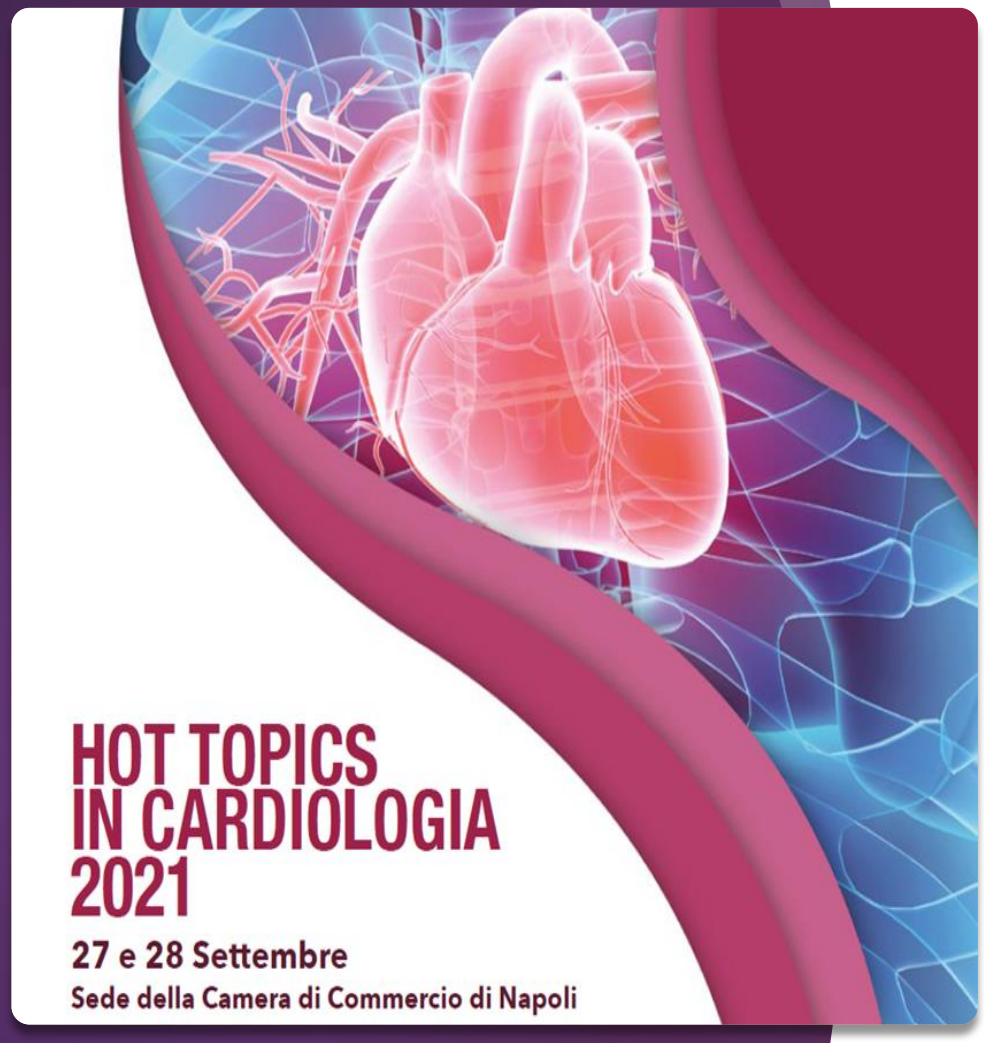
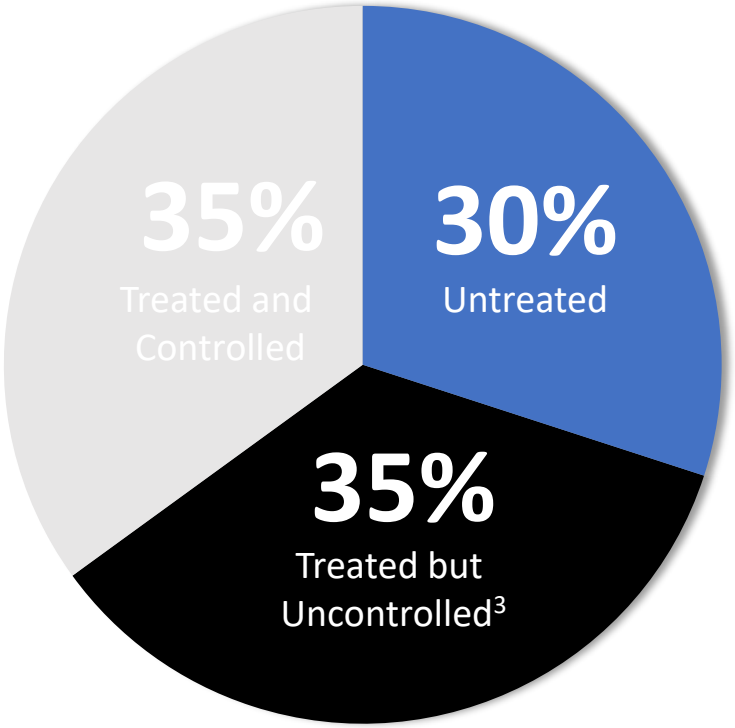


La denervazione renale: una nuova risorsa?

Bruno Villari

HYPERTENSION IS THE SINGLE LARGEST CONTRIBUTOR TO DEATH

HTN is estimated to have **added $18.6B in avoidable costs**[1] to the US health care[2] system alone



HYPERTENSION REMAINS A MAJOR HEALTH BURDEN

1 IN 3 ADULTS HAVE HYPERTENSION[4]

1B PEOPLE WORLDWIDE[5]

1.6B BY 2025[6]

[1]Avoidable costs include emergency, hospital, and outpatient visits that could be avoided with stable adherence.
[3]Uncontrolled defined as ≥140 mm Hg systolic or ≥ 90 mm Hg diastolic. CDC Vital Signs September 2012, NHANES 2003–2010.
[4]Kearney PM, et al. *Lancet*. 2005;365:217–223.
[5]World Health Organization. World Health Report 2002: Reducing risks, promoting healthy life. Geneva, Switzerland.
[6]Messerli FH, et al. *Lancet*. 2007;370:591–603.

Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries

European Journal of Preventive Cardiology

ESC European Society of Cardiology

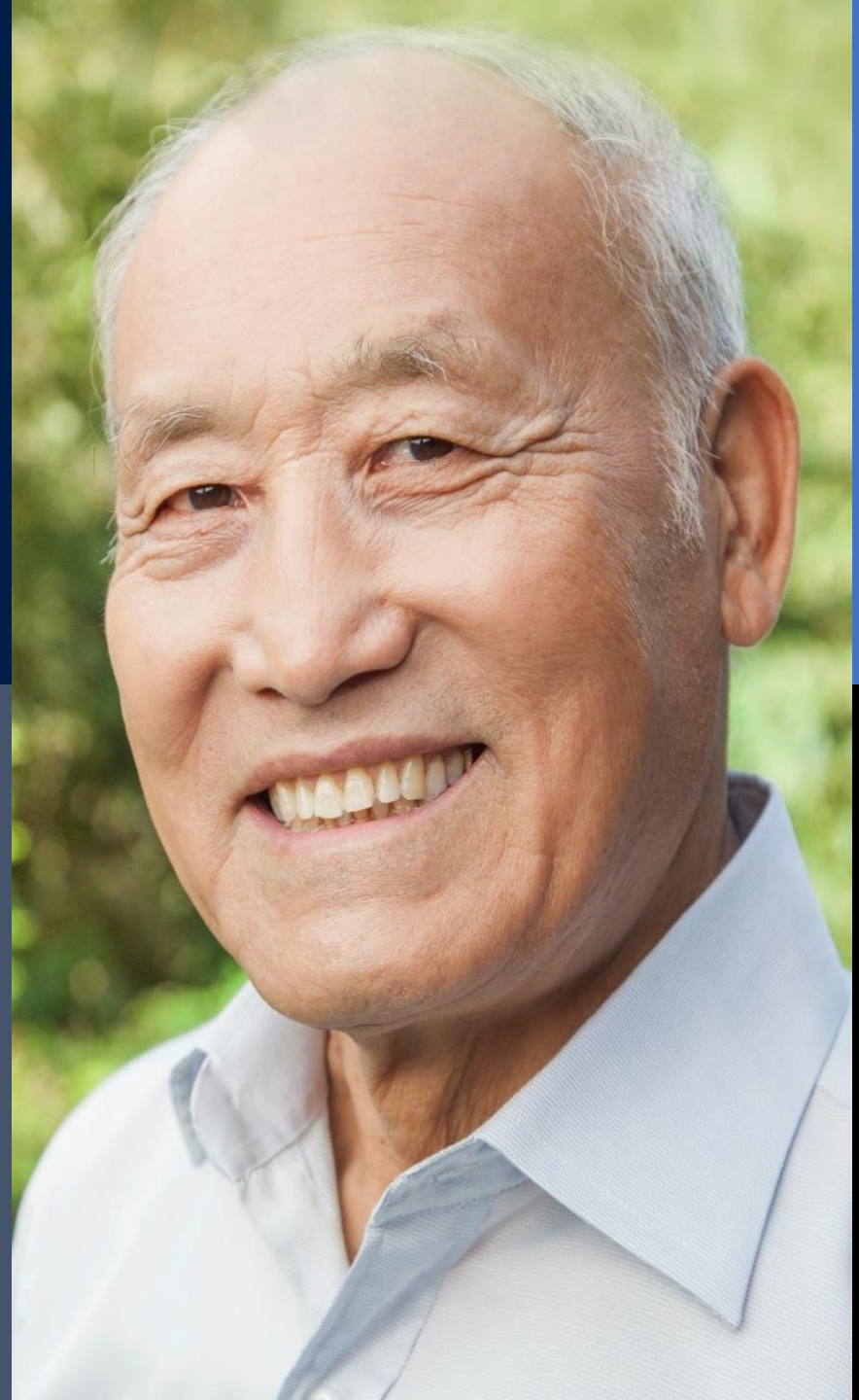
Risk factor	All $n=2759$ %	Gender		Age	
		Men $n=1170$ %	Women $n=1589$ %	<60 years $n=1344$ %	≥60 years $n=1415$ %
BP ≥ 140/90 mm Hg (≥140/85 if diabetes) in patients using antihypertensive drugs	53.0	56.6	50.5[a]	50.4	55.2[b]
BP ≥ 140/90 mm Hg (≥140/85 if diabetes) in patients not using antihypertensive drugs	43.2	48.7	38.7[b]	36.6	52.5[a]
Awareness of BP level in patients using antihypertensive drugs	84.2	83.0	85.0	83.4	84.8
Awareness of BP target in patients using antihypertensive drugs	69.2	69.4	69.0	67.7	70.5
Reporting 100% adherence with BP lowering drugs	64.9	62.5	66.5	61.2	67.9[a]
If blood pressure raised, never been told by a doctor to have high BP	13.0	15.3	11.0	13.8	12.3
BP ≥ 140/90 mm Hg (≥140/85 if diabetes) in obese patients using antihypertensive drugs	60.5	61.5	59.8	61.4	59.7
B ≥ 140/90 mm Hg (≥140/85 if diabetes) in centrally obese patients using antihypertensive drugs	57.0	60.1	55.4	56.7	57.3
BP ≥ 140/90 mm Hg (≥140/85 if diabetes) in obese patients using lipid-lowering drugs	52.7	56.9	48.7	52.0	53.1
BP ≥ 140/90 mm Hg (≥140/85 if diabetes) in centrally obese patients using lipid-lowering drugs	48.0	54.2	43.8[b]	42.5	51.2[b]
LDL-C ≥ 2.6 mmol/l in patients using lipid-lowering drugs	53.1	45.2	59.9[a]	62.2	47.3[a]
LDL-C ≥ 2.6 mmol/l in patients not using lipid-lowering drugs	81.0	77.5	83.3[a]	81.9	79.9
Awareness of total cholesterol level in patients using lipid-lowering drugs	45.3	44.6	45.8	45.8	44.9
Awareness of total cholesterol target in patients using lipid-lowering drugs	29.9	31.4	28.7	32.2	28.5
Reporting 100% adherence with lipid-lowering drugs	61.3	65.3	58.1[b]	54.3	66.1[a]
If LDL-C ≥ 2.6 mmol/l, never been told to have high cholesterol	44.4	46.3	43.2	49.1	39.2[a]
Self-reported previous diabetes	35.8	37.2	34.7	29.2	42.0
In patients with self-reported diabetes, HbA1c ≥ 7.0%	34.8	32.5	36.6	37.0	33.4
Awareness of glucose level in patients with self-reported diabetes	62.9	62.3	63.4	56.0	67.5[a]
Awareness of glucose target in patients with self-reported diabetes	48.0	49.4	46.9	40.5	53.0[a]
Self-monitoring	72.4	72.3	72.5	66.6	76.2
Reporting 100% adherence with glucose-lowering drugs	76.5	75.	77.4	76.2	76.7

BP: blood pressure; LDL-C: low density lipoprotein-cholesterol.
[a] $p < 0.01$; [b] $p < 0.05$.

PATIENT ADHERENCE

IS WORSE THAN YOU MIGHT THINK

Studies have shown doctors overestimate adherence. "Physicians generally tend to overestimate patient's adherence. Studies have demonstrated that clinicians' estimates of non-adherence are very poor, with a positive predictive value of only approximately 30%[1]. In fact, **detecting non-adherence in clinical practice is almost impossible."**



8.2%

OF ADULTS WOULD GIVE UP TWO YEARS OF THEIR LIVES TO AVOID ADDING ONE DAILY PILL[2]

NEARLY

50%

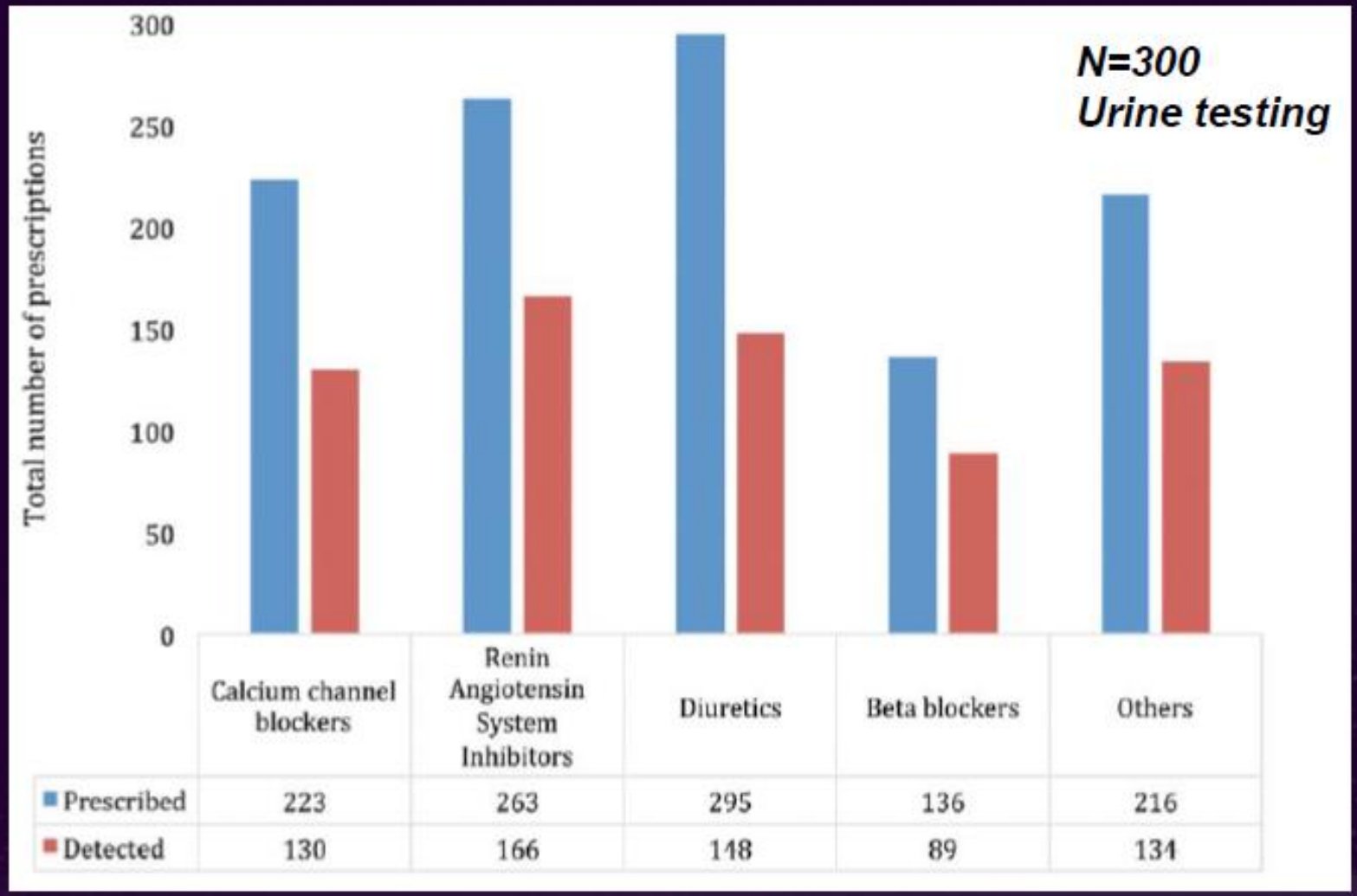
OF PATIENTS BECOME NON-ADHERENT TO ANTIHYPERTENSIVE THERAPY WITHIN ONE YEAR OF INITIATING THERAPY[1]

[1]Jung O, et al. *J Hypertens.* 2013;31:766–774.
[2]Hutchins R, et al. *Circ Cardiovasc Qual Outcomes.* 2015;8:155–163.

NUMBER OF ANTIHYPERTENSIVE DRUGS PRESCRIBED AND DETECTED

Drug Class Differences

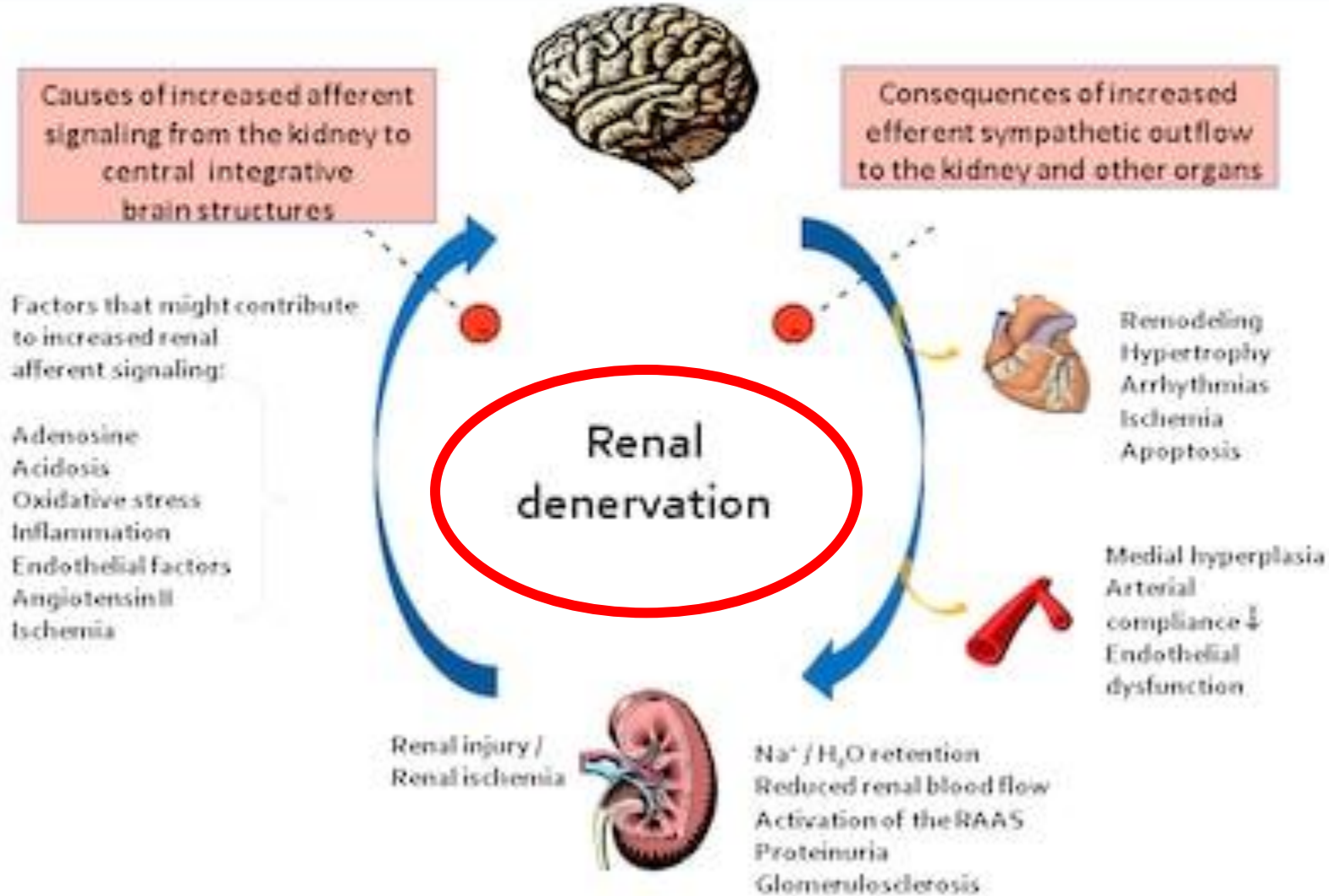
"The majority of patients with apparent treatment resistant hypertension are nonadherent to prescribed treatment."



	Calcium channel blockers	Renin Angiotensin System Inhibitors	Diuretics	Beta blockers	Others
Prescribed	223	263	295	136	216
Detected	130	166	148	89	134

Lawson, et al. J Hypertens .2020.

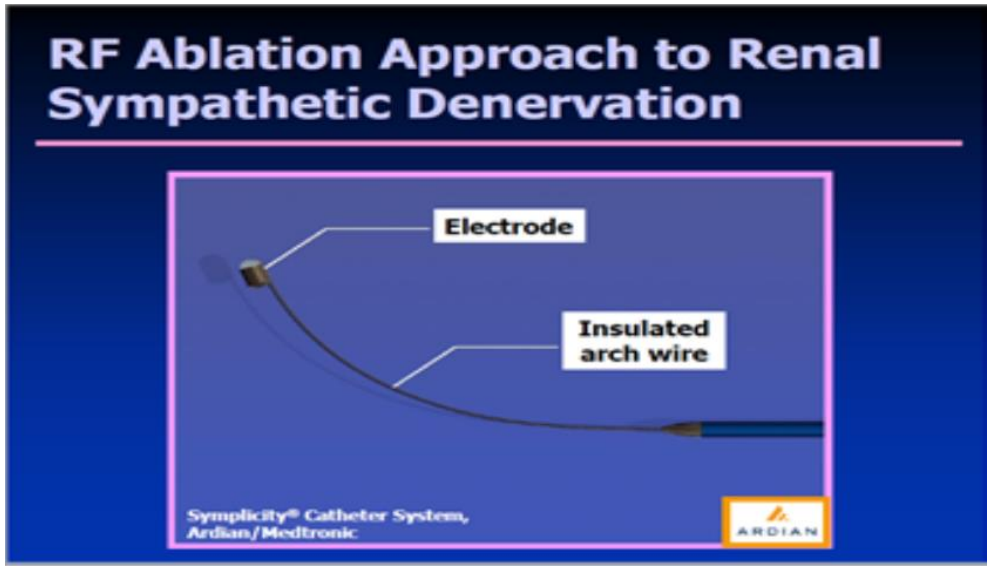
Effects of Increased Sympathetic Tone



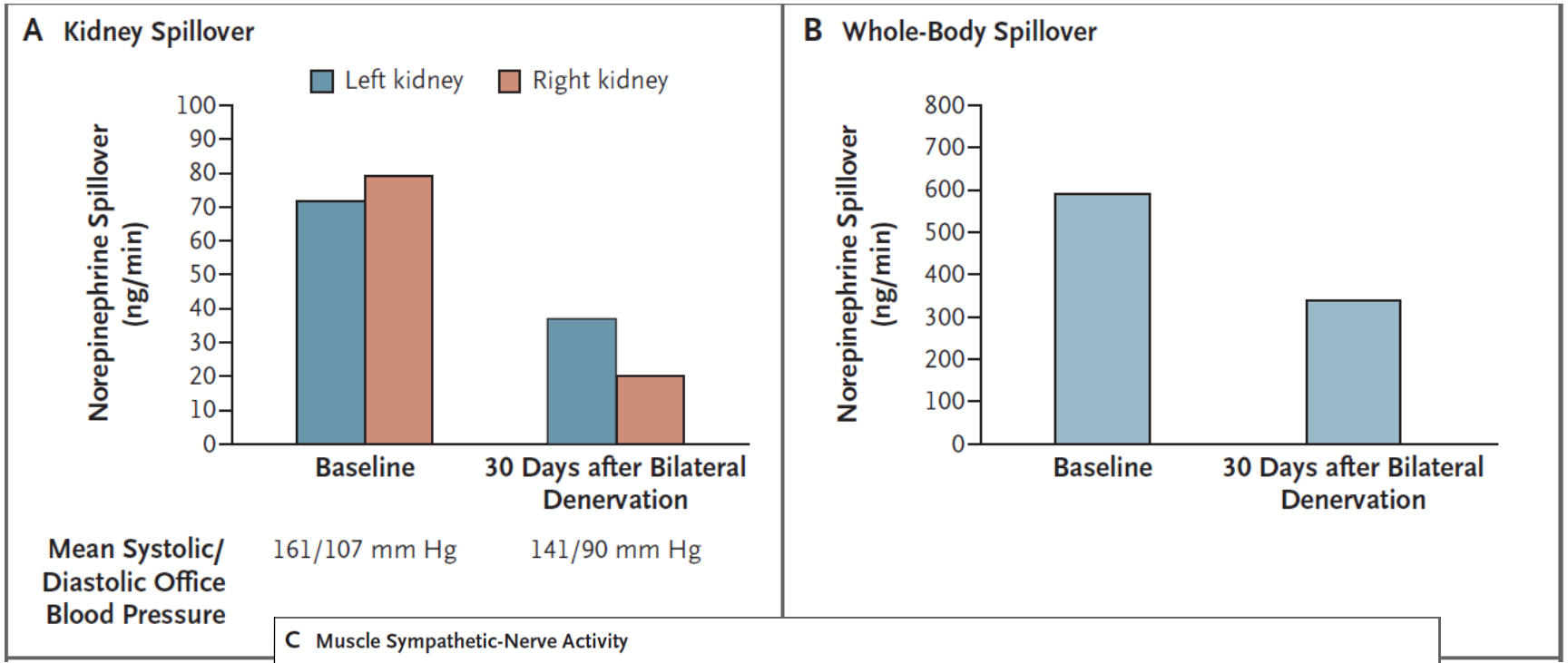
Bohm M, et al. *Nature Rev Cardiol.* 2013;10:465-476. "Reprinted by permission from Springer Nature: Nature Reviews Cardiology Renal sympathetic denervation: applications in hypertension and beyond, Bohm M, et al., Copyright © 2013"

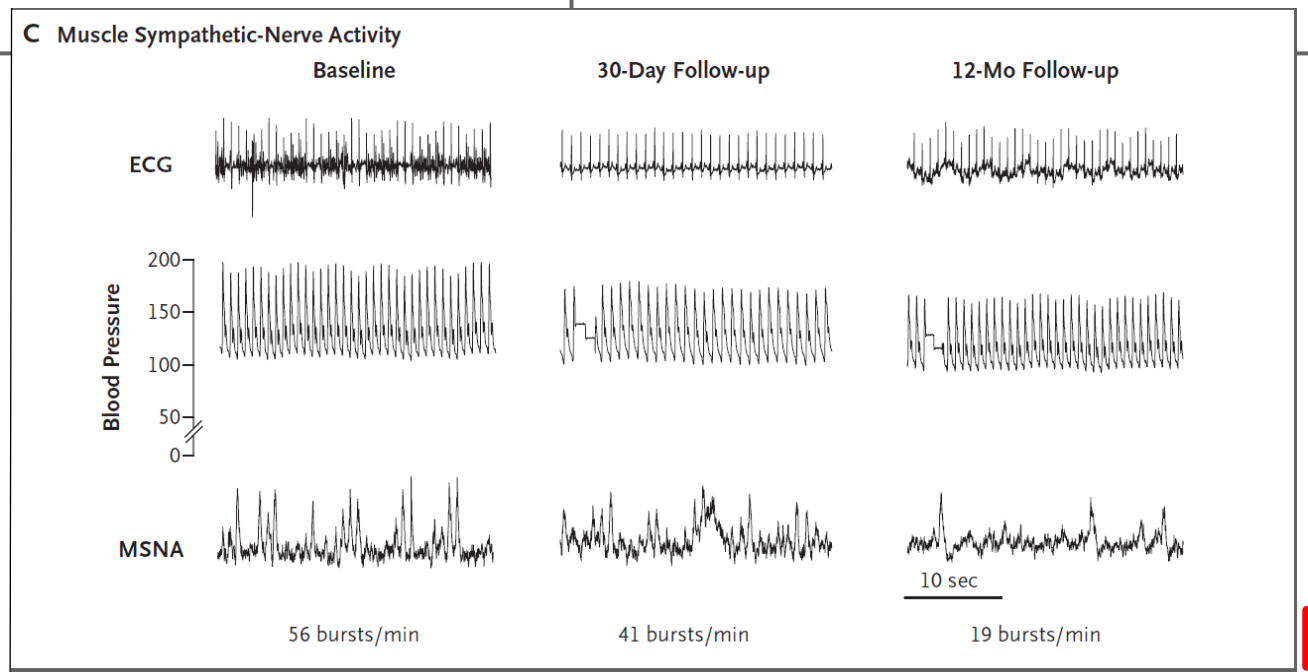
The Beginnings of Renal Denervation (RDN)

- First catheter was the Ardian renal denervation system -- 2005
- Original thoughts were to utilize a catheter to basically do what Smithwick and Thompson had done in a slightly different approach without creating a stepwise function in changes in sympathetic tone
- Catheter-based RDN designed around an RF ablation catheter



Norepinephrine Renal and Whole-Body Spillover and Results of Microneurography before and after Renal- Nerve Ablation

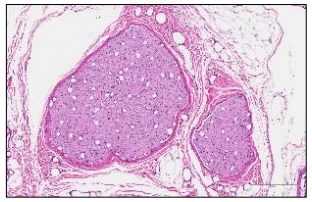
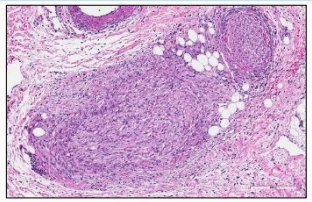
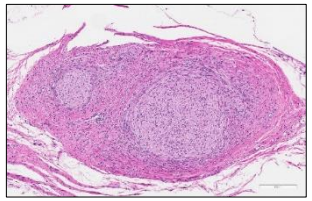
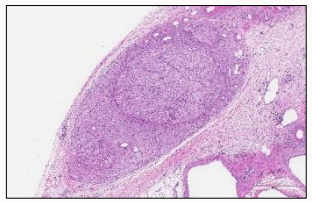




DURABLE RESULTS AFTER RADIO FREQUENCY (RF) RDN OF THE RENAL NERVES

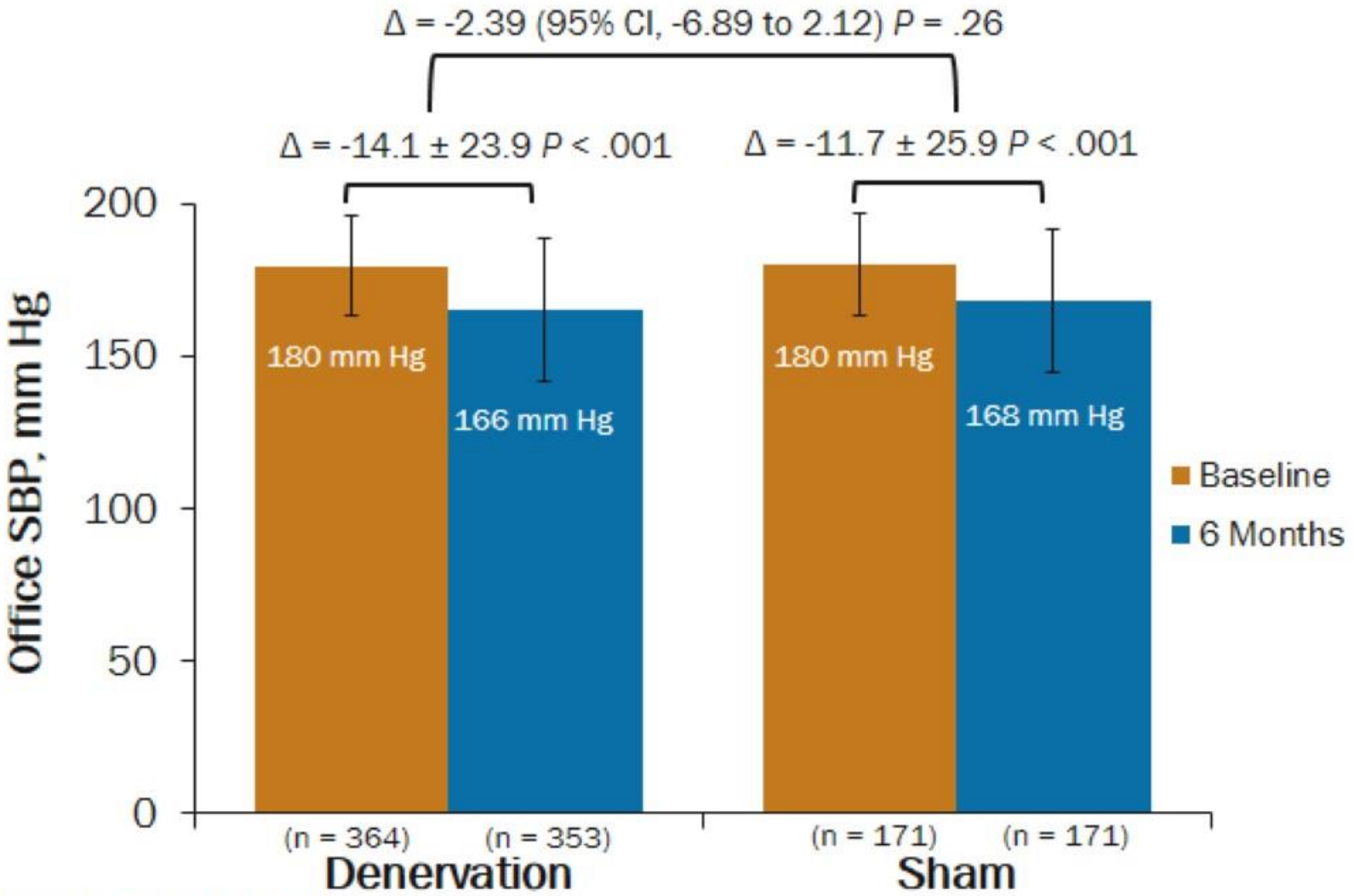
IRREVERSIBLE DESTRUCTION OF AXONS OBSERVED AT DAY 180

Study Design: RF RDN was performed in 164 healthy swine with serial histological tissue samples of the renal arteries obtained at 7, 28, 60 and 180-days

	Histological Tissue Slice	Key Histological Findings
Day 0 (pre-RDN) Normal Nerve Function		• Nerve bundles organized in fascicles • Quiescent Schwann cells • Blood supply intact • Lack of fibrosis
Day 7 Necrosis and inflammation observed		• Obliteration of nerve structure • Cell debris • Loss of blood supply • Intense inflammatory infiltrate • Fibrosis
Day 60 Mature fibrotic infiltration found with disruption to nerve architecture		• Disruption of normal nerve structure • Fibrosis • Hypercellularity
Day 180 Persistent fibrotic infiltration with irreparable nerve architecture. **Functional nerve regrowth is highly unlikely**		• Disruption of normal nerve structure • Fibrosis • Hypercellularity • No restoration of organized nerve bundles

SYMPLICITY HTN-3

Primary Efficacy Endpoint



Bhatt DL, et al. *N Engl J Med*. 2014;370:1393-1401.

2018 ESC/ESH Guidelines

7.6 Device-based hypertension treatment

Device-based therapies for hypertension

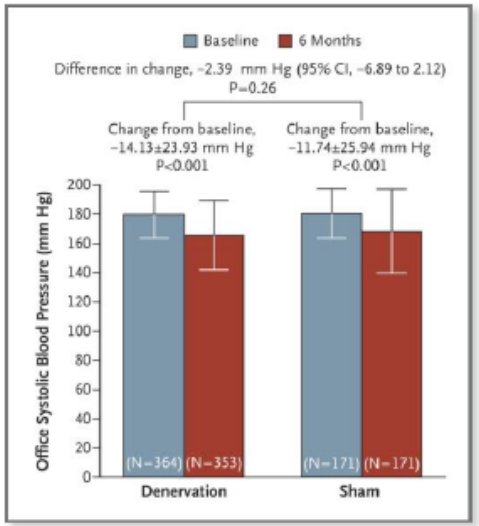
Recommendation	Class[a]	Level[b]
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.[367,368]	III	B

RCT = randomized controlled trial.
[a]Class of recommendation.
[b]Level of evidence.

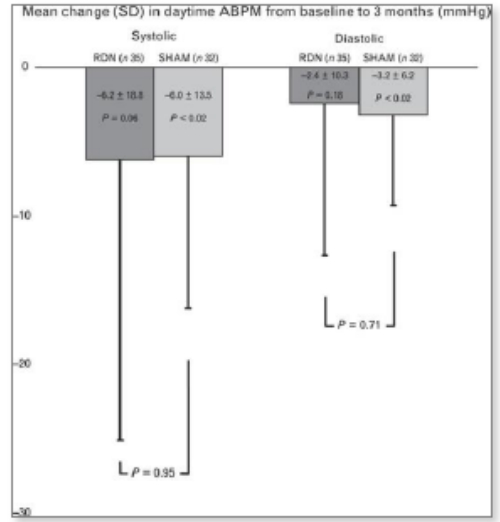
©ESC/ESH 2018

Class III

Evidence or general agreement that the given treatment or procedure is not useful/effective = is not recommended



Ref 367 . Symplicity HTN 3 . NEJM 2014



Ref 368 . Mathiassen ON . J Hyper 2016

Lessons From HTN-3

HTN-3 Factor Identified	Alternative
 Medications	• Obtain off-meds data • Standardize meds • No max dose titration • Measure adherence
 Study Population	• Less severe HTN • Fewer prescribed meds • Focus on ABPM • Patients from across globe • Avoid changing patient behavior
 Procedural	• Spyral™ Catheter • Main + branch vessel treatment • Experienced proceduralists

Circulation

EDITORIAL

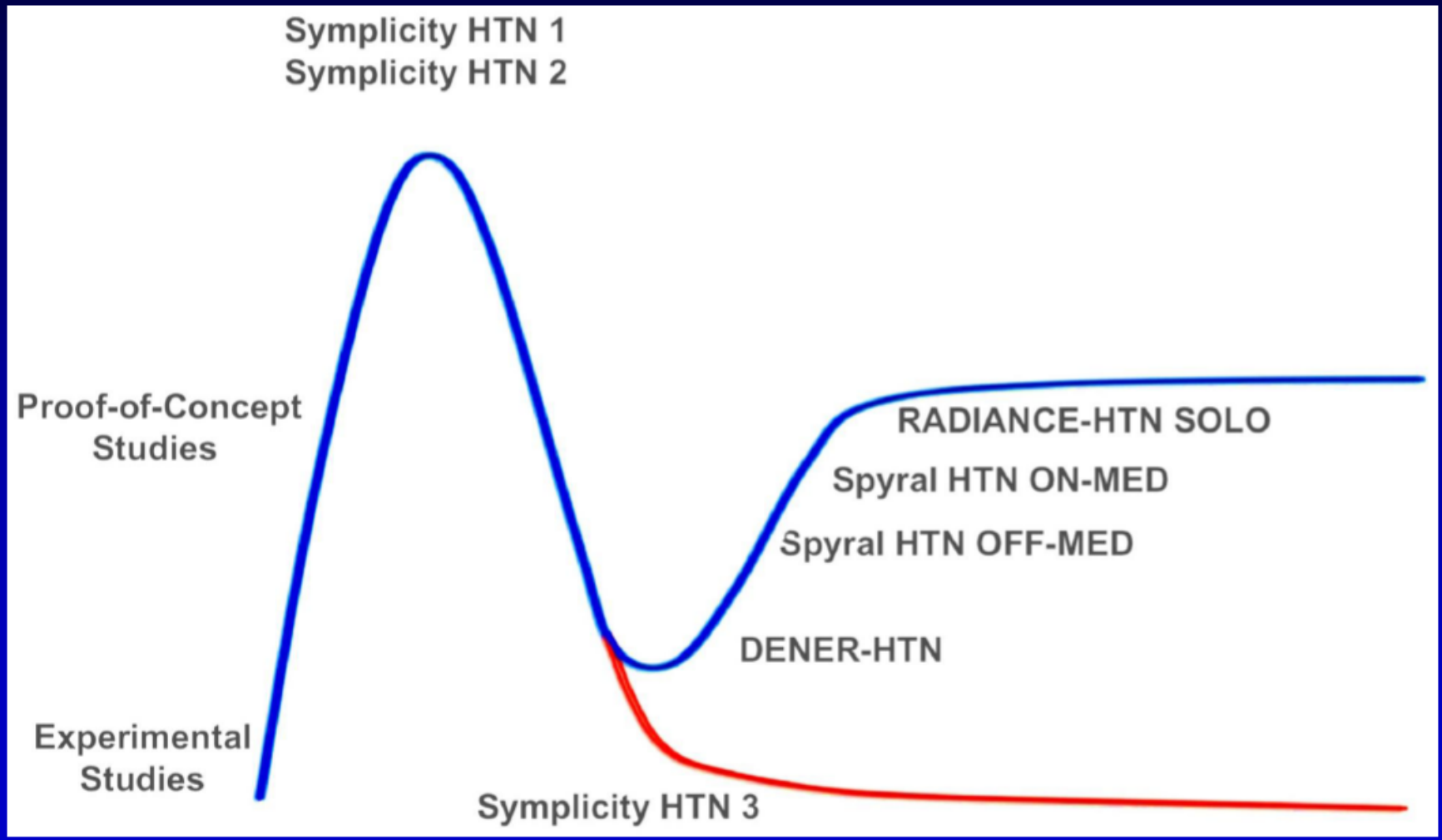
Status of Renal Denervation Therapy for Hypertension

Still in Search of the Magic Bullet

Circulation. 2019;139:601–603. DOI: 10.1161/CIRCULATIONAHA.118.037937

Catheter-based renal denervation: the next chapter begins

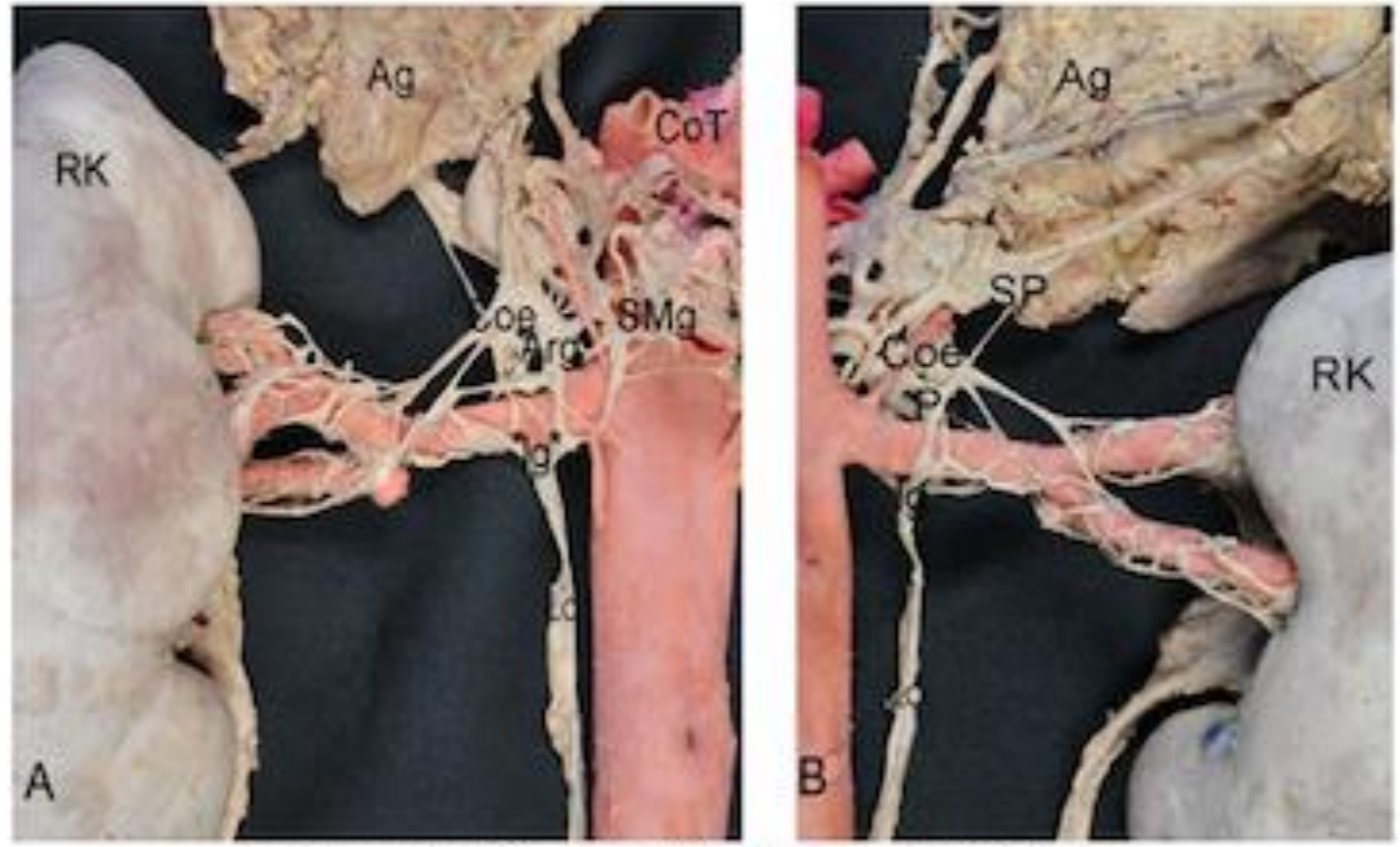
Felix Mahfoud[1,2]*, Markus Schlaich[3,4,5,6], Michael Böhm[1], Murray Esler[7], and Thomas Felix Lüscher[8,9]



