Renal Denervation

by
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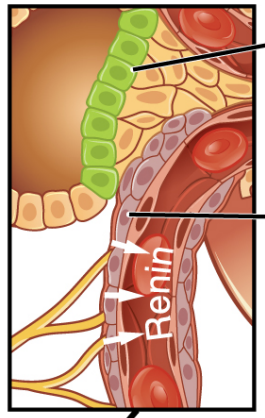
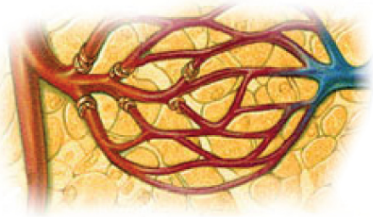


Macula densa senses low fluid flow or low Na^+ concentration

Juxtaglomerular cells secrete renin

Angiotensin-converting enzyme (ACE) in pulmonary blood

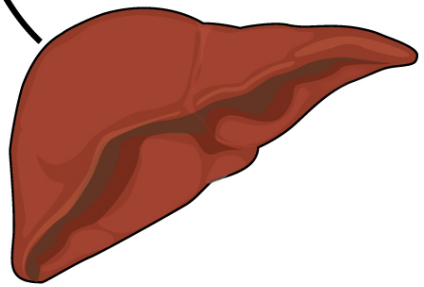


Widespread vasoconstriction

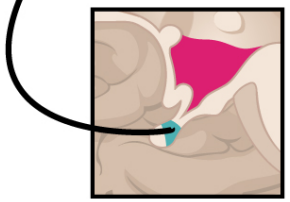
Kidney releases enzyme renin into blood

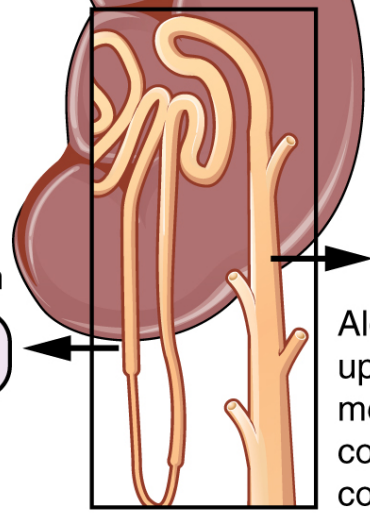
Enzyme reaction → Angiotensin I → Enzyme reaction → Angiotensin II → Stimulates → Adrenal cortex to secrete → Aldosterone

Liver releases angiotensinogen into blood



ADH causes aquaporins to move to the collecting duct plasma membrane, which increases water reabsorption





