Renal denervation

Resistant Hypertension Definition

- **Resistant hypertension**

  > 140/90 mmHg, despite treatmant with 3 drug classes including a diuretic

Confirm Treatment Resistance

Office blood pressure > 140/90 or 130/80 mm Hg in patients with diabetes or chronic kidney disease

and

Patient prescribed 3 or more antihypertensive medications at optimal doses, including if possibe a diuretic

or

Office blood pressure at goal but patient requiring 4 or more antihypertensive medications

AHA Statement Circulation 2008;117:e510ff

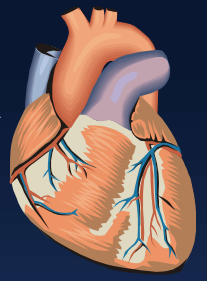
Predictors of Resistant Hypertension

- Advanced age
- High sodium intake
- Obesity
- Renal condition
- Sleep apnea
- Diabetes
- LVH

AHA Statement Circulation 2008;117:e510ff

Renal Sympathetic Afferent Nerves:
Kidney as Origin of Central Sympathetic Drive

Vasoconstriction
Atherosclerosis

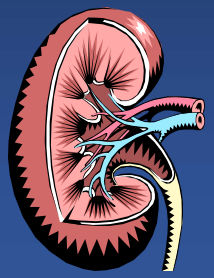


↑ Contractility
↑ Heart rate
Hypertrophy
Arrhythmia
Heart Failure

Efferent Nerves

Afferent Nerves

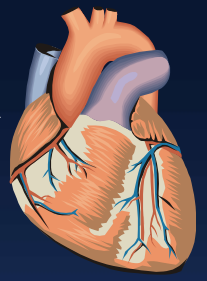
Blood Pressure



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

Concept of Renal denervation

Vasoconstriction
Atherosclerosis

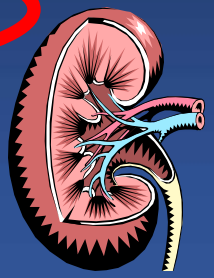


↑ Contractility
↑ Heart rate
Hypertrophy
Arrhythmia
Heart Failure