Mahfoud et al, Eur Heart J 39 (2019): 4144-4149

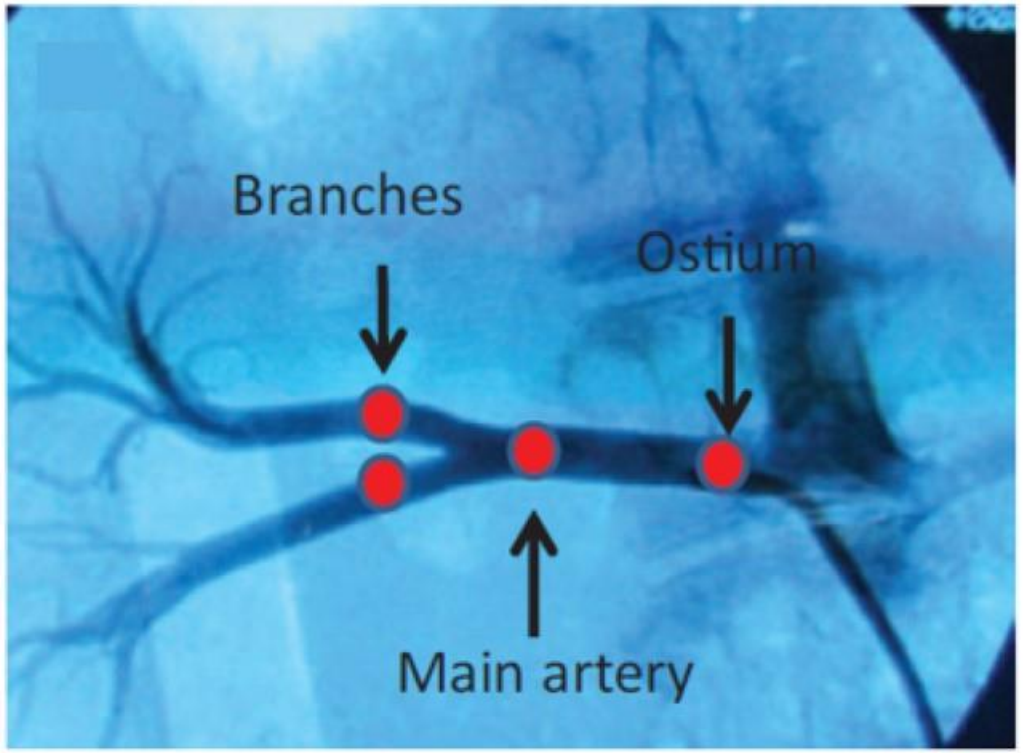
Procedure Changed to Reflect Renal Nerve Anatomy
Distal Nerves Are Closer to the Arterial Lumen

- Renal nerves generally originate from the aorta and arborize toward the kidney
- Nerve fibers do not completely converge on the renal artery until beyond main bifurcation
- Accessory arteries, when present, have similar anatomical innervation patterns that mimic the main renal arteries
- Procedure was changed to ablate as distally as possible where renal nerves congregate closer to artery
- Ablations are only done outside of angiographic shadow of kidney

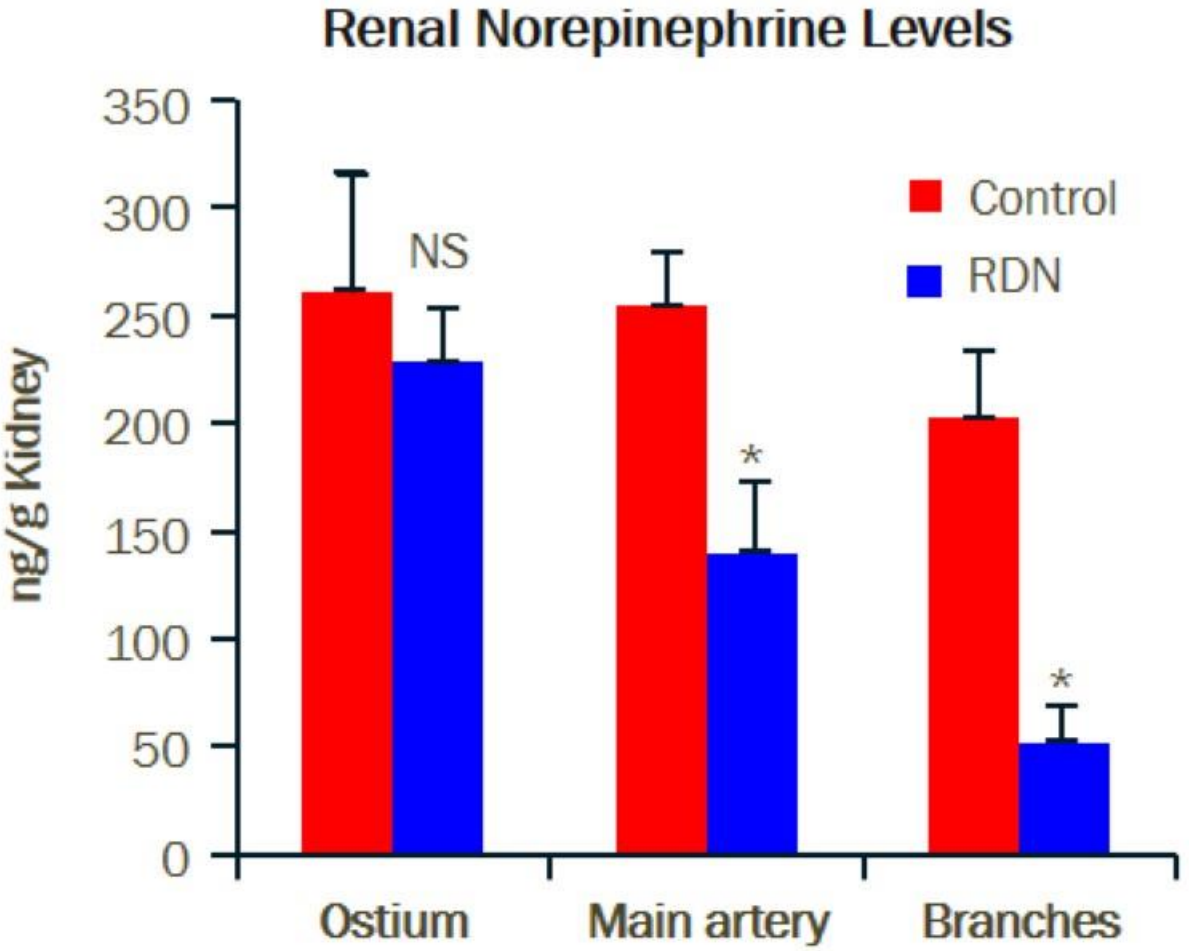


Sympathetic renal plexus of right kidney
(A) anterior (B) posterior

Combined Branch and Main Artery Treatment
Effective in Reducing Renal NE in Normotensive Swine



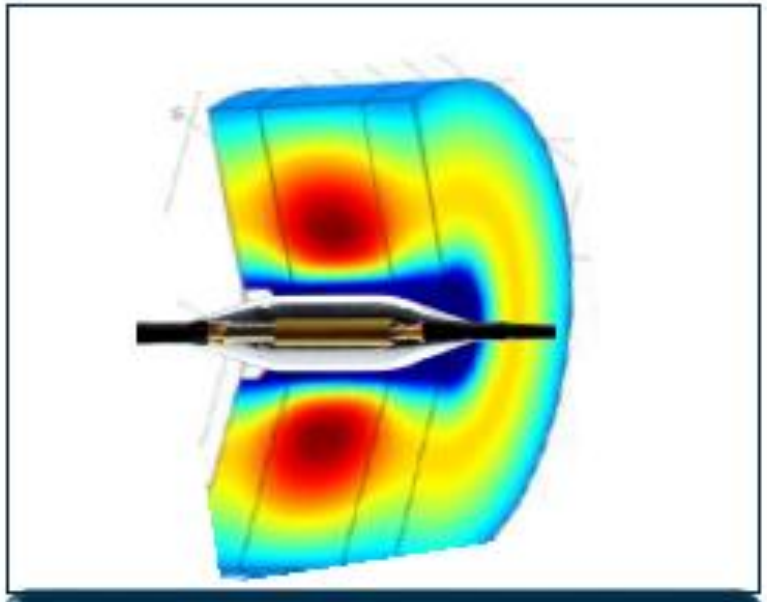
Areas of Renal Denervation



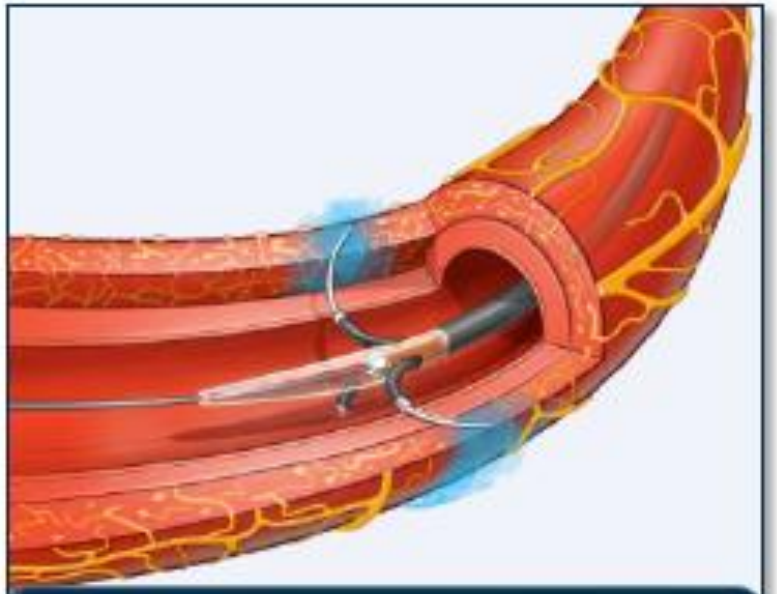
Henegar JR, et al. *Am J Hypertens*. 2015;28:909-914.

Technologies/techniques for renal denervation (RDN)

Radiofrequency denervation

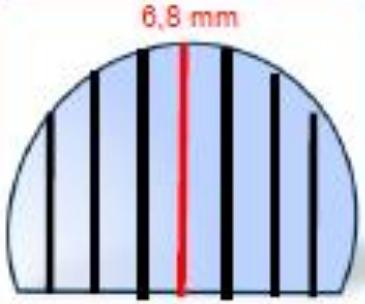
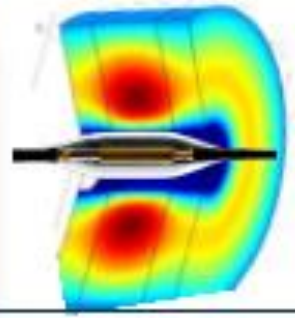
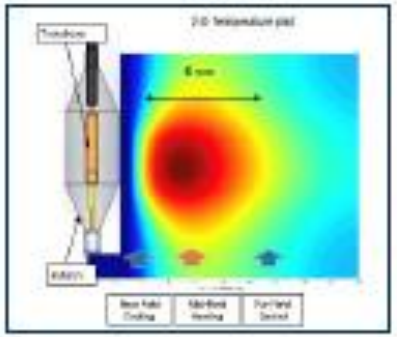
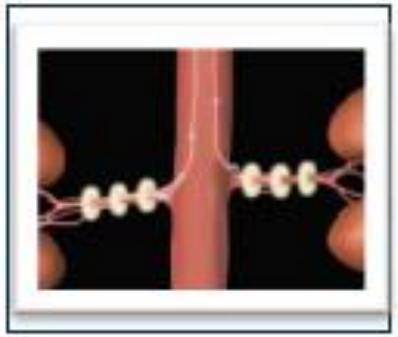


Ultrasound denervation



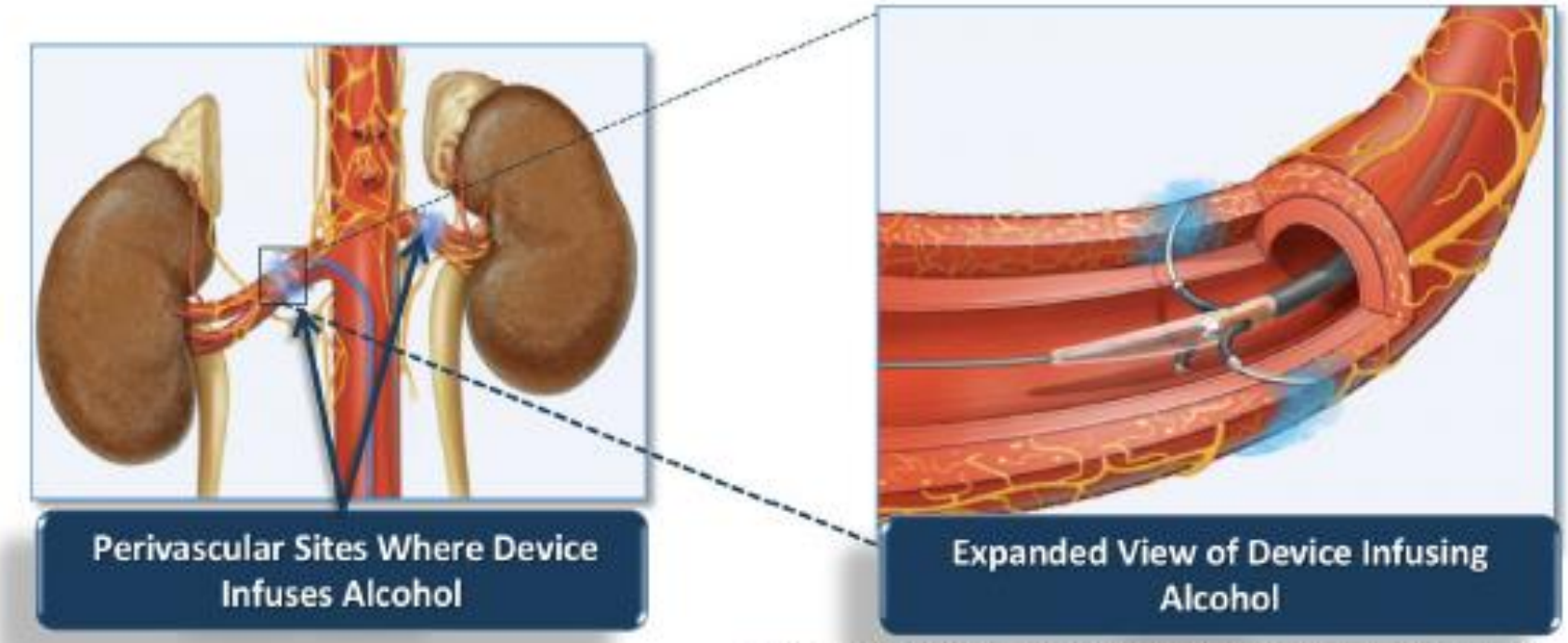
Alcohol mediated denervation

Technologies/techniques for renal denervation (RDN)

	Device	Specifics	Depth	Procedure	Safety
Radiofrequency denervation		▪ Radiofrequency ▪ 4 electrode pattern ablation ▪ 6 F guide catheter compatible ▪ over-the-wire ▪ Vessel diameter range: 3–8 mm			
Ultrasound denervation		▪ Ultrasound ablation ▪ 7 F guide catheter ▪ Ring of energy ▪ Endothelial water cooling ▪ Vessel diameter range: 4–7 mm			

Alcohol mediated denervation

Peregrine System™ Infusion Catheter



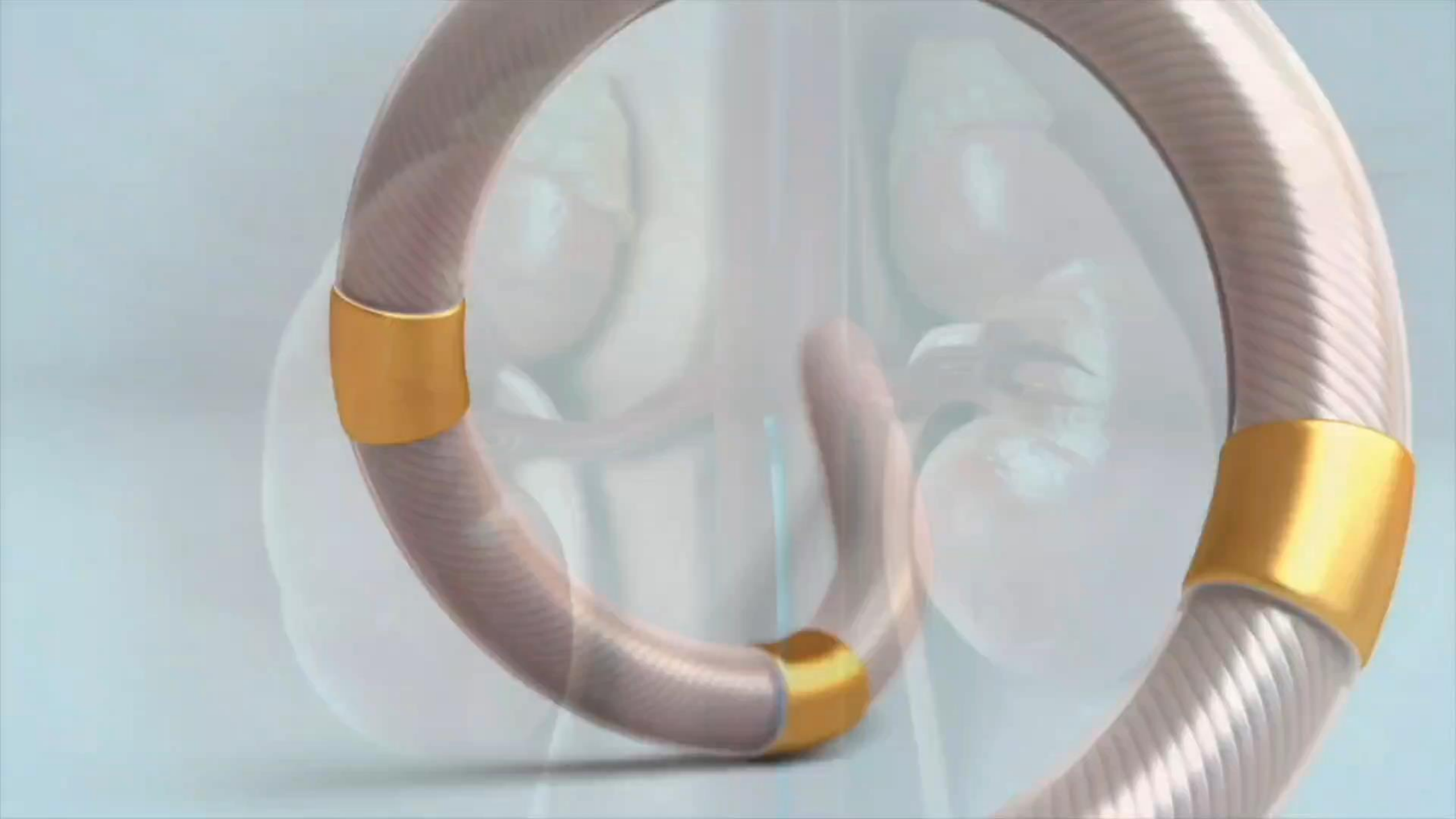
Perivascular Sites Where Device Infuses Alcohol

Expanded View of Device Infusing Alcohol

PVRD Chapter 13; RENAL DENERVATION: A New Approach Treatment – Page 107-116;2015

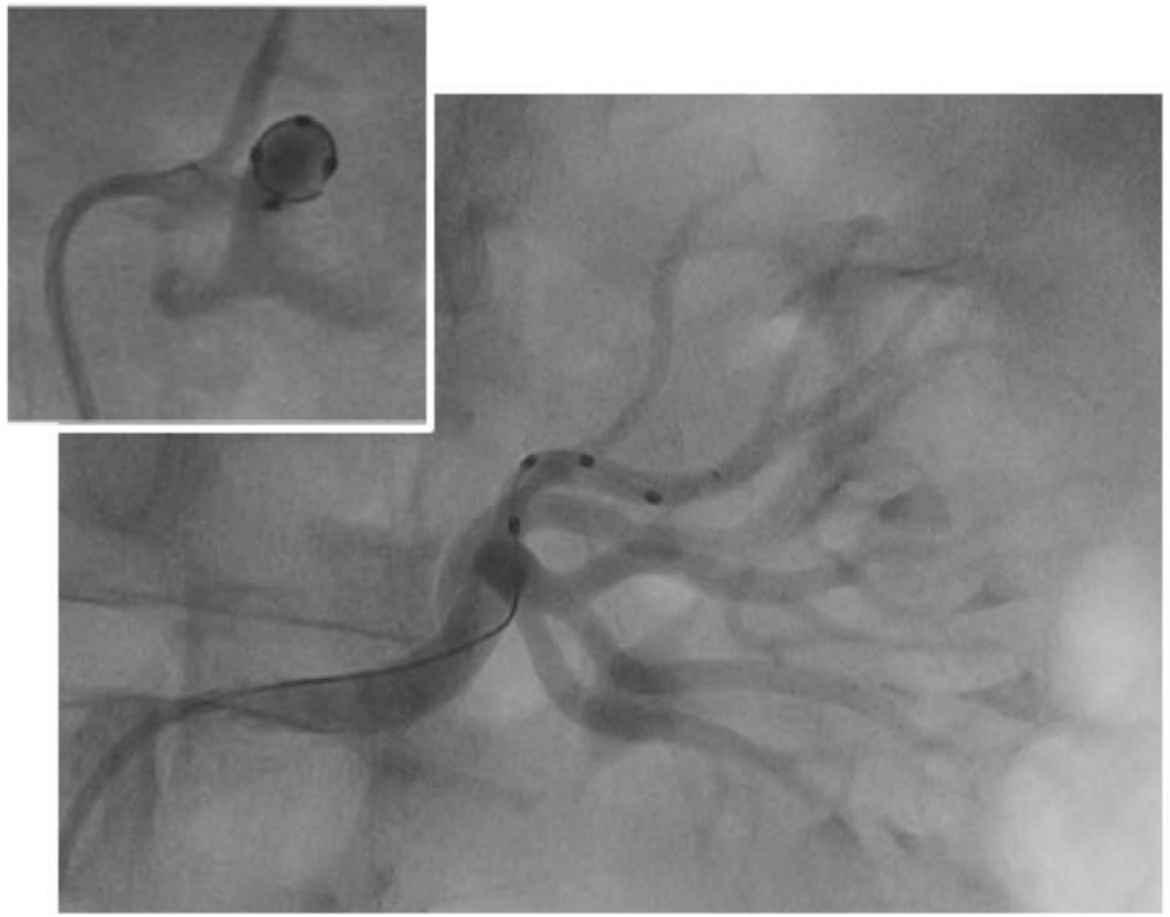
Site-specific delivery of alcohol: Local nerve inactivation

1. Micro-volume (0.3 mL–0.6 mL) infused directly to the perivascular region
2. Extracellular fluid helps spread alcohol circumferentially in the perivascular region
3. Alcohol activity range self-limited through dilution by extracellular fluid



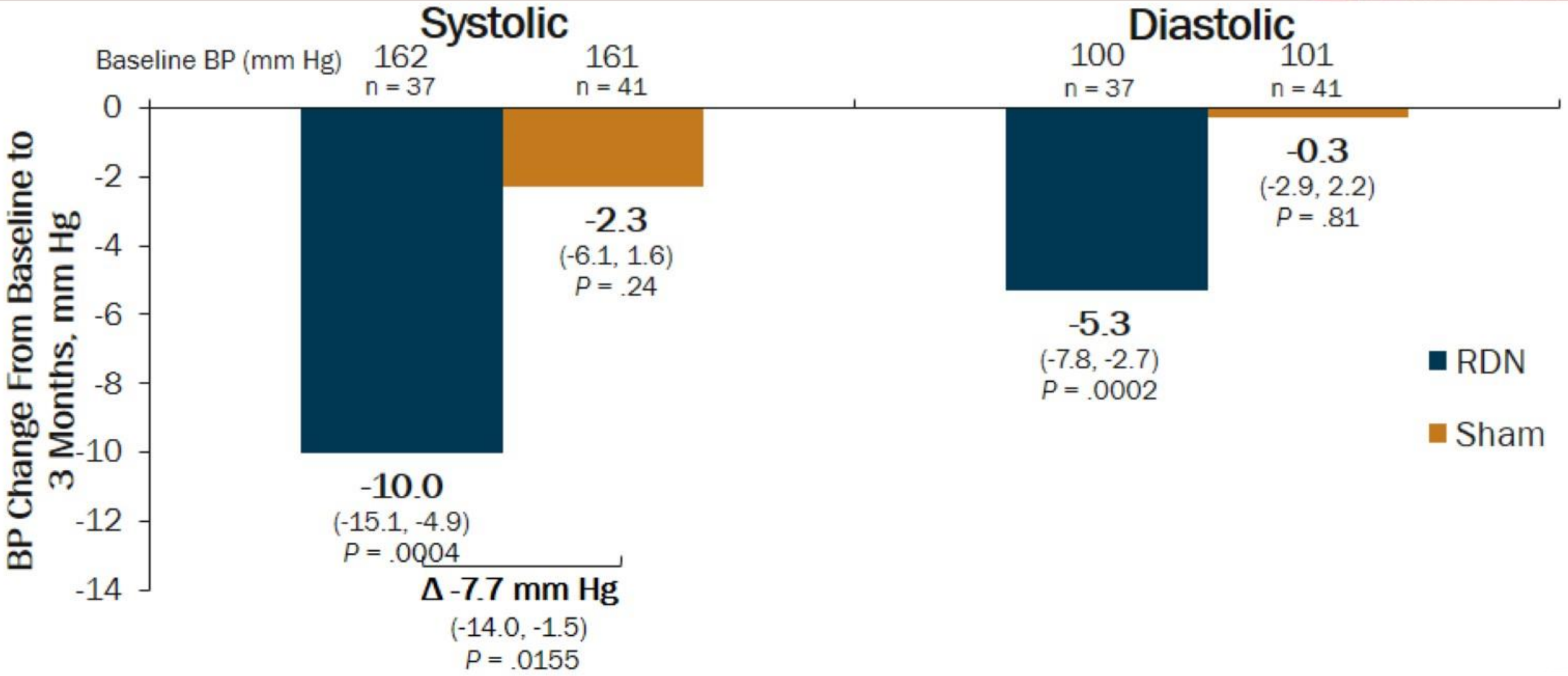
The Symplicity Spyral™ Catheter

- Multi-electrode catheter with quadrantic vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3 mm to 8 mm
- Flexible catheter allows branch treatment
- 6F guiding catheter compatible



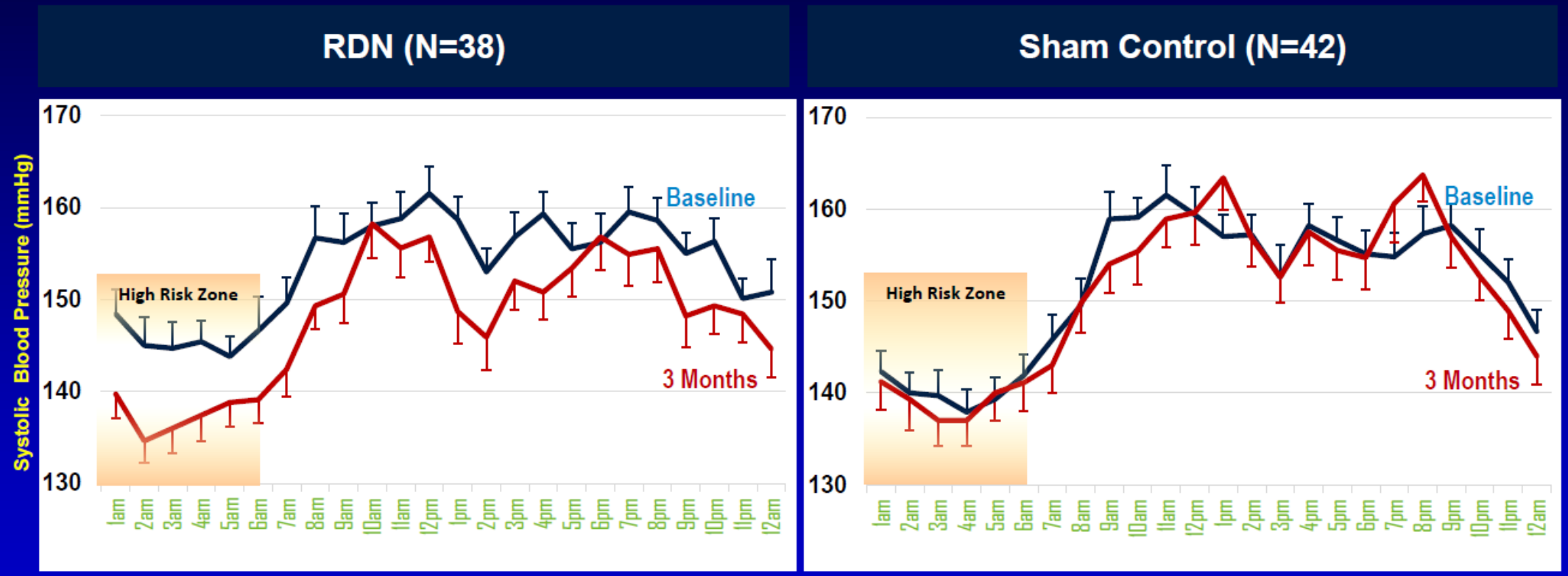
SPYRAL HTN – OFF MED

BP Change From Baseline to 3 Months: Office BP



Townsend RR, et al. *Lancet*. 2017;390:2160-2170.

SPYRAL HTN-OFF MED
24-HOUR ABPM TRENDS



- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events[2,3]

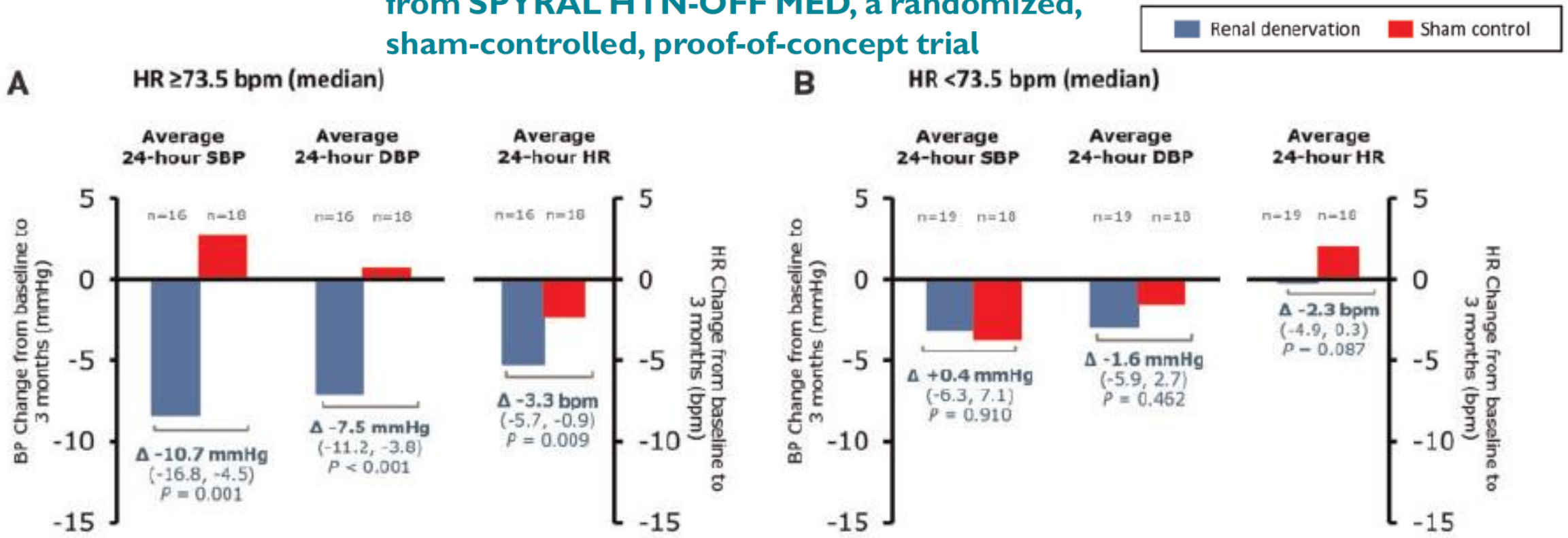
Graphs based on actual clock times. Similar results were observed when 24-hour BP patterns were normalized to patient reported time of waking.

1. Kario K et al, ACC 2018
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

ESC
European Society of Cardiology

Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial

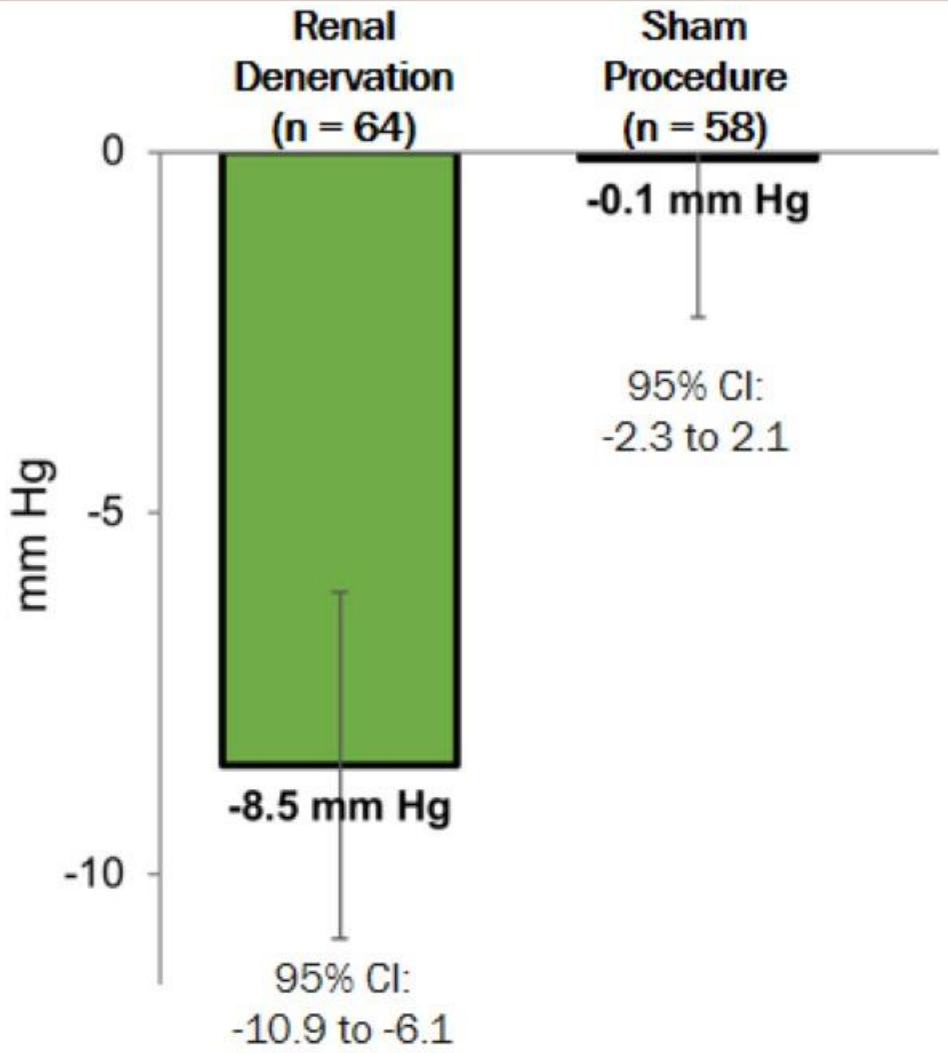
CLINICAL RESEARCH
Hypertension



European Heart Journal (2019) **40**, 743–751

RADIANCE-HTN SOLO

Change in Daytime Ambulatory Systolic BP at 2 Months, Per-Protocol

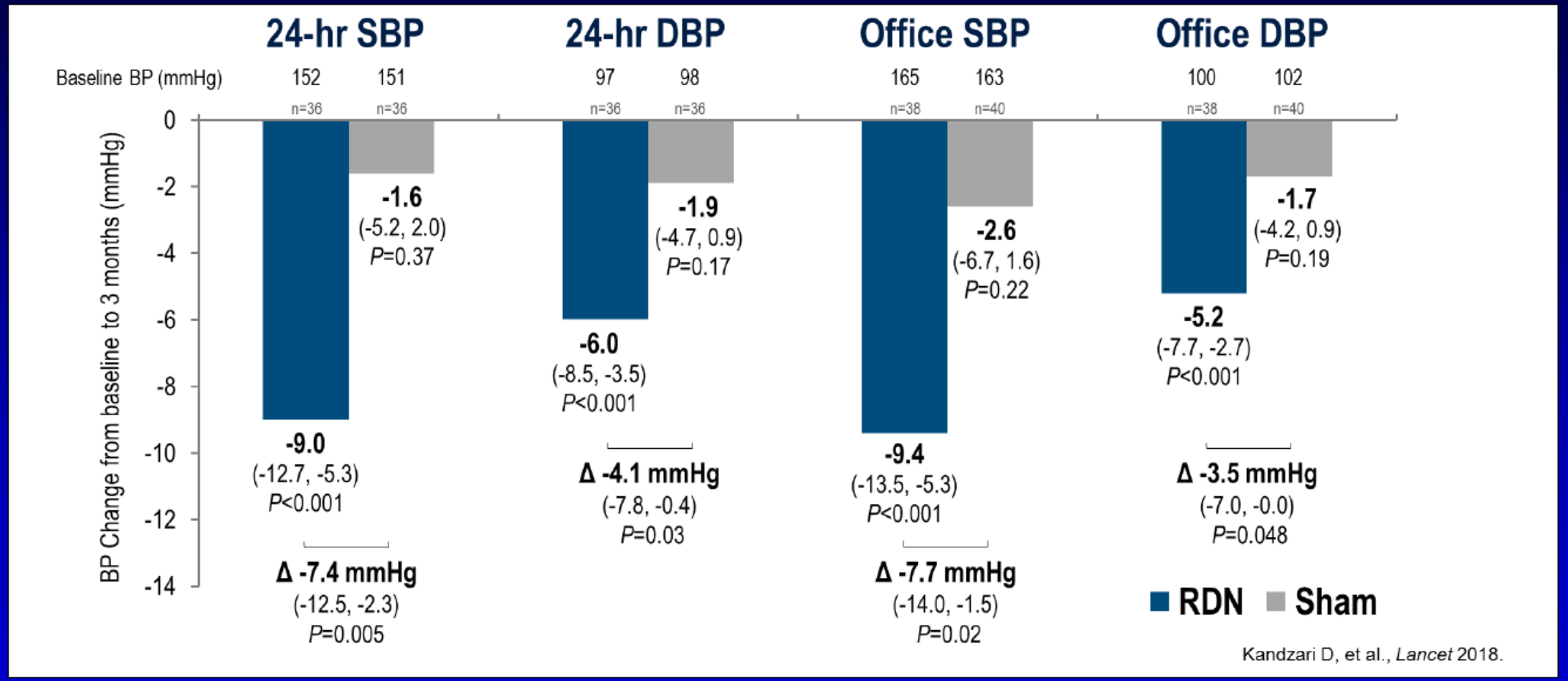


Between group difference adjusted for baseline BP
-8.2 mm Hg
(95% CI, -11.5, -5.0)
P < .0001

Azizi M, et al. *Lancet*. 2018;391:2335-2345.

SPYRAL HTN-ON MED

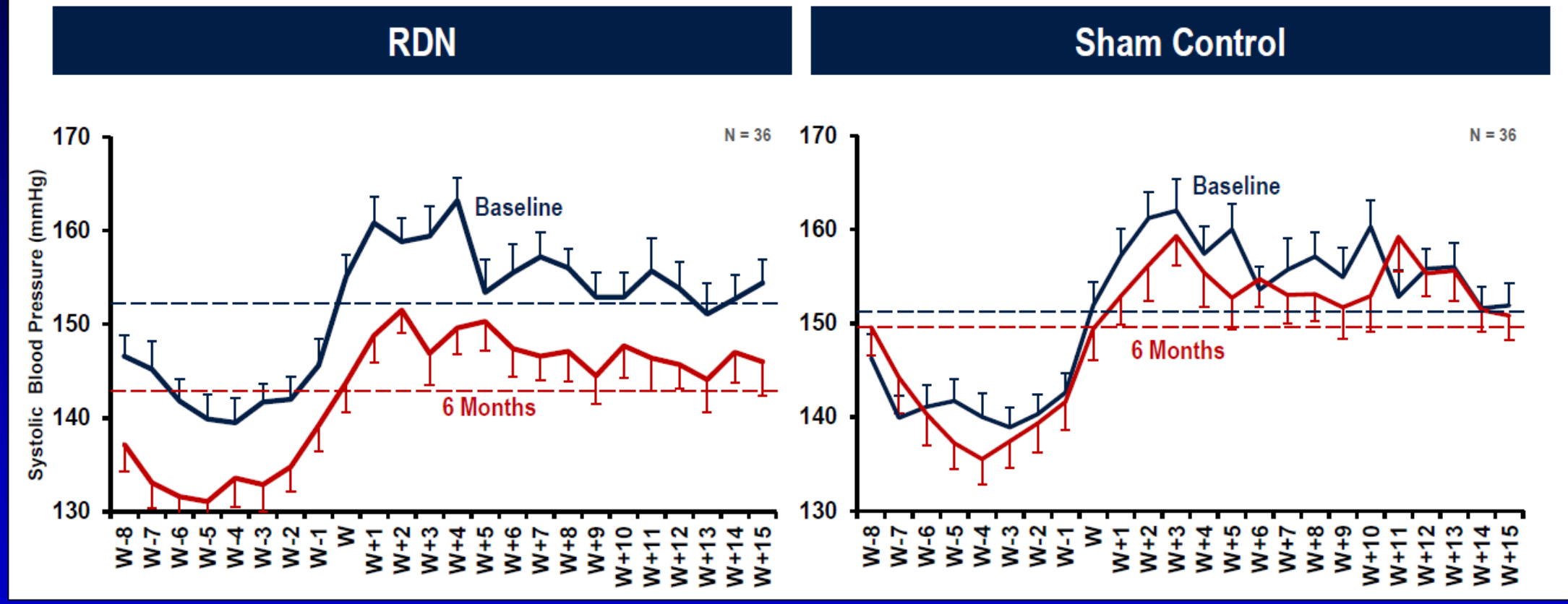
Blood Pressure Change from Baseline to 6 Months



Kandzari D, et al., *Lancet* 2018.