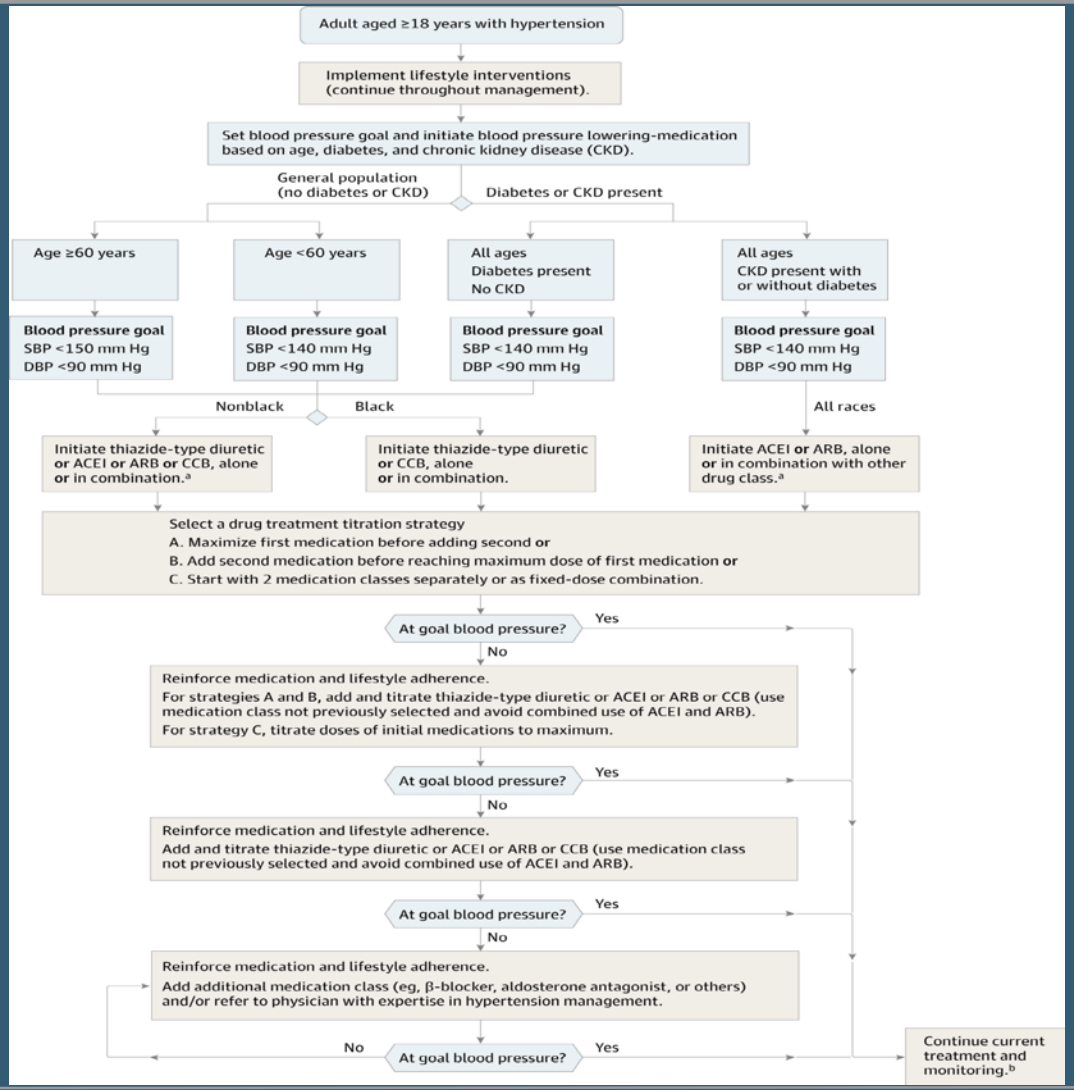
Na^+

H_2O

Aldosterone stimulates Na^+ uptake on the apical cell membrane in the distal convoluted tubule and collecting ducts

The American Heart Association considers a blood pressure reading **below 120/80** to be in the normal range. The chart below shows the range of blood pressure categories.

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
PREHYPERTENSION	120 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	140 – 159	or	90 – 99
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	160 OR HIGHER	or	100 OR HIGHER
HYPERTENSION CRISIS (emergency care needed)	HIGHER THAN 180	or	HIGHER THAN 110



JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

JNC 8 – Recommendation 9

- Thiazide-type diuretic, CCB, ACEI, or ARB.
- If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided.
- Do not use an ACEI and an ARB together in the same patient.
- Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained

Resistant Hypertension

AHA – uncontrolled blood pressure despite the use of a diuretic and at least two other blood pressure medicines.

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Profound Orthostasis

SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.

and

Jesse E. Thompson, M.D., Boston

PHYSIOLOGY IN MEDICINE

A Publication of the American Physiological Society

Sympathetic Nervous System

Lowering of arterial-blood pressure or stimulation of the renal nerves reduces total and cortical renal blood flow and urinary sodium excretion. Conversely, acute renal denervation reduces proximal tubular sodium reabsorption. Sympathetic blocking agents such as phenoxybenzamine hydrochloride (Dibenzyline) induce renal vasodilatation and mild natriuresis in animals and patients with cardiac edema. However, the changes are not large. These observations, in addition to the fact that denervated or transplanted kidneys can maintain normal sodium and water homeostasis and can participate in edema formation in experimental models of heart failure, suggest a facilitative rather than a primary role for the sympathetic nervous system in the pathogenesis of cardiac edema.

REDUCTION OF SYMPATHETIC HYPERACTIVITY BY ENALAPRIL IN PATIENTS WITH CHRONIC RENAL FAILURE

GERRY LIGTENBERG, M.D., PH.D., PETER J. BLANKESTIJN, M.D., PH.D., P. LIAM OEY, M.D., PH.D., INGE H.H. KLEIN, M.D., LIOE-TING DIJKHORST-OEI, M.D., FRANS BOOMSMA, PH.D., GEORGE H. WIENEKE, PH.D., ALEXANDER C. VAN HUFFELEN, M.D., PH.D., AND HEIN A. KOOMANS, M.D., PH.D.

Study 1

14 pts with CKD, HTN vs matched controls

Intervention – Enalapril

Outcome - measured sympathetic nerve activity, plasma renin before and after medication

Study 2

10 pts with CKD, HTN vs matched controls

Intervention – Amlodipine

Outcome - measured sympathetic nerve activity, plasma renin before and after medication

NEJM 1999; 340:1321-8

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH CHRONIC RENAL FAILURE AND THE CONTROL SUBJECTS IN STUDY 1.*

CHARACTERISTIC	PATIENTS (N=14)	CONTROL SUBJECTS (N=14)	P VALUE
Sex (M/F)	9/5	7/7	0.70
Age (yr)	48±6	47±7	0.68
Creatinine clearance (ml/min)	31±18	98±16	<0.001
Serum creatinine (mg/dl)†	3.9±1.9	1.0±0.1	<0.001
Extracellular-fluid volume (ml/kg of lean body mass)‡	305±23	296±27	0.35
Weight (kg)	77±7	76±9	0.74
Systolic blood pressure (mm Hg)	165±20	133±9	<0.001
Diastolic blood pressure (mm Hg)	93±12	72±6	<0.001
Mean arterial pressure (mm Hg)	118±15	92±6	<0.001
Heart rate (beats/min)	68±10	60±9	0.02
Cardiac output (liters/min)	7.5±2.0	8.6±1.8	0.14
Plasma renin activity (ng/ml/hr)§	3.8±2.3	0.7±0.2	<0.001
Plasma norepinephrine (pg/ml)¶	252±111	108±61	0.003
Urinary norepinephrine (μg/24 hr)‖	14±8	41±21	0.006
Muscle sympathetic-nerve activity			
Bursts/min	35±17	19±9	0.004
Bursts/100 heartbeats	53±26	33±17	0.01
Baroreflex sensitivity			
For heart rate (beats/min/mm Hg)	−1.1±1.2	−1.4±1.8	0.54
For muscle sympathetic-nerve activity (bursts/min/mm Hg)	−2.1±1.9	−2.7±1.3	0.36

*Plus–minus values are means ±SD.

