiogram)	×		×	×	×	×	×	×
Oral glucose tolerance test (where appropriate)	×		×	×	×	×	×	×
Echocardiography in patients with heart failure or left ventricular hypertrophy	×		×	×	×	×	×	×
UACR in patients with albuminuria	×	×	×	×	×	×	×	×

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ECG, electrocardiogram; UACR, urine albumin to creatinine ratio.


Future applications of RDN



Behaviour of muscle (MSNA) and skin sympathetic nerve activity (SSNA) in healthy sunjects and in patients with hypertension (HT), obesity (OB), congestive hearth failure (CHF), methabolic syndrome (MS) or renal failure (RF)

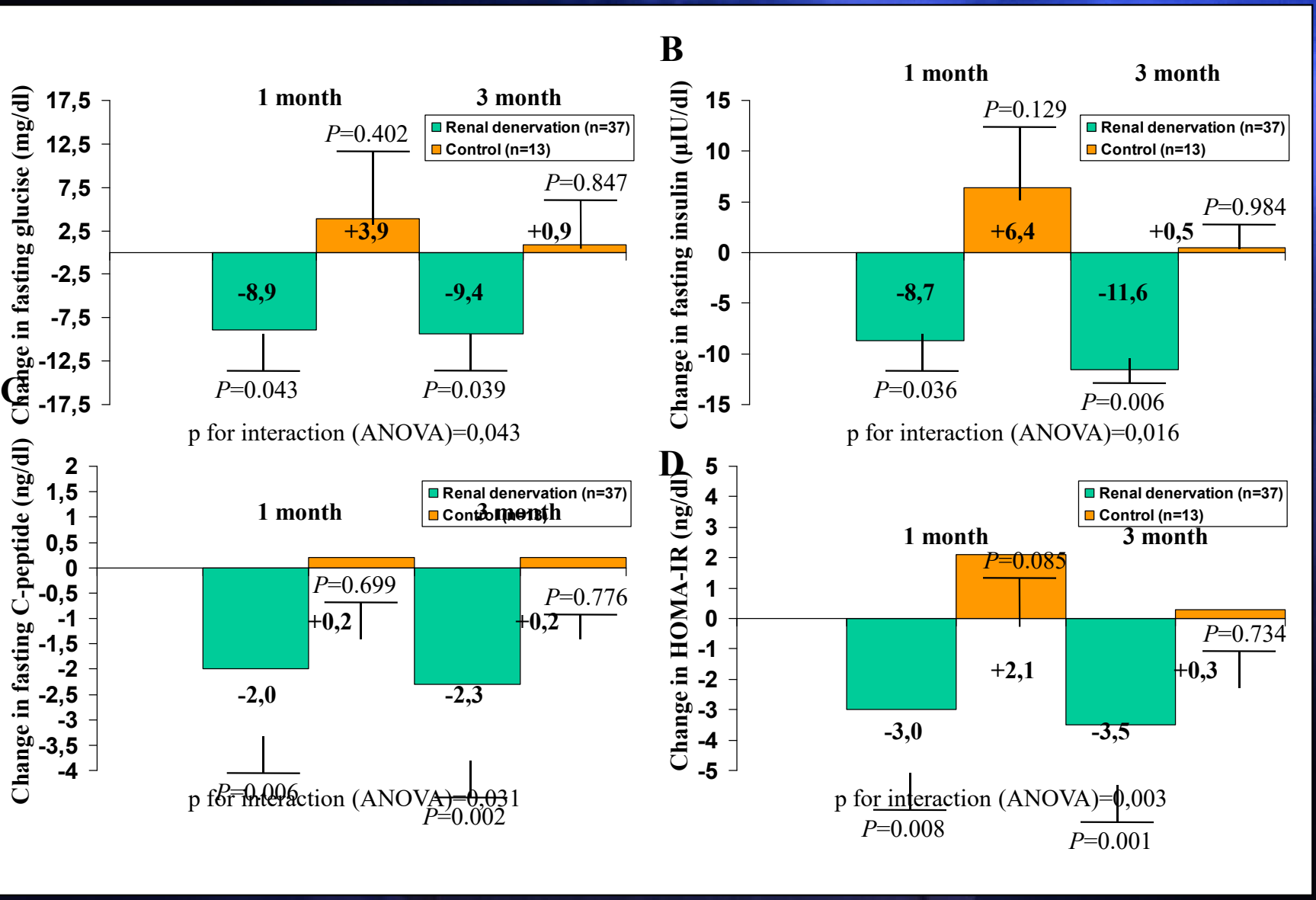
Grassi G. et al.; Exp Physiol 2009

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

Mahfoud F. et al.; Circulation 2011



Mahfoud F. et al.: Circulation 2011

Renal sympathetic nerve ablation for the treatment of difficult-to-control or refractory hypertension in a haemodialysis patient

Nicola Di Daniele[1], Marianna De Francesco[1], Leano Violo[1], Alessio Spinelli[2] and Giovanni Simonetti[2]

NDT 2012

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*†‡

JACC 2012

The Role of Renal Denervation in the Treatment of Heart Failure

Paul A. Sobotka · Henry Krum · Michael Böhm ·
Darrel P. Francis · Markus P. Schlaich

Curr Cardiol Rep 2012

Renal Denervation in Moderate to Severe CKD

Dagmara Hering,*† Felix Mahfoud,‡ Antony S. Walton,§ Henry Krum,§ Gavin W. Lambert,* Elisabeth A. Lambert,* Paul A. Sobotka,‖¶ Michael Böhm,‡ Bodo Cremers,‡ Murray D. Esler,*§ and Markus P. Schlaich*§

*Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Australia; †Department of Hypertension and Diabetology, Medical University of Gdansk, Poland; ‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §Heart Centre Alfred Hospital, Melbourne, Australia; ‖Department of Medicine and Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; and ¶Medtronic ARDIAN Inc., Mountain View, California

ABSTRACT

Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) < 45 ml/min per 1.73 m^2 is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3–4 CKD (mean eGFR, 31 ml/min per 1.73 m^2). We used CO_2 angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO_2 angiography. Mean baseline BP ± SD was 174±22/91±16 mmHg despite the use of 5.6±1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were −34/−14, −25/−11, −32/−15, and −33/−19 mmHg, respectively. Night-time ambulatory BP significantly decreased ($P<0.05$), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3–4 CKD and resistant hypertension.

J Am Soc Nephrol 2012

Limitations

- RDN does not cause universal BP lowering
- Only a small number of patients have been exposed to RDN and the follow-up is short
- Lacking of randomized blinded studies
- Lacking of any procedural marker that might identify good responders to RDN
- Lacking of standardized certification of RDN centers