AS-av17-0818

SPYRAL HTN-ON MED
24-Hr Systolic Blood Pressure

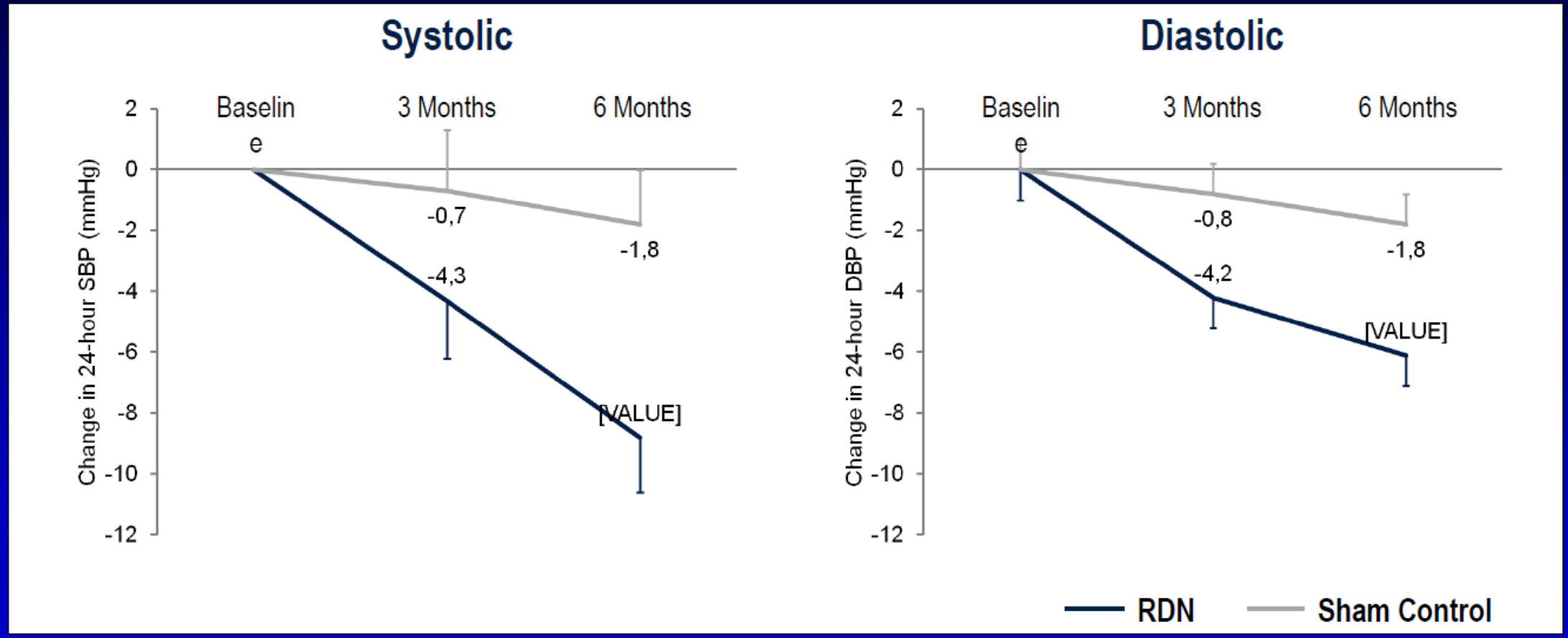


Dashed line represents the 24-hr mean at baseline (blue) and 6 months (red)
W = Self reported wake time or 7:00AM if not reported

Kandzari D, et al., *Lancet* 2018.

SPYRAL HTN-ON MED

24-Hr ABPM – Progressive Change Over Time



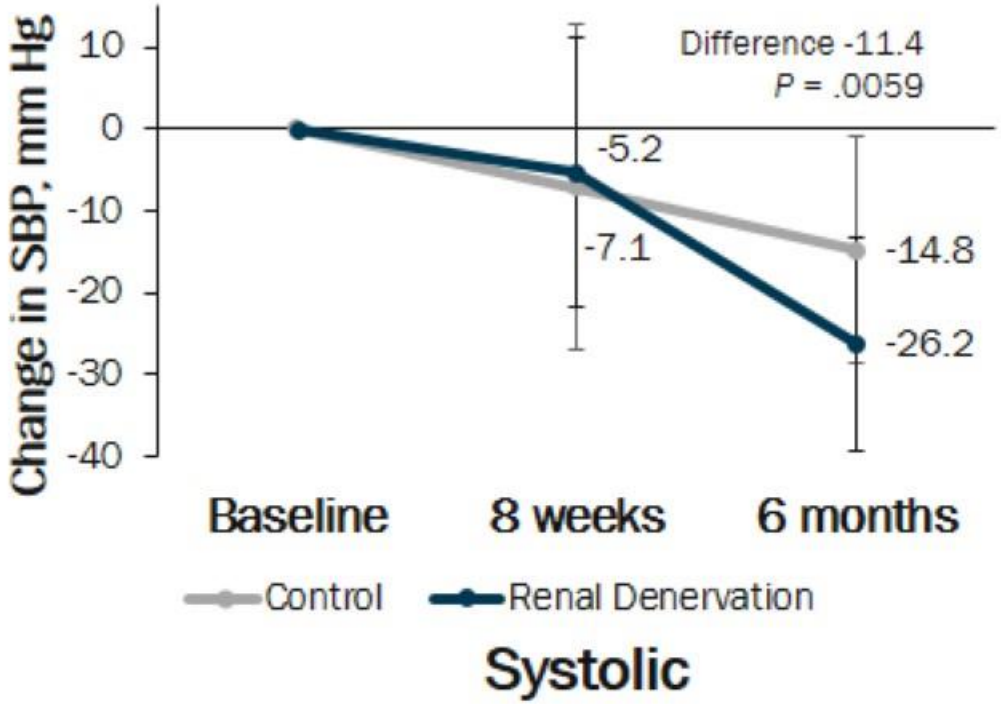
ANCOVA adjusted analysis

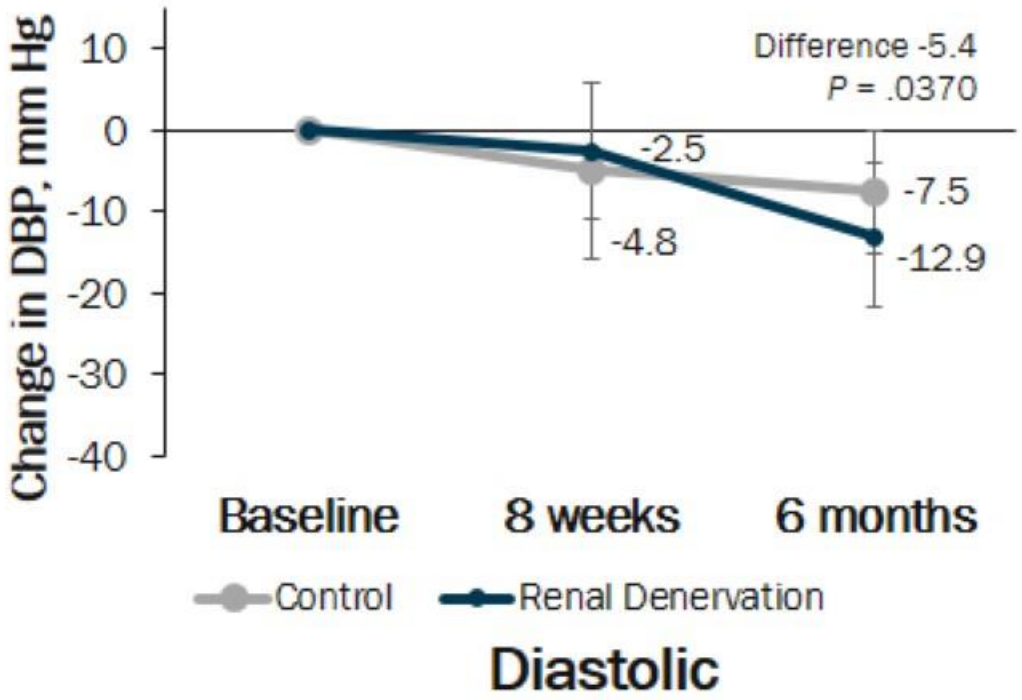
Kandzari D, et al., *Lancet* 2018.

REDUCE HTN: REINFORCE

Change in Office BP

Baseline BP, mm Hg	Systolic	Diastolic
Vessix	166.3 ± 9.0	94.9 ± 11.8
Control	166.2 ± 8.8	94.9 ± 11.1



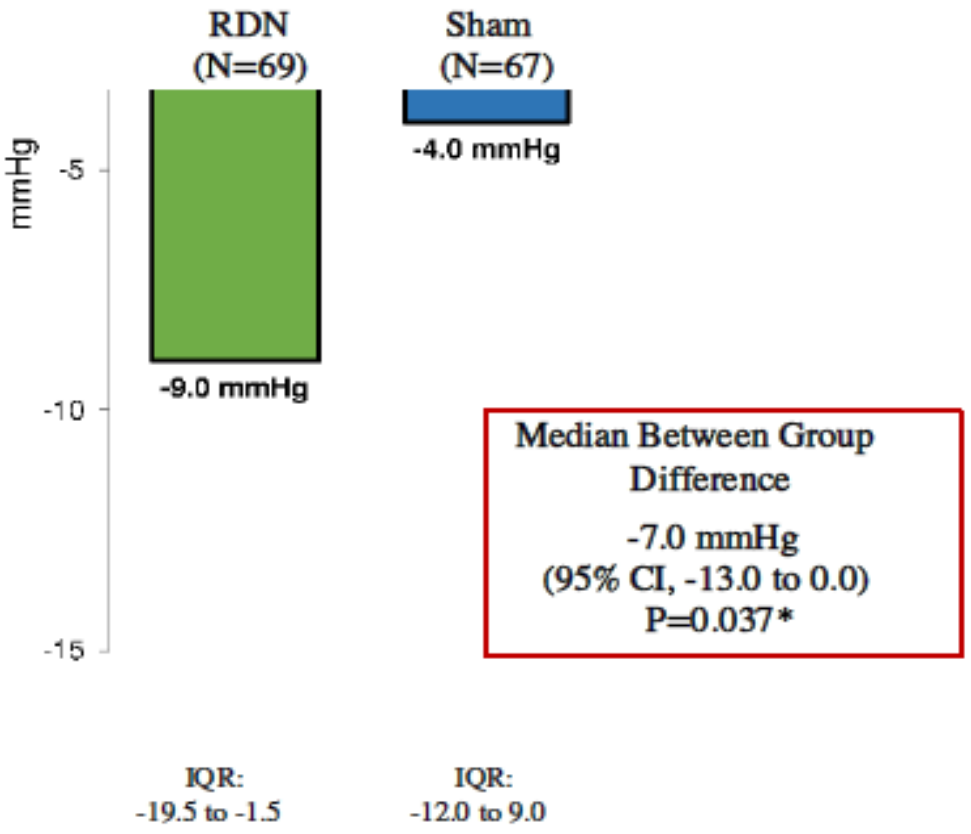


8-week data point includes rescued subjects with last antihypertensive medication-free reading carried forward to 8 weeks.

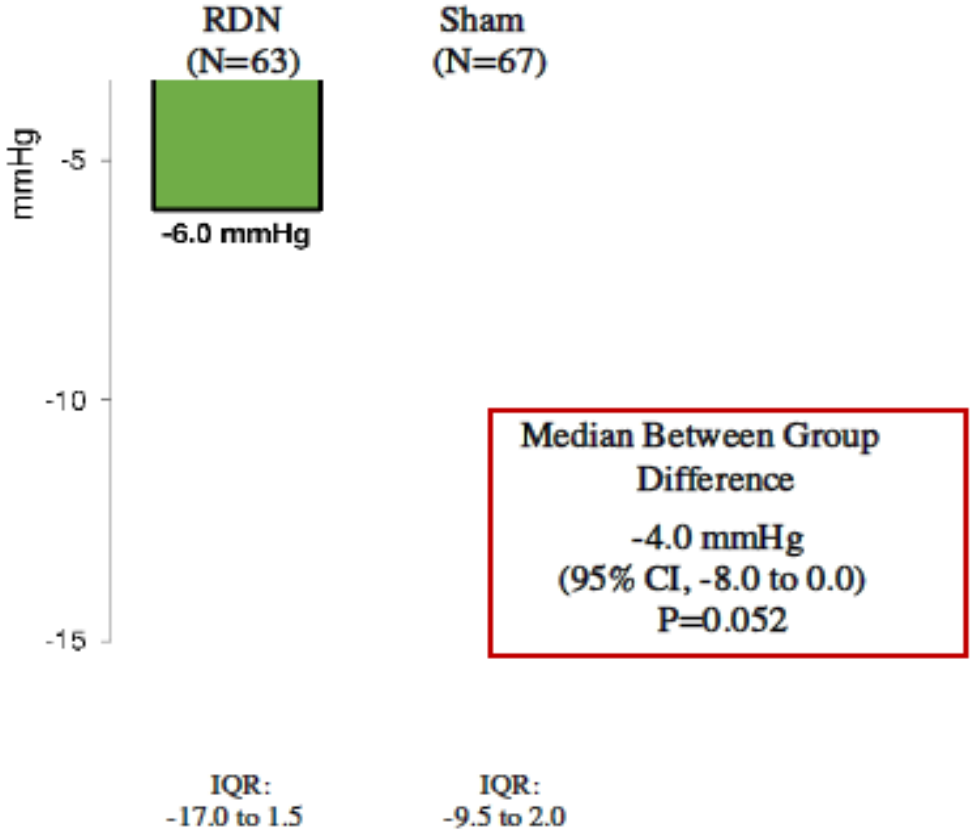
Weber MA, et al. *JACC Cardiovasc Interv*. 2020;13:461-470.

Change in Office and Home SBP at 2 Months

Office SBP



Home SBP

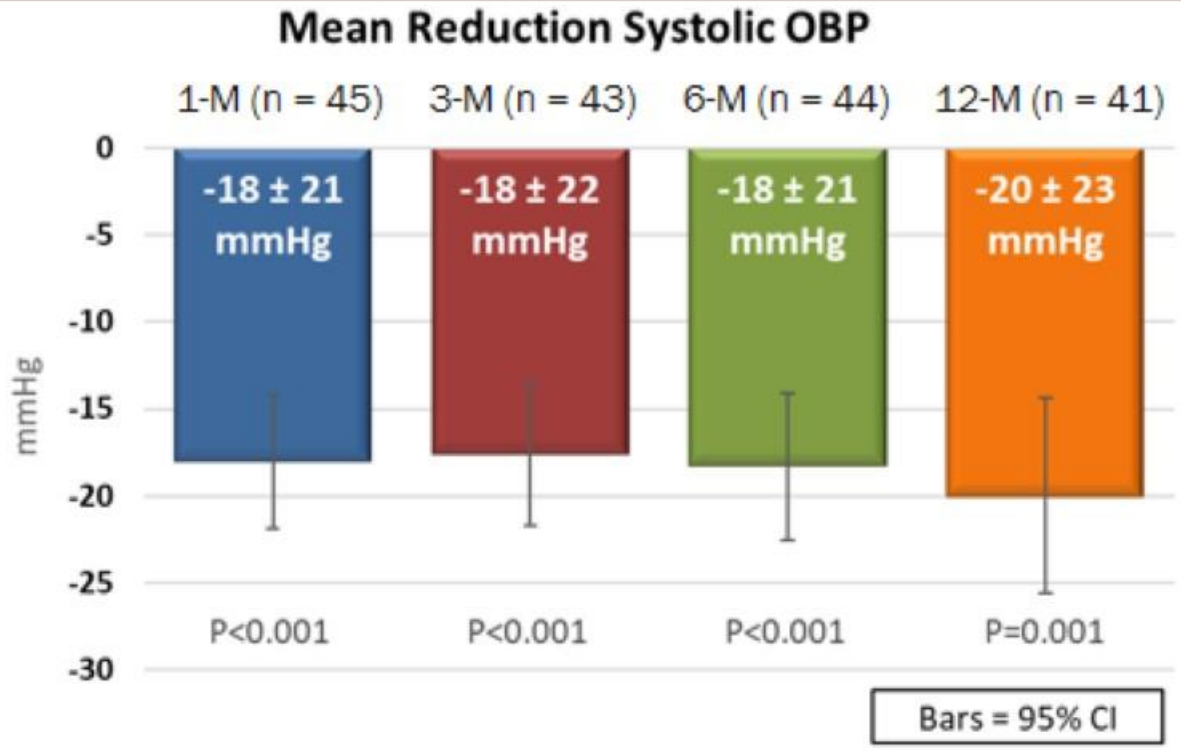


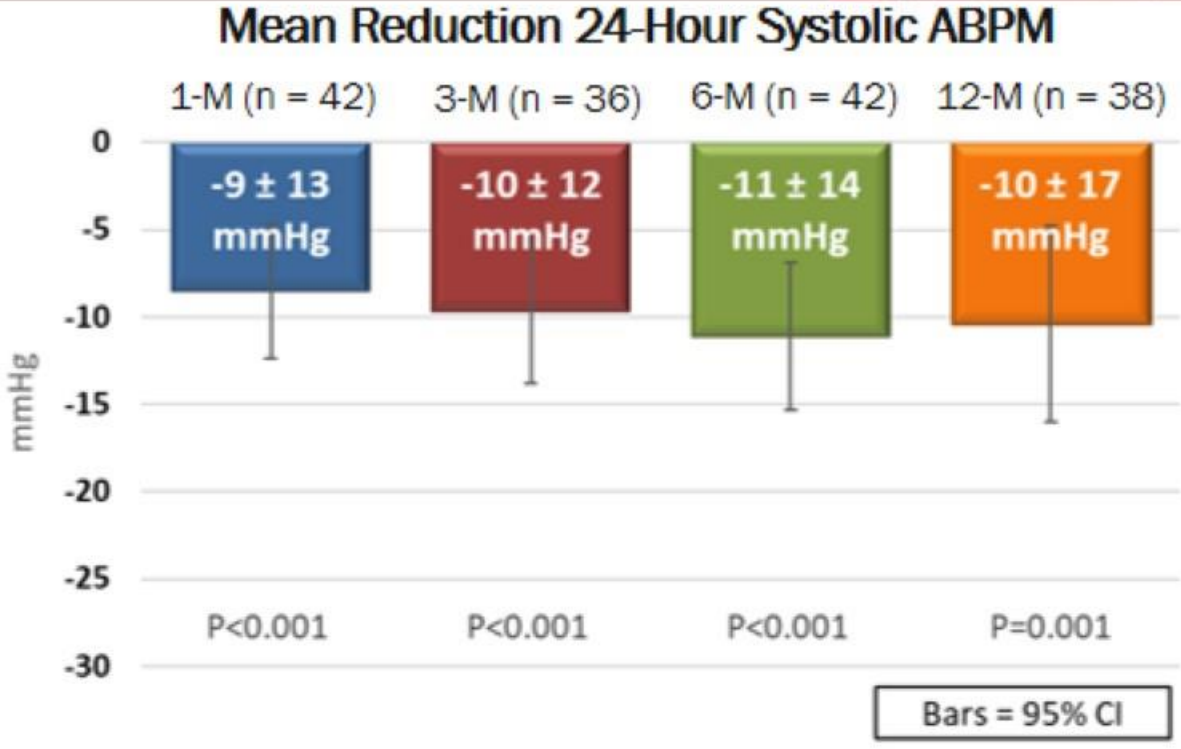
*Baseline-adjusted ANCOVA on the ranks due to non-normality of distribution

Lancet 2021, 397: 2476

Peregrine Catheter/Extra-Arterial Alcohol Perfusions

Systolic BP Reduction at 1, 3, 6, and 12 Months





Baseline OBP: 169 ± 15 mm Hg (n = 45)

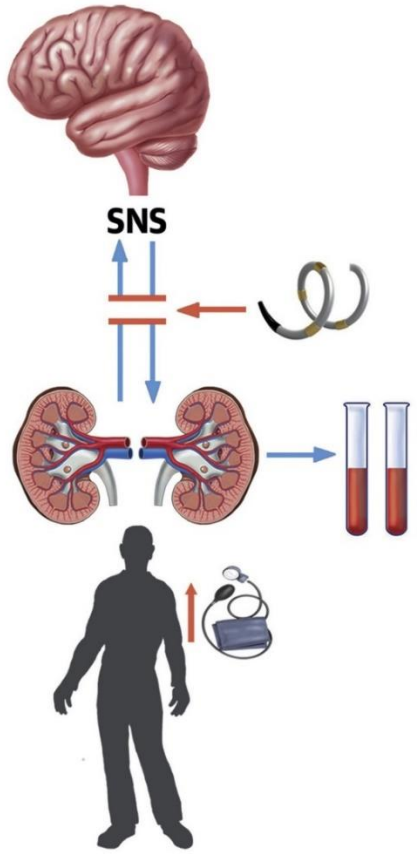
Baseline ABPM: 151 ± 14 mm Hg (n = 44)

Responders*:	**69%**	**58%**	**61%**	**71%**	**64%**	**67%**	**71%**	**61%**

*Responders are defined as ≥ 10 mm Hg drop for OBP and ≥ 5 mm Hg drop for ABPM.
Note: The Peregrine System is an investigational product not approved in the US.
Mahfoud F, et al. *JACC Cardiovasc Interv*. 2020;13:471-484.

Changes in Plasma Renin Activity After Renal Artery Sympathetic Denervation

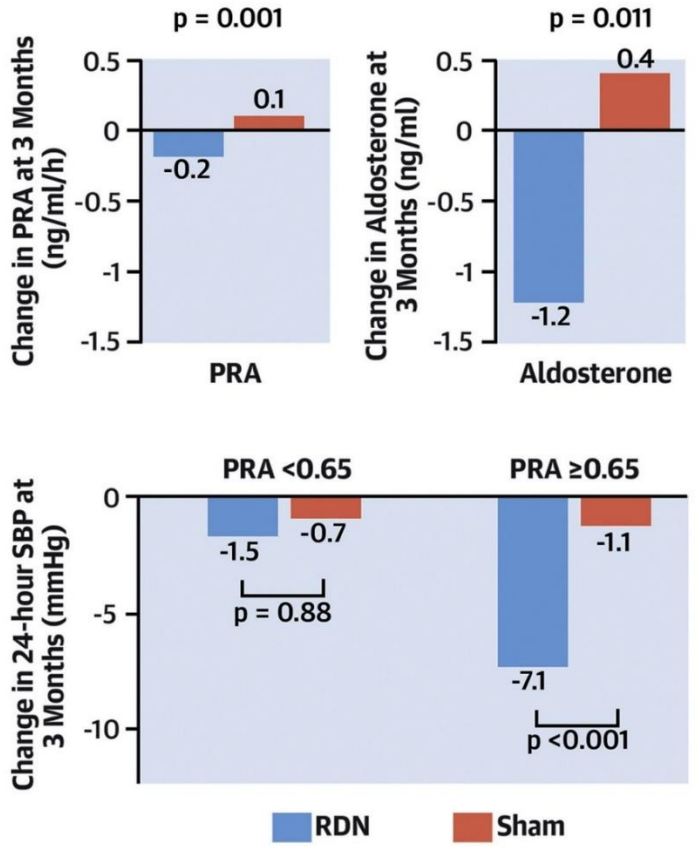
CENTRAL ILLUSTRATION: Impact of Renal Denervation on Plasma Renin Activity, Aldosterone, and Blood Pressure Reduction at 3 Months



Renal denervation resulted in lower plasma renin activity (PRA) and aldosterone compared with sham at 3 months

Patients with higher baseline PRA had greater drops in blood pressure compared with sham at 3 months

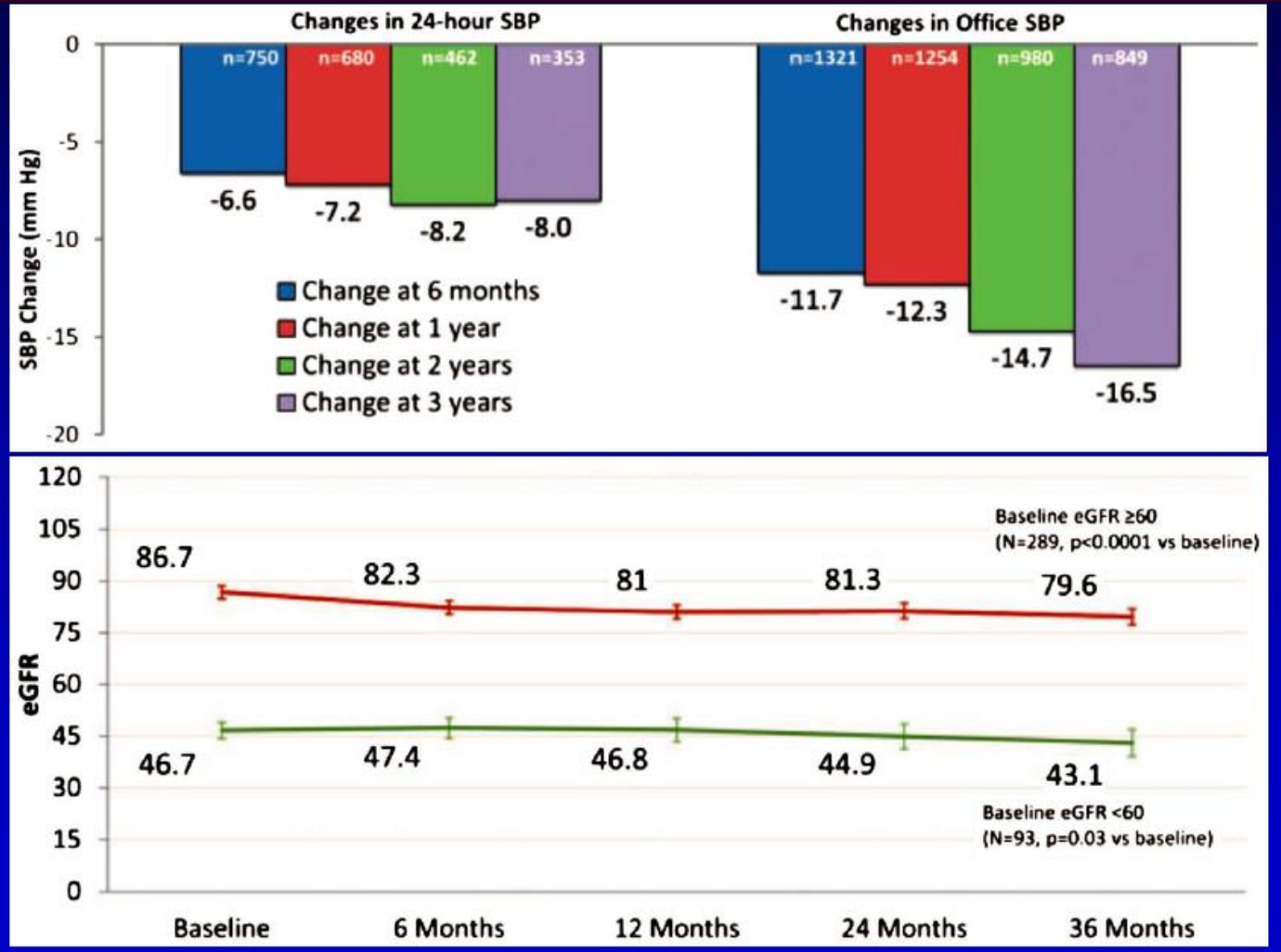
226 patients with uncontrolled hypertension without concomitant antihypertension medication



Mahfoud, F. et al. J Am Coll Cardiol. 2021;77(23):2909-19.

Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry

Felix Mahfoud[1]*, Michael Böhm[1], Roland Schmieder[2], Krzysztof Narkiewicz[3], Sebastian Ewen[1], Luis Ruilope[4], Markus Schlaich[5], Bryan Williams[6], Martin Fahy[7], and Giuseppe Mancia[8]



Mahfoud et al, Eur Heart J (2019): [doi:10.1093/eurheartj/ehz118]

Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry

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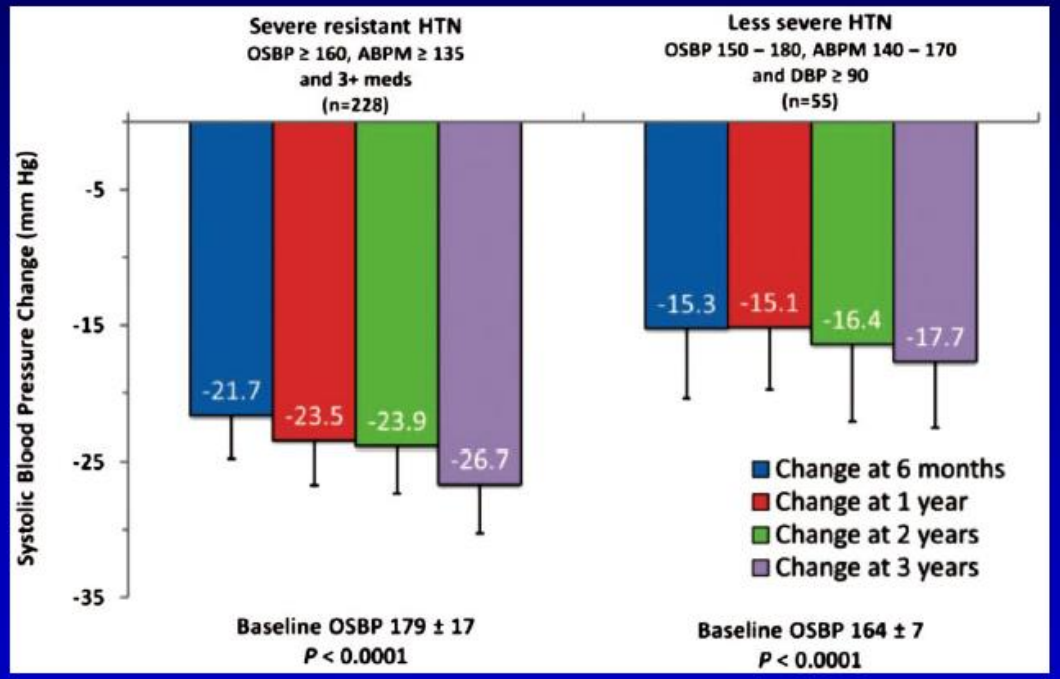
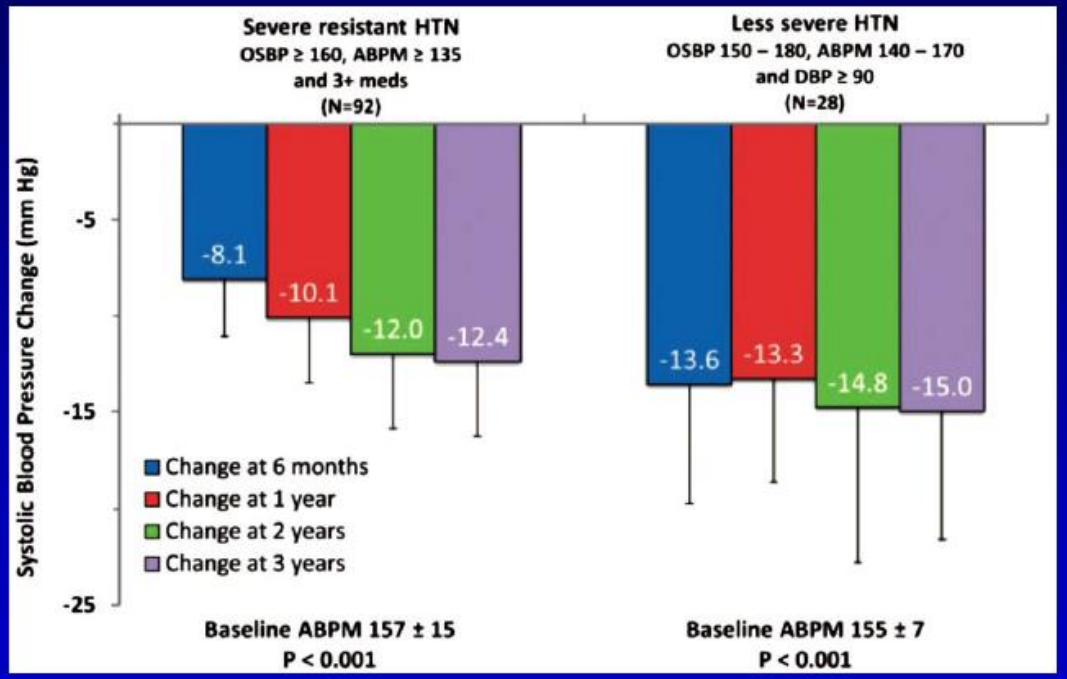
Change in Office SBP



Change in 24h Ambulatory SBP



Mahfoud et al, Eur Heart J (2019): [doi:10.1093/eurheartj/ehz118]

Controlling hypertension is critically important

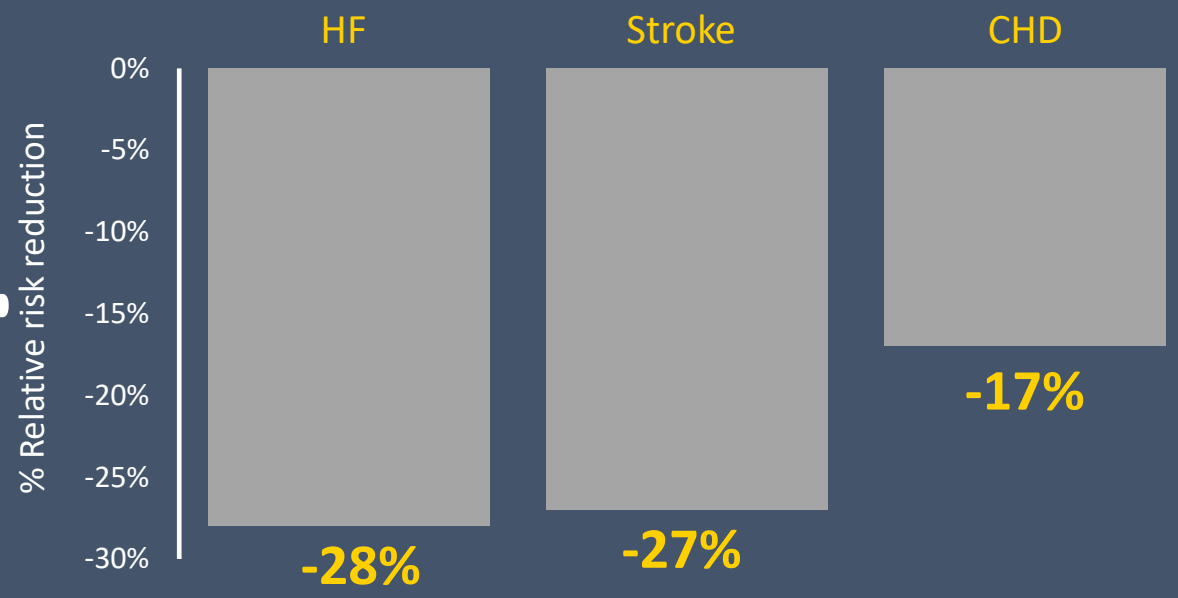
BLOOD PRESSURE CONTROL REDUCES THE RISK OF DEBILITATING SIDE EFFECTS

10 MM HG DECREASE IN MEAN OFFICE SBP:

20%
Reduction in relative risk of
major cardiovascular events

+

13%
Reduction in relative risk of
all-cause mortality



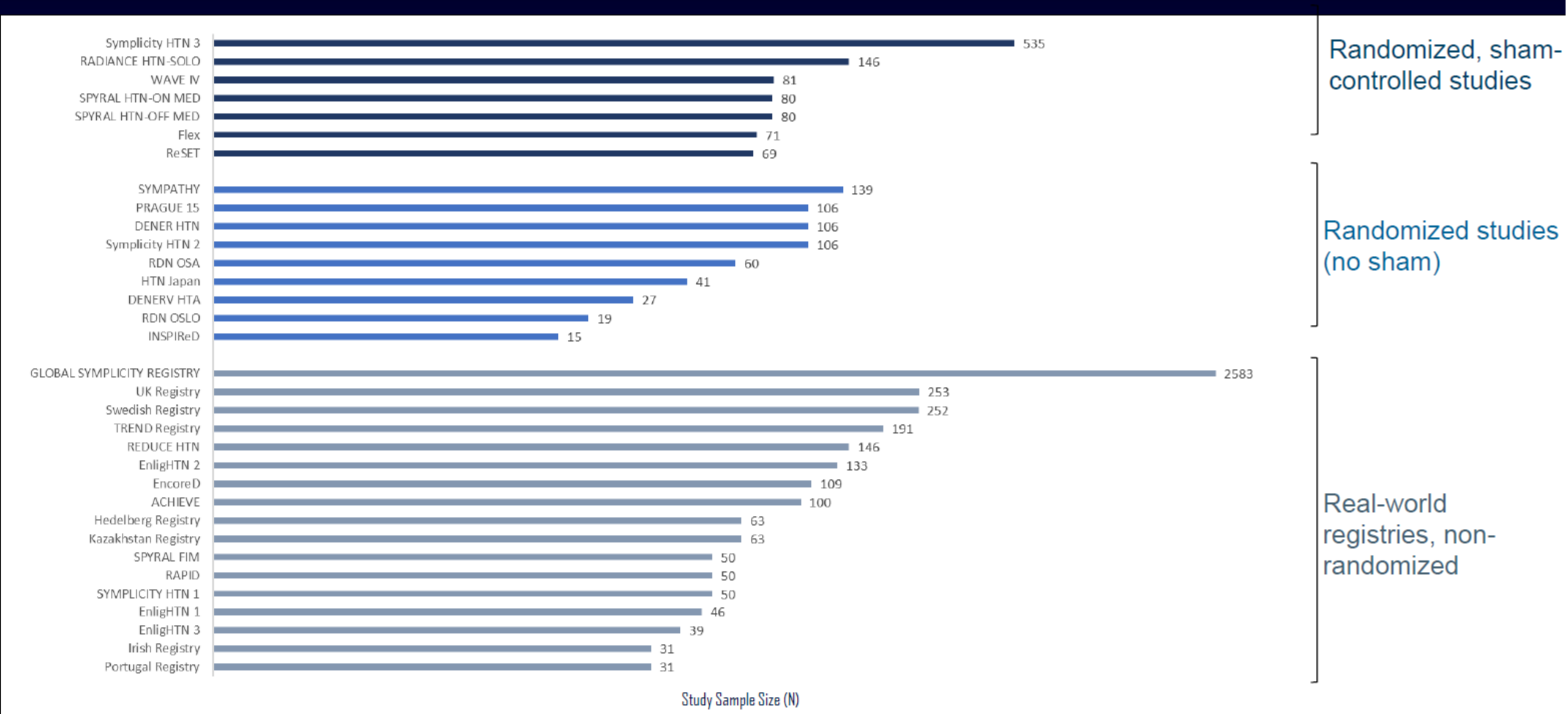
Ettehad D, et al. *Lancet*. 2016,387:957–967

CLINICAL EVENT REDUCTIONS IN HIGH-RISK HYPERTENSION PATIENTS TREATED WITH RENAL DENERVATION: A MODEL-BASED ESTIMATE BASED ON 36-MONTH DATA FROM THE GLOBAL SYMPLICITY REGISTRY

	Resistant Hypertension (RH)				Type-II Diabetes Mellitus (T2DM)			
	Global Symplicity Registry Observed (36M)	Calculated RR	Calculated control (Baseline SBP)	Calculated NNT	Global Symplicity Registry Observed (36M)	Calculated RR	Calculated control (Baseline SBP)	Calculated NNT
Death	5.7%	0.91	6.3%	181	7.1%	0.92	7.7%	172
Cardiovascular death	2.8%	0.78	3.6%	128	4.0%	0.84	4.8%	130
MI	2.3%	0.74	3.1%	121	3.5%	0.79	4.5%	105
Stroke	4.8%	0.58	8.4%	28	4.0%	0.66	6.1%	49
New-onset end-stage renal disease	1.9%	0.89	2.1%	426	2.8%	0.91	3.1%	363
Major adverse cardiac events (calculated)	9.9%	0.66	15.1%	19	11.5%	0.75	15.3%	27

JACC May 11, 2021
Volume 77, Issue 18

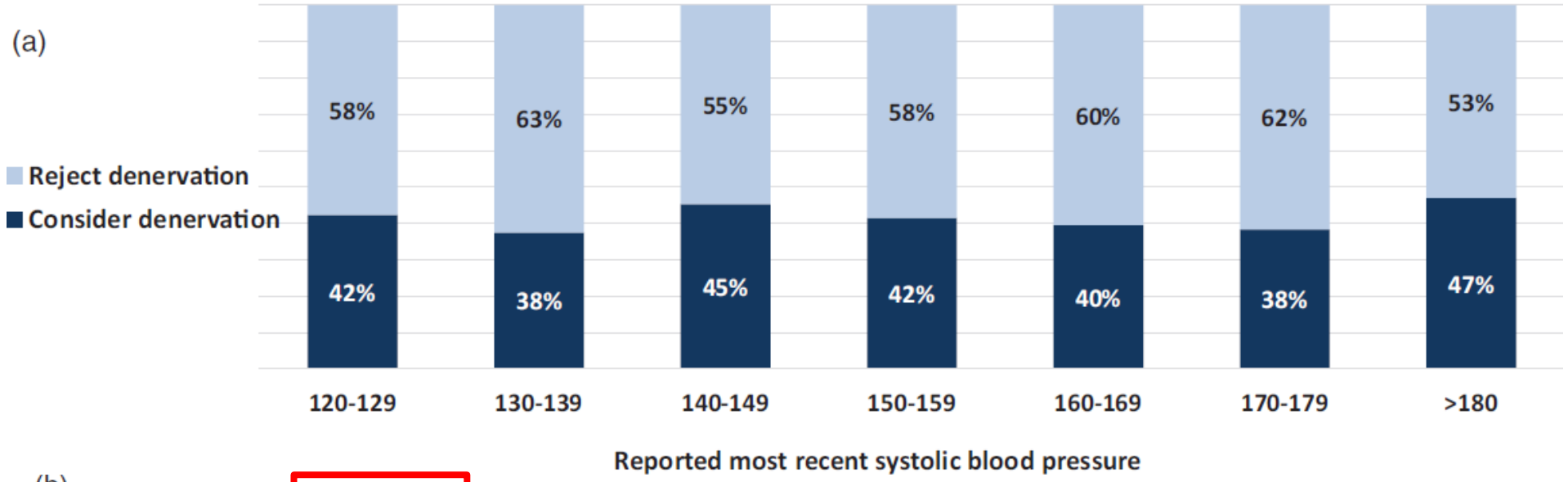
Over 5,800 Patients in Published trials of RDN for hypertension

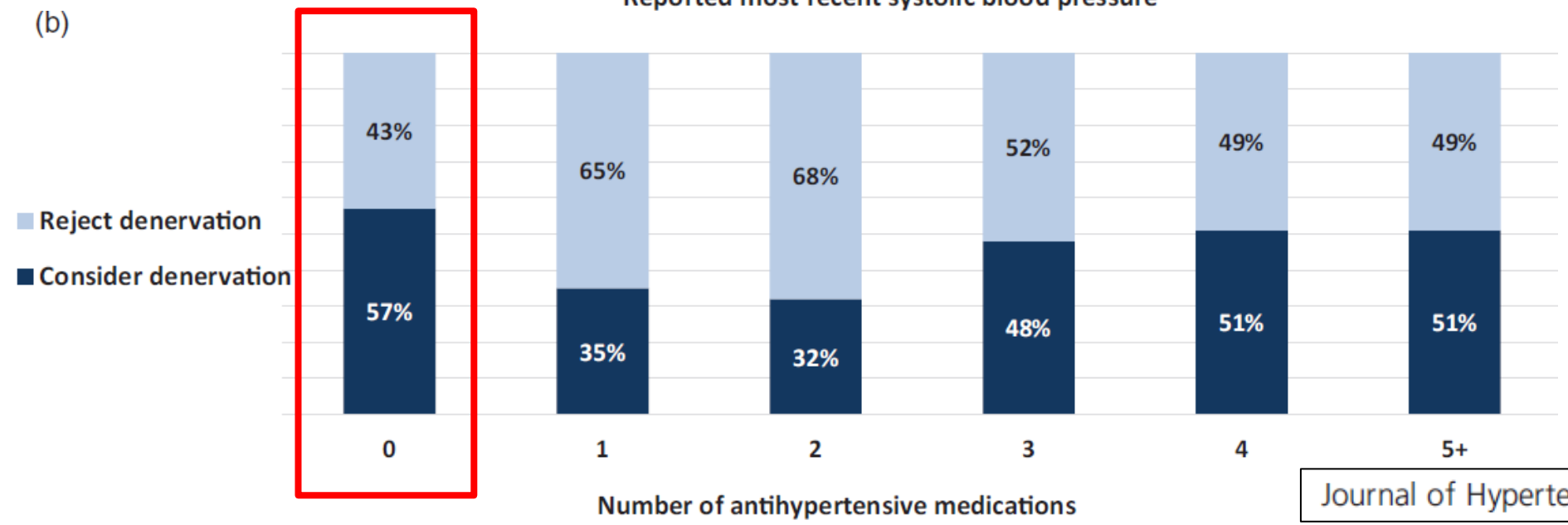


Renal Denervation for Treating Hypertension

- Renal nerve ablation is achieved by radiofrequency or ultrasound energy or by alcohol perfusion delivered by catheters through the walls of the renal arteries
- Improved understanding of renal nerve anatomy, new generation catheters, and updated ablation procedures have all added to the effectiveness of RDN
- The techniques now used are effective in patients not taking oral antihypertensive drugs, as well as in patients with uncontrolled hypertension despite being on these drugs
- Although effects of the procedure can sometimes be seen almost immediately, full reductions in blood pressure may not be apparent for up to 6 months
- Registry data demonstrate efficacy is maintained for at least 3 years
- There have been no major safety issues reported with the RDN procedures

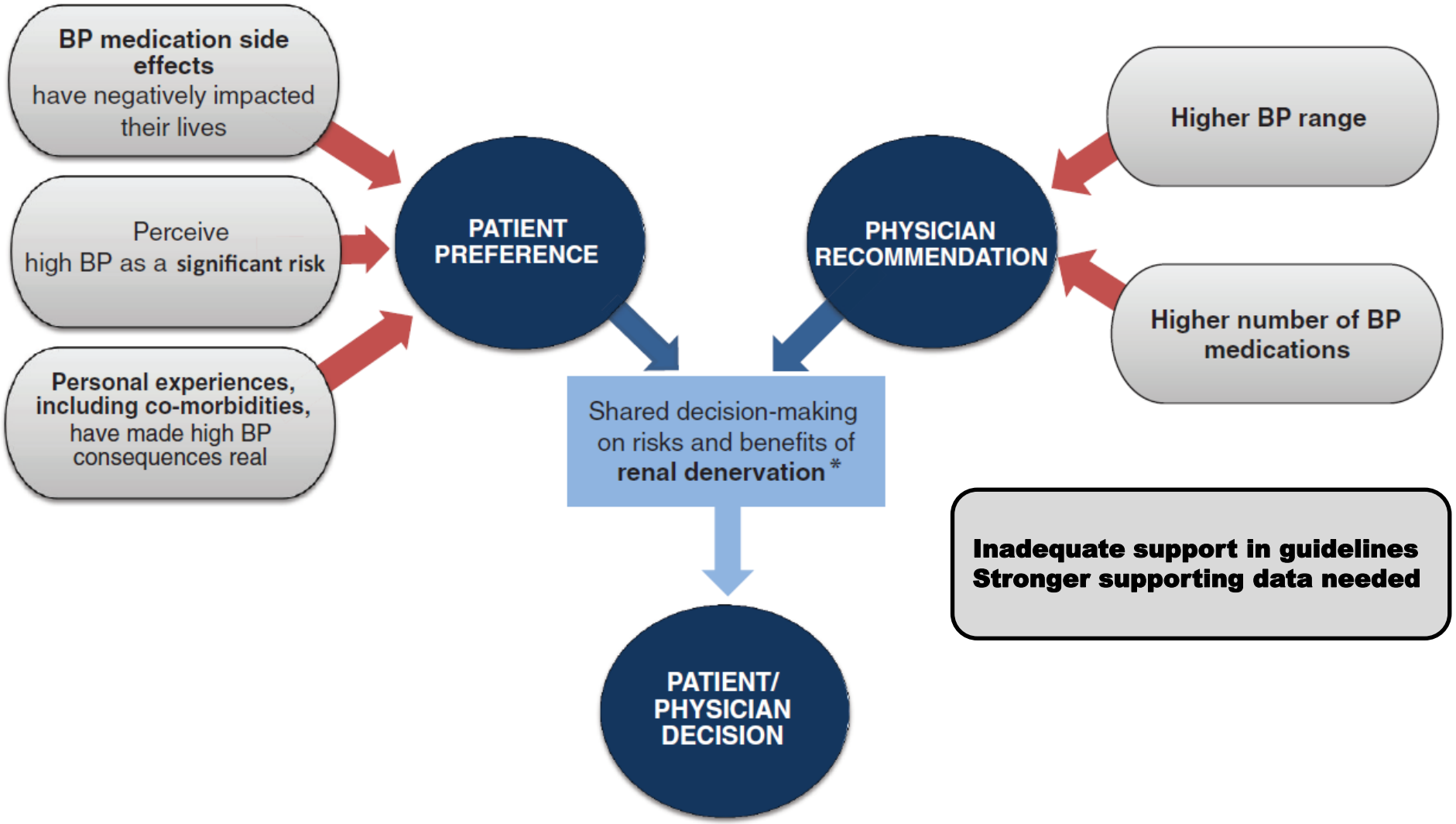
Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension





Journal of Hypertension 2021, 39:162–168

Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension



Journal of Hypertension 2021, 39:162–168

nuove posizioni

POSITION PAPER

Check for updates

Italian Society of Arterial Hypertension (SIIA) Position Paper on the Role of Renal Denervation in the Management of the Difficult-to-Treat Hypertensive Patient

Rosa Maria Bruno[1,2] · Stefano Taddei[1] · Claudio Borghi[3] · Furio Colivicchi[4] · Giovambattista Desideri[5] · Guido Grassi[6] · Alberto Mazza[7] · Maria Lorenza Muiesan[8] · Gianfranco Parati[9,10] · Roberto Pontremoli[11] · Bruno Trimarco[12] · Massimo Volpe[13,14] · Claudio Ferri[5]

8 internisti
4 cardiologi
1 nefrologo

… nel futuro è quindi necessario un forte programma di sviluppo scientifico e clinico che ci porti a poter considerare la denervazione renale una delle opzioni terapeutiche nella pratica clinica quotidiana

High Blood Pressure & Cardiovascular Prevention . 2020

European Society of Hypertension position paper on renal denervation 2021

Consensus Document

BOX 1: Position Statement in 2021

- On the basis of consistent results of several sham-controlled clinical trials, renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and blood pressure lowering drugs.
- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, that is to effectively reduce an elevated blood pressure and achieve blood pressure targets.
- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available up to 3 years.
- Renal denervation is an alternative or additive, not a competitive treatment strategy.
- A structured pathway for clinical use of RDN in daily practice is recommended.
- Patients' perspective and preference as well as patients' stage of hypertensive disease including comorbidities should lead to an individualized treatment strategy in a shared decision-making process, that carefully includes the various options of treatment, including renal denervation.