NEJM 1999; 340:1321-8

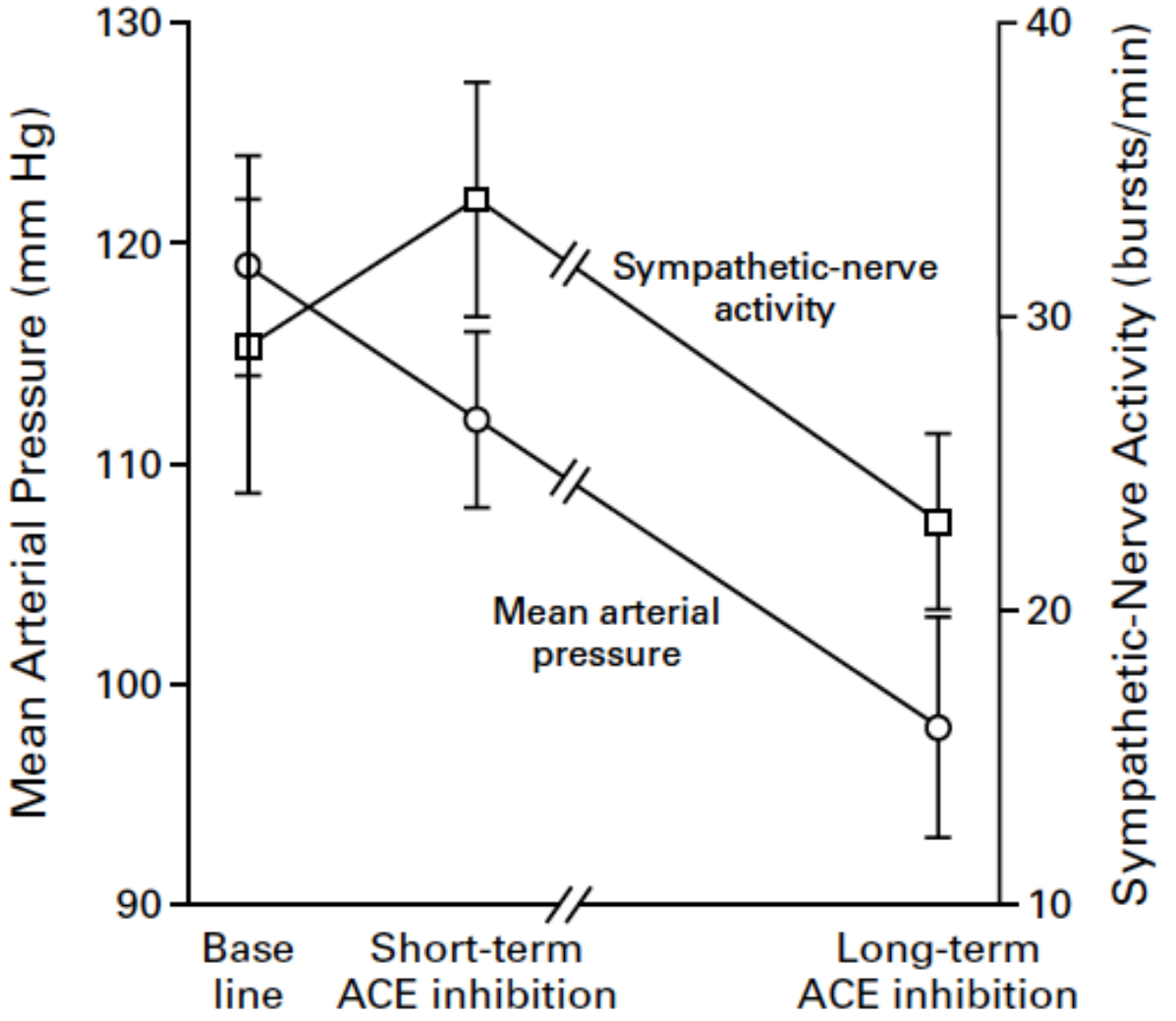


Figure 2. Changes in Mean Arterial Pressure and Muscle Sympathetic-Nerve Activity during an Intravenous Infusion of Enalaprilat and during Long-Term Treatment with Enalapril in Nine Patients with Chronic Renal Failure.