Efferent Nerves

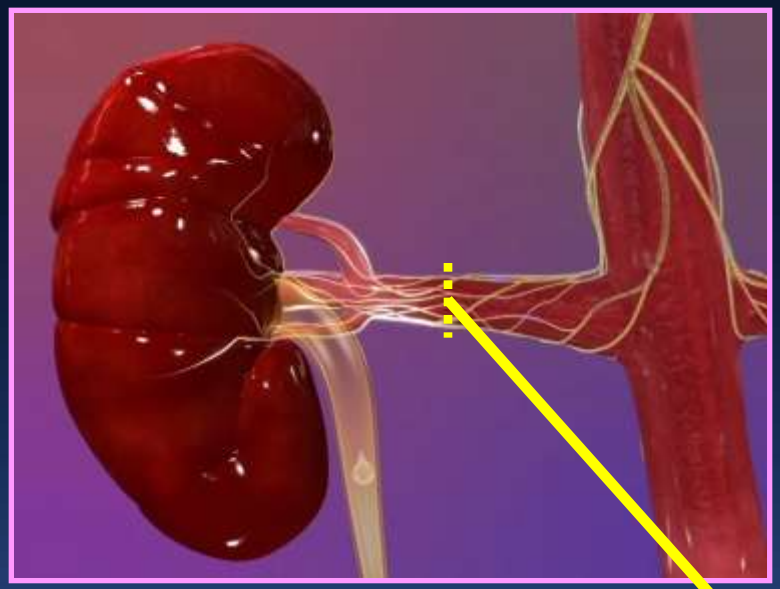
Afferent Nerves

Renal denervation

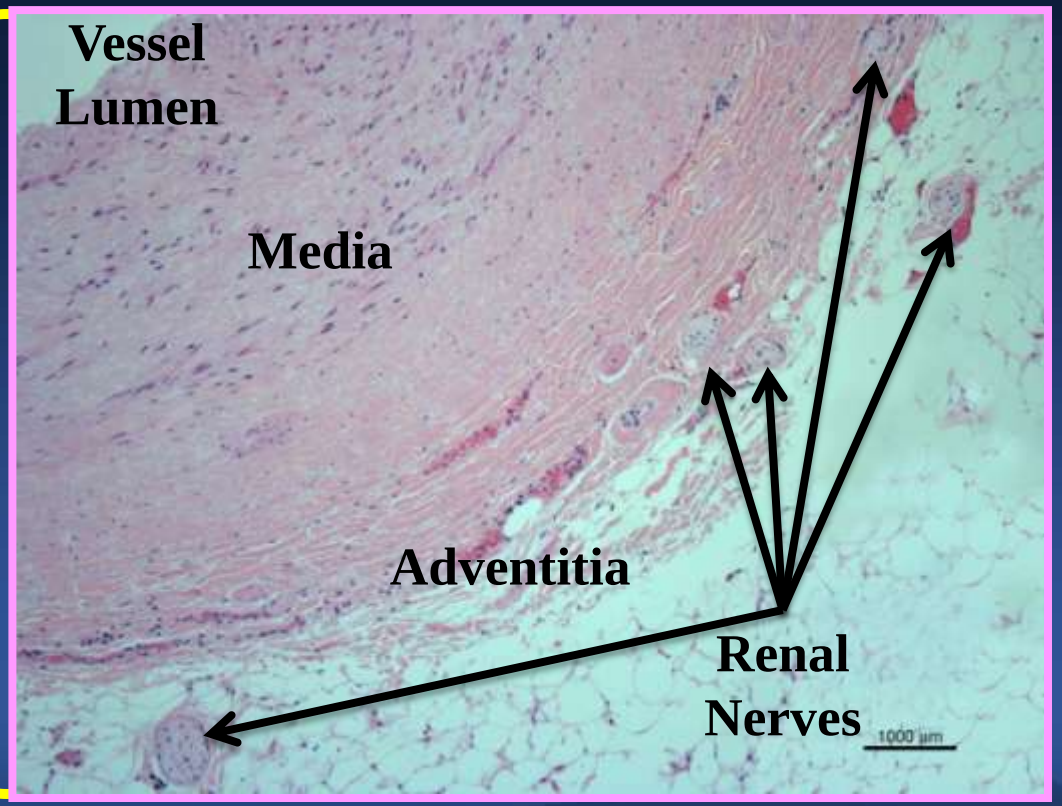


↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
↓ Kidney function

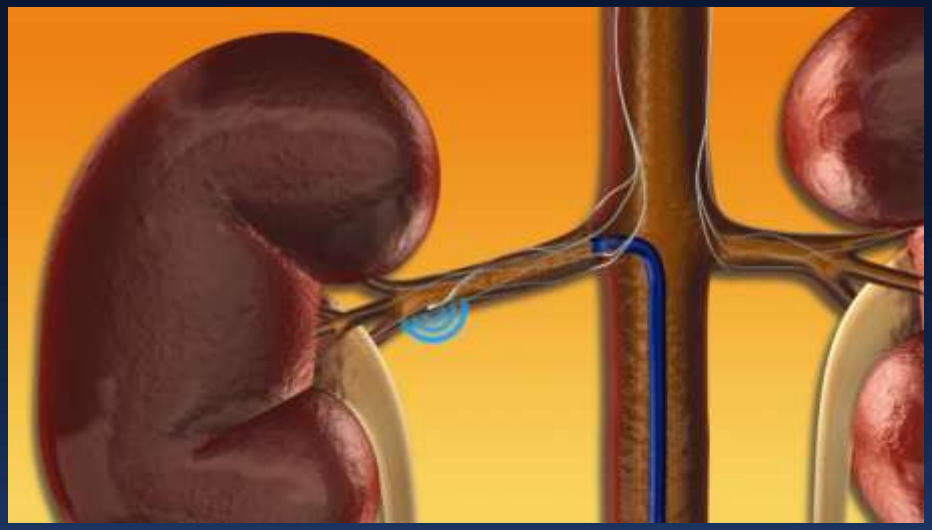
Anatomy of Renal Sympathetic Nerves

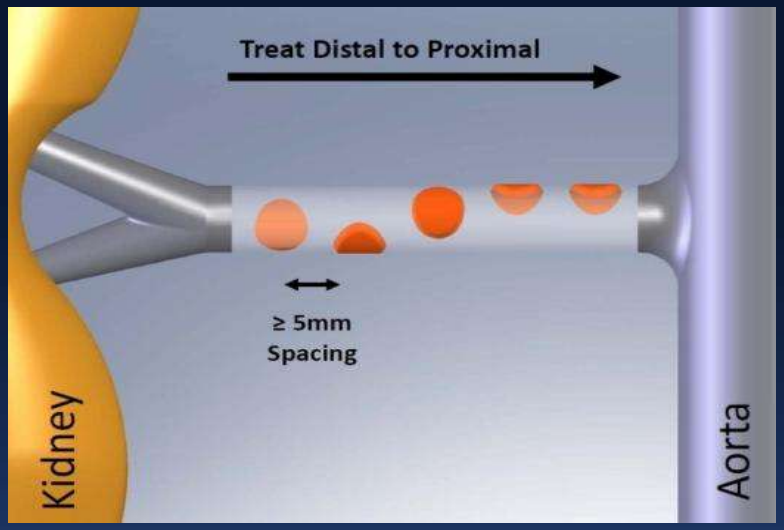


Location of renal nerves allows
Catheter based approach

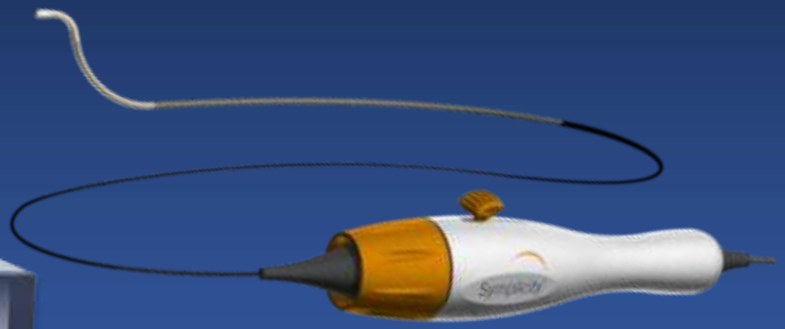


Catheter-based Approach

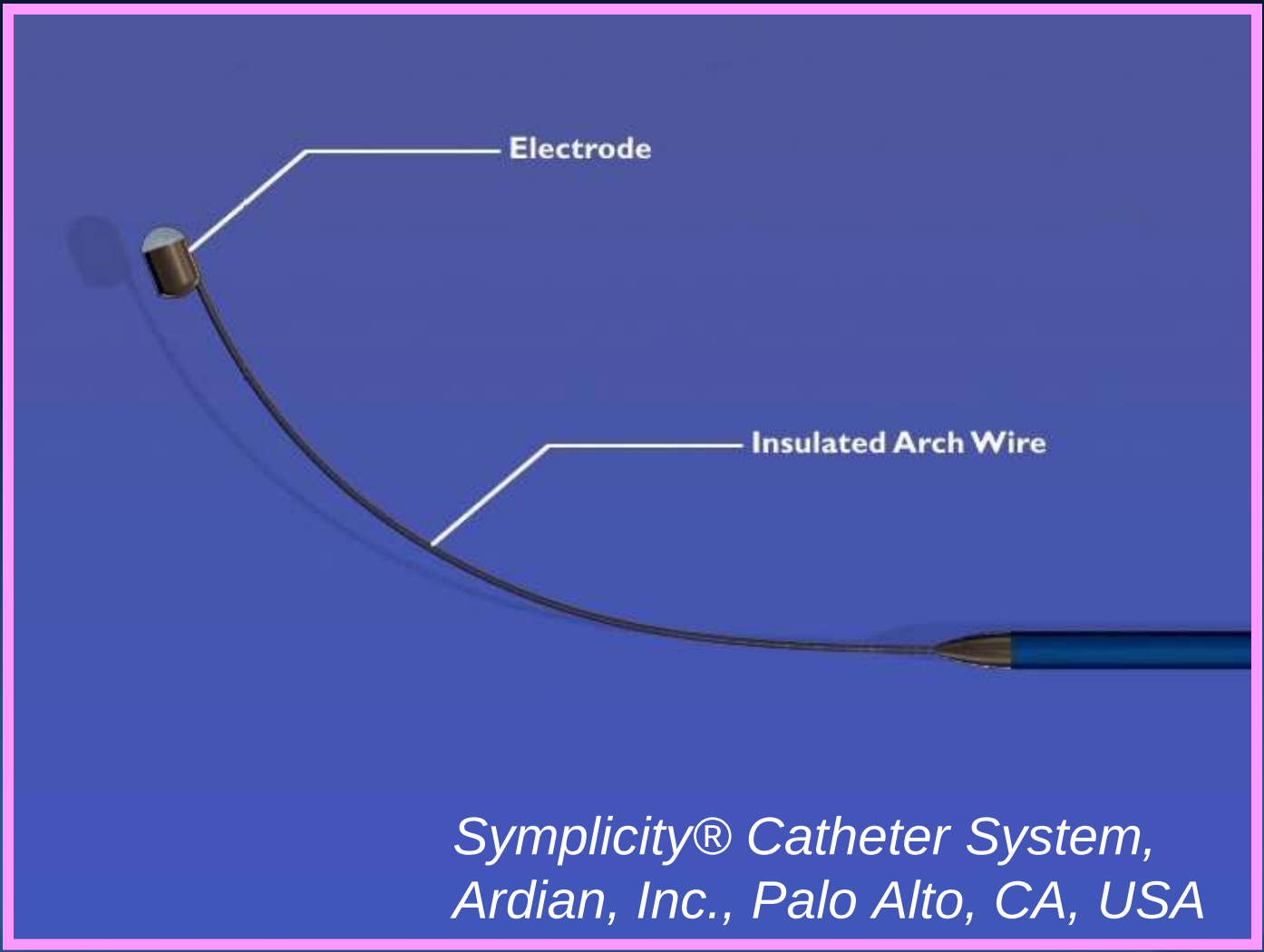




- Standard femoral access (6F)
- 4~6 series of 2-minute energy deliveries per each renal artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