Journal of Hypertension 2021, 39:000–000

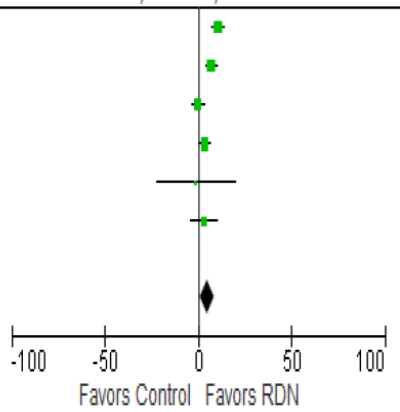
Introduction

- Catheter-guided renal artery denervation (RDN) works on sympathetic system deactivation
- It can treat resistant hypertension and modulate sympathetic system hyper stimulation of heart failure patients with reduced ejection fraction (HFrEF)
- Current medical therapy aim to inhibit the RAAS
- RDN can be an alternative to medical therapy

LVEF Improvement

Study or Subgroup	RDN Mean	RDN SD	RDN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Chen.2016	41.9	7.9	30	31.2	5.5	30	20.7%	10.70 [7.26, 14.14]
Dai.2015	45	3	10	38	4	10	21.5%	7.00 [3.90, 10.10]
Drozdz.2019	32	3	10	32	5	10	20.3%	0.00 [-3.61, 3.61]
Gao.2018	39.1	7.3	30	35.6	3.3	30	22.0%	3.50 [0.63, 6.37]
Spadaro.2019	32.2	8.2	9	33.3	20.8	4	2.6%	-1.10 [-22.18, 19.98]
Taborsky.2012	31.14	14	26	28	12	25	12.8%	3.14 [-4.01, 10.29]
Total (95% CI)			115			109	100.0%	4.87 [1.25, 8.48]

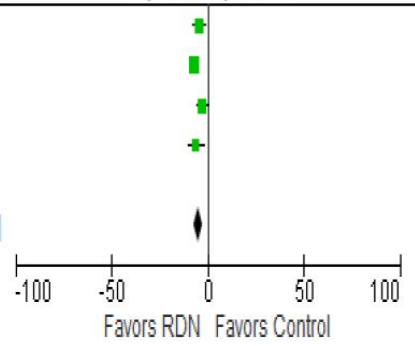
Heterogeneity: Tau² = 13.35; Chi² = 21.06, df = 5 (P = 0.0008); I² = 76%
Test for overall effect: Z = 2.64 (P = 0.008)



LVEDD

Study or Subgroup	RDN Mean	RDN SD	RDN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Chen.2016	59.4	7	30	63.9	5	30	24.2%	-4.50 [-7.58, -1.42]
Dai.2015	60	3	10	67	0.4	10	34.1%	-7.00 [-8.88, -5.12]
Gao.2018	60	6.7	30	62.5	4.5	30	25.6%	-2.50 [-5.39, 0.39]
Taborsky.2012	60	7	26	66	9	25	16.2%	-6.00 [-10.44, -1.56]
Total (95% CI)			96			95	100.0%	-5.08 [-7.31, -2.85]

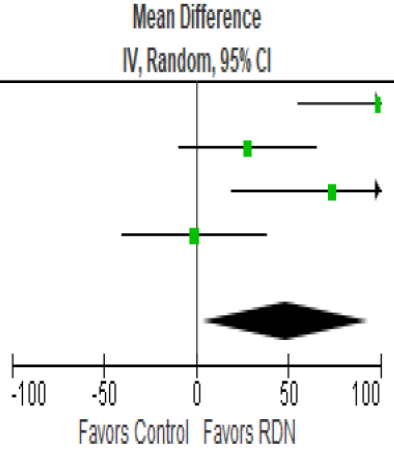
Heterogeneity: Tau² = 2.88; Chi² = 7.05, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 4.47 (P < 0.00001)



6 Minutes Walk

Study or Subgroup	RDN Mean	RDN SD	RDN Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Chen.2016	374.9	91.9	30	275.3	82	30	24.9%	99.60 [55.53, 143.67]
Drozdz.2019	350	45	10	322	40	10	26.8%	28.00 [-9.32, 65.32]
Gao.2018	301.2	139.5	30	227.2	65	30	22.0%	74.00 [18.93, 129.07]
Spadaro.2019	200	57.2	9	201	11.3	4	26.3%	-1.00 [-39.98, 37.98]
Total (95% CI)			79			74	100.0%	48.35 [3.29, 93.40]

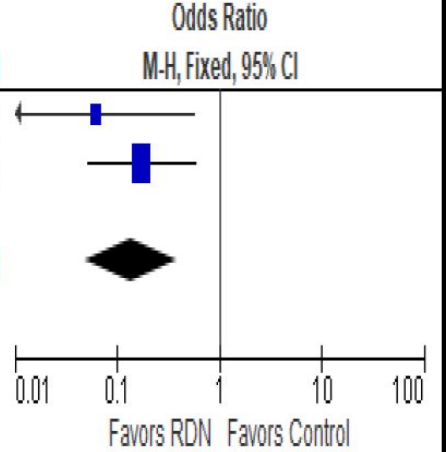
Heterogeneity: Tau² = 1612.63; Chi² = 13.07, df = 3 (P = 0.004); I² = 77%
Test for overall effect: Z = 2.10 (P = 0.04)



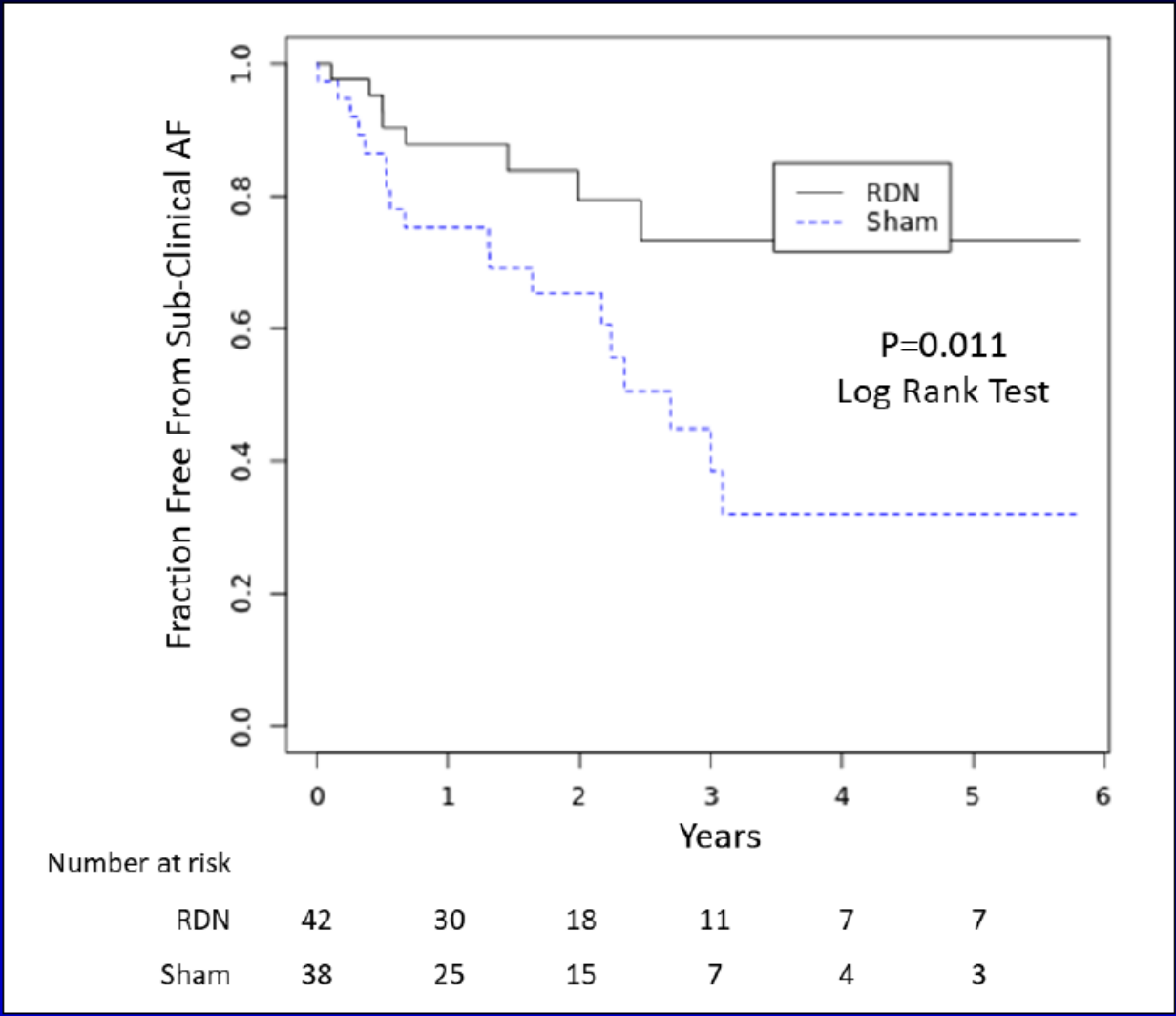
Hospitalizations

Study or Subgroup	RDN Events	RDN Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dai.2015	2	10	8	10	33.5%	0.06 [0.01, 0.56]
Taborsky.2012	8	26	18	25	66.5%	0.17 [0.05, 0.58]
Total (95% CI)		36		35	100.0%	0.14 [0.05, 0.39]
Total events	10		26			

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)



RESULTS: Primary Endpoint: Subclinical AF*



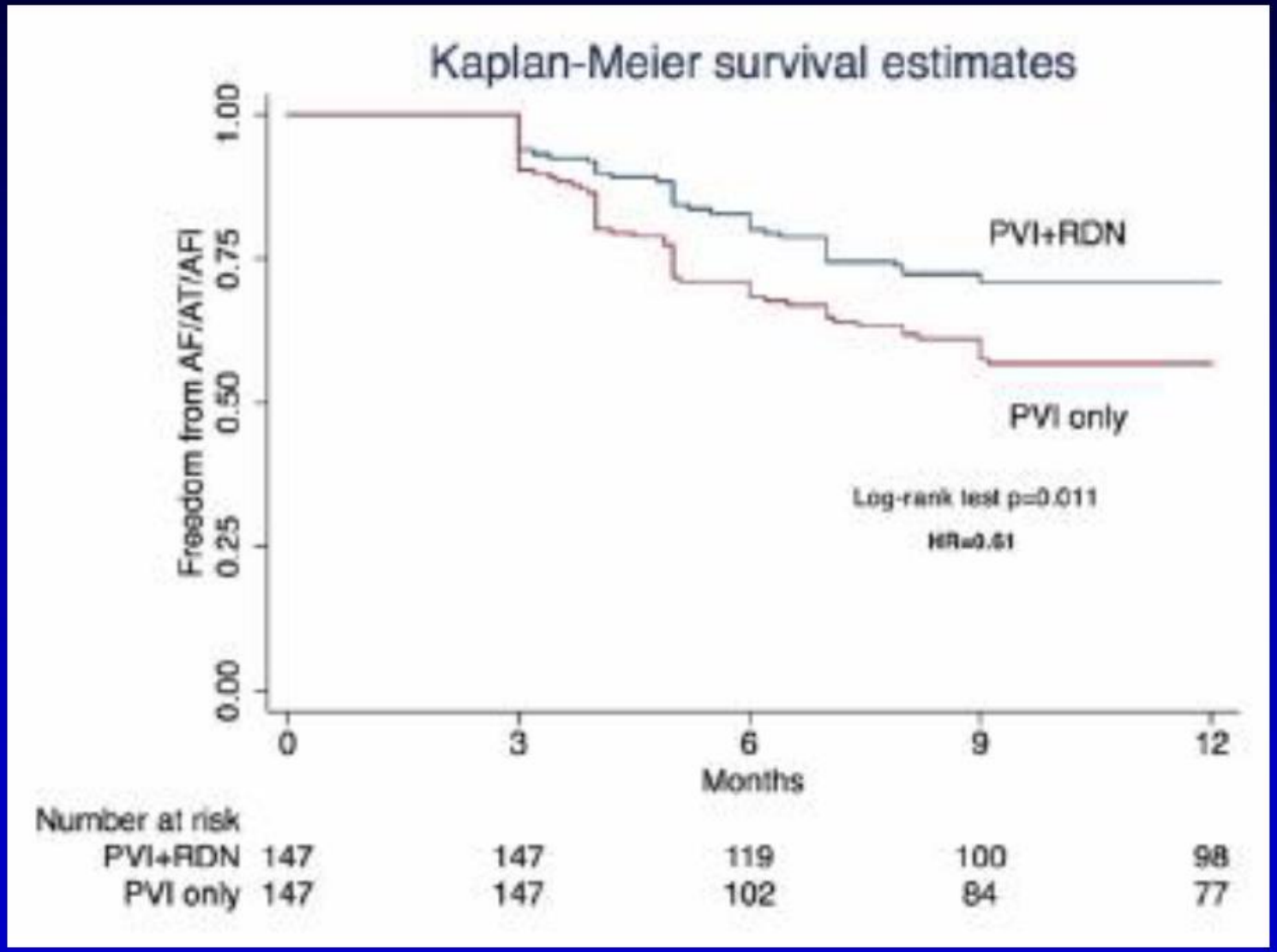
Cumulative incidence of primary endpoint after average 3 years follow up:

- RD: 8 of 42 (19%)
- Sham RD: 18 of 38 (47%)
- RR: 0,4 (95% CI: 0,22-0,73)
- RRR= 60%
- NNT: 3,5 to prevent one event

*identified via ILR

Heradien et al., Euro PCR 2019

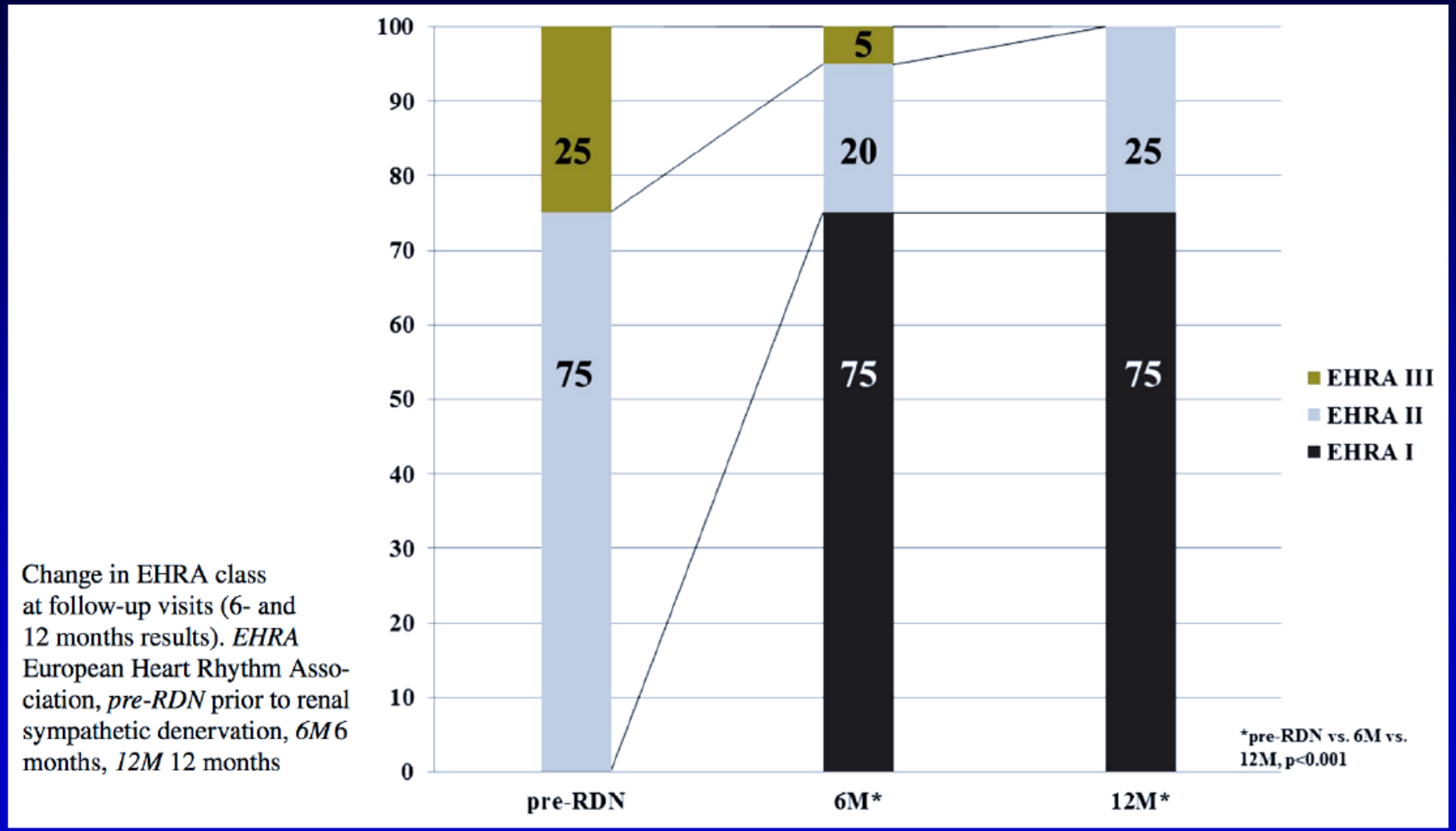
RDN reduced AF recurrence after Pulmonary Vein Isolation



Steinberg J, et al. Presented at HRS 2019.

Atrial fibrillation reduction by renal sympathetic denervation: 12 months' results of the AFFORD study

Lida Feyz[1] · Dominic A. Theuns[1] · Rohit Bhagwandien[1] · Mihai Strachinaru[1] · Isabella Kardys[1] · Nicolas M. Van Mieghem[1] · Joost Daemen[1]



Change in EHRA class at follow-up visits (6- and 12 months results). *EHRA* European Heart Rhythm Association, *pre-RDN* prior to renal sympathetic denervation, *6M* 6 months, *12M* 12 months

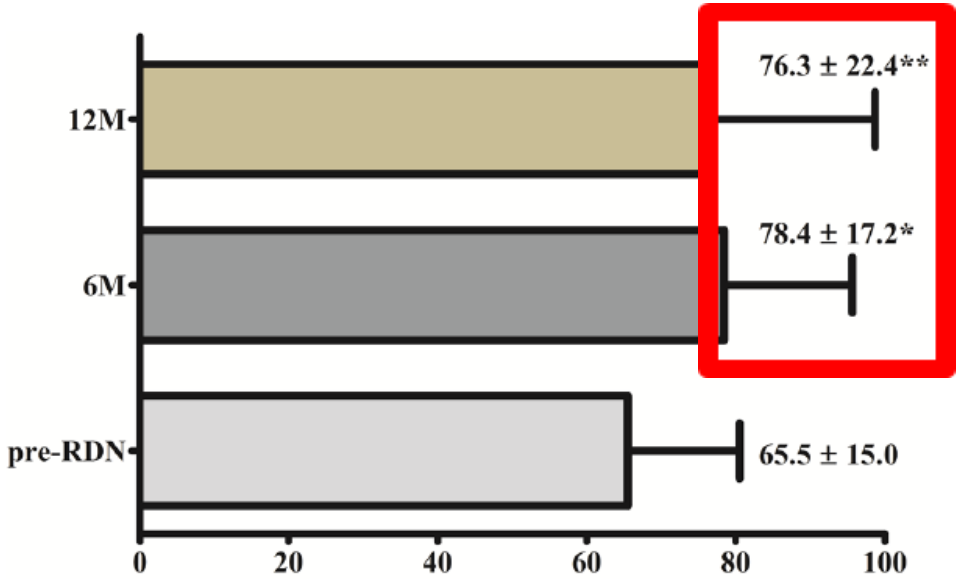
Feyz et al, Clin Res Cardiol 108 (2019): 634-642

Atrial fibrillation reduction by renal sympathetic denervation: 12 months' results of the AFFORD study

	Pre-RDN	6 months	12 months	*p**	*p***
AF episodes (*n*)	1 (0–11)	1 (0–11)	3 (0–16)	0.84	0.31
Total episodes AF (min)	125 (2–978)	44 (0–2833)	84 (0–544)	0.64	0.03
AF min/day	1.39 (0–10.9)	0.67 (0–31.6)	0.94 (0–6.0)	0.64	0.03
Highest VRR (bpm)	127 (105–145)	117 (104–141)	106 (75–126)	0.09	0.01

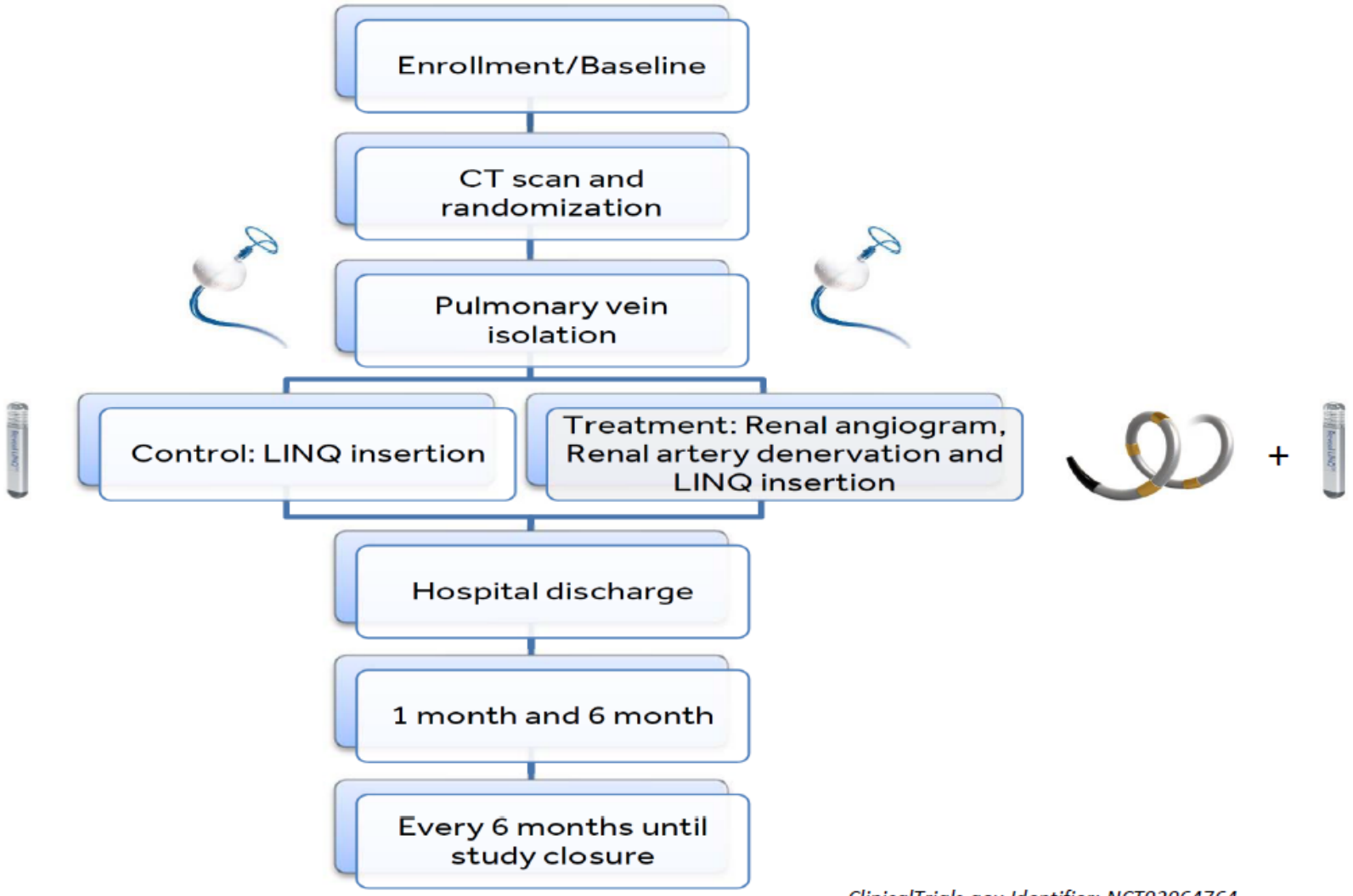
24 h-holter monitoring for (S)VE beats

	Pre-RDN	6 months	12 months	*p**	*p***
Heart rate (bpm)	71 ± 15	66 ± 8	70 ± 12	0.15	0.63
SVE (beats)	187 (82–948)	137 (43–1096)	79 (13–763)	0.36	0.05
VE (beats)	35 (3–153)	22 (3–86)	42 (5–134)	0.57	0.73



Clinical Research in Cardiology (2019) 108:634–642

Specific Outcomes: Symplicity AF: Study Design



Renal denervation: which patient?

FINE

ESC European Society of Cardiology

Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies

CURRENT OPINION
Hypertension

Potential predictors of response to RDN therapy

Baseline characteristics

- Systolic blood pressure
  - Amplitude
  - Variability
- Combined versus isolated systolic hypertension
- Pulse wave velocity
- Heart rate
  - Basal rate
  - Variability
- Antihypertensive medication
- Poor drug adherence despite extensive counselling
- Ethnicity
- Risk factors
- Obstructive sleep apnoea
  - Chronic kidney disease
  - Obesity

Procedural variables

- Number of treatment ablations
- Anatomic site
  - Distal branch vessels for RF treatment
  - Accessory renal arteries

Biomarkers

- Ghrelin, MR-proadrenomedullin, Neuropeptide-Y, Brain-derived neurotrophic factor, intercellular cell adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM)
- mircoRNA
- Muscle sympathetic nerve activity

Invasive/provocative testing

- Renal resistance and wave speed
- Drug challenge (e.g. clonidine)
- Baroreceptor sensitivity
- Blood pressure response to orthostasis
- Electrical renal nerve stimulation

Imaging

- Meta-iodobenzylguanidine scintigraphy (kidney/heart)
- Renal artery diameter
- Presence of accessory arteries

European Heart Journal (2020) 41, 1588–1599

RDN . from resistant hypertension to the difficult-to-treat-patient

Clinical profiles of patient candidates to RDN

(a) Essential hypertensive patient uncontrolled by an association RAS-blocker/calcium-channel blocker/diuretic at maximally tolerated doses (recommended)	[36, 60]
Additional features	
Adverse effects with spironolactone	[37]
Poor drug adherence despite extensive counseling	[56]
Systo-diastolic hypertension	[34]
No extensive vascular damage	[57, 58]
High/very high lifetime cardiovascular risk	
Patient preferences	

(b) Grade 1–2, systo-diastolic, essential hypertensive patient, untreated or uncontrolled by 1–2 BP-lowering drugs (possible)	[39–41]
Additional features	
Multiple intolerance to BP-lowering drugs/adverse effects	
Poor drug adherence despite extensive counseling	
High/very high lifetime cardiovascular risk	
Paroxysmal atrial fibrillation and planned ablation	[63]
Patient preferences	

TWO CLINICAL PROFILES OF PATIENTS CANDIDATES TO RDN

1

RECOMMENDED

Essential hypertensive patient uncontrolled by an association

- RAS-blocker
- calcium-channel blocker
- diuretic

at maximally tolerated doses

Additional features:

- Adverse effects with spironolactone
- Poor drug adherence despite extensive counseling
- Systo-diastolic hypertension
- No extensive vascular damage
- High/very high lifetime cardiovascular risk
- Patient preferences

Evidence from Symplicity trials; GSR; DENERHTN; Prague-15; Azizi M et al, Circulation 2016; Mahfoud F et al Eur Heart J 2017, GSR ACC2019, …

2

POSSIBLE

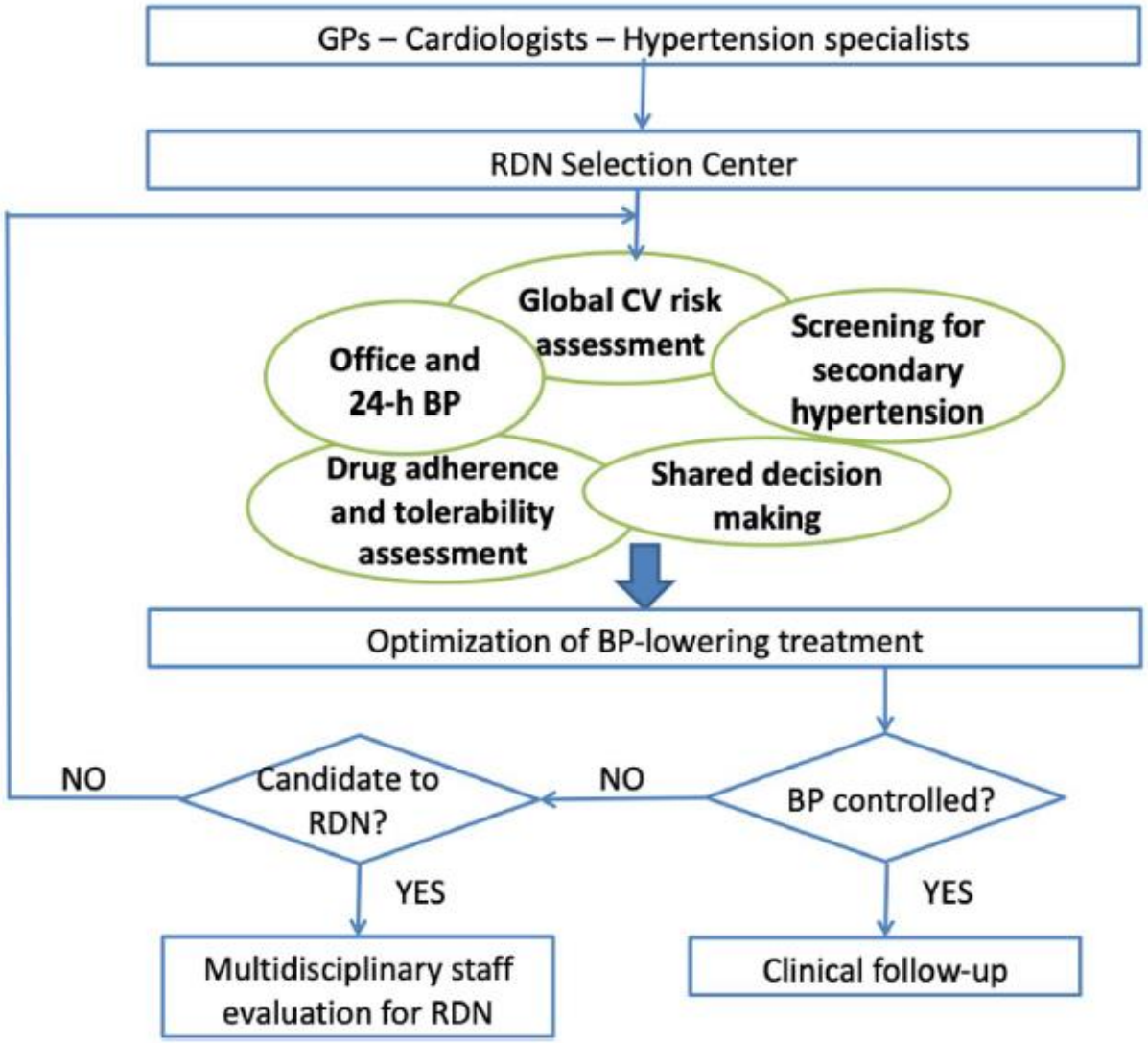
Grade 1–2, systo-diastolic, essential hypertensive patient, untreated or uncontrolled by 1–2 BP lowering drugs

Additional features:

- Multiple intolerance to BP-lowering drugs/adverse effects
- Poor drug adherence despite extensive counseling
- High/very high lifetime cardiovascular risk
- Paroxysmal atrial fibrillation and planned ablation
- Patient preferences

Evidence from Spyral OFF-med, ON-med, Radiance solo; Bohm et al,Eur Heart J. 2019; Atti V et al. J C Electrophysiol 2019

FLOWCHART FOR THE DIFFICULT-TO-TREAT HYPERTENSIVE PATIENT

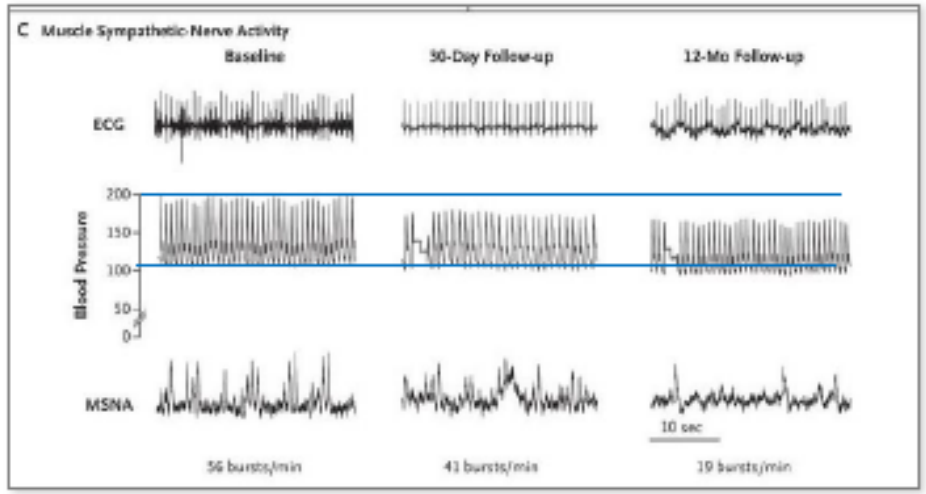


Clinical Case

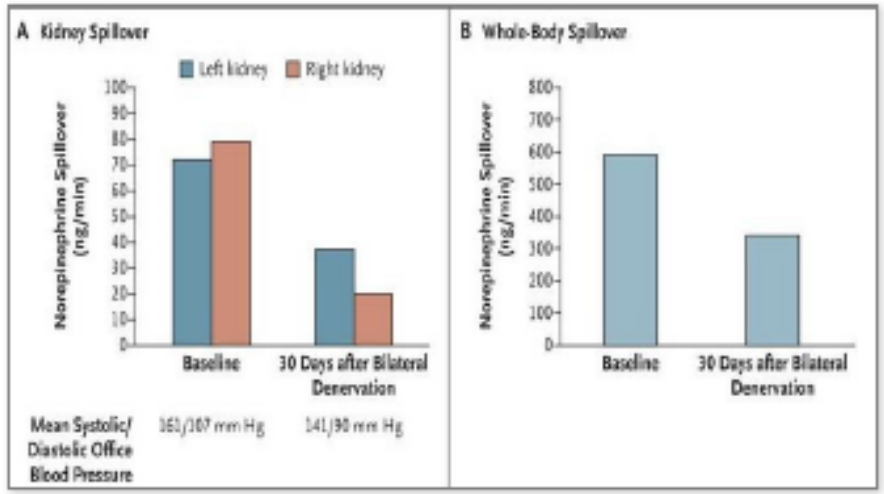
59 y, previous TIA and untreated OSAS . Mean office BP 161/107 (on top of Tx)

Bilateral RDN

Attività Nervosa Simpatica Muscolare



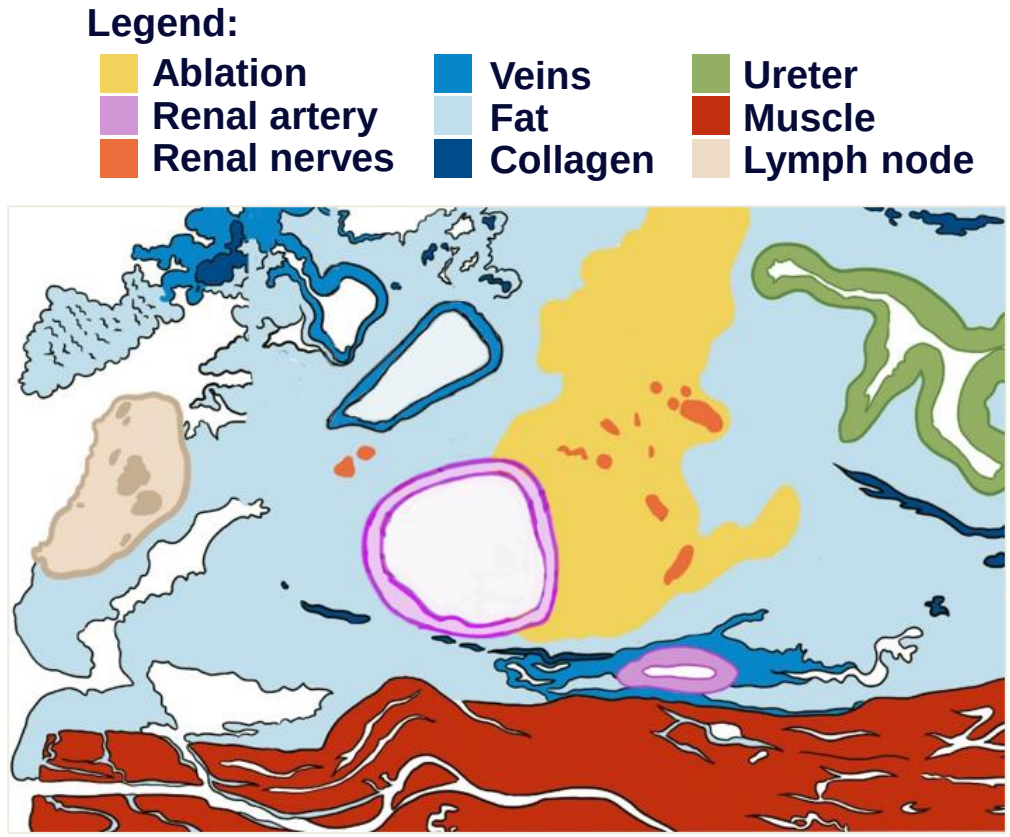
Spillover della Norepinefrina



MP Schlaich, NEJM 2009

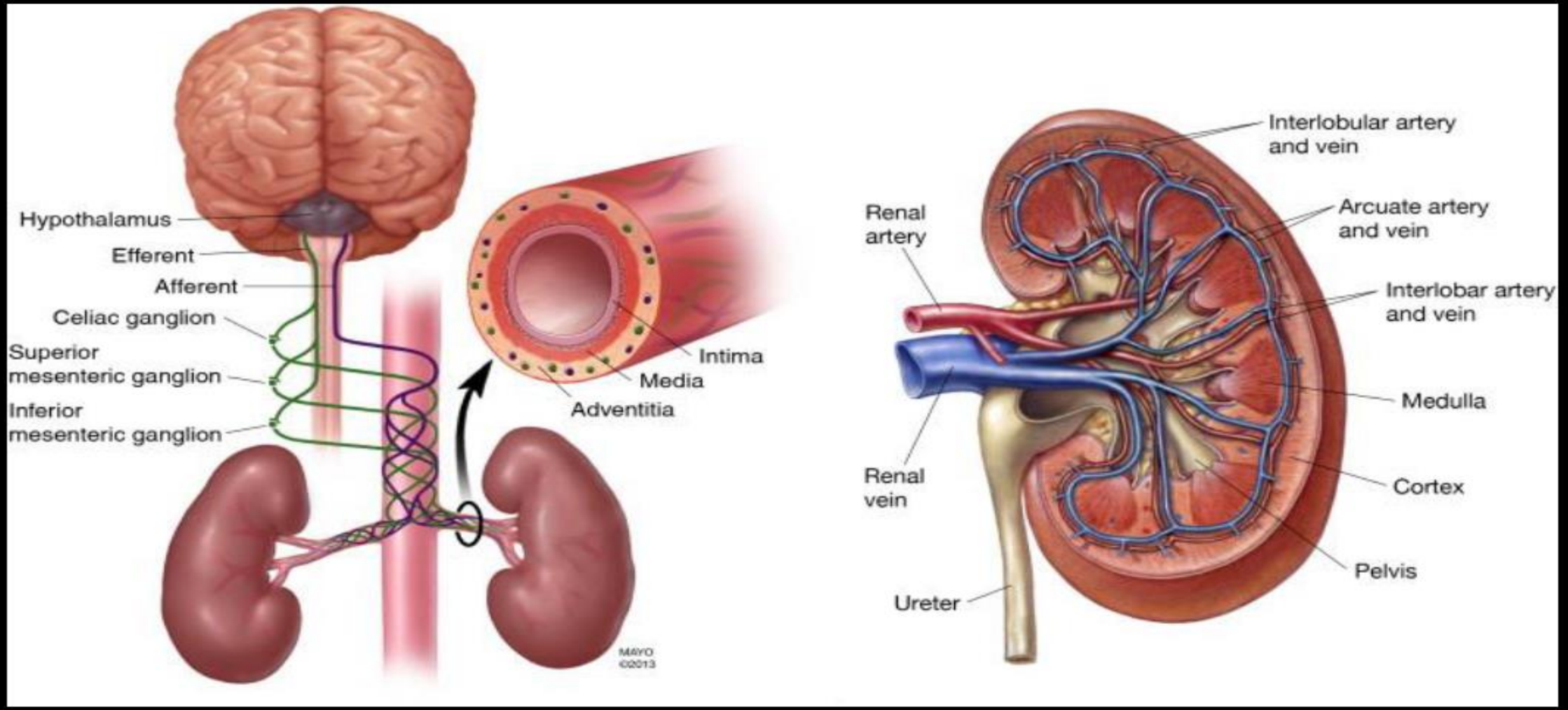
Key Characteristics of Radio Frequency (RF) Ablation