NEJM 1999; 340:1321-8

TABLE 3. CHARACTERISTICS OF THE CONTROL SUBJECTS AND THE PATIENTS WITH CHRONIC RENAL FAILURE IN STUDY 2.*

CHARACTERISTIC	CONTROL SUBJECTS (N=10)	PATIENTS (N=10)		P VALUE†	P VALUE‡
		BEFORE AMLODIPINE	DURING AMLODIPINE		
Sex (M/F)	6/4	7/3		1.00	
Age (yr)	46±9	47±12		0.80	
Serum creatinine (mg/dl)§	0.9±0.2	3.3±1.6	3.6±1.8	<0.001	0.25
Creatinine clearance (ml/min)	92±13	41±22	39±19	<0.001	0.40
Extracellular-fluid volume (ml/kg of lean body mass)¶	288±24	296±26	306±27	0.40	0.33
Body weight (kg)	75±11	74±11	74±11	0.81	0.33
Systolic blood pressure (mm Hg)	133±7	165±10	143±14	<0.001	<0.001
Diastolic blood pressure (mm Hg)	72±7	94±6	83±8	<0.001	0.003
Mean arterial pressure (mm Hg)	91±6	118±7	103±8	<0.001	<0.001
Heart rate (beats/min)	58±9	65±9	69±9	0.10	0.03
Plasma renin activity (ng/ml/hr)‖	0.7±0.2	5.1±4.6	9.2±7.8	<0.001	0.04
Muscle sympathetic-nerve activity					
Bursts/min	21±9	41±19	56±14	0.01	0.02
Bursts/100 heartbeats	37±18	62±26	81±16	0.02	0.03
Baroreflex sensitivity					
For heart rate (beats/min/mm Hg)	−1.1±0.8	−1.3±0.6	−0.8±0.8	0.61	0.21
For muscle sympathetic-nerve activity (bursts/min/mm Hg)	−2.4±1.6	−2.3±1.3	−2.2±2.0	0.93	0.82