RF ablation catheter

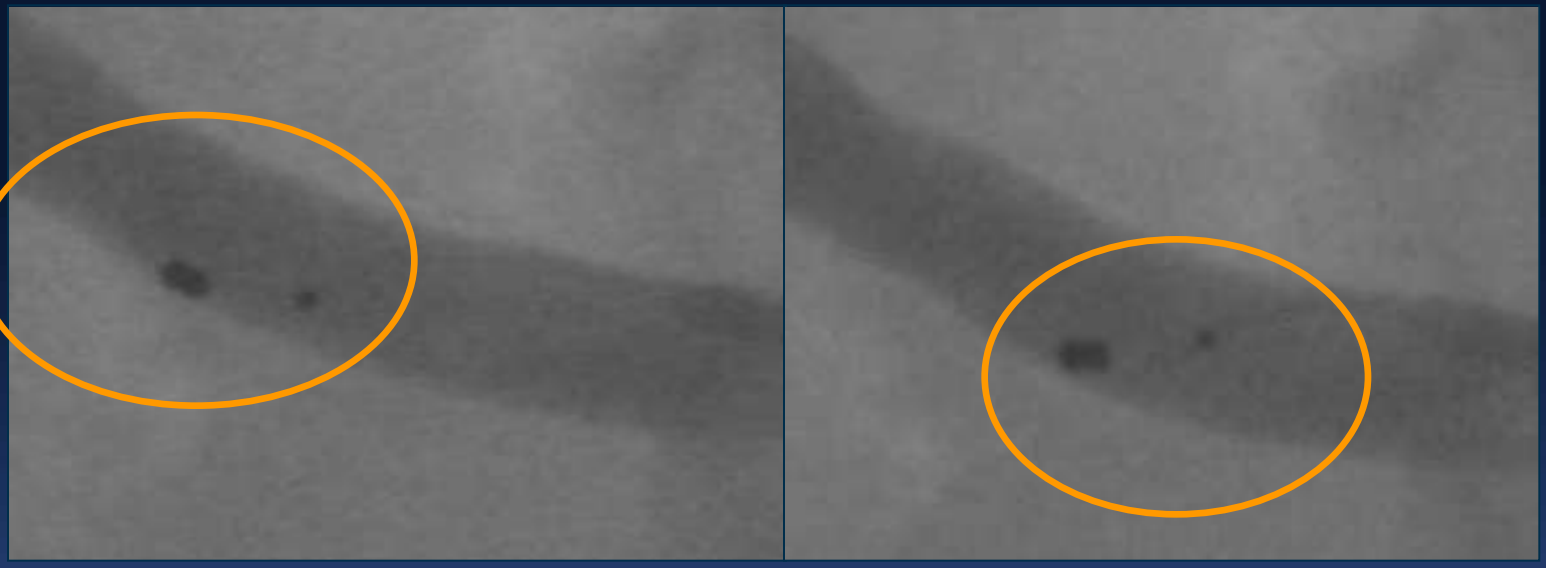


Symplicity® Catheter System,
Ardian, Inc., Palo Alto, CA, USA

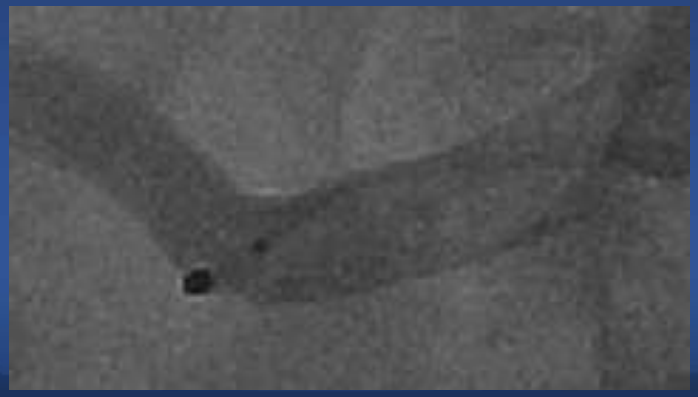
Placement of Renal RF Catheter

Wall Contact

Sufficient Wall Contact