- Renal nerves are embedded in perivascular fat
- RF ablation preferentially occurs in the fat
- By providing some cooling, structures like veins contribute to the creation of safe lesions
- Ablation area is a key metric
- Endothelial healing is observed



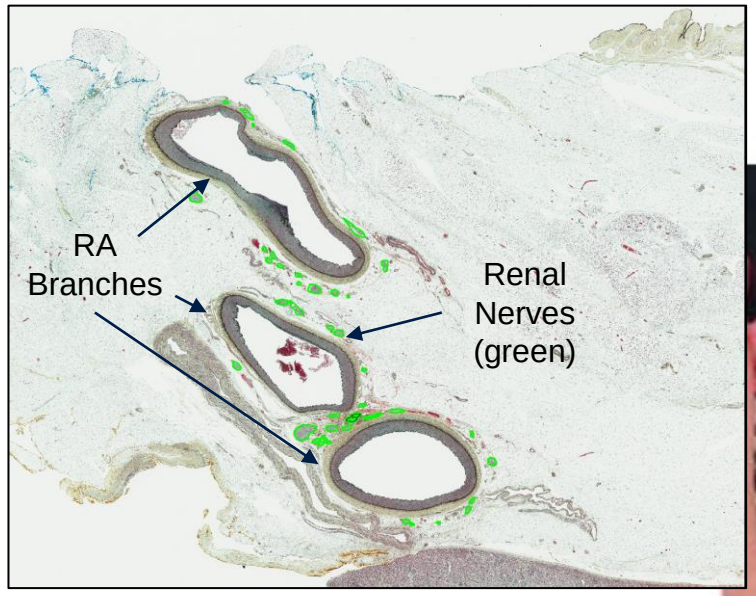
Cartoon image derived from actual histological section from porcine model

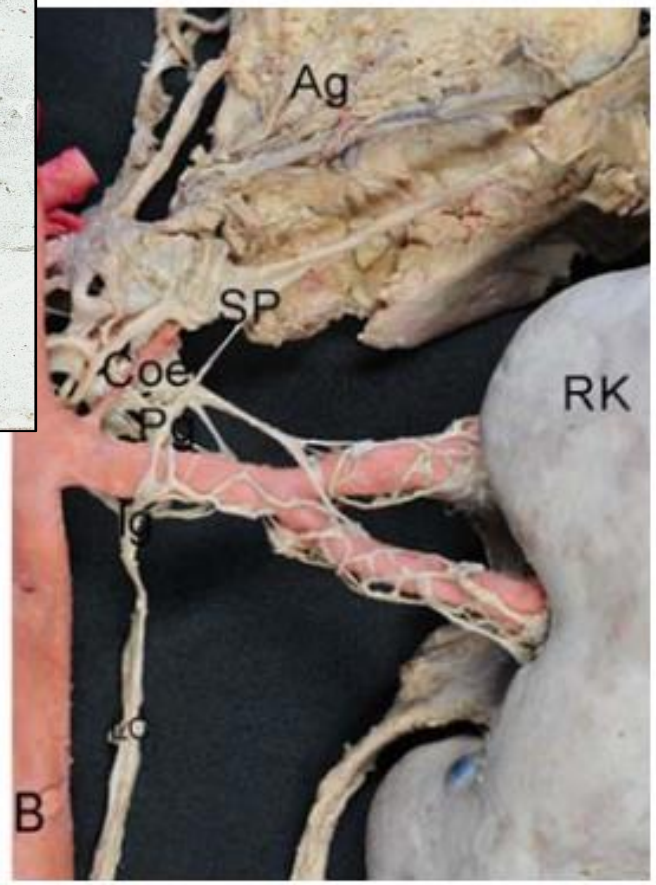
Sharp A. TCT 2020


Hypothalamus
Efferent
Afferent
Celiac ganglion
Superior mesenteric ganglion
Inferior mesenteric ganglion
Intima
Media
Adventitia
MAYO ©2013
Interlobular artery and vein
Renal artery
Arcuate artery and vein
Interlobar artery and vein
Medulla
Renal vein
Cortex
Pelvis
Ureter

Procedural strategy to reflect renal nerve anatomy
Distal nerves are closer to the arterial lumen

- Renal nerves generally originate from the aorta and arborise towards the kidney
- Nerve fibers do not completely converge on the renal artery until beyond the main bifurcation
- Ablations are performed outside of the angiographic shadow of the kidney



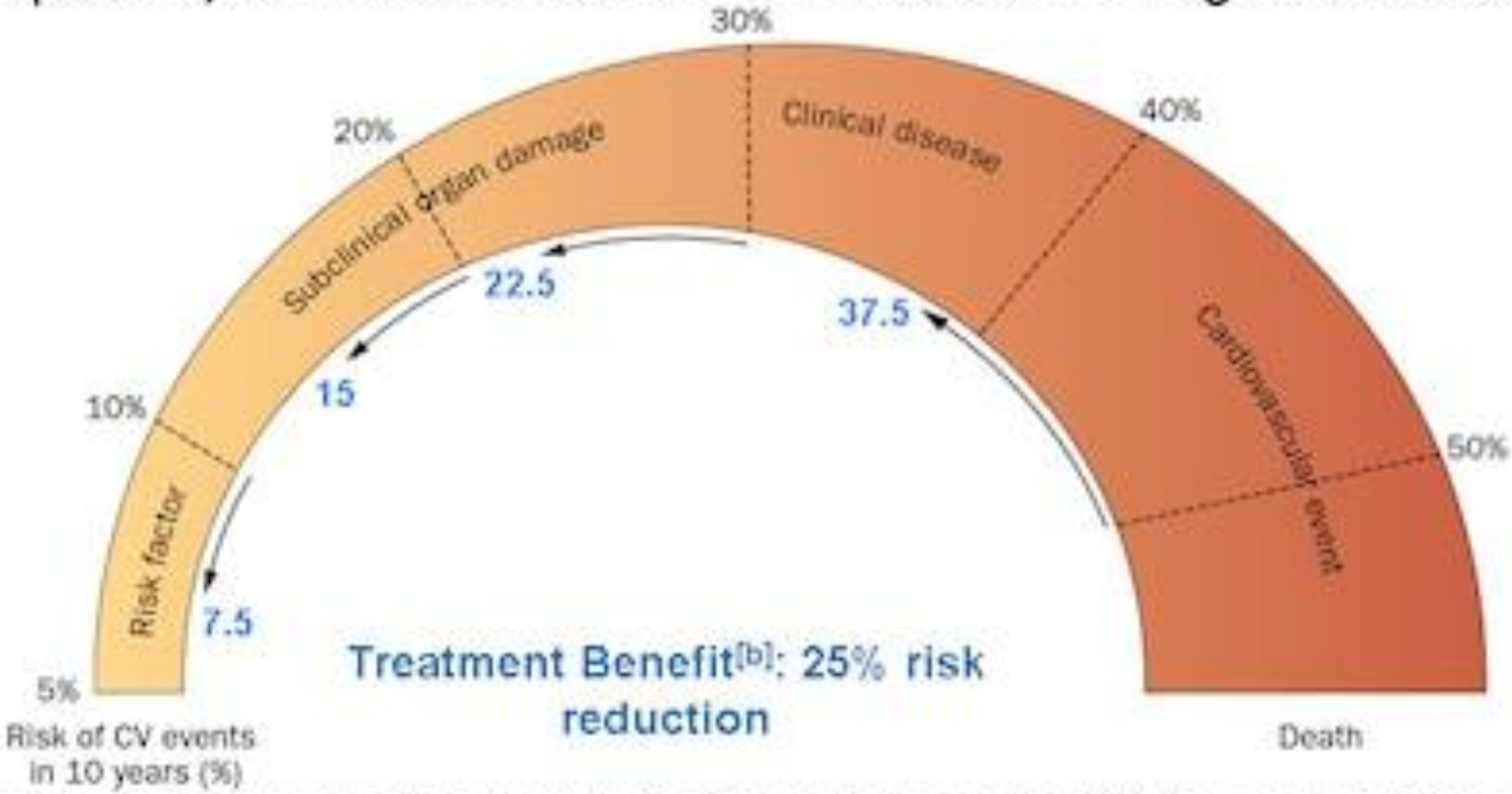


Human cadaver specimens

Mompeo B, et al. *Clin Anat*. 2016;29:660–664.
Sharp et al. TCT 2019

CV Continuum: Start Therapy Earlier

In high-risk patients, small relative risk reductions translate into large absolute benefits[a]



- Subclinical organ damage left untreated results in clinical (symptomatic) disease and CV events (stroke, MI, HF) and death[a]
- Risk can be reduced depending on when treatment is initiated[a]

Do we over treat mild hypertension?, Zanchetti A., *Nat Rev Cardiol.* Volume 16, 2015 - Issue 8, 2010 reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com). a. Zanchetti A. *Nat Rev Cardiol.* 2010;7:66-67; b. Law MR, et al. *BMJ.* 2009;338:1665-1683.

Proof of Principle
Quantifying Human SNS Activity

Central Sympathetic Nerve Activity

1. Muscle Sympathetic Nerve Activity (MSNA)

Renal Sympathetic Nerve Activity

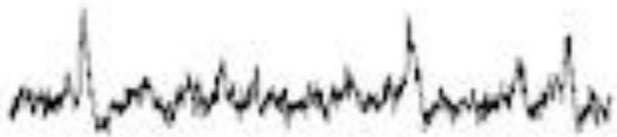
2. Adrenal Vein Sampling (NE spillover)

"Testing is best done by recording postganglionic nerve traffic… and measuring transmitter release from sympathetic nerves to plasma (NE 'spillover')"

Esler M. *J Appl Physiol.* 2010;108:227-237. Journal of Applied Physiology, Esler M et al, vol. 109, 2010, and pg 1996-1998

RDN and Reduction in Central Sympathetic Drive

Muscle Sympathetic Nerve Activity (MSNA) in a Patient With Resistant HTN

	** 59-year-old man on 7 HTN meds*	MSNA (burst/min)		BP (mm Hg)
Baseline		56	→	161/107
1 mo		41 (-27%)	→	141/90 (-20/-17)
12 mo		19 (-66%)	→	127/81 (-34/-26)

Reduction of renal contribution to central sympathetic drive to normal BP

*Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 → 11.7 msec/mm Hg).
Schlaich MP, et al. *N Engl J Med*. 2009;361:932-934.

Concept

Resistant HTN
Sympathetic Tone

Surgery

- Open procedure
- Overmodulation
- Higher risk

RDN

- Catheter procedure
- Controlled modulation
- Low-risk vascular access
- Renal arteries are robust

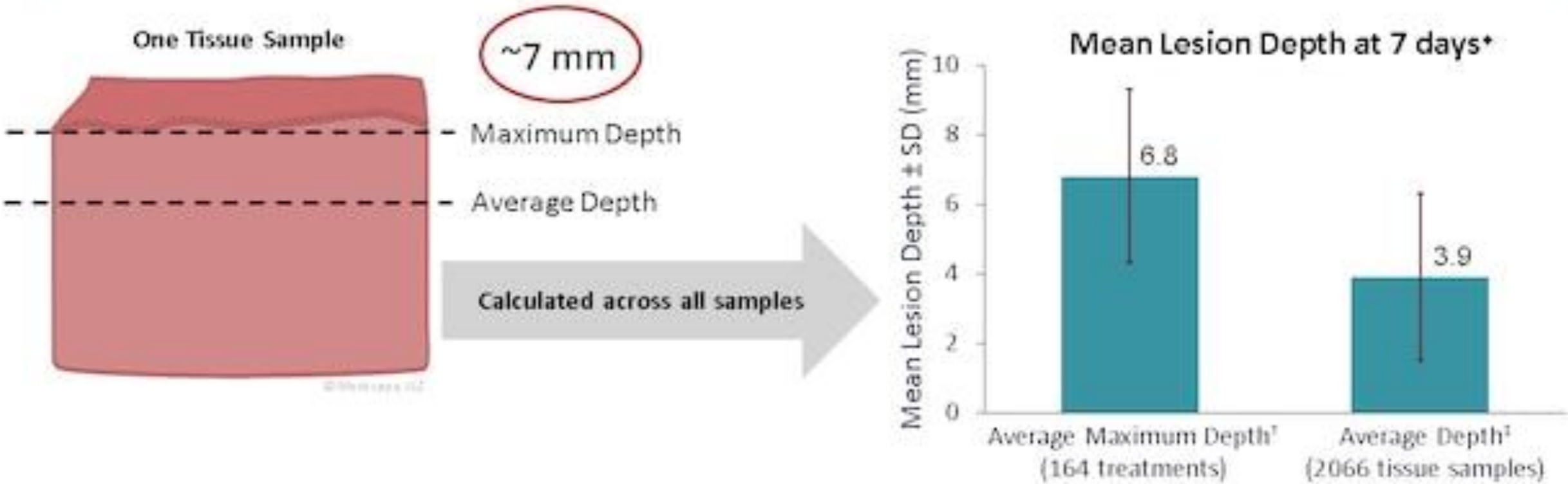
RDN With RF Was Developed With Extensive and Rigorous Testing

Tissue Properties Make RF an Attractive Choice for RDN

- > 400 swine and 10 human cadaver studies have been used to develop and understand effective RDN with RF[b]
- RDN with RF selectively heats perivascular adipose tissue that leads to denervation

a. Finn A, et al. EuroPCR 2019; b. Sharp ASP, et al. TCT 2019.

RF Is a Safe and Effective Method to Achieve RDN



- Refined technology allows reliable delivery of energy, 360° around the artery, reaching greater depth

*Mean lesion depth created by the Symplicity Spyral™ multi-electrode catheter and Symplicity G3 RF Generator (not approved for use in the USA).
†For each RF lesion, multiple lengths are measured and the longest (maximum) length is identified. The mean of the maximum measurements across all lesions is calculated and reported as the Maximum Depth. ‡Measured lesion lengths for 2066 tissue samples are aggregated to calculate an Average Depth.
Sharp ASP, et al. TCT 2019.

"Lesion Depth" Is a Limited Measure of Denervation Efficacy

Lesion safety and efficacy depend on several factors:

- RDN placement along renal artery
- Energy duration
- Lesion size and 3-dimensional shape
- Surrounding structures contribute to nonuniform lesion formation
  - Location of structures varies throughout the length of the renal artery

Lesion samples should be evaluated at 7 days, the peak of the inflammatory response due to RF energy

"Lesion area" is a more appropriate measure of denervation efficacy

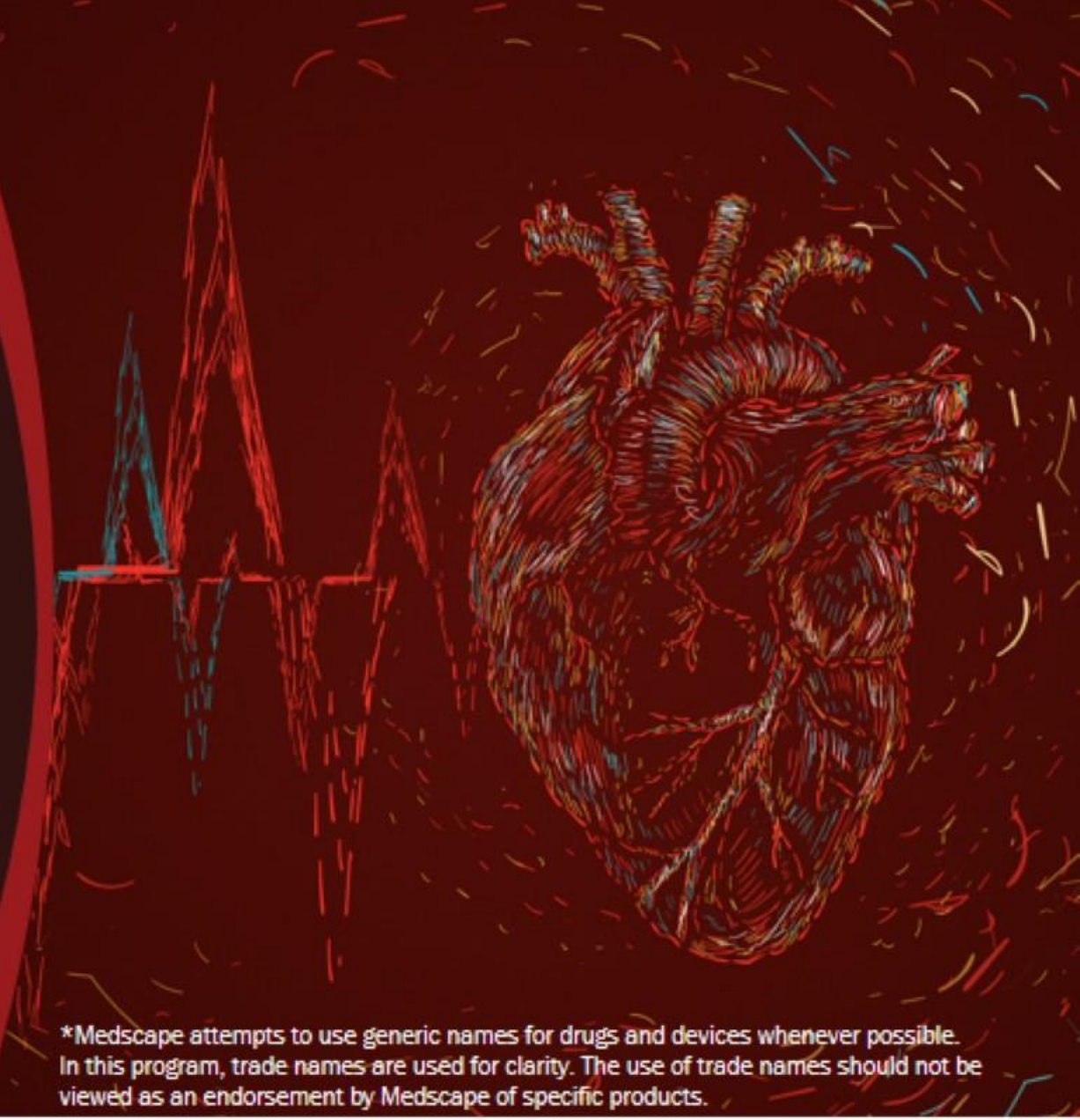
Sharp ASP, et al. TCT 2019.

Conclusions and Take-Home Messages

- RDN has a solid and valid research physiological background
- There is much more to learn
- Catheter-based approaches are very safe and effective in achieving renal denervation, as supported now by both clinical and registry data
- A deeper understanding of the anatomy and physiology of sympathetic nerves has facilitated further technical advances with improved algorithms for use
- Ongoing studies are looking at patients who are on medications with a variety of approaches to management and catheter use

A Medscape LIVE! CONFERENCE

Renal Denervation for Treating Hypertension: Alive and Well



*Medscape attempts to use generic names for drugs and devices whenever possible. In this program, trade names are used for clarity. The use of trade names should not be viewed as an endorsement by Medscape of specific products.

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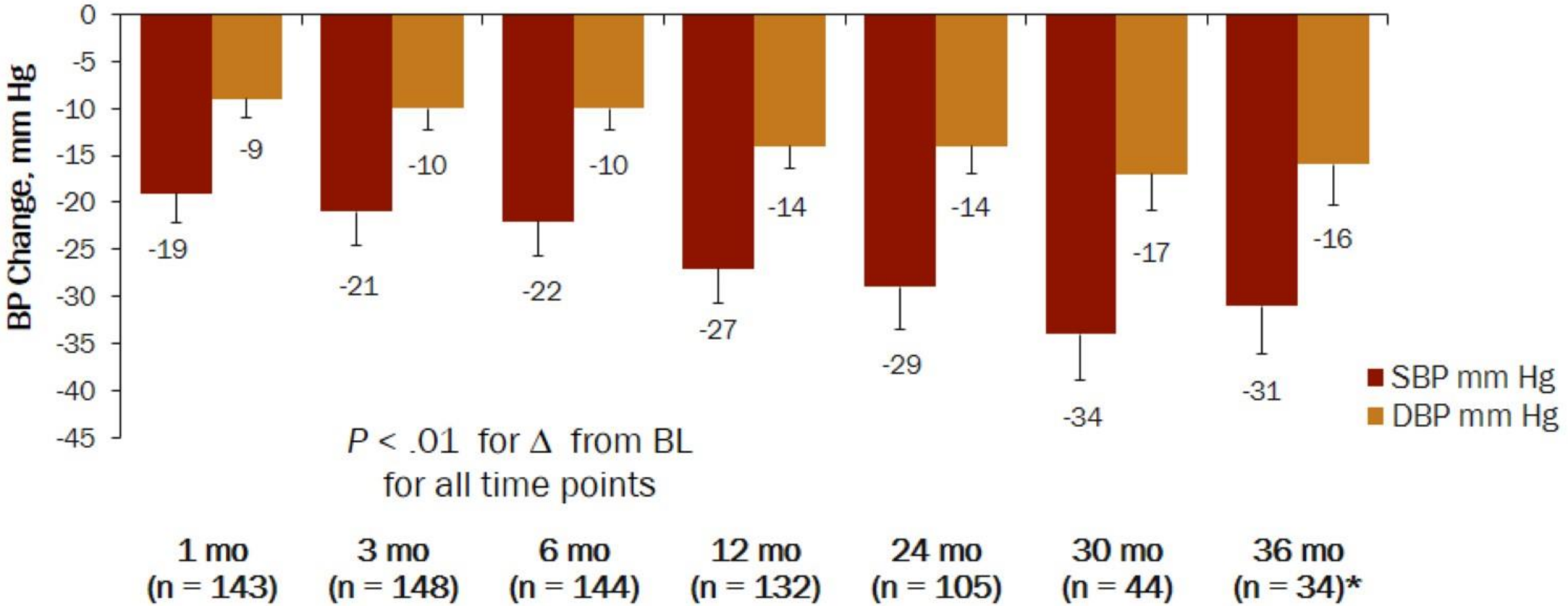
Division of Cardiovascular Medicine
Department of Medicine
Downstate Medical Center
State University of New York
Brooklyn, New York

theheart.org
Medscape Cardiology

SYMPLICITY HTN-2

Change in Office BP by 36 Months in Treatment-Resistant HTN

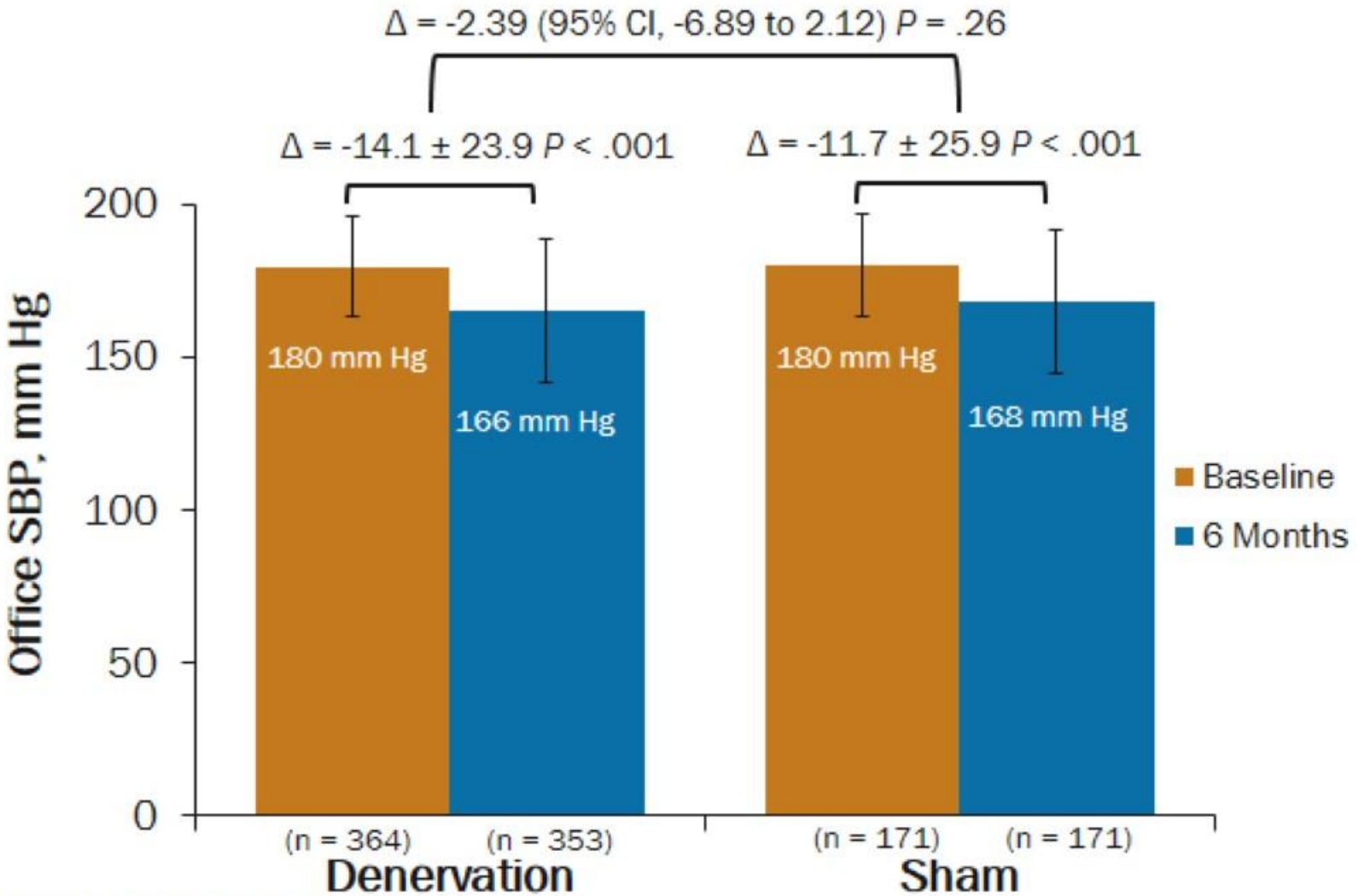


*Reported as mean with 95% confidence intervals.

Esler MD, et al. *Eur Heart J*. 2014;35:1752-1759.

SYMPLICITY HTN-3

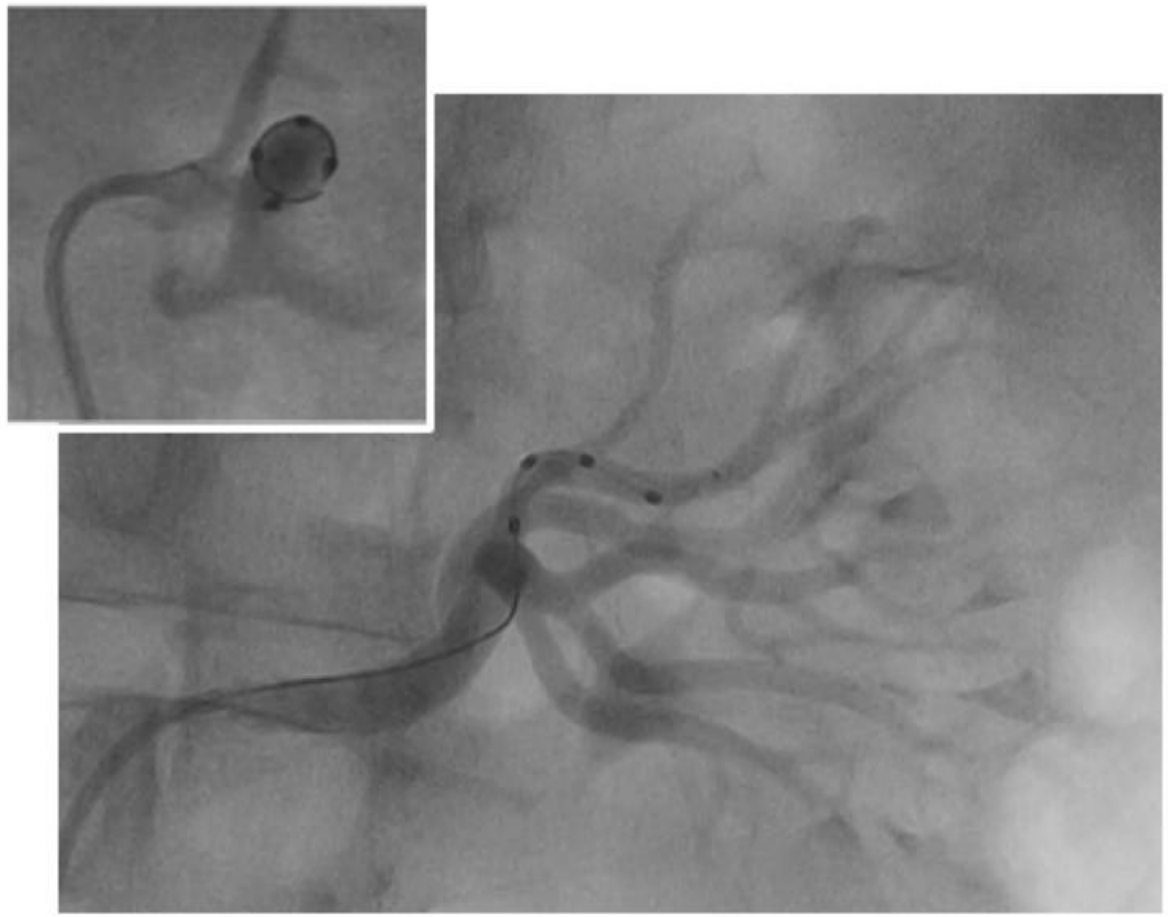
Primary Efficacy Endpoint



Bhatt DL, et al. *N Engl J Med*. 2014;370:1393-1401.

The Symplicity Spyral™ Catheter

- Multi-electrode catheter with quadrantic vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3 mm to 8 mm
- Flexible catheter allows branch treatment
- 6F guiding catheter compatible



Renal Denervation Trials – Restart

EDITORIAL

Renal Denervation for the Treatment of Hypertension: Making a New Start, Getting It Right

Michael A. Weber, MD;[1] Ajay Kirtane, MD;[2] Laura Mauri, MD;[3] Raymond R. Townsend, MD;[4] David E. Kandzari, MD;[5] Martin B. Leon, MD[2]

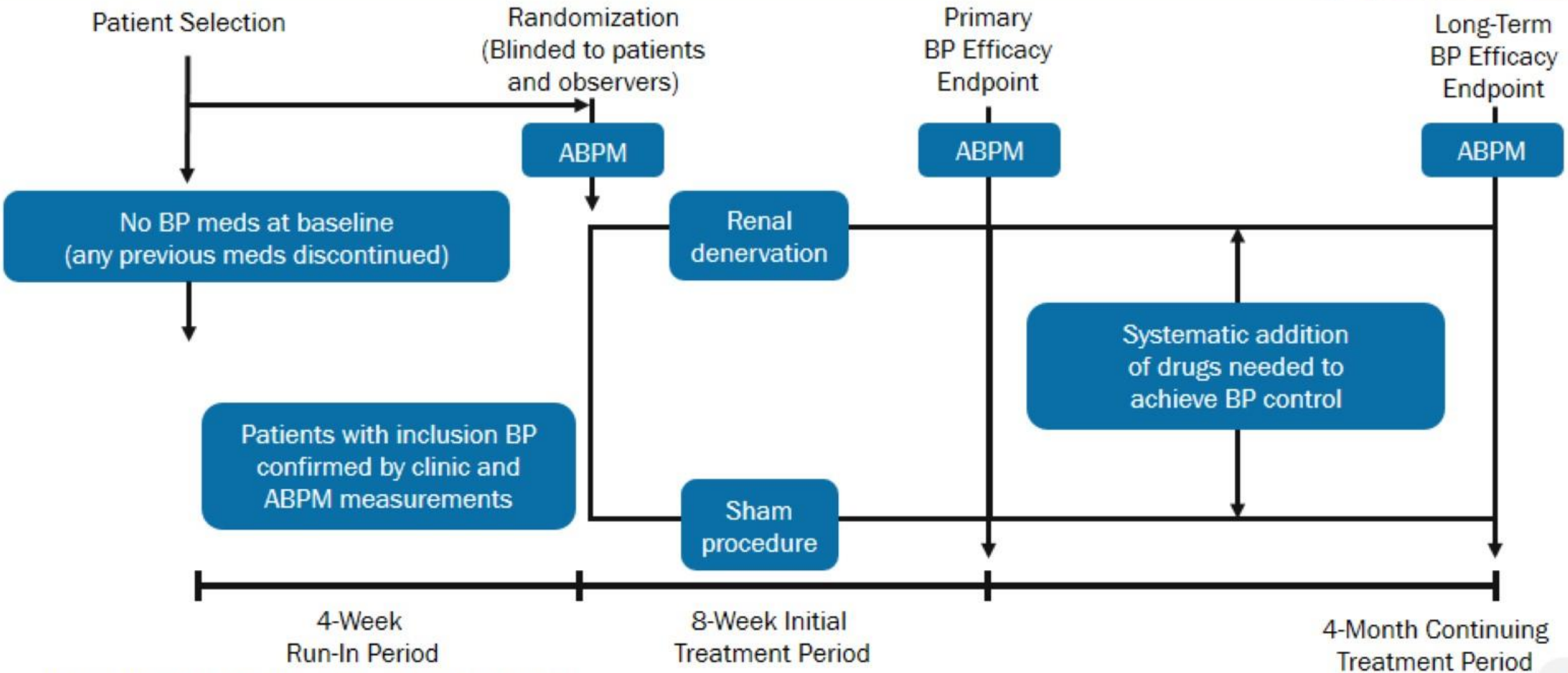
From the Cardiovascular Division, Downstate Medical Center, State University of New York, Brooklyn, NY;[1] Center for Interventional Vascular Therapy, Columbia University Medical Center, New York, NY;[2] Brigham and Women's Hospital, Harvard Clinical Research Institute and Harvard Medical School, Boston, MA;[3] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA;[4] and Piedmont Heart Institute, Atlanta, GA[5]

A strategy based on the widely followed protocol for antihypertensive drug development:

- Demonstrate safety and efficacy of RDN as a single therapy
- Demonstrate safety and added efficacy of RDN when combined with BP-lowering drugs

Weber MA, et al. *J Clin Hypertens*. 2015;17:743-750.

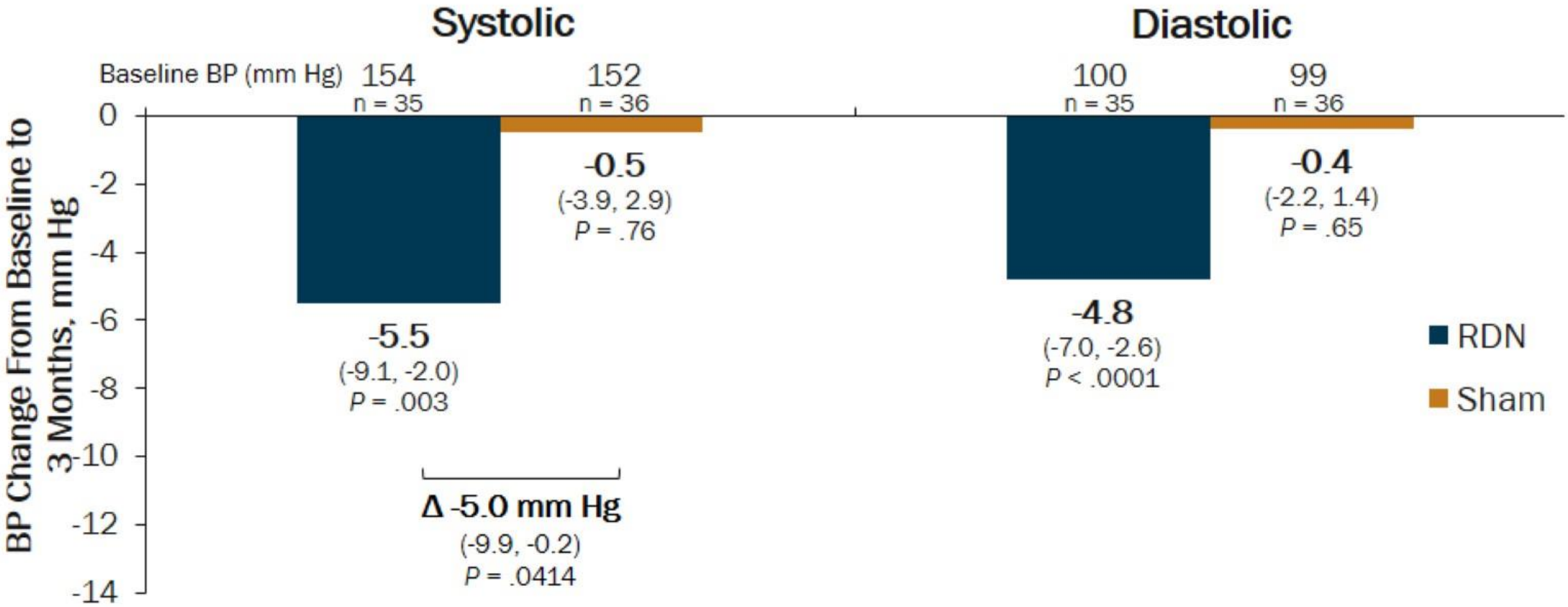
Focused Protocols for RDN in Hypertension



Weber MA, et al. *J Clin Hypertens*. 2016;17:743-750.

SPYRAL HTN – OFF MED

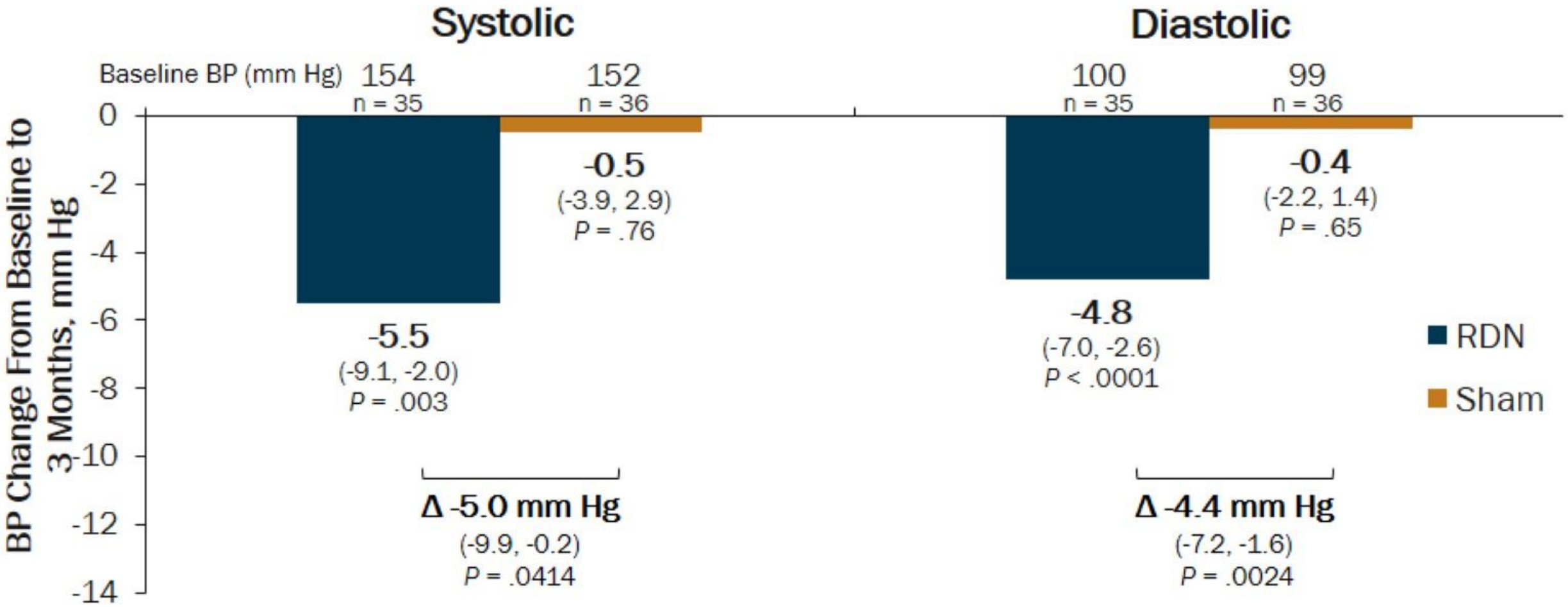
BP Change From Baseline to 3 Months: 24-Hr ABPM



Townsend RR, et al. *Lancet*. 2017;390:2160-2170.

SPYRAL HTN – OFF MED

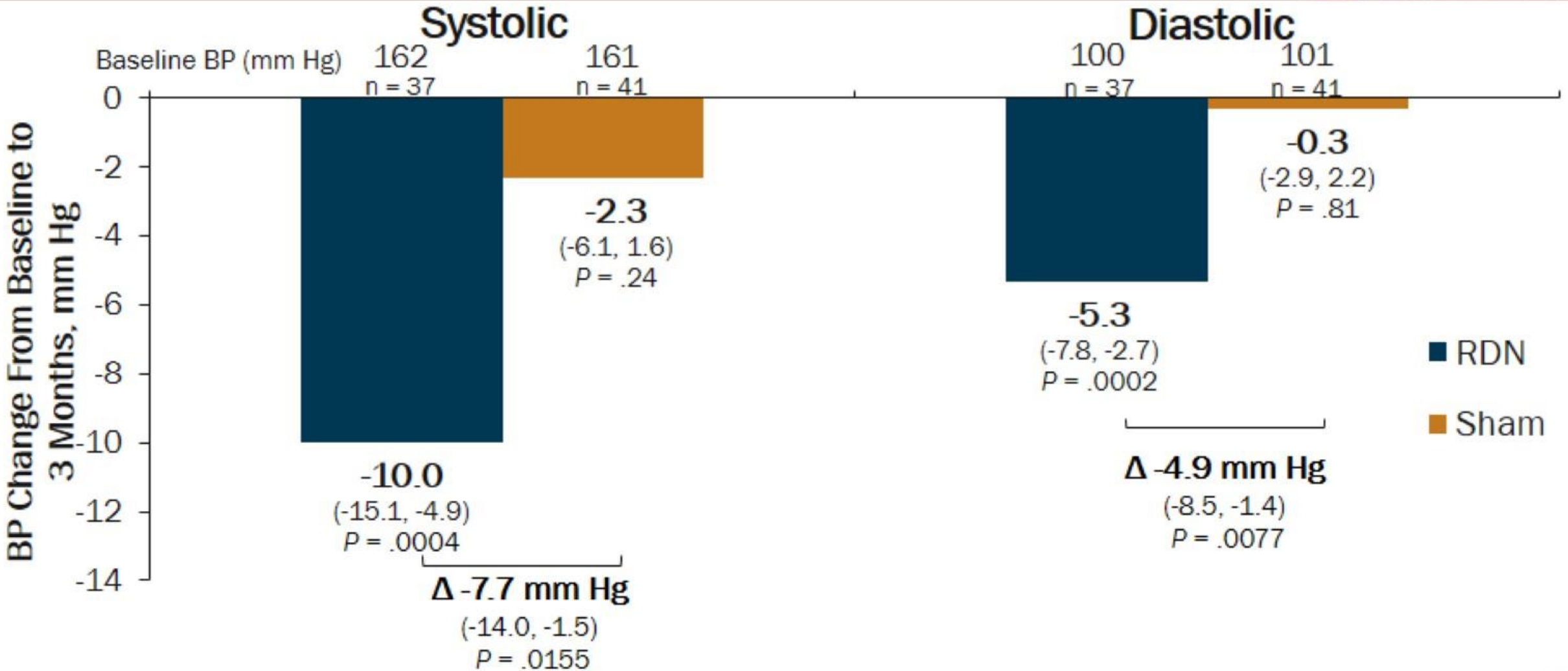
BP Change From Baseline to 3 Months: 24-Hr ABPM



Townsend RR, et al. *Lancet*. 2017;390:2160-2170.