NEJM 1999; 340:1321-8

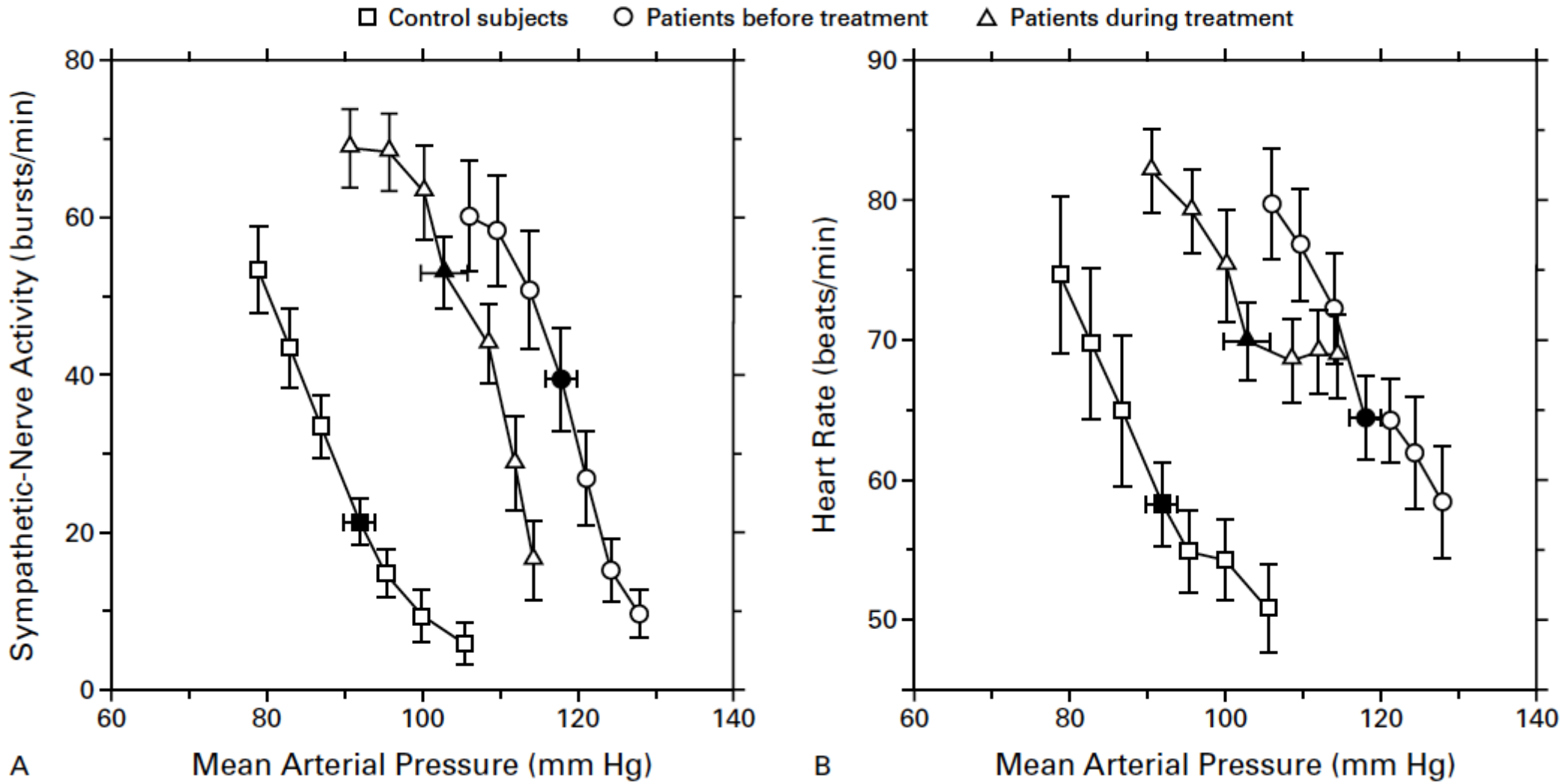
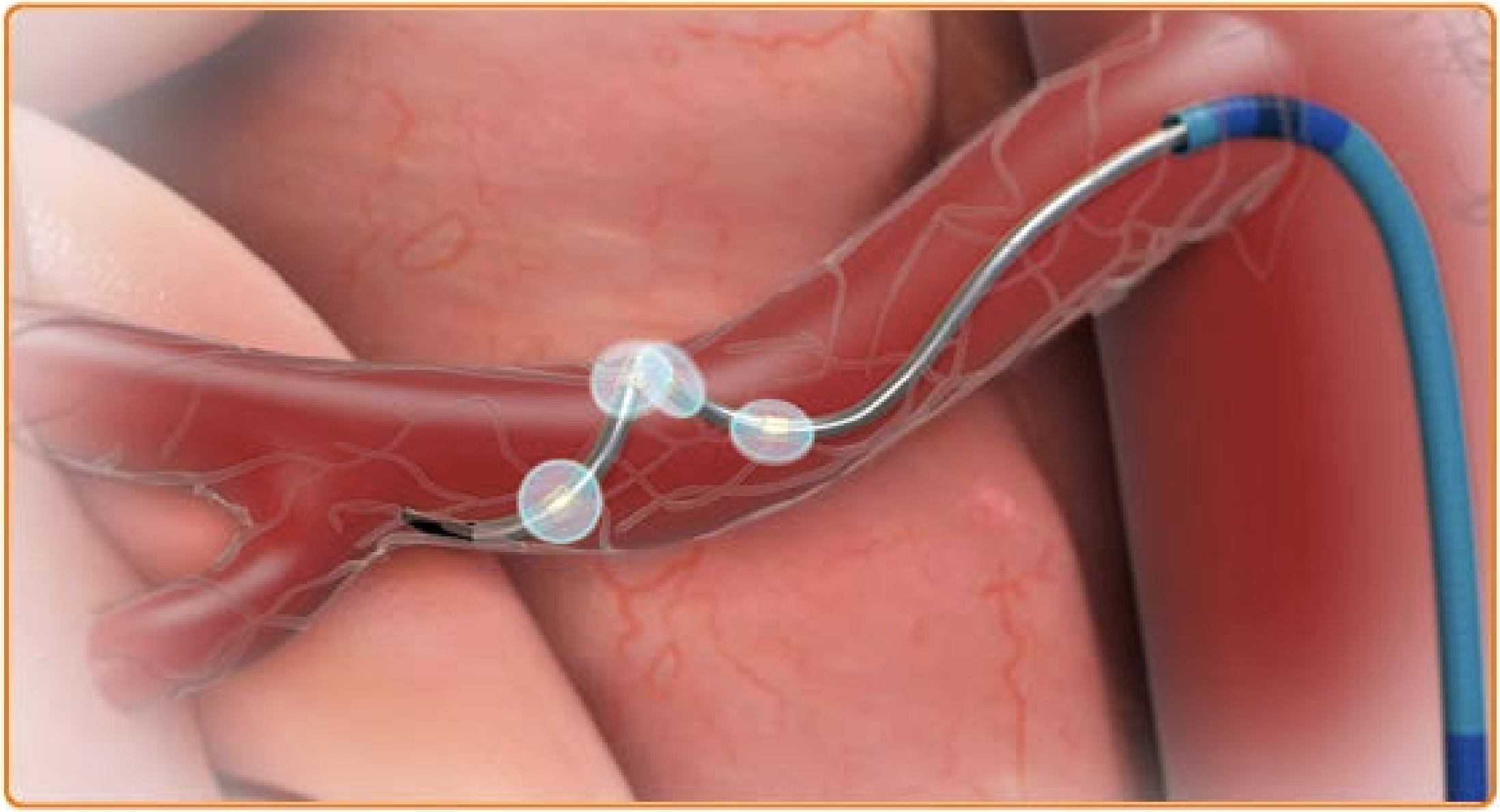


Figure 3. Baroreflex Response to Changes in Mean Arterial Pressure in 10 Patients with Chronic Renal Failure before and during Long-Term Treatment with Amlodipine and in 10 Control Subjects.

Conculsions

- ↑ sympathetic activity & renin with Amlodipine
- ↓ sympathetic activity & renin with Enalapril
- Renin contributed to increased sympathetic activity
- ACE-I decreased renal sympathetic activity by improving renal perfusion



Symplicity HTN-2 Trial

- Multi-center trial, randomized
- Resistant hypertension
- 1:1 ratio; intervention or previous treatment
- Primary end point – office based blood pressure at 6 months

Esler et al. Lancet 2010;376:1903-9

Results

Intervention

- 52 patients enrolled
- 41/49 – reduction of SBP of >10 mm Hg
- P< 0.0001 difference

Control

- 54 patients enrolled
- 18/51 – reduction of SBP of >10 mm Hg

Esler et al. Lancet 2010;376:1903-9

A Controlled Trial of Renal Denervation for Resistant Hypertension

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

N Engl J Med 2014;370:1393-401.