Excessive Wall Contact
(avoid distending vessel wall with electrode)



CardioVascular Research Foundation
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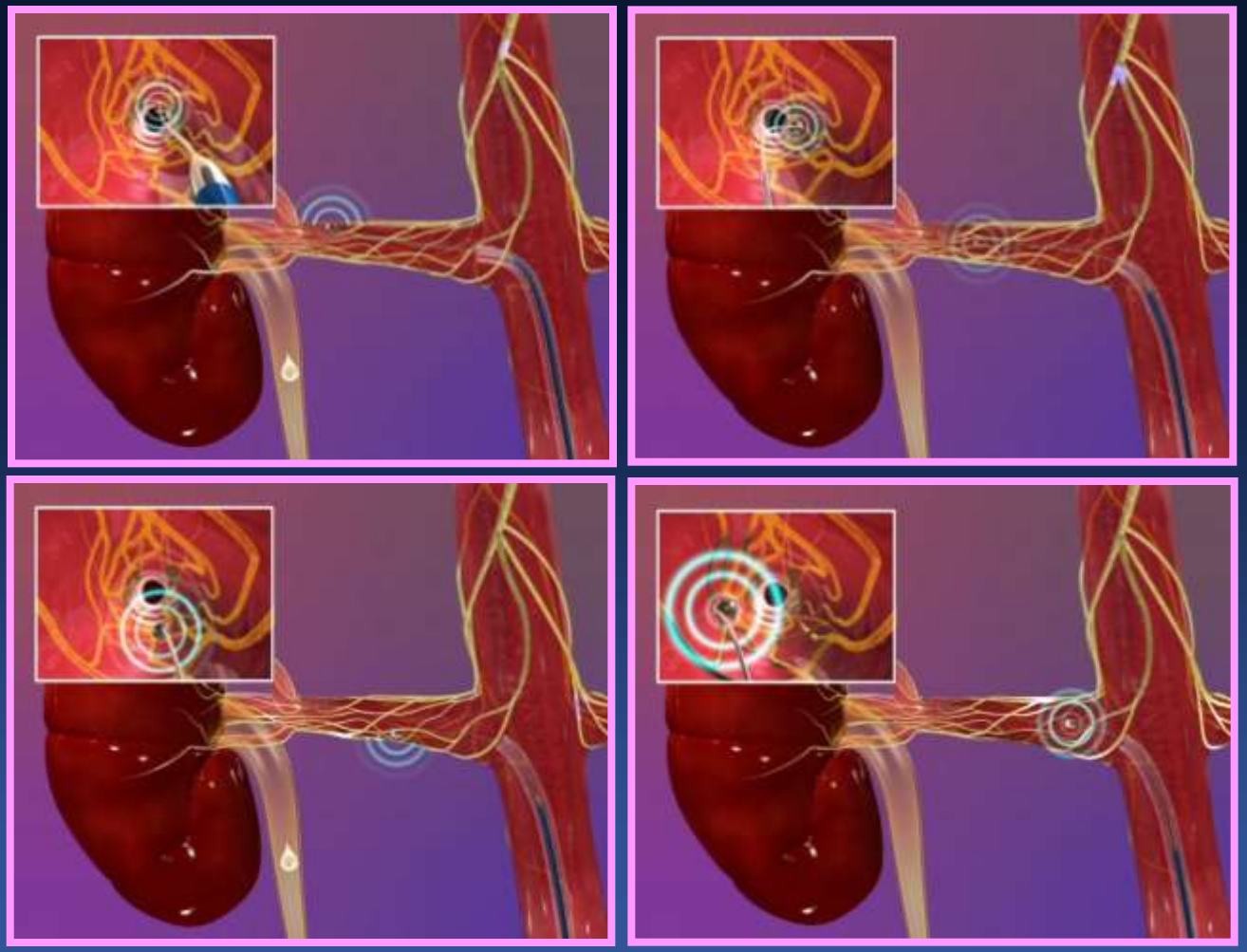
ASAN Medical Center