SPYRAL HTN – OFF MED

BP Change From Baseline to 3 Months: Office BP

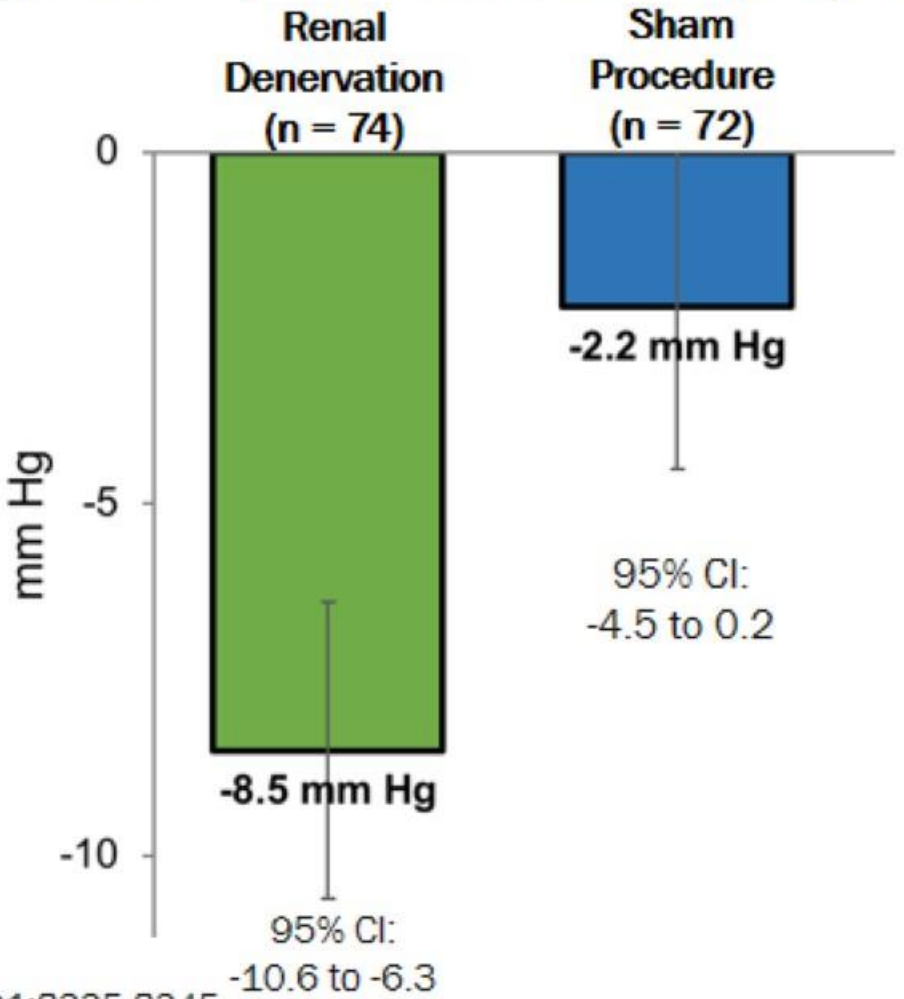


Townsend RR, et al. *Lancet*. 2017;390:2160-2170.

RADIANCE-HTN SOLO

Primary Efficacy Endpoint (No Medications)

Change in Daytime Ambulatory Systolic BP at 2 Months, ITT

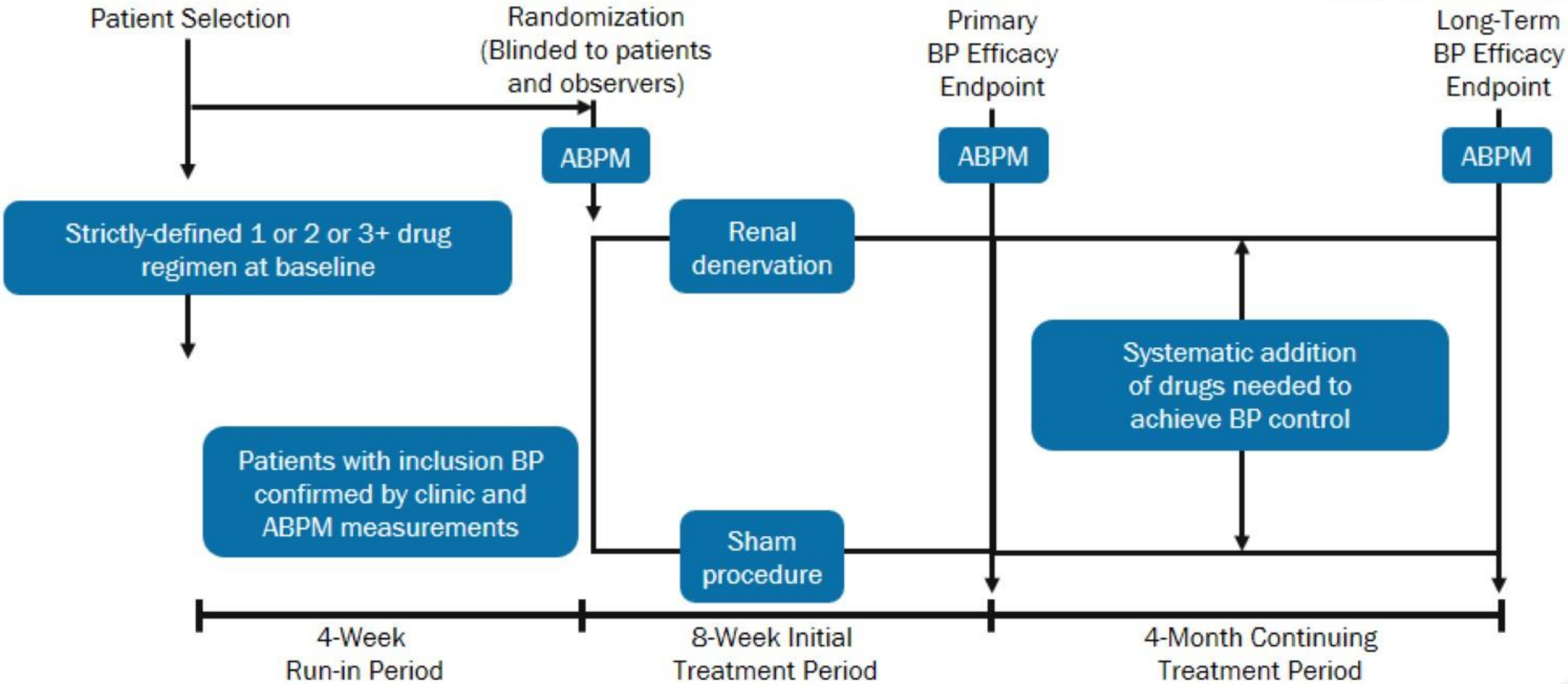


Between group difference adjusted for baseline BP
-6.3 mm Hg
(95% CI, -9.4, -3.1)
P = .0001

Azizi M, et al. *Lancet*. 2018;391:2335-2345.

Focused Protocols for Renal Denervation

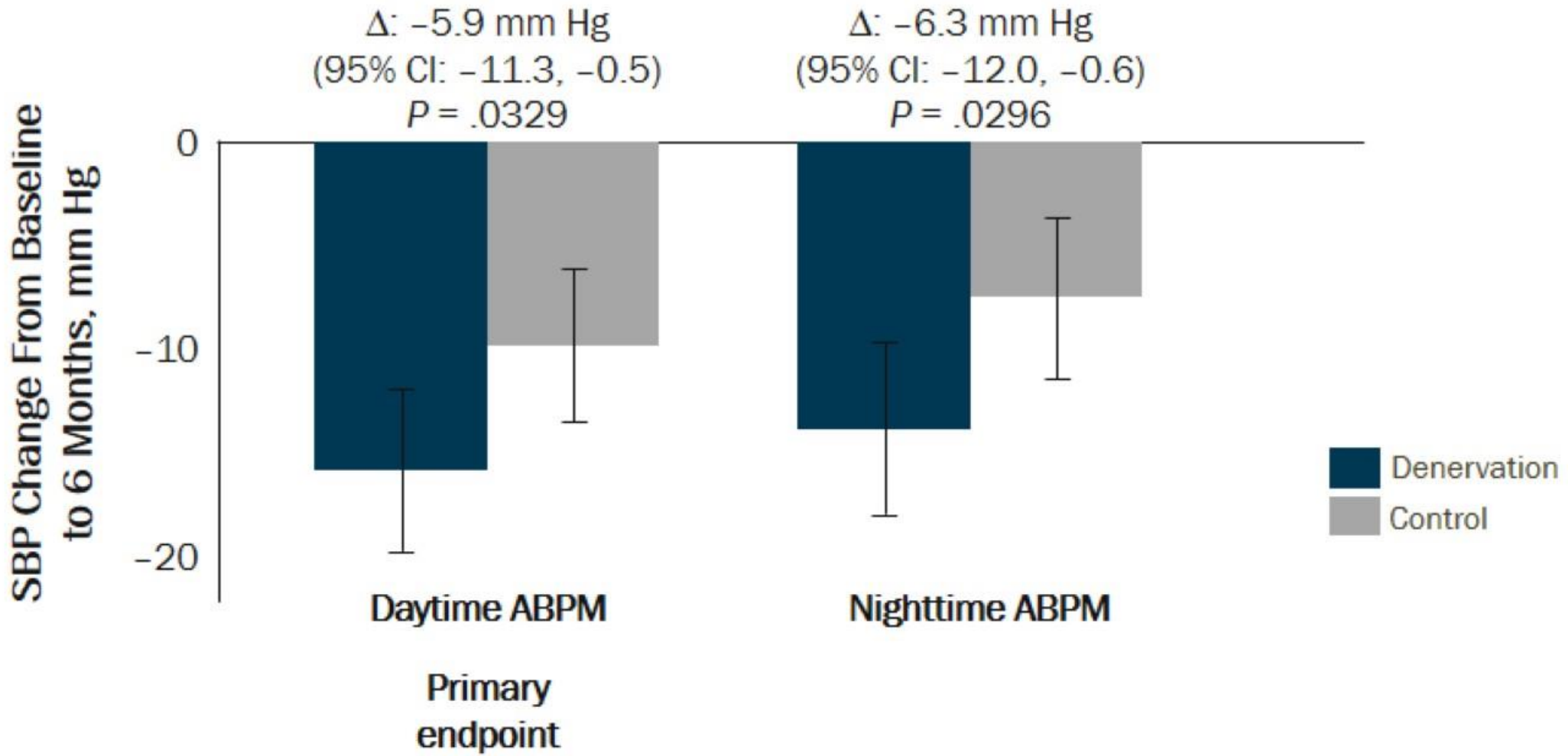
Adding Denervation to Drug Therapy



Weber M, et al. *J Clin Hypertens (Greenwich)*. 2015;17:743-750.

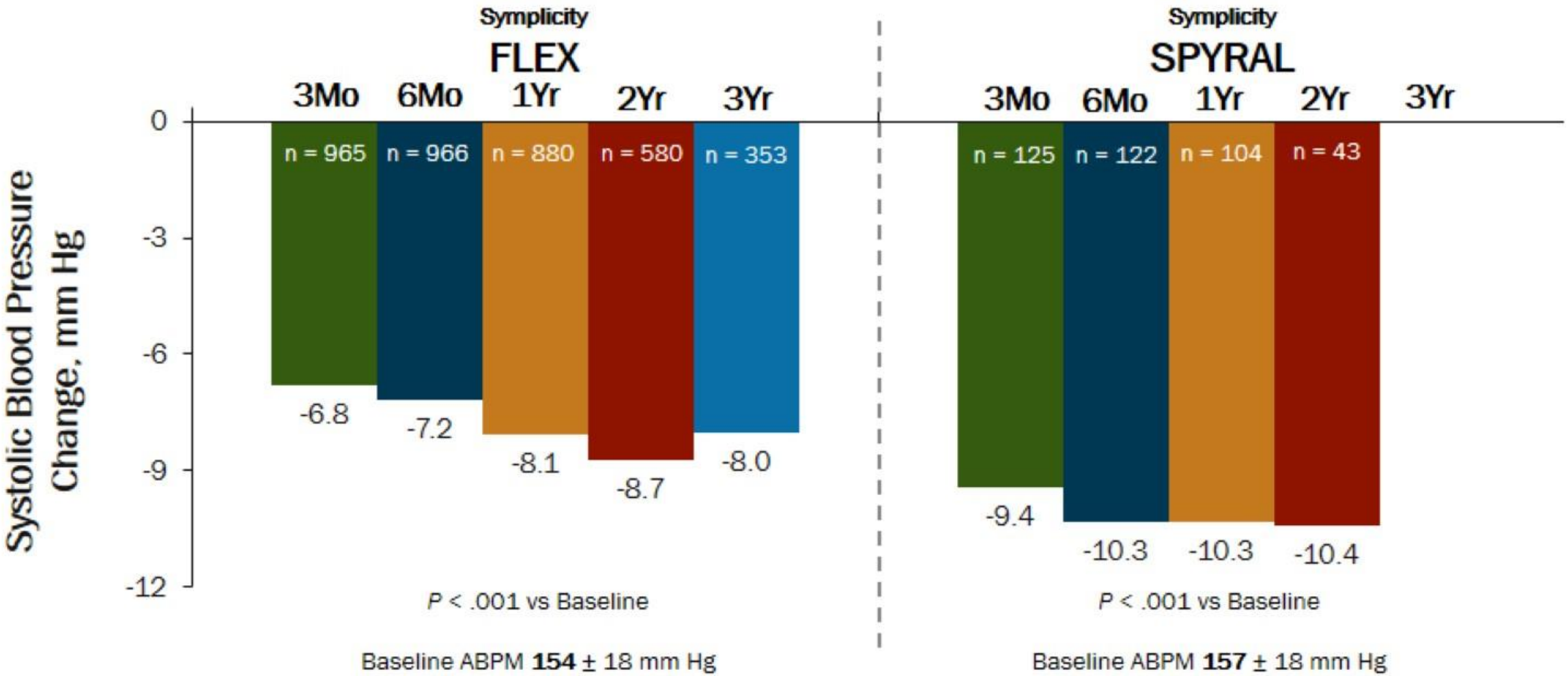
DENERHTN

First Successful Controlled Trial of RD in Treatment-Resistant HTN



Required 1416 referred resistant patients to yield 106 eligible for the trial (1:13).
Azizi M, et al. *Lancet*. 2015;385:1957-1965.

Global SYMPLICITY Registry
ABPM Change



Mahfoud F, et al. *Eur Heart J*. 2019;40:3474-3482.

Single-Center Experience With RDN

57 Uncontrolled Hypertensive Patients Treated by One Operator

Effects on Office BP

System	Number	SBP/DBP, mm Hg			
		Baseline	Δ at 6 Months	Δ at 12 Months	Δ at 24 Month
Vessix	19	155/87	-19/-8	-29/-7	-29/-13
SYMPLICITY	24	173/89	-25/-5	-22/-4	-22/-2
EnligHTN	14	175/94	-29/-9	-36/-11	-42/-14

The Vessix System is an investigational device and not available for sale in the US.

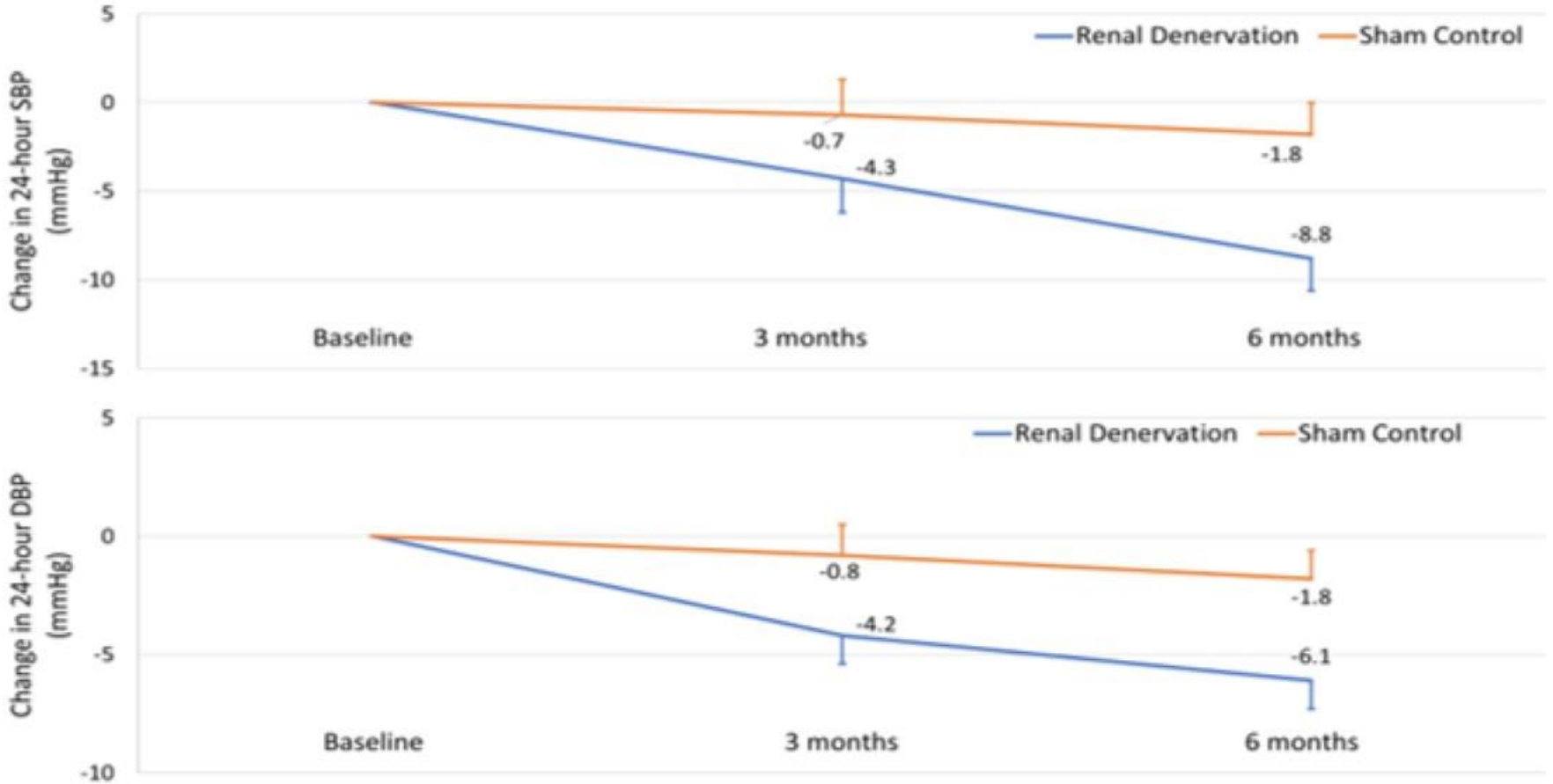
Denegri A, et al. *J Clin Hypertens (Greenwich).* 2018;20:627-633.

Time-to-Effect

- Data from 2 reported trials, the SPYRAL ON-MED study and the Vessix trial, reported that in the presence of oral medications the effect of renal denervation at 3 months was not significant, but became significant when compared with control by 6 months

Changes in 24-Hour ABPM

At 3 and 6 Months, Adjusted for Baseline Values

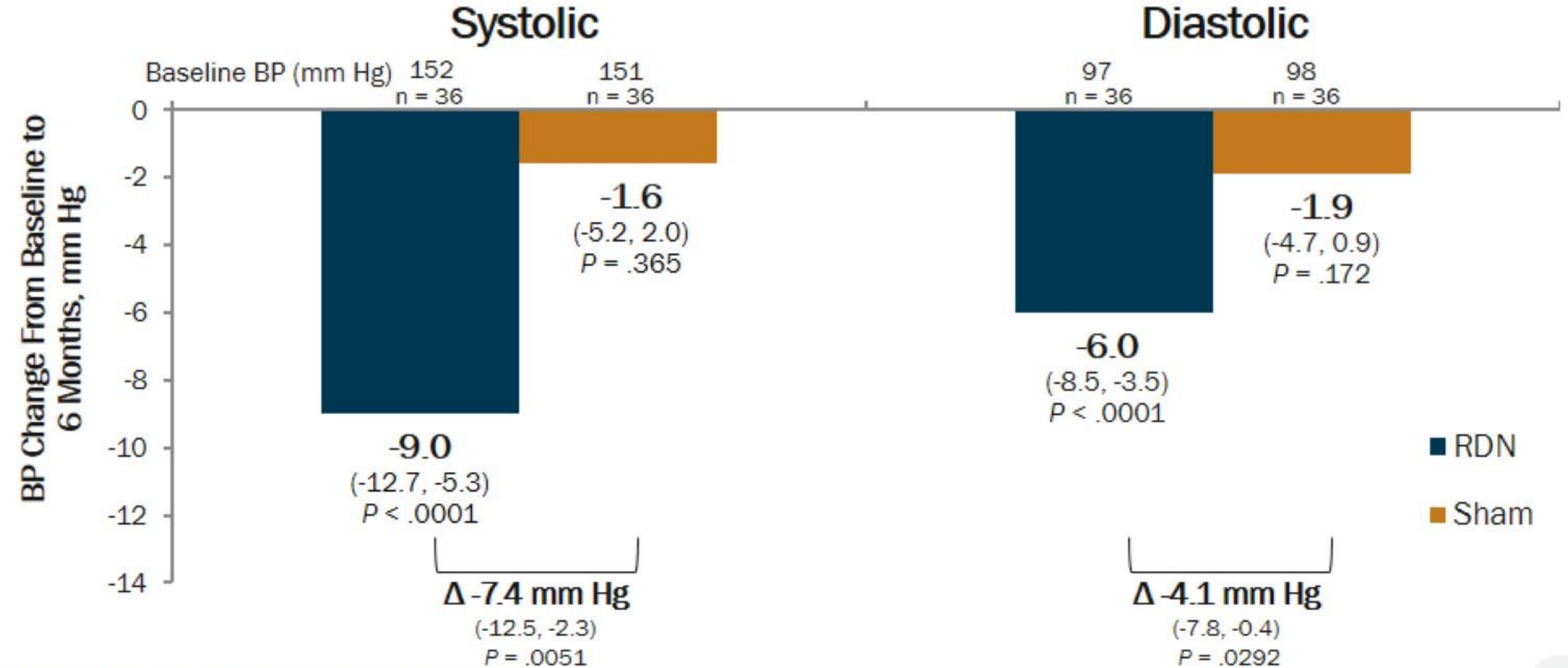


Comparison of changes in 24-hour blood pressure measurements -- BP reduction for the renal denervation group was greater at 6 months compared to 3 months

Kandzari DE, et al. *Lancet*. 2018;391:2346-2355.

SPYRAL HTN – ON MED

24-Hour ABPM Change From Baseline to 6 Months



Kandzari DE, et al. *Lancet*. 2018;391:2346-2355.

Abbreviations

ABPM = ambulatory blood pressure monitoring

BL = baseline

BP = blood pressure

COVID-19 = coronavirus disease 2019

CVD = cardiovascular disease

DBP = diastolic blood pressure

HTN = hypertension

ITT = intention to treat

NE = norepinephrine

NS = not significant

OBP = office blood pressure

RDN = renal denervation

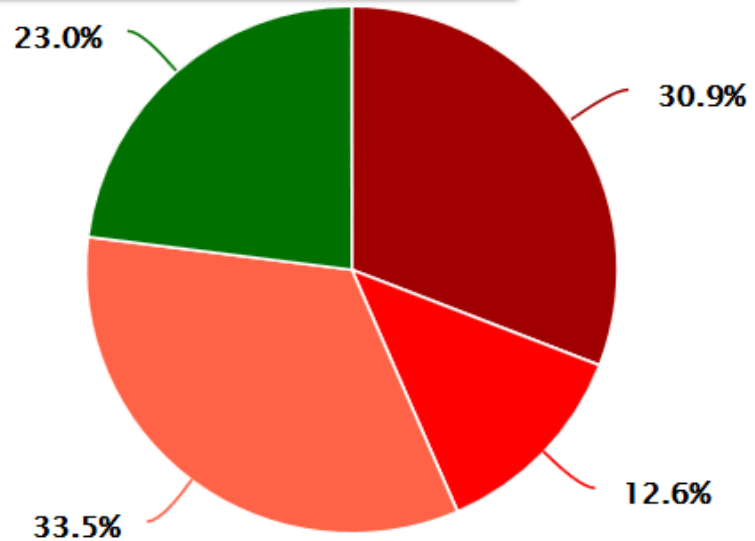
SBP = systolic blood pressure

Ipertensione

Ipertesione – Consapevolezza ed adeguatezza del trattamento Uomini – Italia

Periodo: 2008–2012 – Età: 35–79
Livello di istruzione: Tutti

consapevoli adeguatamente trattati
Percentuale: 23.0%



non consapevoli
consapevoli non trattati
consapevoli non adeguatamente trattati
consapevoli adeguatamente trattati

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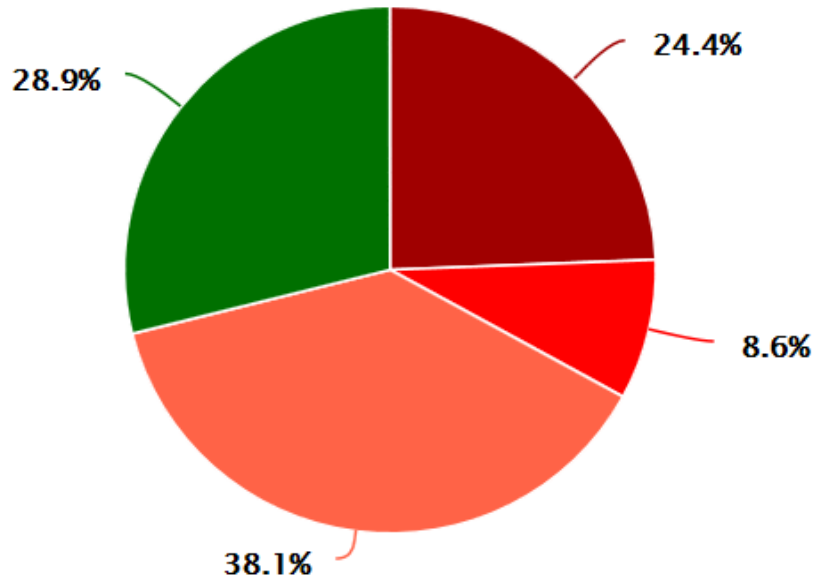
Ipertesi – Consapevolezza ed adeguatezza del trattamento Donne – Italia

Periodo: 2008–2012 – Età: 35–79
Livello di istruzione: Tutti



non consapevoli
consapevoli non trattati
consapevoli non adeguatamente trattati
consapevoli adeguatamente trattati

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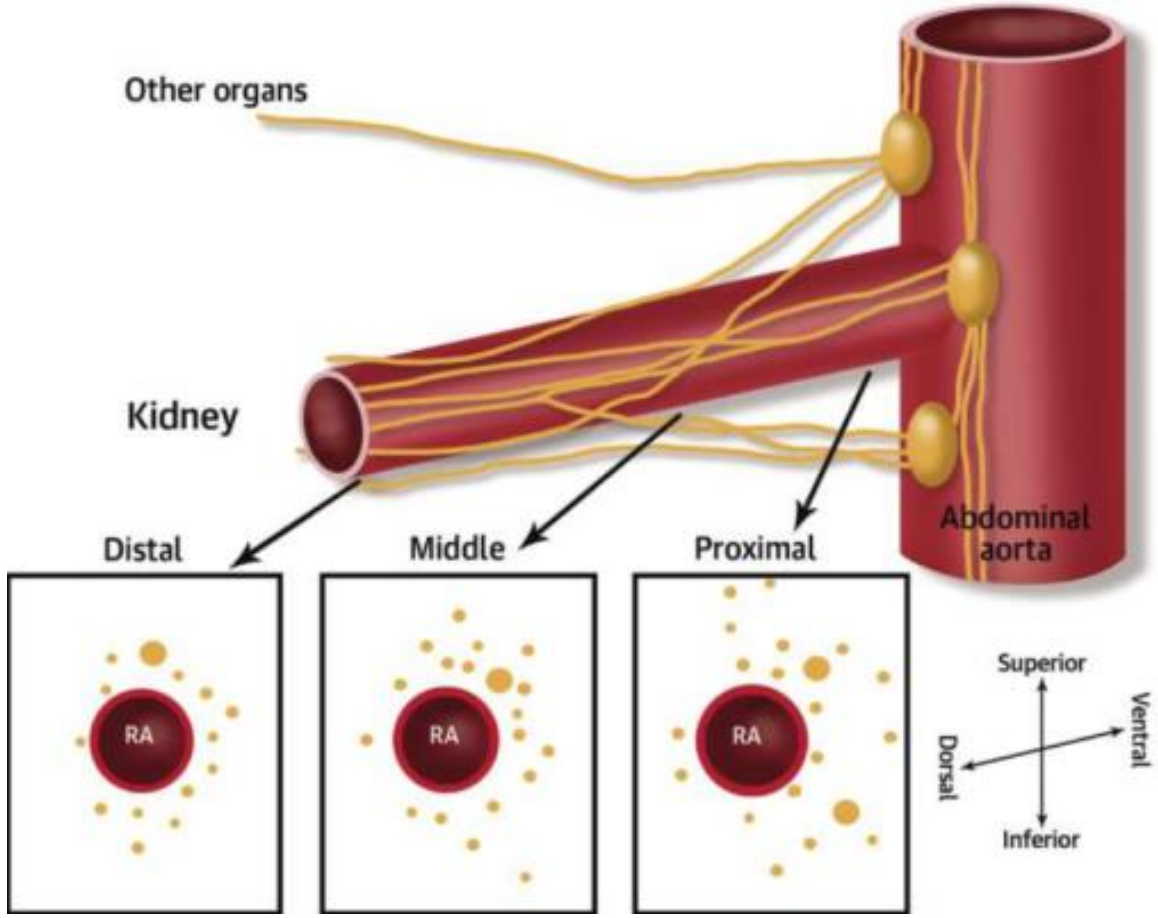
Distal renal nerves are closer to the arterial lumen

Renal nerves may have a positional bias on radial distance from arterial lumen; distal nerves are closer



Sakakura K, et al. *J Am Coll Cardiol*. 2014.64:634–643.

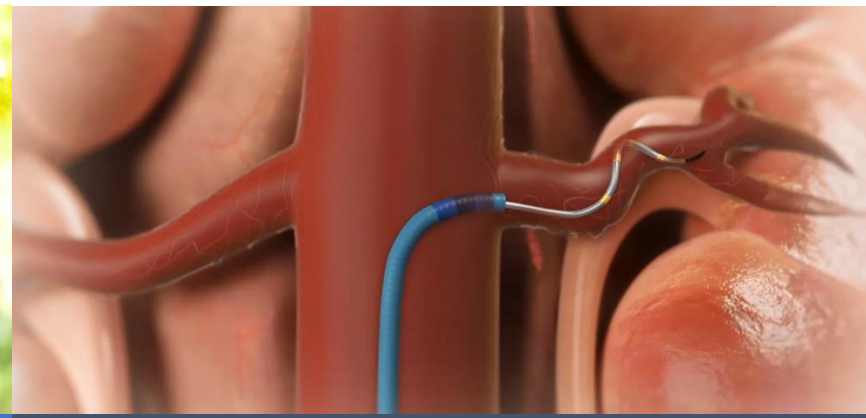
Sources of variance learned from HTN-3

DRUG CHANGES AND VARIABLE PATIENT ADHERENCE

- OBTAIN OFF-MED DATA
- STANDARDISE MEDS
- NO MAX DOSE TITRATION
- MEASURE ADHERENCE

PATIENT POPULATION

- LESS SEVERE HYPERTENSION
- PATIENTS ON FEWER PRESCRIBED MEDS
- FOCUS ON AMBULATORY BLOOD PRESSURE
- PATIENTS FROM ACROSS GLOBE
- AVOID CHANGING PATIENT BEHAVIOR



PROCEDURAL EXPERIENCE AND VARIABILITY

- SYMPLICITY SPYRAL™ CATHETER
- MAIN AND BRANCH VESSEL TREATMENT
- EXPERIENCED PROCEDURALISTS

Symplicity HTN 3

535 pts *with severe hypertension SBP >160 mmHg on 3 or more tx incluse a diuretic* – **RCT . sham control**

Punti critici e confondenti

1. **Trattamento Farmacologico .** Aderenza (<50%) e Modifiche (40%) alla terapia, Antialdosterone e Vasodilatatori diretti (+6% e +8% gruppo Sham)

2. **Popolazione in Studio .** Sham Placebo Effect, Africani di America∼30%, Ipertensione Sistolica Isolata 36%

3. **Procedura e Device .** 43% degli operatori aveva eseguito solo 1 RDN; catetere Flex scarsamente performante e molto operatore dipendente

Nuovi aspetti tecnici

- Nuovi Cateteri Ablatori

(+ performanti; - operatore dipendenti)

SPYRAL (radiofrequenza)

PARADISE (ultrasuoni)

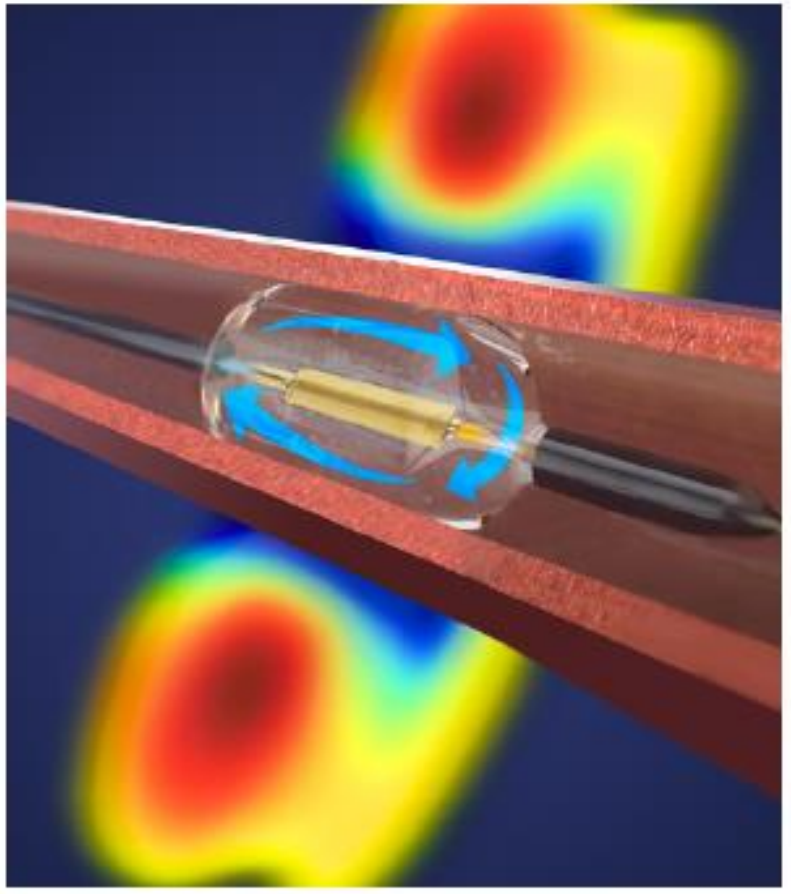
- Nuovi Concetti Procedurali
  - Ablazione più completa *(15-20 punti per arteria)*
  - Ablazione più periferica *(MB + Diramazioni)*
  - Ablazione circonferenziale *(Pattern 4 Quadranti)*

Paradise Ultrasound Renal Denervation System

- Ring of ablative energy (depth of 1-6 mm) to interrupt renal nerve traffic
- Arterial wall protected by water circulating through balloon
- 2-3 sonications lasting 7 seconds each are delivered to each main renal artery

Thermal Profile

Ultrasonic Heating + Water Cooling



Major Adverse Events

Major Adverse Events	RDN (N=69)	Sham (N=67)
30-Day Major Adverse Events		
Death	1 (1%) [1]	0 (0%)
End stage renal disease, the need for permanent renal replacement therapy	0 (0%)	0 (0%)
Doubling of plasma creatinine	1 (1%) [2]	0 (0%)
Embolic event resulting in end organ damage	0 (0%)	0 (0%)
Renal artery complication requiring intervention	0 (0%)	0 (0%)
Major access site complications requiring intervention	1 (1%) [3]	0 (0%)
Hypertensive emergency resulting in hospitalization	0 (0%)	0 (0%)
Other Major Adverse Events Measured Through 2 Months		
New onset renal artery stenosis of greater than 70%	0 (0%)	0 (0%)

[1] Sudden death unrelated to device or procedure 21 days post-procedure
[2] Transient acute renal injury 25 days post-procedure associated with spironolactone use and resolved upon discontinuation of spironolactone
[3] Femoral access site pseudoaneurysm post-procedure resolved with thrombin injection

- Real-world data from the Global SYMPLICITY Registry (GSR) showed clinically meaningful, statistically significant, and sustained blood pressure reductions in patients with **resistant hypertension**[1]
  - Office systolic blood pressure (OSBP) **decreased 24 mmHg** through 3 years ($p<0.001$)
  - 55% of patients achieved blood pressures below 150mmHg at 3 years without increasing medication burden
- GSR is the **largest** investigation of RDN with 2800+ patients enrolled and complements data from the randomized, sham-controlled trials
- Radio Frequency (RF) RDN ablation is effective and durable, as demonstrated by histological animal data[2]
  - Functional nerve regrowth is absent after RF RDN, including **permanent axonal destruction**, observed through 180 days
- Anatomical targets for successful RDN should include the **renal branches and accessory arteries**[3]
  - 63% of kidneys had renal nerves that bypass the main renal artery
  - 30% accessory arteries present and highly innervated

1. Schlaich M, et al. TCT Connect 2020.
2. Sharp A, et al. TCT Connect 2020.
3. Garcia-Touchard A, et al. TCT Connect 2020.

SIIA position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient

Table of contents

SIIA Consensus Paper 2020

SIIA position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient

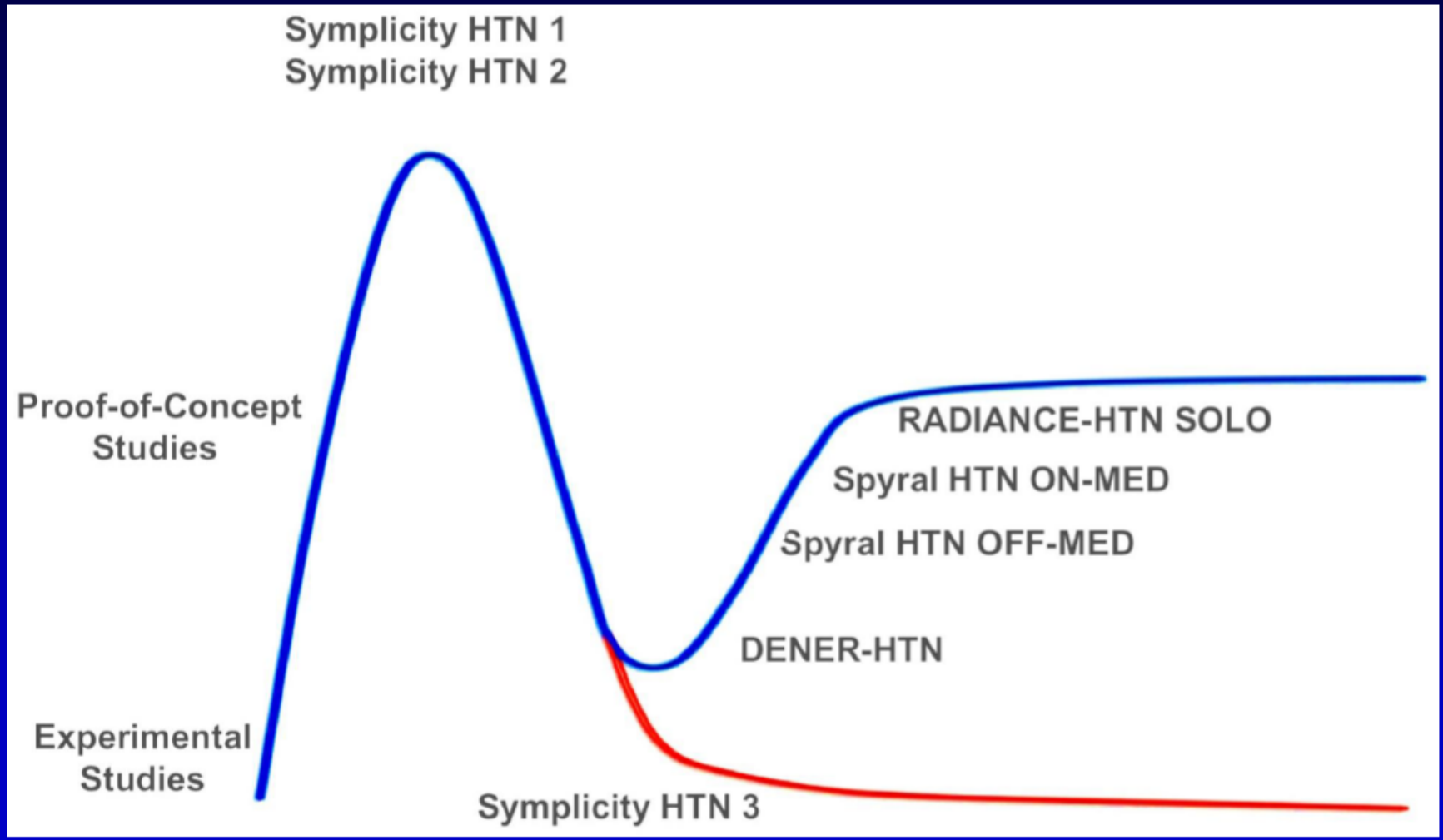
Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

Bruno RM [1], Taddei S [1], Borghi C [2], Colivicchi F [3], Desideri G [4], Grassi G [5], Mazza A [6], Muiesan ML [7],Parati G [8], Pontremoli R [9],Trimarco B [10], Volpe M [11], Ferri C [4]

[1] University of Pisa, Pisa, [2] University of Bologna, Bologna, [3] Ospedale San Filippo Neri, Roma, [4] University of L'Aquila, L'Aquila,, [5] University of Milano-Bicocca, Milano, [6] AUSL Rovigo, Rovigo, Italy, [7] University of Brescia, Brescia, [8] Istituto Auxologico Italiano ,IRCCS & Department of Medicine and Surgery, University of Milano Bicocca, Milano, [9] University of Genova, Genova, [10] University of Napoli, Napoli, [11] University of Rome "La Sapienza", Roma

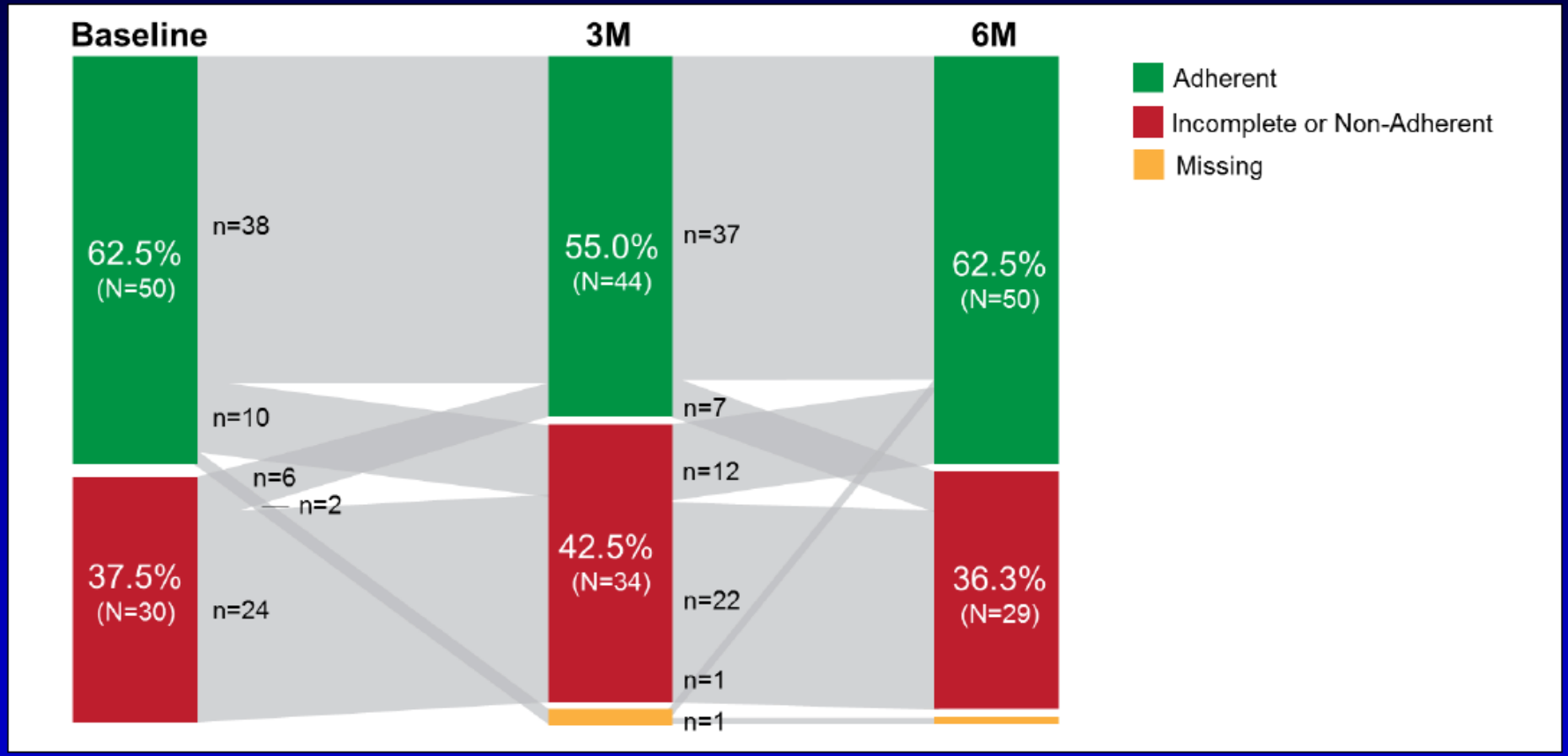
Catheter-based renal denervation: the next chapter begins

Felix Mahfoud[1,2]*, Markus Schlaich[3,4,5,6], Michael Böhm[1], Murray Esler[7], and Thomas Felix Lüscher[8,9]



Mahfoud et al, Eur Heart J 39 (2019): 4144-4149

SPYRAL HTN-ON MED
Medication Adherence

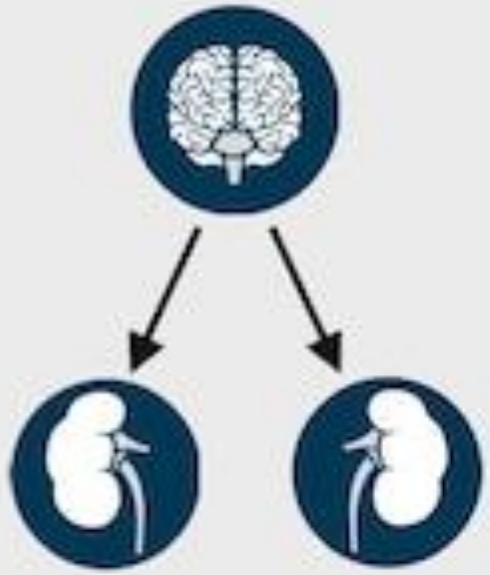


Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.