Study Design

- Multiple center single blinded trial
- 18 – 80 yrs & Resistant hypertension
- 2:1 ratio to undergo renal denervation or sham procedure
- 6 month f/u period
- Primary Efficacy end point – Office based systolic blood pressure
- Secondary efficacy end point – Changed in mean ambulatory systolic blood pressure
- Safety end point – composite of death, ESRD, embolic events, renovascular HTN

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4

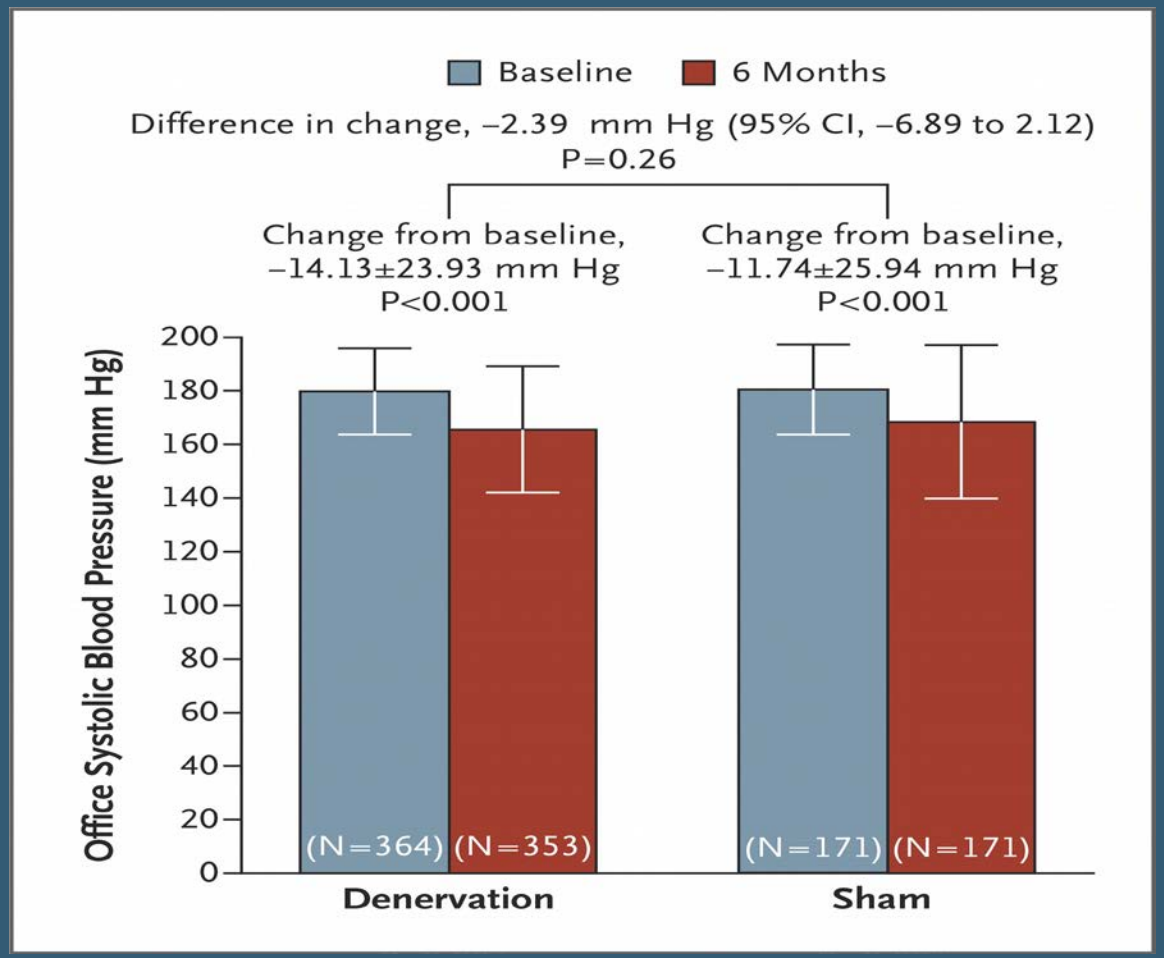
N Engl J Med 2014;370:1393-401.

Table 1. (Continued.)

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Type of antihypertensive medication — no. (%)		
ACE inhibitor		
Patients taking medication	179 (49.2)	71 (41.5)
Patients taking maximally tolerated dose	167 (45.9)	64 (37.4)
Angiotensin-receptor blocker		
Patients taking medication	182 (50.0)	91 (53.2)
Patients taking maximally tolerated dose	180 (49.5)	88 (51.5)
Aldosterone antagonist	82 (22.5)	49 (28.7)
Alpha-adrenergic blocker	40 (11.0)	23 (13.5)
Beta-blocker	310 (85.2)	147 (86.0)
Calcium-channel blocker		
Patients taking medication	254 (69.8)	125 (73.1)
Patients taking maximally tolerated dose	208 (57.1)	109 (63.7)
Centrally acting sympatholytic agent	179 (49.2)	75 (43.9)
Direct-acting renin inhibitor	26 (7.1)	12 (7.0)
Direct-acting vasodilator	134 (36.8)	77 (45.0)
Diuretic		
Patients taking medication	363 (99.7)	171 (100)
Patients taking maximally tolerated dose	351 (96.4)	167 (97.7)

N Engl J Med 2014;370:1393-401.