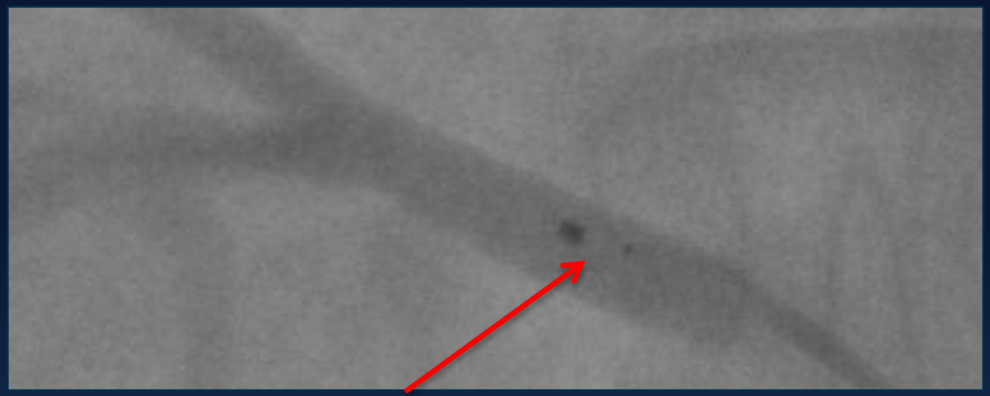
Treatment by Renal RF Catheter



Distal to Proximal / Circumferential coverage

Example Treatment Sites

Distal locations in straight vessels may require more deflection to achieve Vessel wall contact



Unable to confirm adequate contact visually (may need to rely on impedance to assess for sufficient wall contact)

Because of added guide catheter support, proximal locations may require less deflection to achieve vessel wall contact

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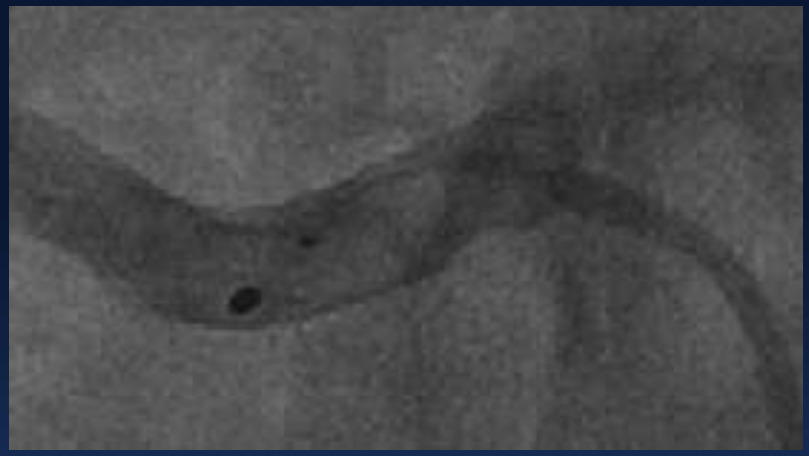
ASAN Medical Center