Kandzari D, et al., Lancet 2018.

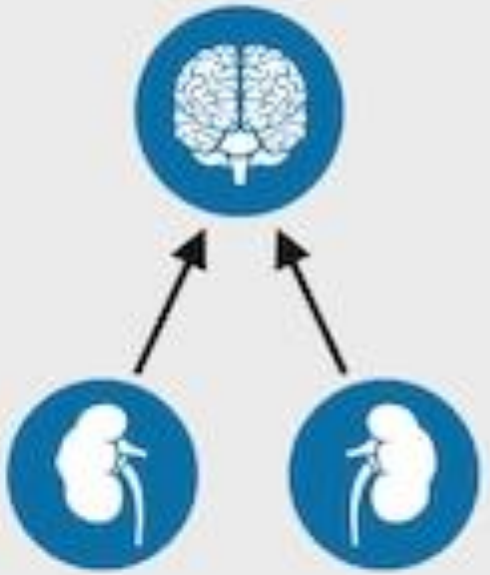
Renal Nerves and the Sympathetic Nervous System

Efferent sympathetics



Sympathetic signals from the CNS modulate the physiology of the kidneys

Afferent renal sympathetics



The kidney is a source of central sympathetic activity, sending signals to the CNS

Adapted from Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

Razionale

- Background

Presupposto . L'iperattività del Sistema Nervoso Simpatico contribuisce allo sviluppo

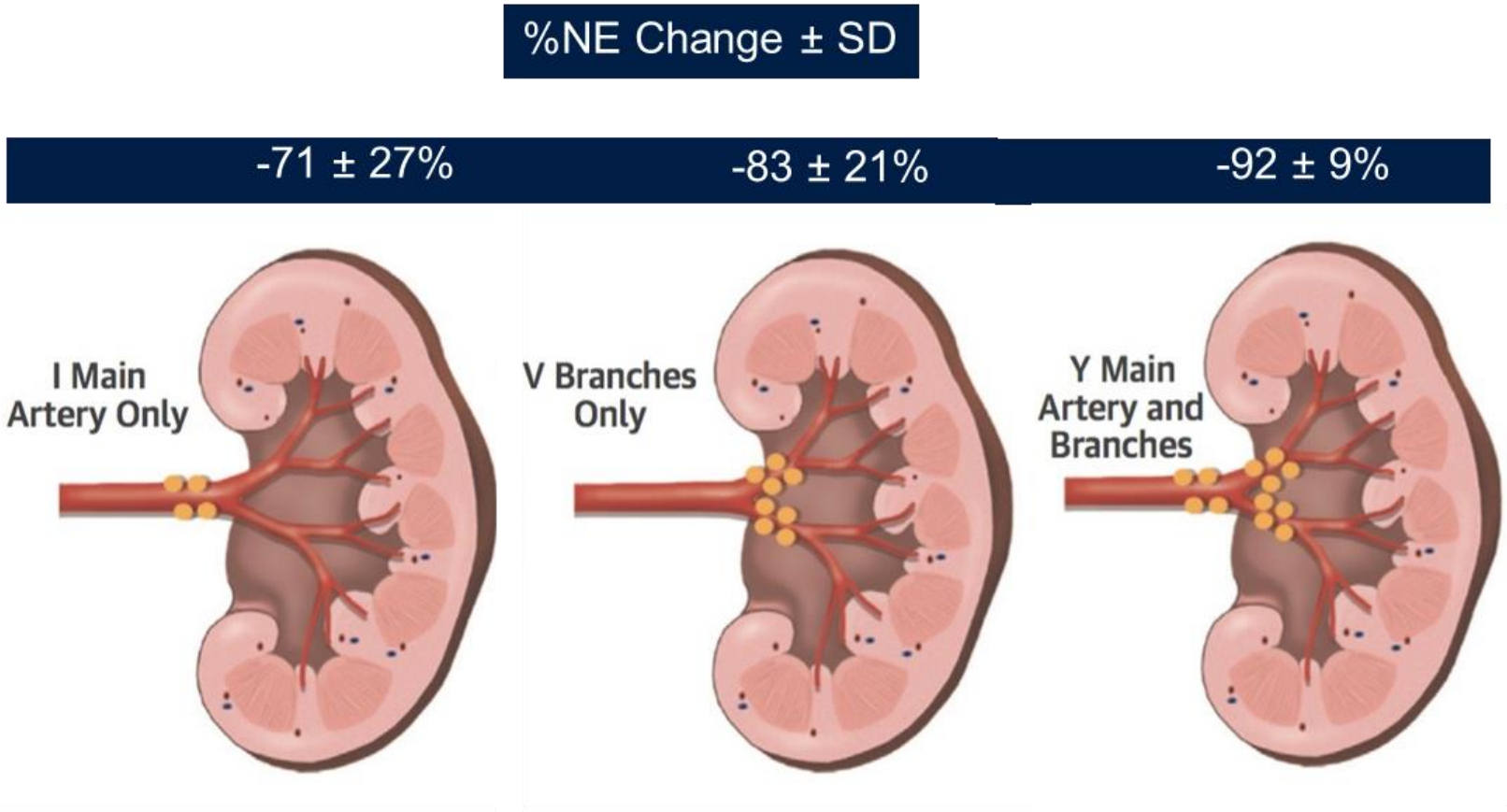
e al mantenimento di uno stato Ipertensivo Arterioso

Concetto/Deduzione . L'interruzione della trasmissione del segnale *nervoso simpatico* può contrastare lo stato tensivo pressorio SNS mediato

Lessons From HTN-3

HTN-3 Factor Identified	Alternative
 Medications	• Obtain off-meds data • Standardize meds • No max dose titration • Measure adherence
 Study Population	• Less severe HTN • Fewer prescribed meds • Focus on ABPM • Patients from across globe • Avoid changing patient behavior
 Procedural	• Spyral™ Catheter • Main + branch vessel treatment • Experienced proceduralists

IVY Trial: Distal ablation was associated with greater reduction in sympathetic nerve activity (porcine model)



Pre-clinical data show significantly greater reductions in renal sympathetic activity with combined proximal and distal therapy application.

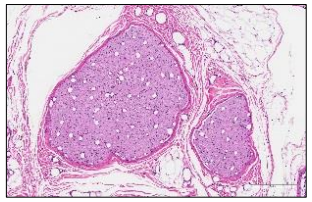
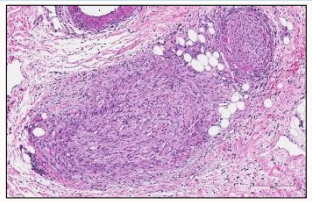
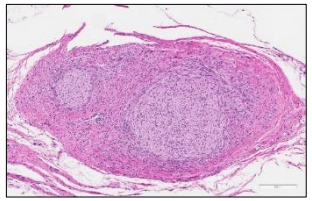
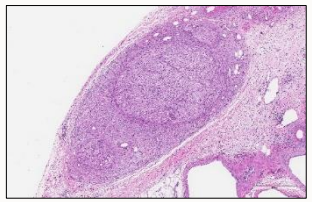
Distal renal nerves are closer to the arterial lumen

Mahfoud F et al. *J Am Coll Cardiol*. 2015;66:1766-75.

DURABLE RESULTS AFTER RADIO FREQUENCY (RF) RDN OF THE RENAL NERVES

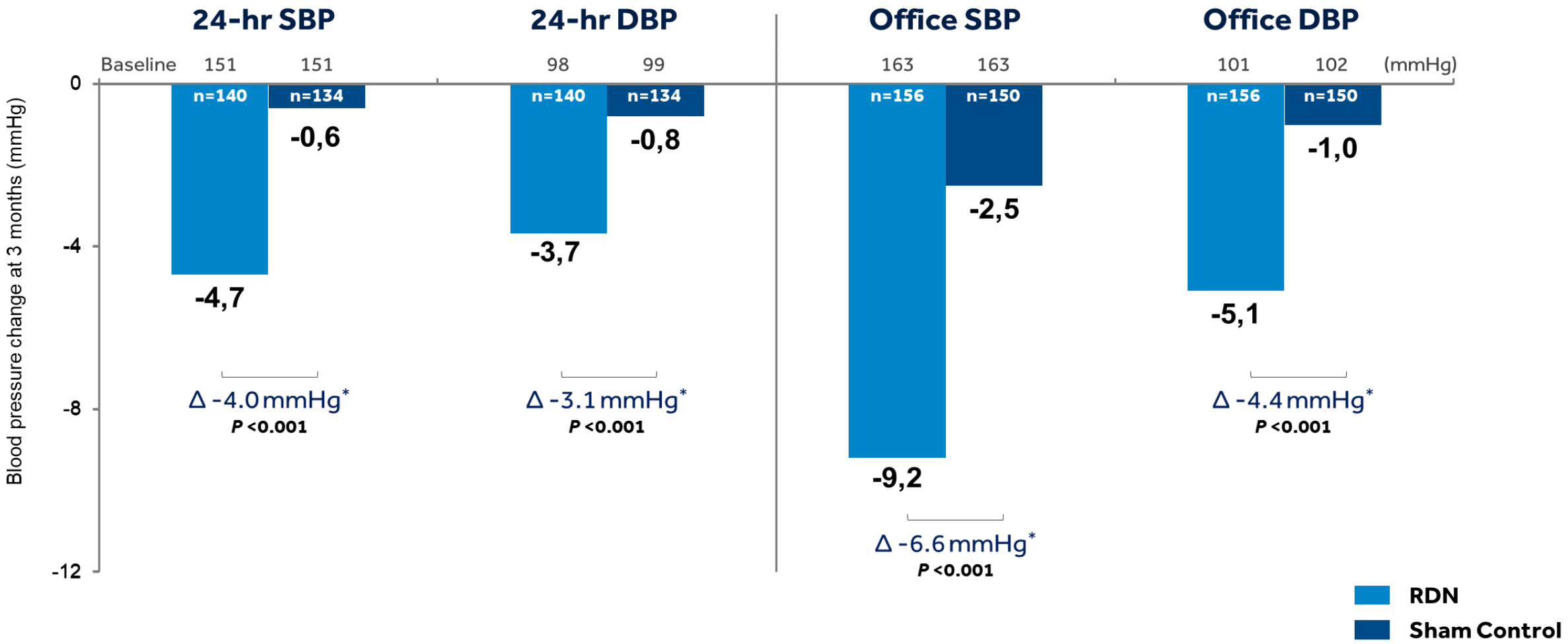
IRREVERSIBLE DESTRUCTION OF AXONS OBSERVED AT DAY 180

Study Design: RF RDN was performed in 164 healthy swine with serial histological tissue samples of the renal arteries obtained at 7, 28, 60 and 180-days

	Histological Tissue Slice	Key Histological Findings
Day 0 (pre-RDN) Normal Nerve Function		• Nerve bundles organized in fascicles • Quiescent Schwann cells • Blood supply intact • Lack of fibrosis
Day 7 Necrosis and inflammation observed		• Obliteration of nerve structure • Cell debris • Loss of blood supply • Intense inflammatory infiltrate • Fibrosis
Day 60 Mature fibrotic infiltration found with disruption to nerve architecture		• Disruption of normal nerve structure • Fibrosis • Hypercellularity
Day 180 Persistent fibrotic infiltration with irreparable nerve architecture. **Functional nerve regrowth is highly unlikely**		• Disruption of normal nerve structure • Fibrosis • Hypercellularity • No restoration of organized nerve bundles

RDN showed significant reductions in all bp measures

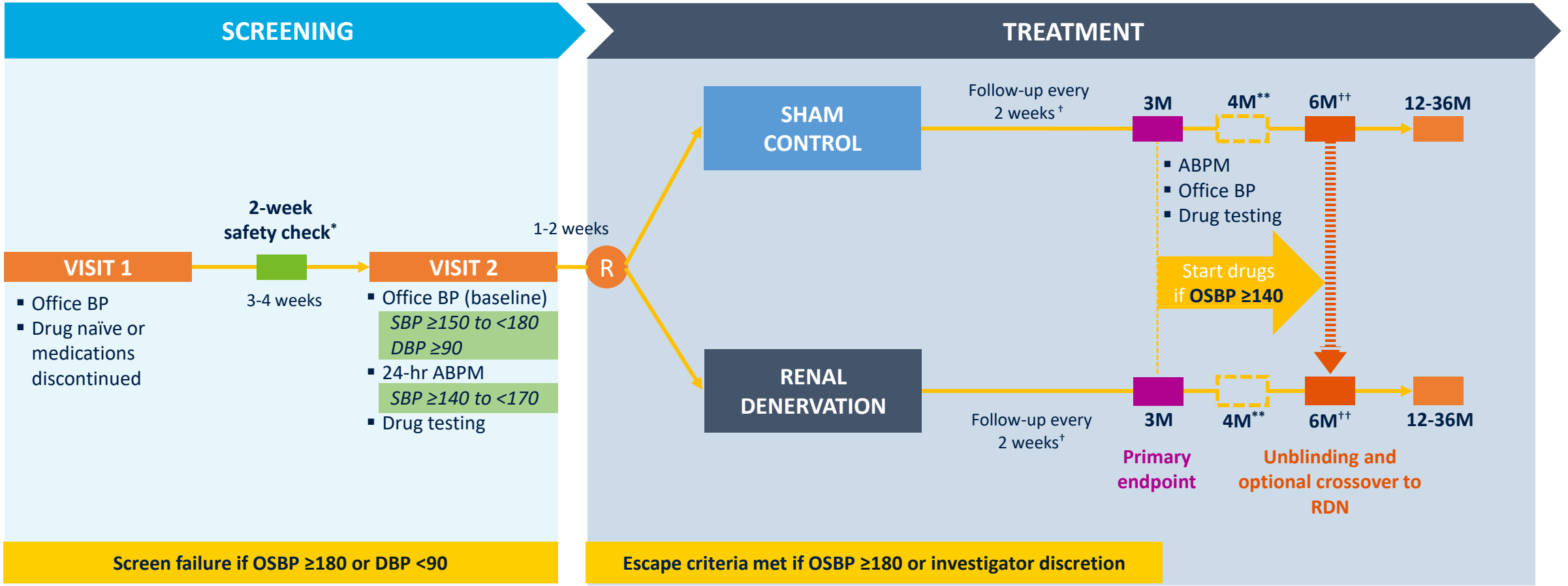
BLOOD PRESSURE CHANGE FROM BASELINE AT 3 MONTHS



Bohn et al, Lancet 2020

SPYRAL HTN-off med Pivotal trial

RANDOMIZED, SHAM-CONTROLLED[1]



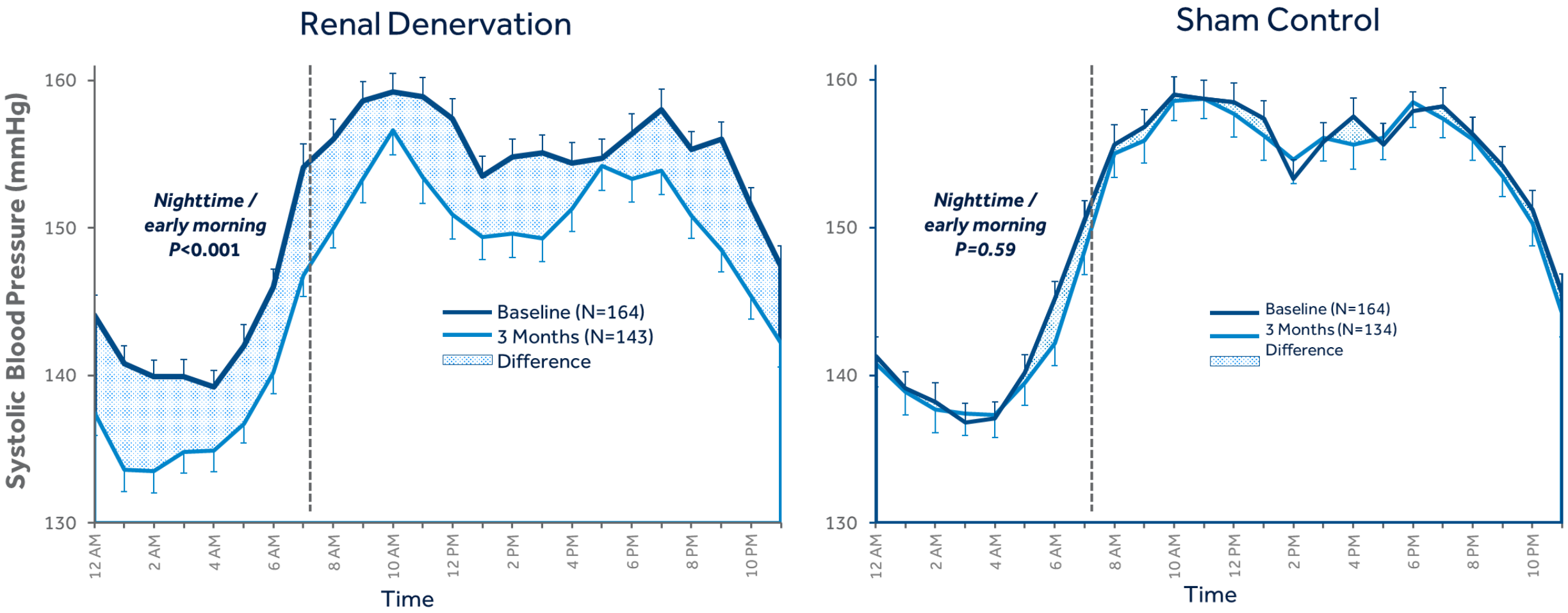
*Only for patients discontinuing anti-hypertensive medications
†Optional follow-up at weeks 6 and/or 10 if the patient is not controlled
**Only for patients with BP ≥140 mm Hg at 3M

††6 and 12 month renal imaging

Böhm et al. Clin Res in Card, 2020

RDN demonstrated an “always on” effect on 24-hour Bp lowering

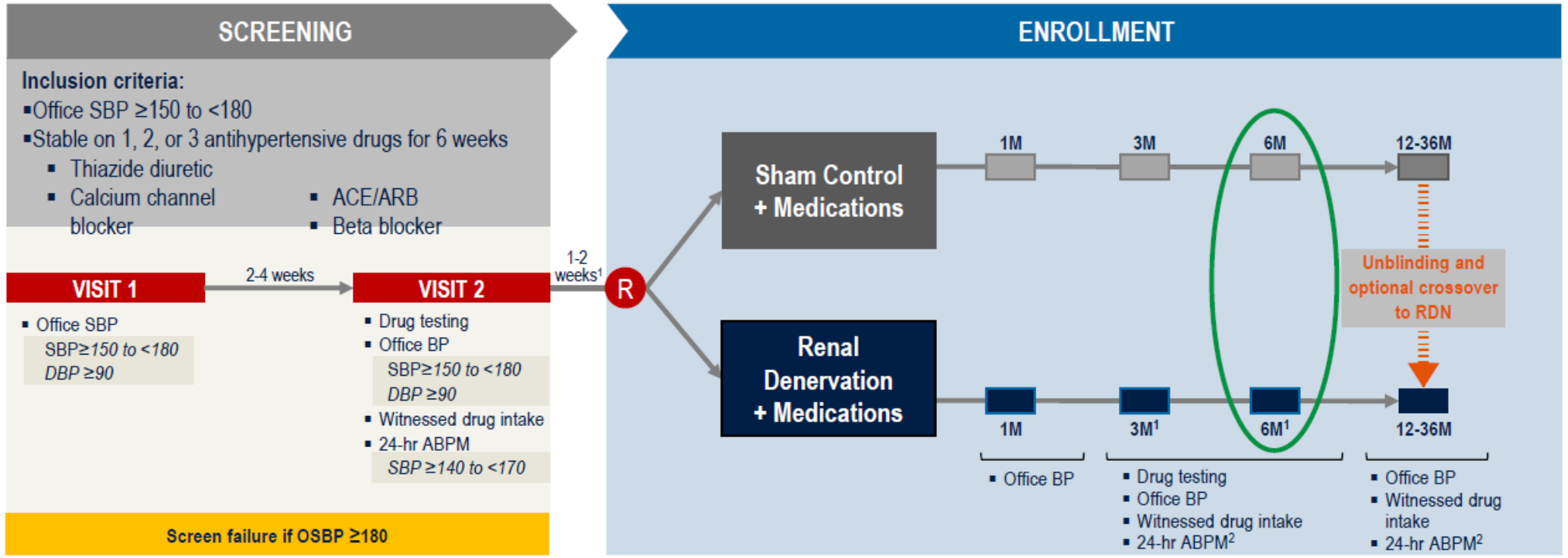
24-HOUR SYSTOLIC ABPM TREND AT 3 MONTHS



1. Böhm et al. The Lancet, 2020.
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

SPYRAL HTN-ON MED

RANDOMIZED, SHAM-CONTROLLED TRIAL

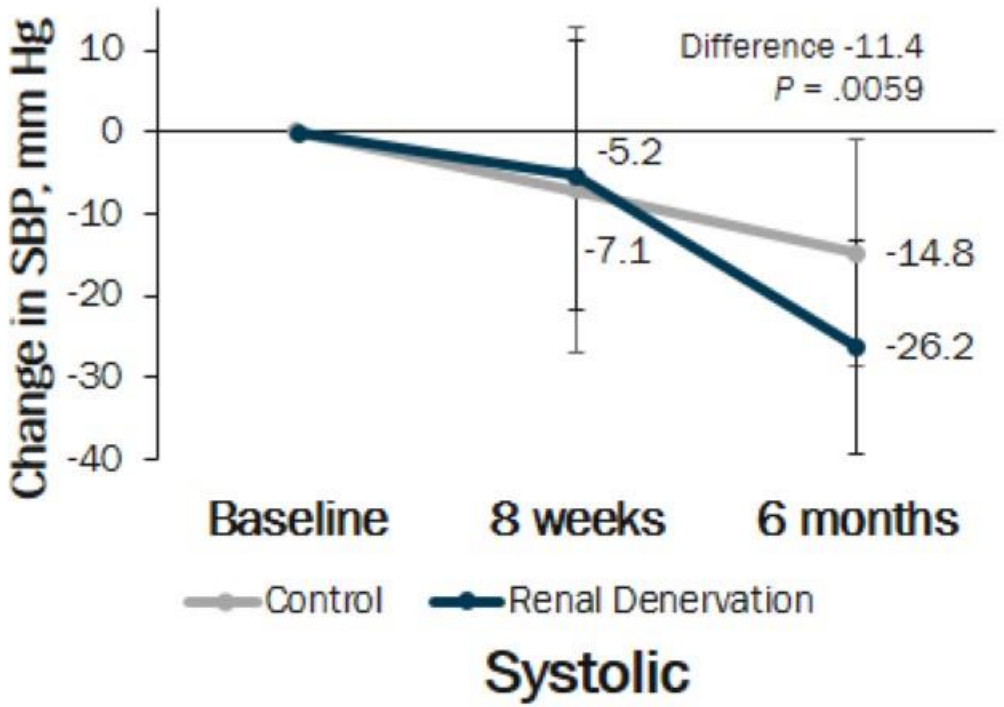


[1]According to scheduling
Clinicaltrials.gov NCT02439775
Kandzari D, et al. *Am Heart J*. 2016;171:82-91.

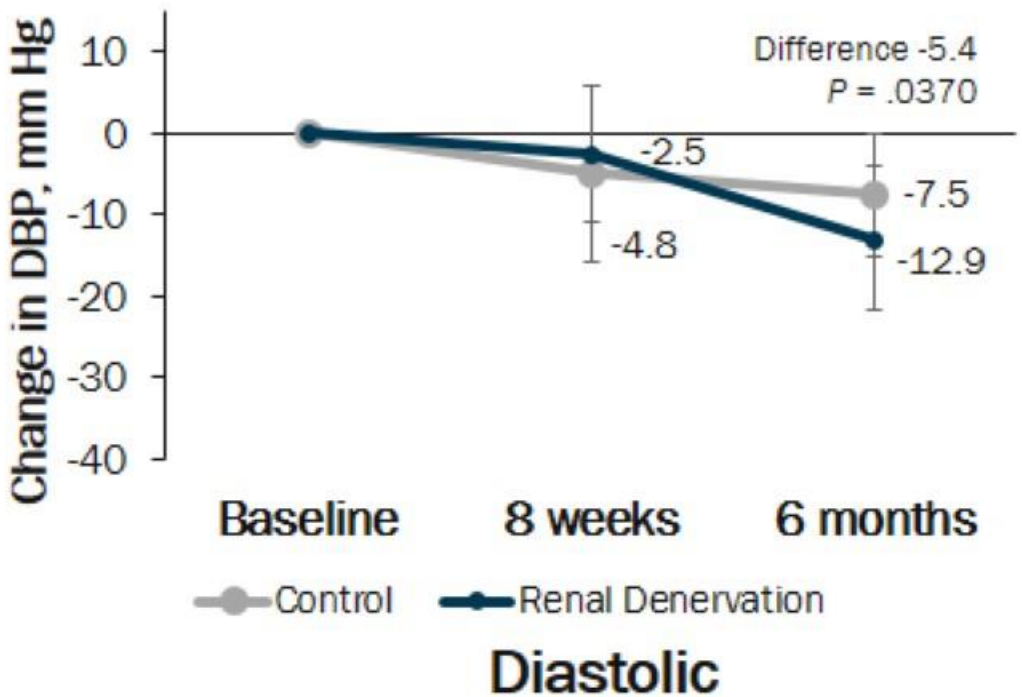
REDUCE HTN: REINFORCE

Change in Office BP

Baseline BP, mm Hg	Systolic	Diastolic
Vessix	166.3 ± 9.0	94.9 ± 11.8
Control	166.2 ± 8.8	94.9 ± 11.1



Systolic



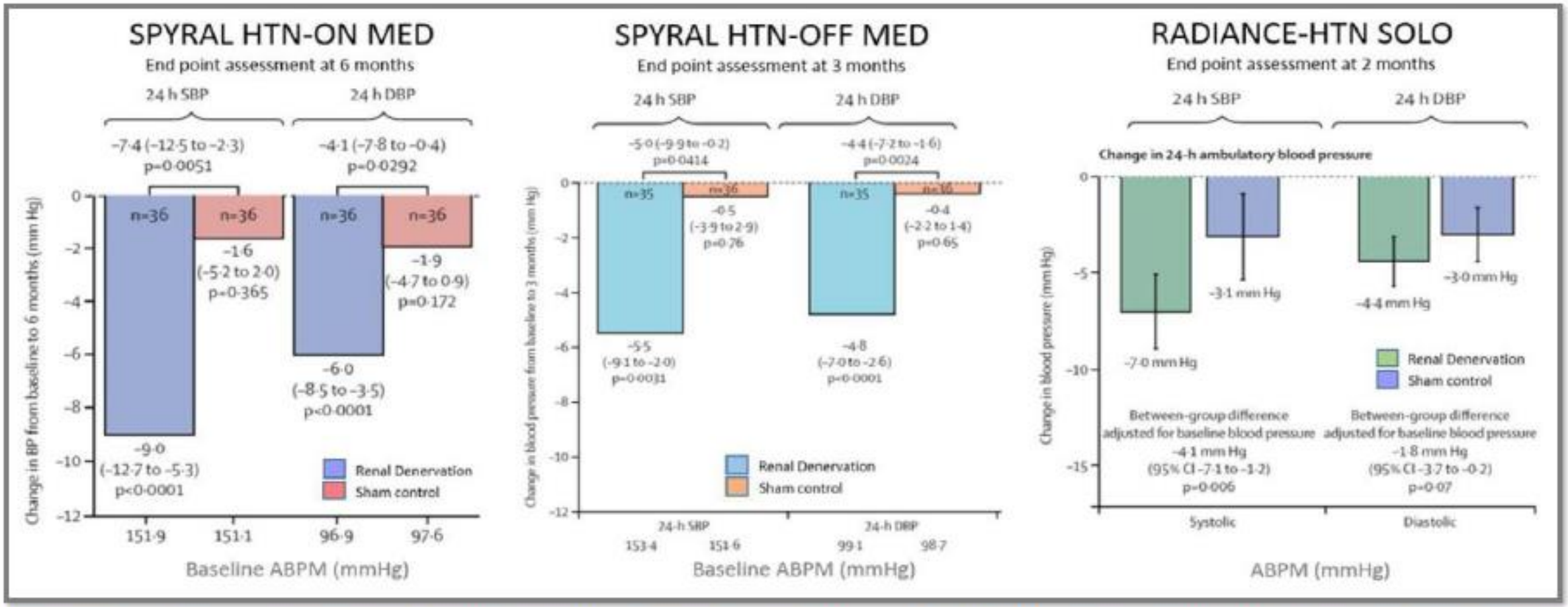
Diastolic

8-week data point includes rescued subjects with last antihypertensive medication-free reading carried forward to 8 weeks.

Weber MA, et al. *JACC Cardiovasc Interv*. 2020;13:461-470.

2017-2018 . 3 nuovi trial clinici – 306 RH pts

(≠ disegno (wash-out Tx) e popolazione in studio (IA lieve-moderata), devices e tecniche procedurali)



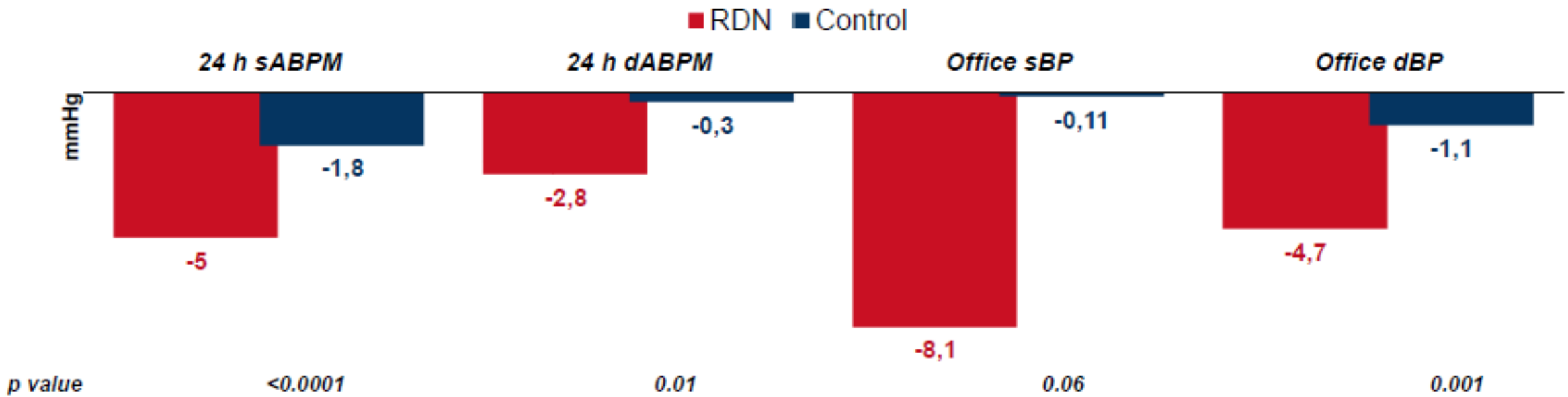
this results <u>show a convincing and clinically relevant reduction of 24hsBP</u> compared with sham-control group in the absence and presence of concomitant antihypertensive medication

nuove evidenze . Metanalisi 1

7 Randomized Sham-Controlled Trial

1098 Hypertensive Patients → 660 RDN . 438 Control

f.u. 2-6 months – 71% RF devices, 40% first generation RF devices



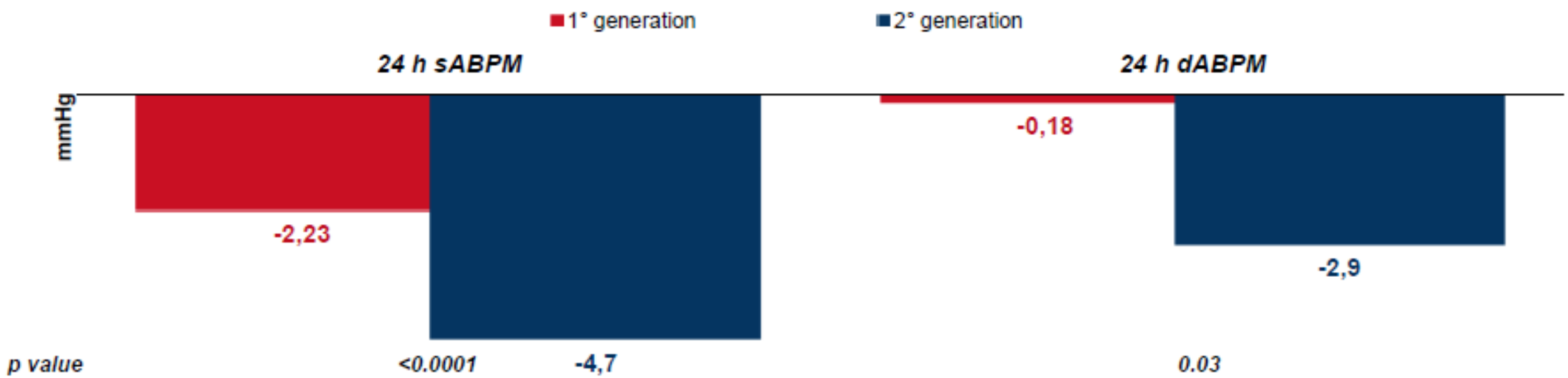
RDN significantly reduces ambulatory BP and office BP in patients with hypertension

nuove evidenze . Metanalisi 2

6 Randomized Sham-Controlled Trial

981 Hypertensive Patients → 585 RDN . 396 Control

- comparing first and second generation devices -



The overall benefit noted with RDN can be attributed mostly to the 2° generation studies

Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry

Felix Mahfoud[1]*, Michael Böhm[1], Roland Schmieder[2], Krzysztof Narkiewicz[3], Sebastian Ewen[1], Luis Ruilope[4], Markus Schlaich[5], Bryan Williams[6], Martin Fahy[7], and Giuseppe Mancia[8]

Baseline characteristics

Characteristics	Global SYMPLICITY Registry (n = 2237)
Male (%)	58.0
Age (years)	61 ± 12
Body mass index (kg/m^2)	31 ± 6
Current smoking (%)	9.8
History of cardiac disease (%)	48.4
Estimated GFR (mL/min/1.73 m^2)	76.3 ± 25.0
Chronic kidney disease stage ≥3 (%) (eGFR <60 mL/min/1.73 m^2)	20.9
Obstructive sleep apnoea (%)	10.6
Atrial fibrillation (%)	12.7
Diabetes Type 2 (%)	38.0
Office blood pressure (mmHg)	
Systolic	166 ± 25
Diastolic	90 ± 17
24-h ambulatory blood pressure (mmHg)	
Systolic	154 ± 18
Diastolic	86 ± 14
True hypertension (%)	83
Masked hypertension (%)	11
White coat-hypertension (%)	4

Results are presented as % or mean ± SD.
eGFR, estimated glomerular filtration rate.

Mahfoud et al, Eur Heart J (2019): [doi:10.1093/eurheartj/ehz118]

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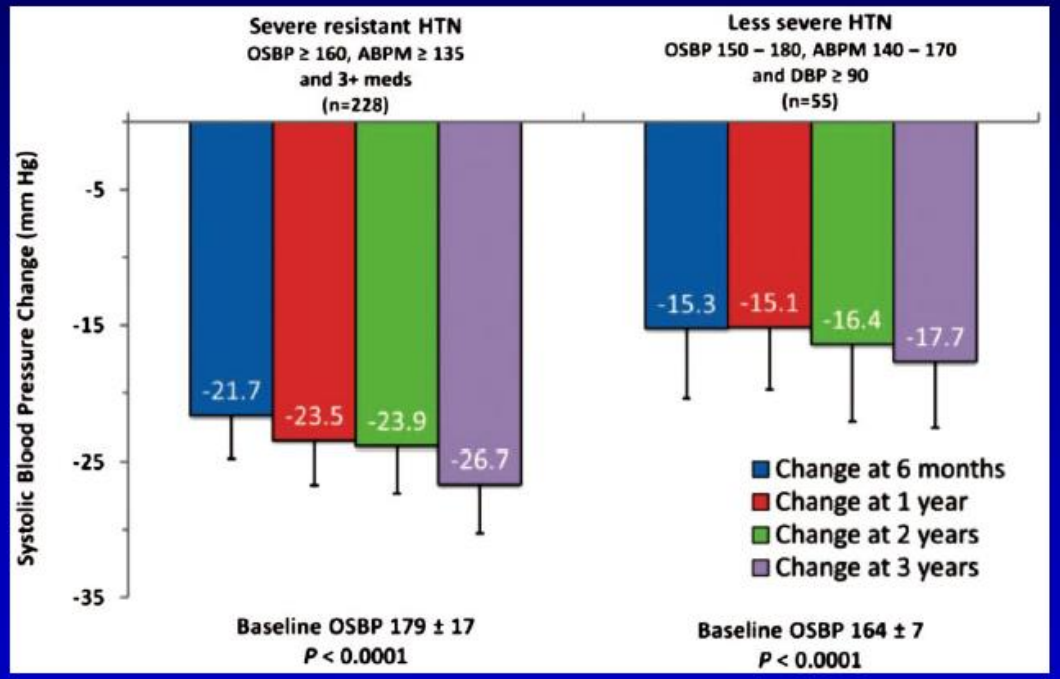
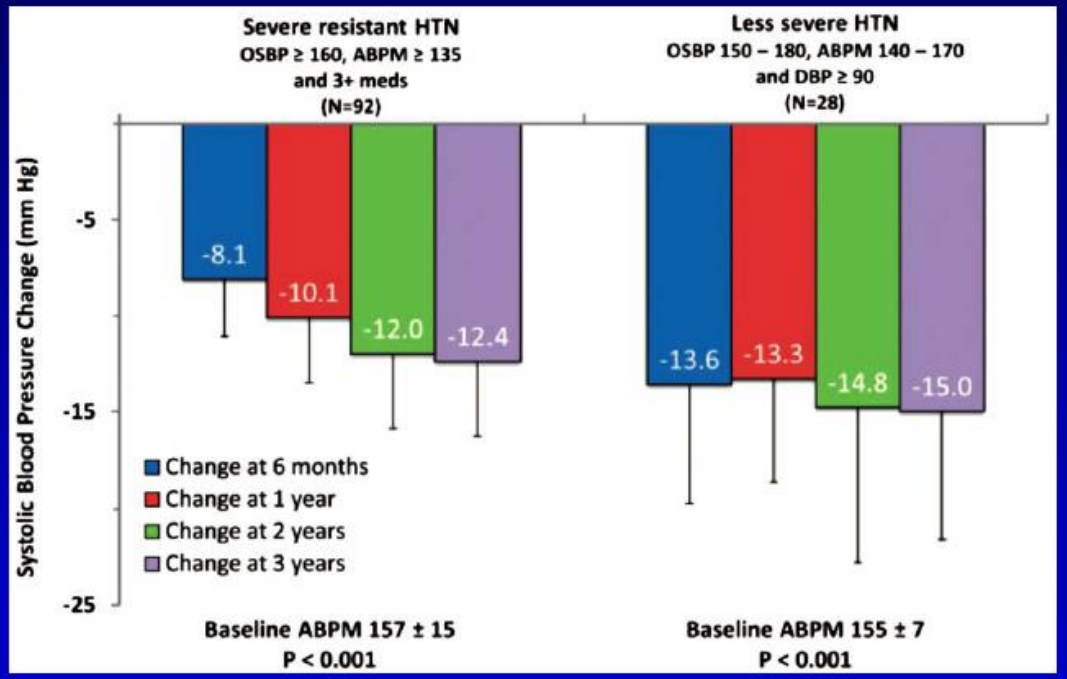
Change in Office SBP



Change in 24h Ambulatory SBP



Mahfoud et al, Eur Heart J (2019): [doi:10.1093/eurheartj/ehz118]

Global SYMPLICITY Registry

CLINICAL TRIAL DESIGN

Prospective, open-label, single-arm, multi-center, all-comer observational registry

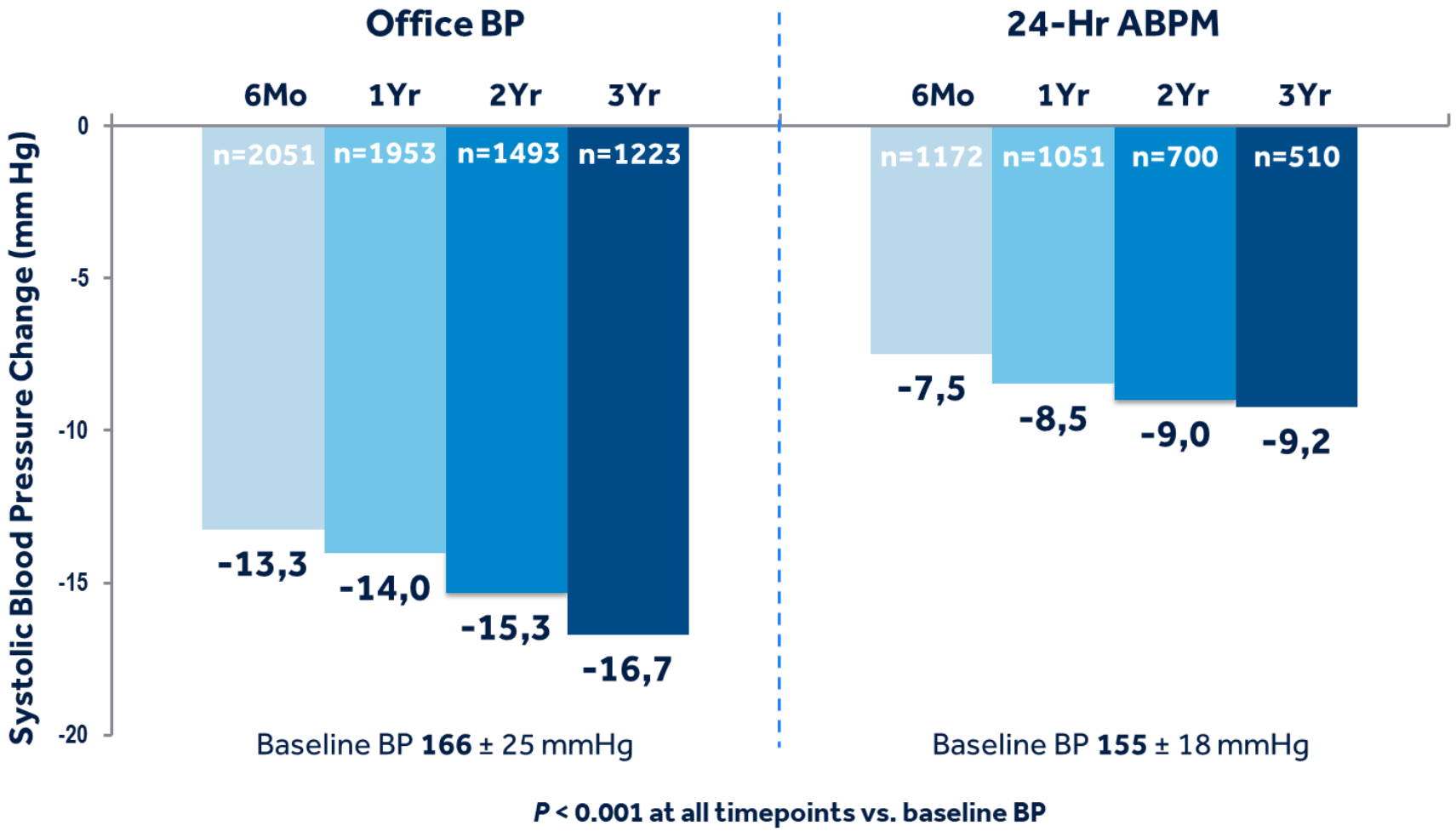
3000 Consecutive patients with uncontrolled hypertension
or other conditions associated with increased sympathetic activity
treated with Symplicity™ (Flex or Spyral) RDN system