Primary Efficacy End Point.



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

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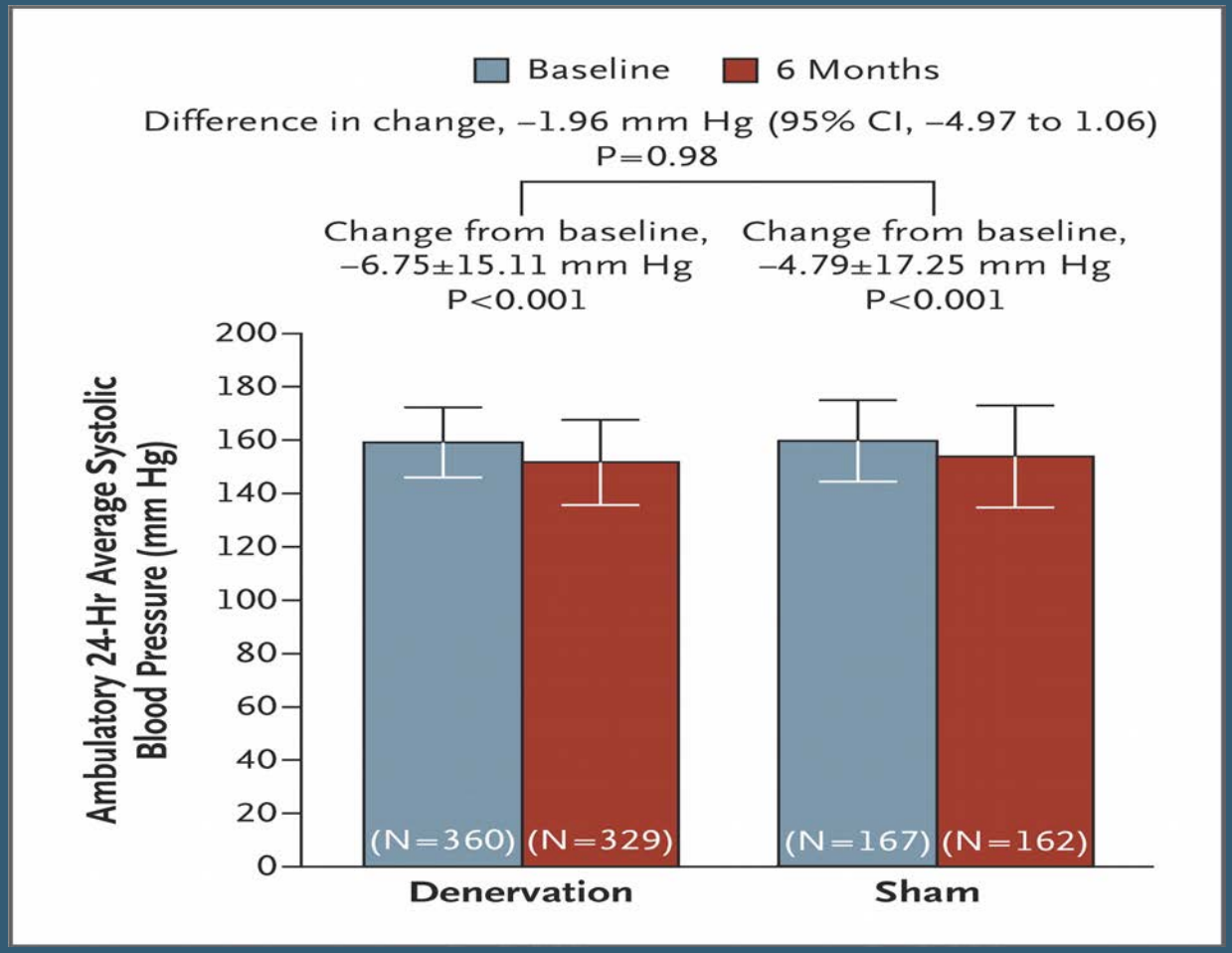
Secondary Efficacy End Point.



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

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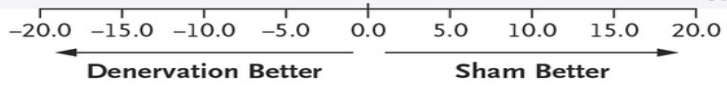
Selected Subgroup Analyses.

Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 to 2.62)	0.26	
Sex					0.37
Male	208	108	−2.30 (−7.63 to 3.03)	0.40	
Female	142	61	−6.64 (−14.94 to 1.65)	0.12	
Black race					0.09
Yes	85	49	2.25 (−7.27 to 11.78)	0.64	
No	264	120	−6.63 (−11.81 to −1.44)	0.01	
Body-mass index					0.77
<30	91	42	−2.77 (−11.47 to 5.93)	0.53	
≥30	259	126	−4.36 (−9.76 to 1.03)	0.11	
Receiving aldosterone antagonist at baseline					0.36
Yes	76	47	−8.05 (−17.63 to 1.52)	0.10	
No	274	122	−3.24 (−8.42 to 1.93)	0.22	
Estimated GFR					0.31
<60 ml/min/1.73 m^2	68	38	0.54 (−8.29 to 9.37)	0.90	
≥60 ml/min/1.73 m^2	282	131	−5.22 (−10.51 to 0.06)	0.05	
Age					0.27
<65 yr	246	128	−5.73 (−11.06 to −0.40)	0.04	
≥65 yr	104	41	0.09 (−8.80 to 8.99)	0.99	
Any medication change					0.68
Yes	132	70	−5.41 (−13.49 to 2.67)	0.19	
No	218	99	−3.44 (−8.83 to 1.96)	0.21	



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Safety End Points.

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (–0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	–1.9 (–6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (–1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (–2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	–2.7 (–6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (–2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (–1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (–0.3 to 0.9)

* CI denotes confidence interval.

† The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data. The rate in the renal-denervation group was 1.4% with an upper boundary of the one-sided 95% CI of 2.9%; therefore, the performance criterion was met with a P value of <0.001.

‡ This end point was a composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis of more than 70% within 6 months.

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

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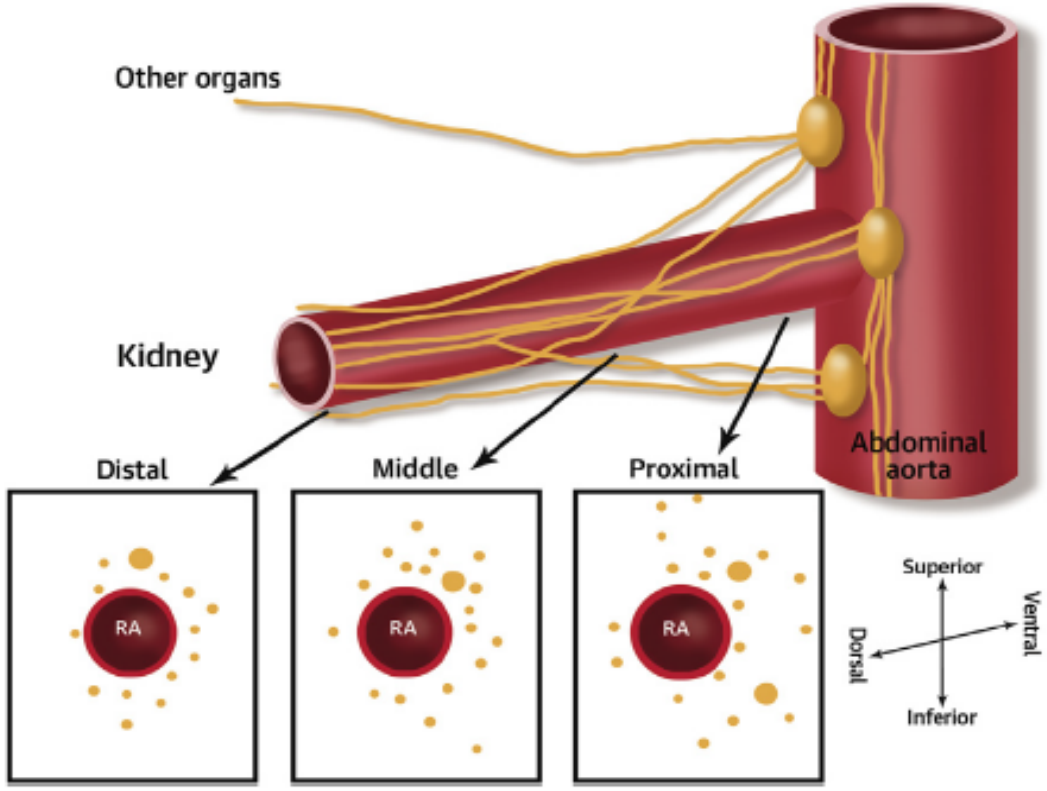
Conclusions

- Renal Denervation is safe
- No difference in systolic BP reduction between groups
- Placebo effect?
- Better adherence to medication in “resistant hypertensive” patients

Renal Denervation

- Is it a plausible alternative to treatment of resistant HTN?
- Essential hypertension?
- Patients with CKD?
- Non-compliant patient?
- More cost effective than long term antihypertensive meds?
- Safe?



CENTRAL ILLUSTRATION **Proposed Diagram of Renal Artery and Circumferential Peri-Arterial Nerve Location**

Although there were fewer nerves surrounding the renal artery (RA) in the distal segments compared with the proximal and middle segments, the mean distance from RA lumen to nerve location is least in the distal segments compared with the proximal and middle segments.

Sakura et al. JACC;2014;64:635-43.

SPYRAL HTN-ON MED

- Phase 2 clinical trial
- Patients on three antihypertensive agents
- Recruiting 20 – 80 yrs old
- Randomized, multi-center, single blind (patient)
- Renal denervation with multi-electrode vs sham procedure
- Primary Outcome – Δ in ambulatory SBP and 36 month safety for major adverse events
- Secondary Outcome - Δ in office SBP, Δ in office DBP, Δ in ambulatory DBP

SPYRAL HTN-OFF MED

- Phase 2 clinical trial
- Patients off hypertensive meds
- Recruiting 20 – 80 yrs old
- Randomized, multi-center, single blind (patient)
- Renal denervation with multi-electrode vs sham procedure
- Primary Outcome – Δ in ambulatory SBP and 36 month safety for major adverse events
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THANK YOU!