Follow-up	3M	6M	1Y	2Y	3Y
Follow-up eligible to date:					
Patients treated with Symplicity Flex™ catheter	2231	2226	2211	2207	
Patients treated with Symplicity Spyral™ catheter	516	472	381	323	
Total	**2747**	**2698**	**2592**	**2530**	

Mahfoud F, et al. PCR e-Course. 2020

Significant blood pressure reductions were sustained out to 3 years

BLOOD PRESSURE CHANGE IN ALL PATIENTS



***P* < 0.001 at all timepoints vs. baseline BP**

Mahfoud F, et al. PCR e-Course. 2020

Controlling hypertension is critically important

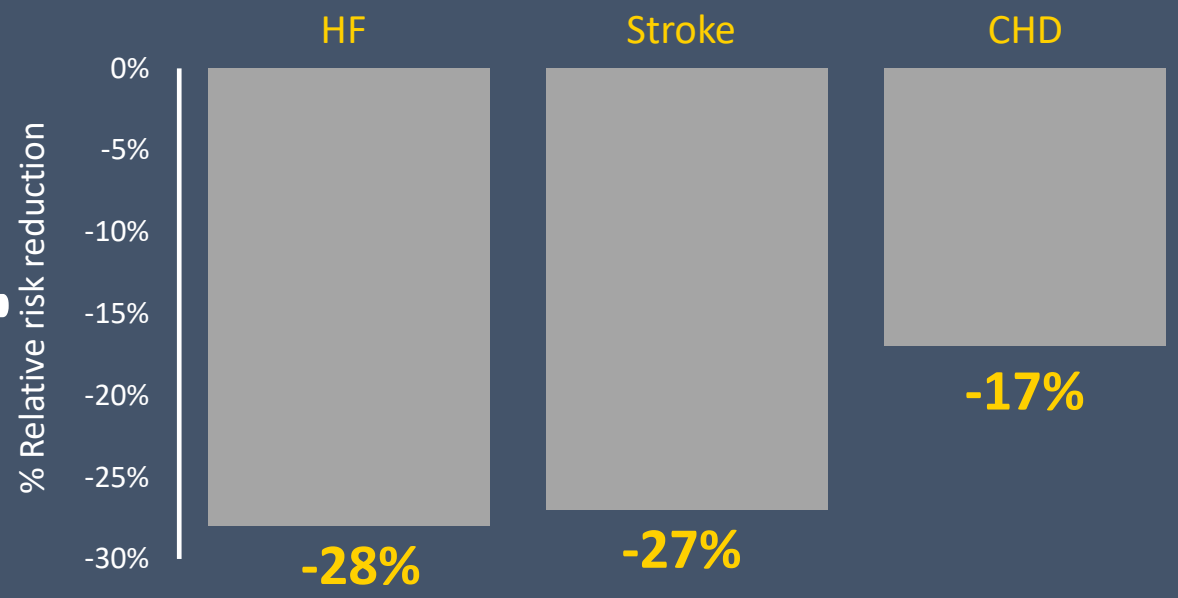
BLOOD PRESSURE CONTROL REDUCES THE RISK OF DEBILITATING SIDE EFFECTS

10 MM HG DECREASE IN MEAN OFFICE SBP:

20%
Reduction in relative risk of
major cardiovascular events

+

13%
Reduction in relative risk of
all-cause mortality



Ettehad D, et al. *Lancet*. 2016,387:957–967

nuove posizioni

POSITION PAPER

Check for updates

Italian Society of Arterial Hypertension (SIIA) Position Paper on the Role of Renal Denervation in the Management of the Difficult-to-Treat Hypertensive Patient

Rosa Maria Bruno[1,2] · Stefano Taddei[1] · Claudio Borghi[3] · Furio Colivicchi[4] · Giovambattista Desideri[5] · Guido Grassi[6] · Alberto Mazza[7] · Maria Lorenza Muiesan[8] · Gianfranco Parati[9,10] · Roberto Pontremoli[11] · Bruno Trimarco[12] · Massimo Volpe[13,14] · Claudio Ferri[5]

8 internisti
4 cardiologi
1 nefrologo

… nel futuro è quindi necessario un forte programma di sviluppo scientifico e clinico che ci porti a poter considerare la denervazione renale una delle opzioni terapeutiche nella pratica clinica quotidiana

High Blood Pressure & Cardiovascular Prevention . 2020

RDN . from resistant hypertension to the difficult-to-treat-patient

Clinical profiles of patient candidates to RDN

(a) Essential hypertensive patient uncontrolled by an association RAS-blocker/calcium-channel blocker/diuretic at maximally tolerated doses (recommended) [36, 60]

Additional features

- Adverse effects with spironolactone [37]
- Poor drug adherence despite extensive counseling [56]
- Systo-diastolic hypertension [34]
- No extensive vascular damage [57, 58]
- High/very high lifetime cardiovascular risk
- Patient preferences

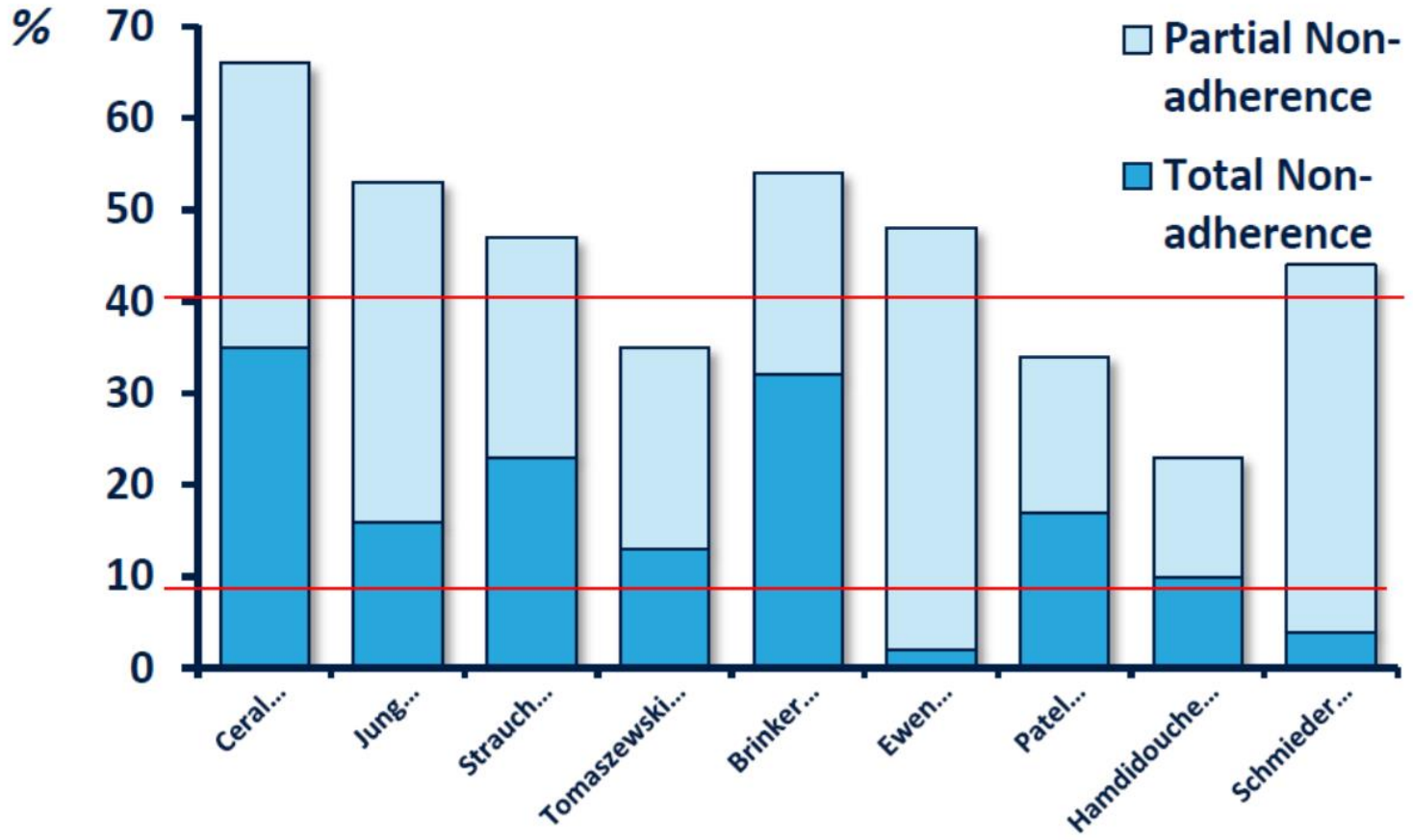
(b) Grade 1–2, systo-diastolic, essential hypertensive patient, untreated or uncontrolled by 1–2 BP-lowering drugs (possible) [39–41]

Additional features

- Multiple intolerance to BP-lowering drugs/adverse effects
- Poor drug adherence despite extensive counseling
- High/very high lifetime cardiovascular risk
- Paroxysmal atrial fibrillation and planned ablation [63]
- Patient preferences

Non-Adherence to prescribed antihypertensive drugs in clinical studies:

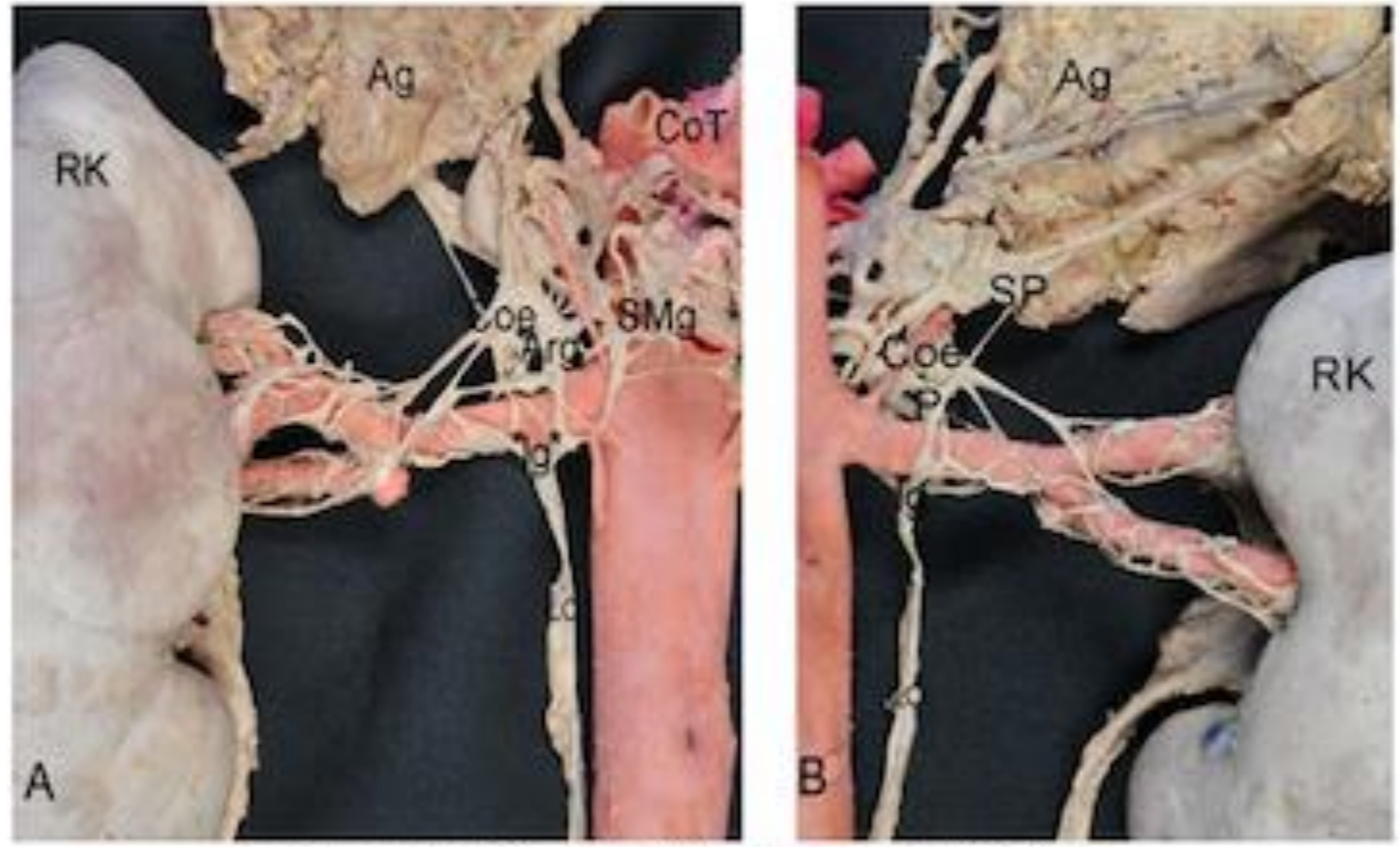
- Up to 50% non-adherence rates across trials
- Poor and dynamic adherence introduces variability to trial endpoints



Berra E, et al. Hypertension. 2016;68:297-306

Procedure Changed to Reflect Renal Nerve Anatomy
Distal Nerves Are Closer to the Arterial Lumen

- Renal nerves generally originate from the aorta and arborize toward the kidney
- Nerve fibers do not completely converge on the renal artery until beyond main bifurcation
- Accessory arteries, when present, have similar anatomical innervation patterns that mimic the main renal arteries
- Procedure was changed to ablate as distally as possible where renal nerves congregate closer to artery
- Ablations are only done outside of angiographic shadow of kidney



Sympathetic renal plexus of right kidney
(A) anterior (B) posterior

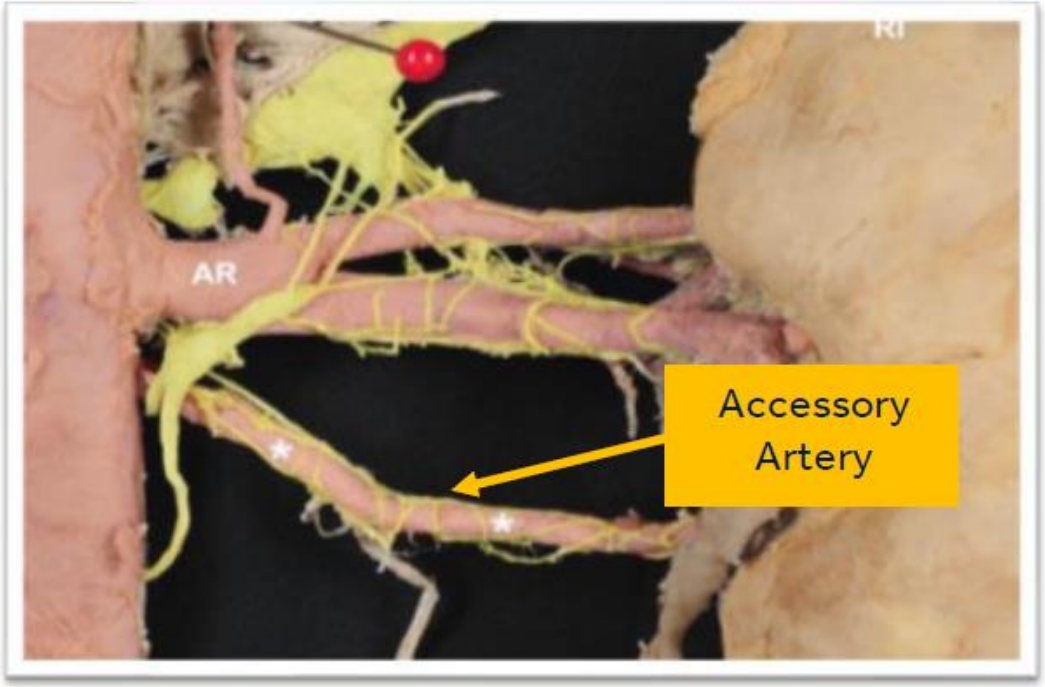
EFFECTIVE RDN INCLUDES TREATMENT IN THE BRANCHES AND ACCESSORIES

RENAL NERVES OFTEN BYPASS THE MAIN RENAL ARTERY AND JOIN AT THE BRANCHES

Study Design:

- Sixty kidneys from 30 human cadavers were systematically microdissected
- Each dissection required over 40 hours of careful, meticulous work

63% of kidneys had renal nerves that joined distal to the main renal artery bifurcation

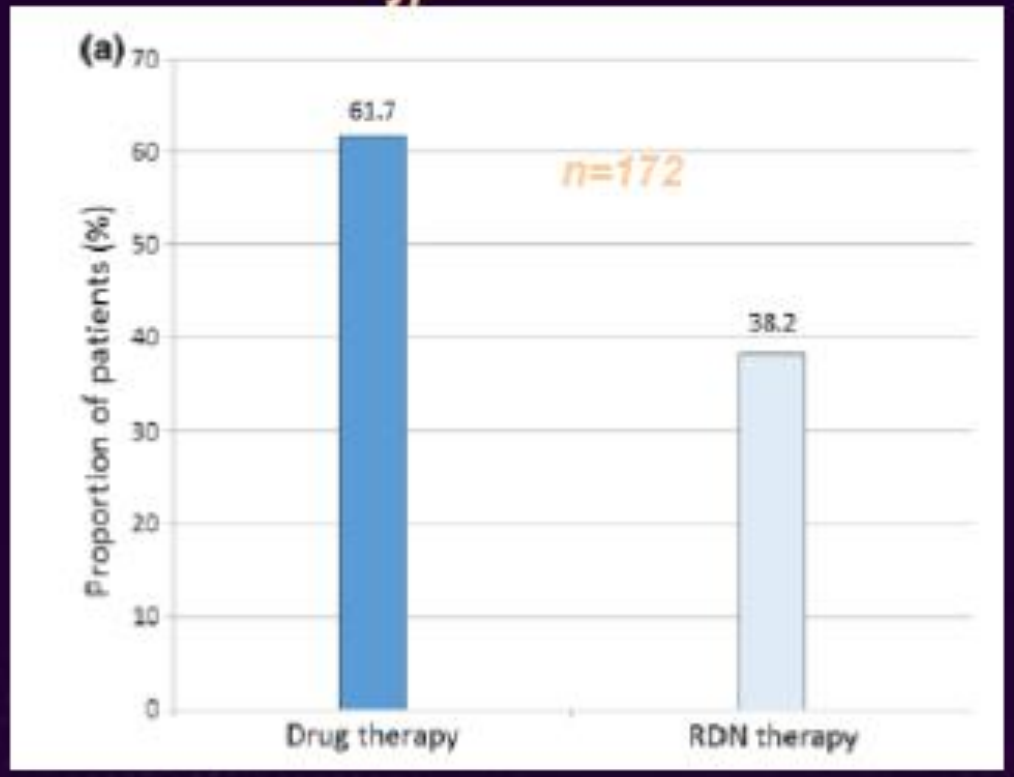


30% of cadavers had accessory arteries and were highly innervated

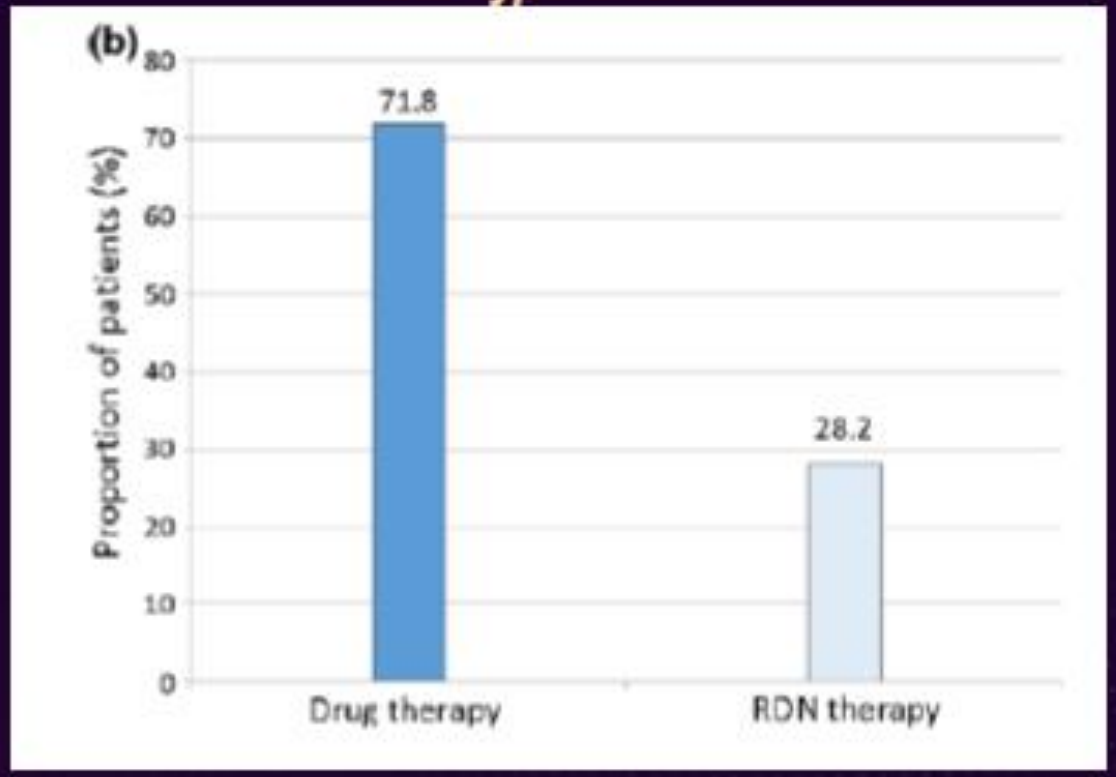
Garcia-Touchard A, et al. TCT Connect 2020.

PATIENT PREFERENCE FOR DRUG THERAPY VERSUS RENAL DENERVATION
MANY PATIENTS WOULD PREFER DEVICE TREATMENT

Patients not taking antihypertensive medication



Patients prescribed ≥1 anti-hypertensive medication

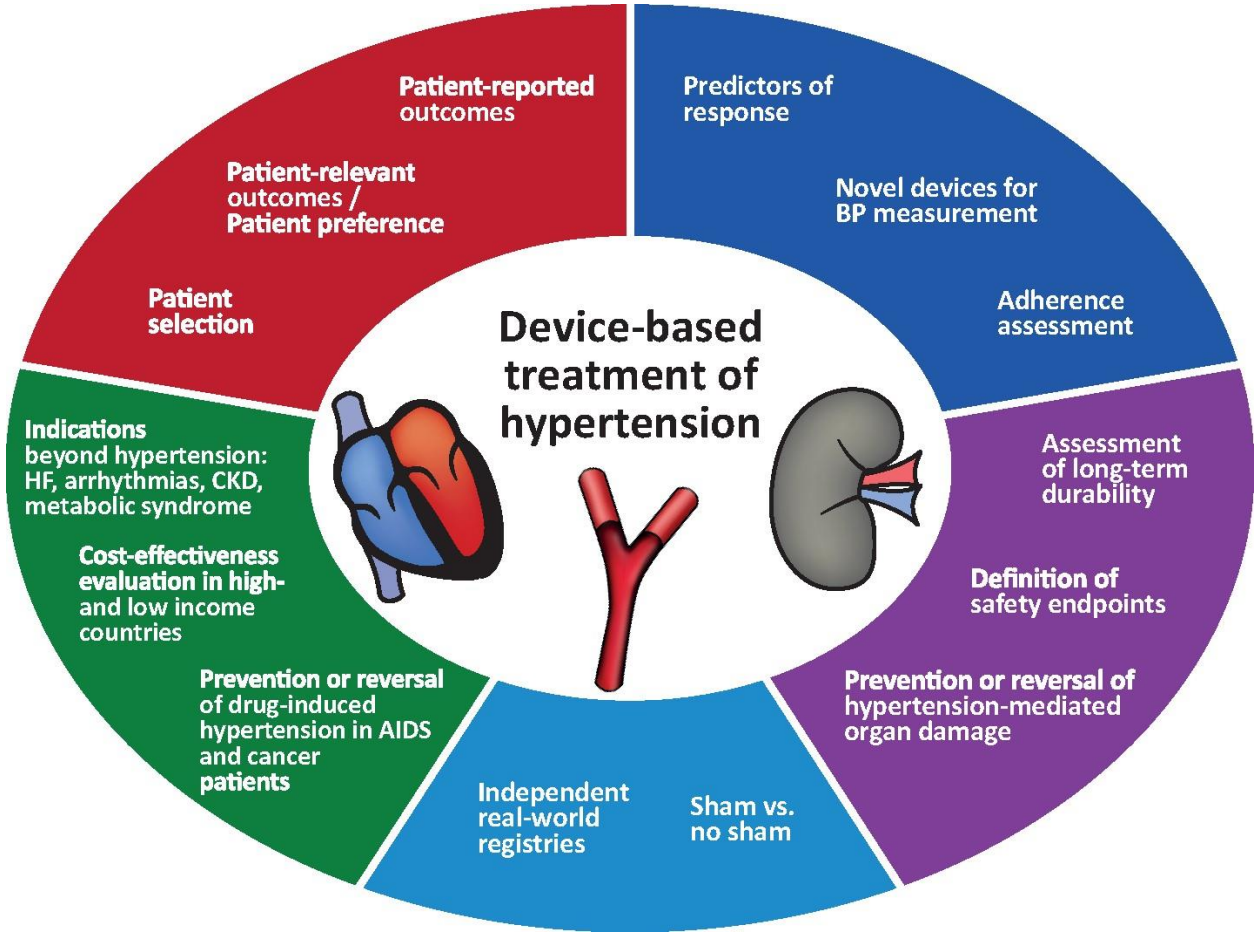


n=839

Questionnaire-based cross-sectional survey in patients with elevated blood pressure in Germany (

Schmieder R, et al. Clin Res Cardiol. 2019. https://doi.org/10.1007/s00392-018-01468-0

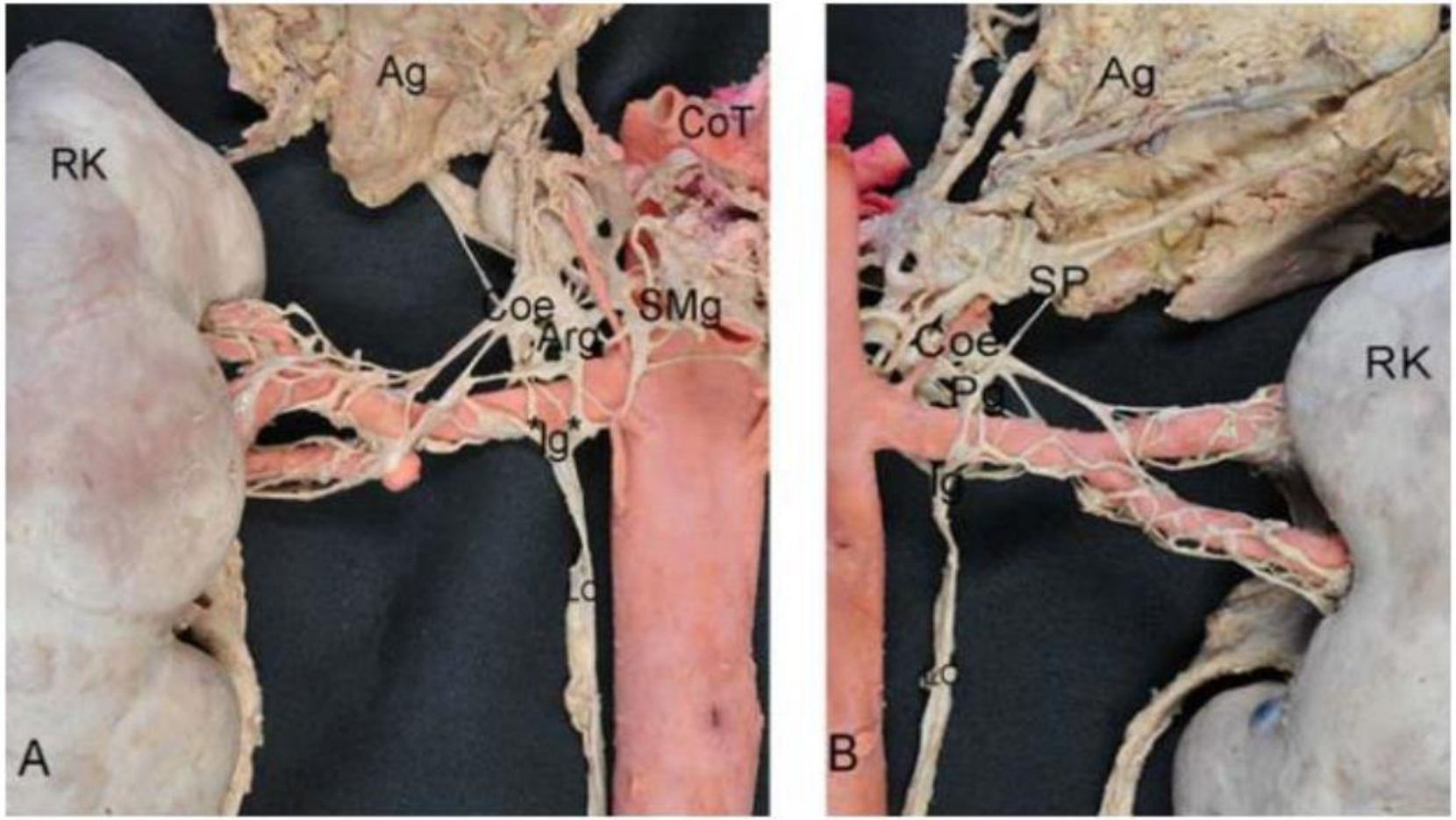
500308



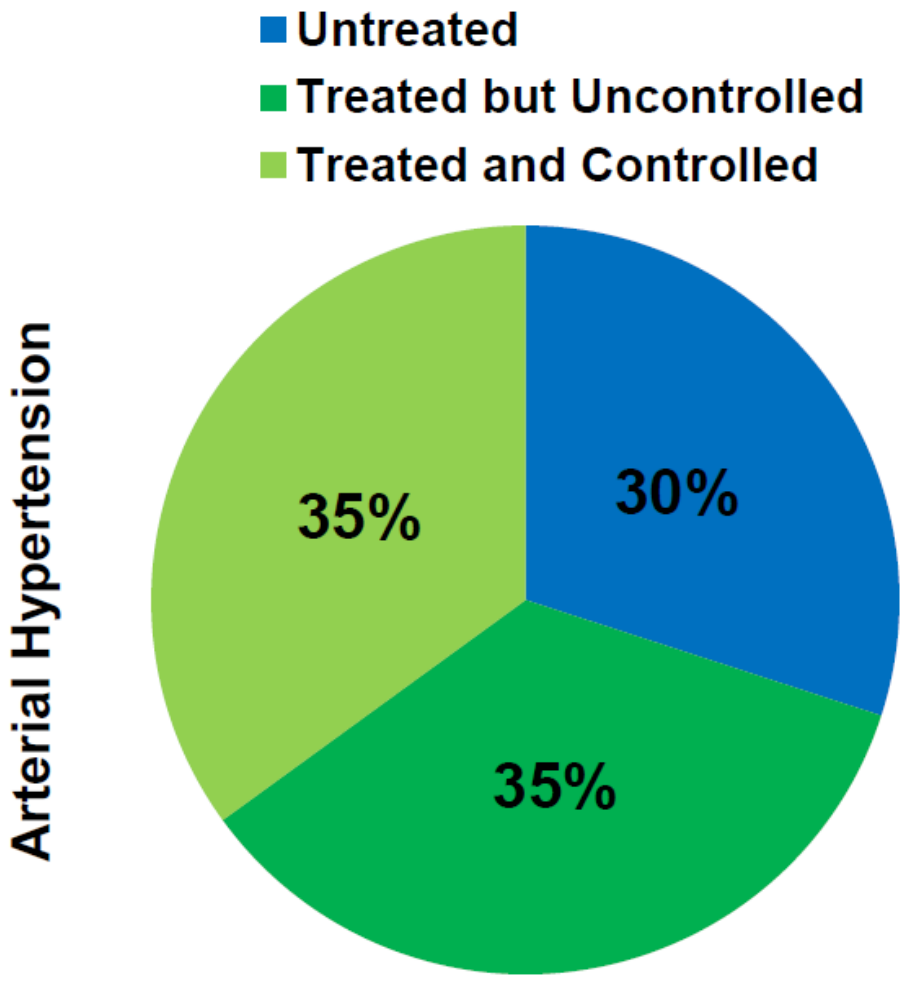
Eur Heart J, Volume 41, Issue 16, 21 April 2020, Pages 1588–1599, https://doi.org/10.1093/eurheartj/ehaa121

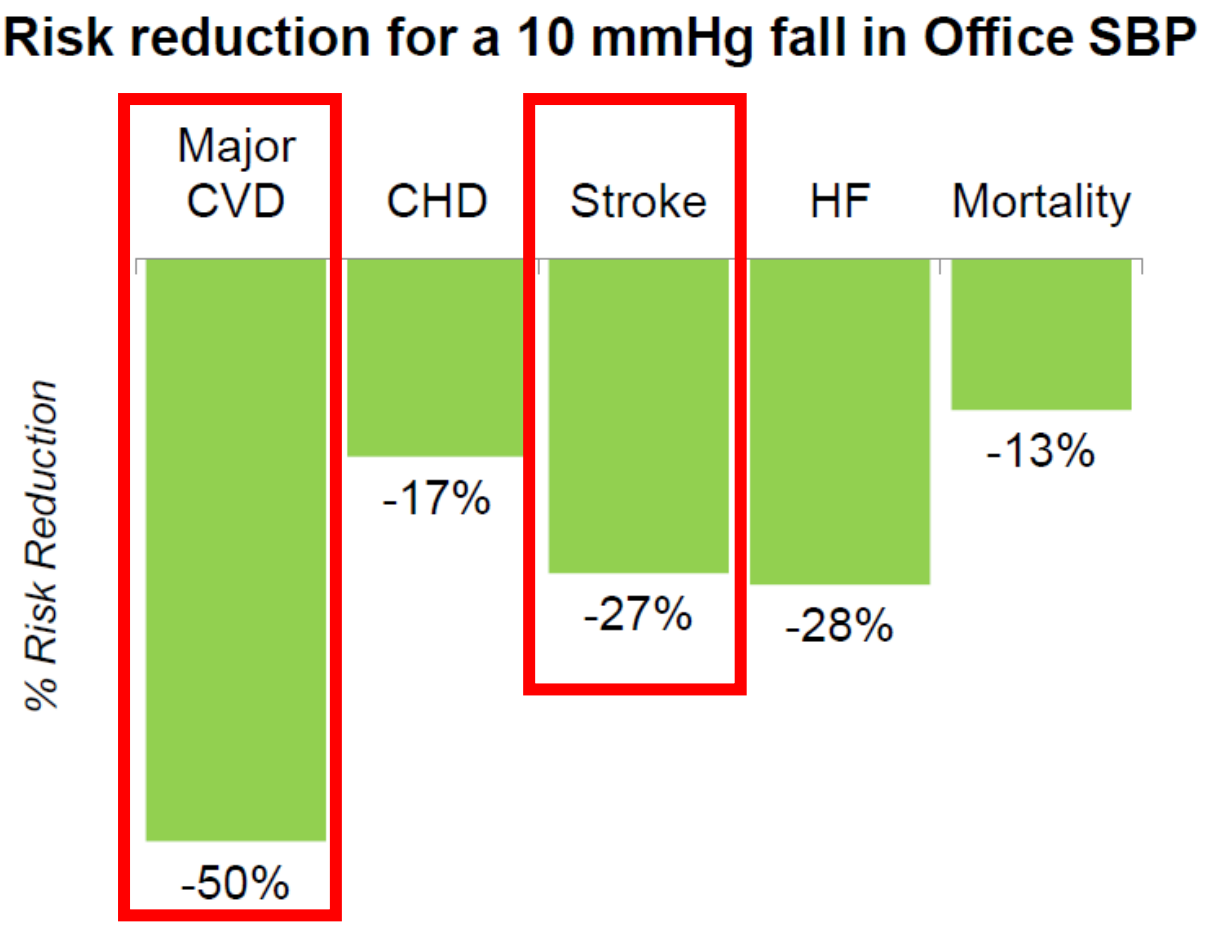
Anatomical consideration for efficacy

Circumferential ablation



Mompeo , et al, Clinical Anatomy. 2016. doi: 10.1002/ca.22720.



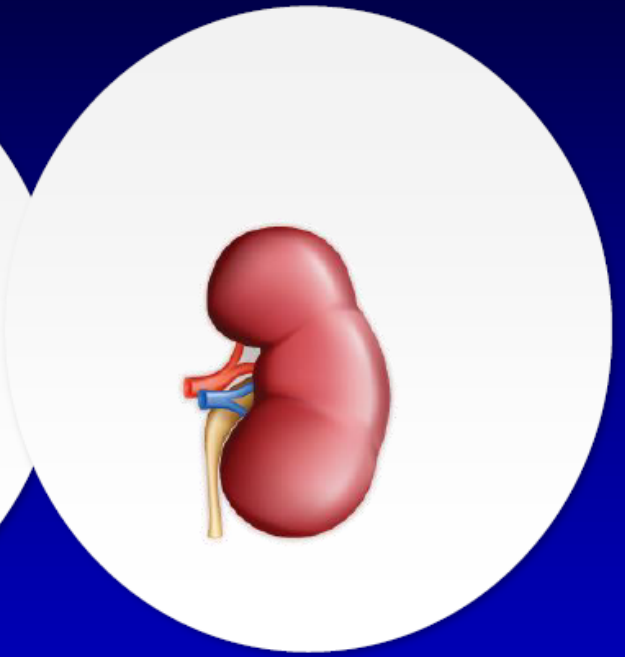


Ettehad D. Lancet 2016

Confounding factors

Medication

Study population

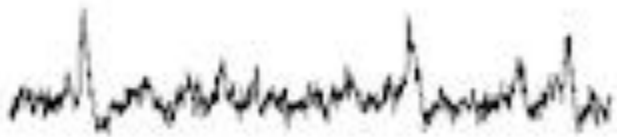


Procedure

White et al, J Am Soc Hypertens. 2015;9(5):341-50.Mahfoud et al., Eur Heart J. 2015,36:2219-2227
Mahfoud et al., Eur Heart J. 2017,37:3272-3281

RDN and Reduction in Central Sympathetic Drive

Muscle Sympathetic Nerve Activity (MSNA) in a Patient With Resistant HTN

	** 59-year-old man on 7 HTN meds*	MSNA (burst/min)		BP (mm Hg)
Baseline		56	→	161/107
1 mo		41 (-27%)	→	141/90 (-20/-17)
12 mo		19 (-66%)	→	127/81 (-34/-26)

Reduction of renal contribution to central sympathetic drive to normal BP

*Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 → 11.7 msec/mm Hg).
Schlaich MP, et al. *N Engl J Med*. 2009;361:932-934.

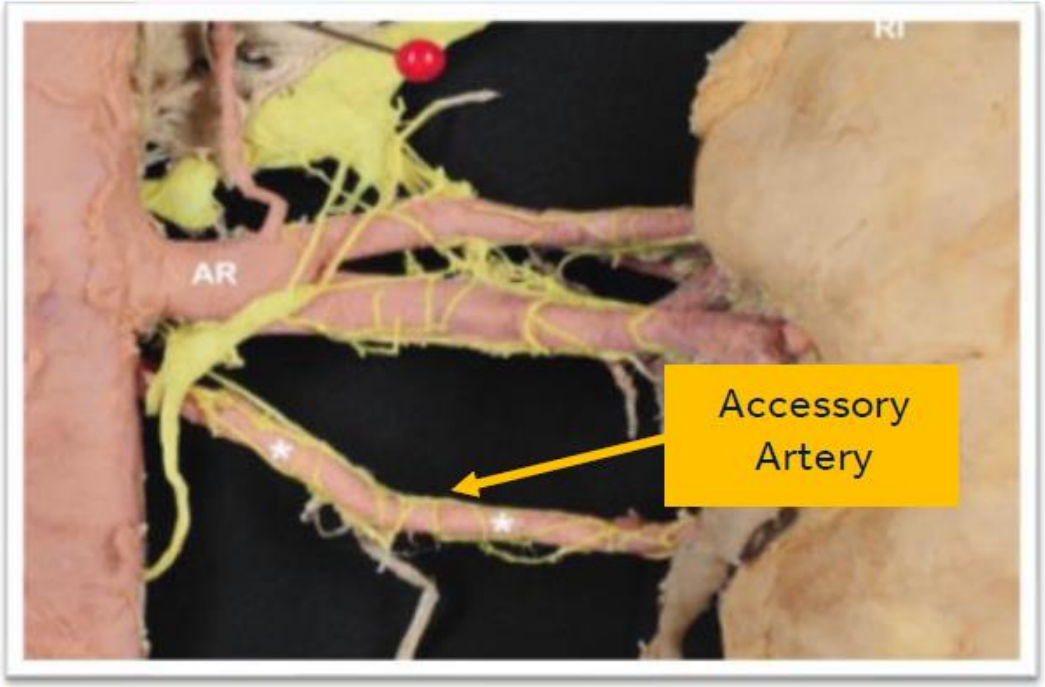
EFFECTIVE RDN INCLUDES TREATMENT IN THE BRANCHES AND ACCESSORIES

RENAL NERVES OFTEN BYPASS THE MAIN RENAL ARTERY AND JOIN AT THE BRANCHES

Study Design:

- Sixty kidneys from 30 human cadavers were systematically microdissected
- Each dissection required over 40 hours of careful, meticulous work

63% of kidneys had renal nerves that joined distal to the main renal artery bifurcation

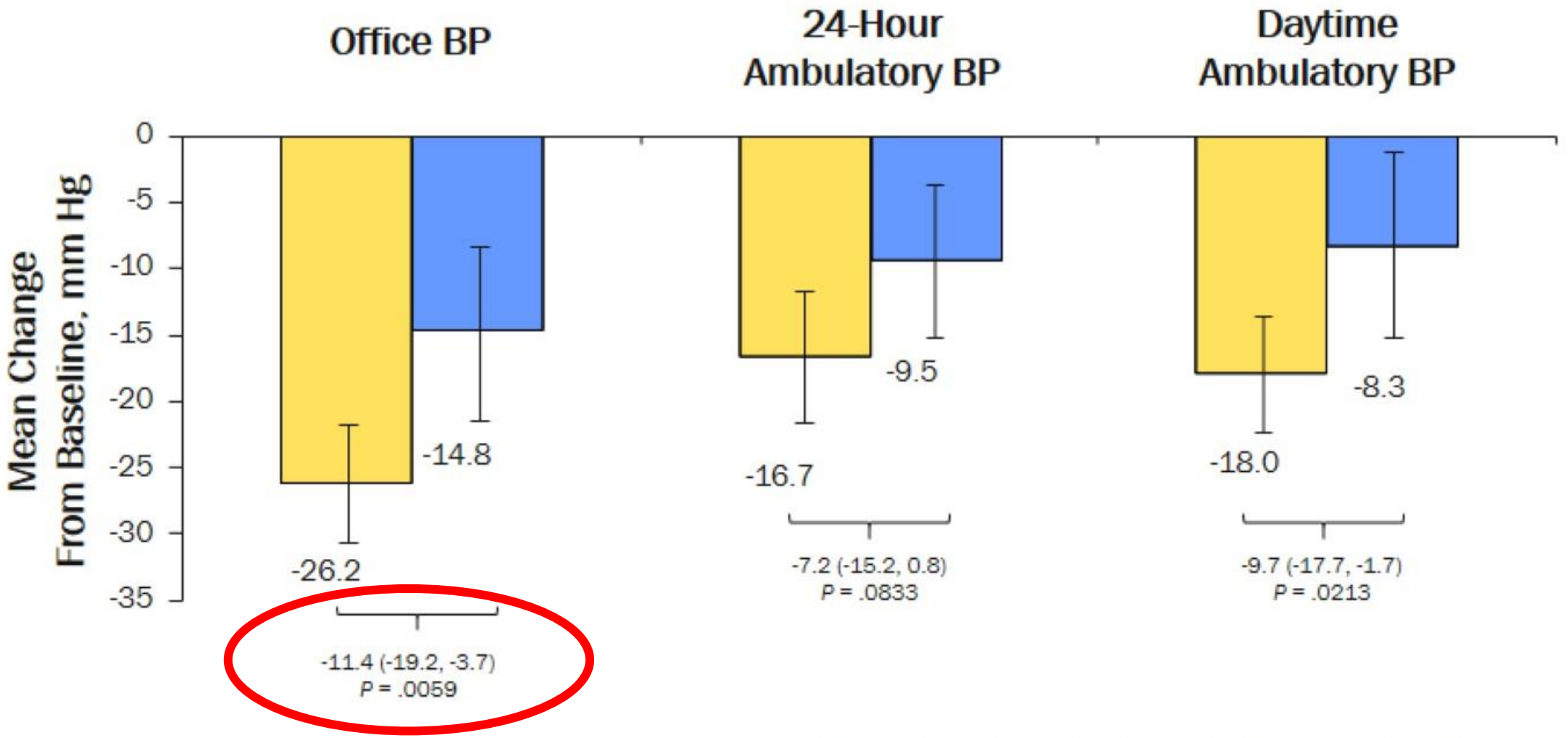


30% of cadavers had accessory arteries and were highly innervated

Garcia-Touchard A, et al. TCT Connect 2020.

REDUCE HTN: REINFORCE

Change in BP at 6 Months



Weber MA, et al. *JACC Cardiovasc Interv*. 2020;13:461-470.