Optimizing Treatment Sites: Impedance

- Impedance may be used to confirm stable wall contact:
  - Higher impedance may indicate better wall contact
  - In an early superior or inferior location with good visible wall contact, note “reference impedance” for comparison with future positions
  - Stable impedance over a respiratory cycle (Δ < 15–20 ohms) may indicate consistent wall contact
  - Abnormally high impedance may indicate electrode is in a side-branch



- Impedance varies by patient and vessel. Care should be taken to notice range of available impedance readings within each vessel

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ASAN Medical Center

Initiate First Treatment

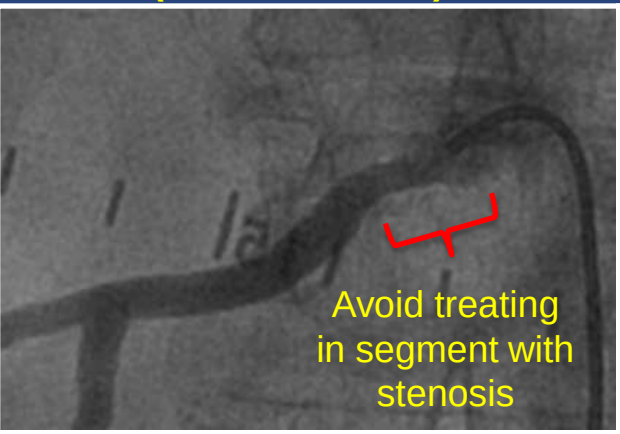
- **Medications:**
  - IA nitroglycerine
  - Fentanyl or morphine (or similar)
  - Sufficient anticoagulation (confirm ACT > 250)
  - Document each treatment site using cine.
  - If contrast is used, wait 3-5 seconds for contrast to clear
- **Initiate energy delivery**:
  - Stabilize catheter – do not move during treatment
  - Press foot pedal (or RF button) once to activate catheter
  - Do not inject contrast *during* active treatment (alters impedance)
- **Generator will automatically control RF energy delivery:**
  - Power automatically ramped and maintained (5-8W)
  - Continuously monitors temperature and impedance
  - Automatically shuts off after 2 min or when either impedance or te mperature exceed program limits
  - To manually stop RF delivery, depress foot pedal or press RF button once

Areas to Avoid

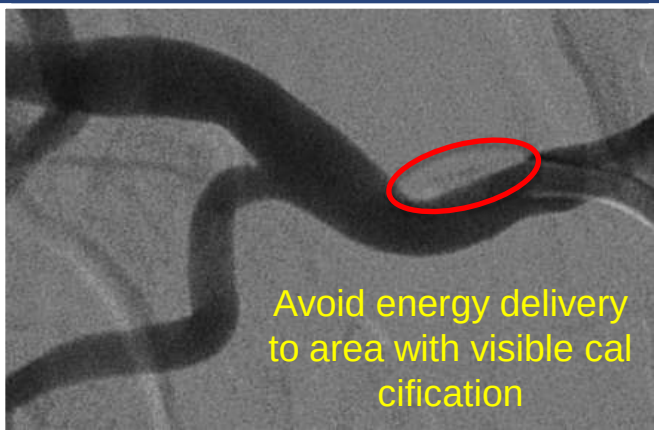
- Avoid placing the electrode at the ostium of small branch arteries, such as those perfusing the adrenal glands
- Avoid treating in very distal segments of the renal artery, in particular, segments beyondsignificant renal artery branch points and segments that may be in close proximity to structures such as the ureter or kidney.
- There is no clinical experience treating near any areas of visible atherosc lerosis, calcification, or fibromuscular dysplasia.

  Avoid treating areas of visible disease.
- There is no clinical experience treating in vessels with renal artery aneurysms

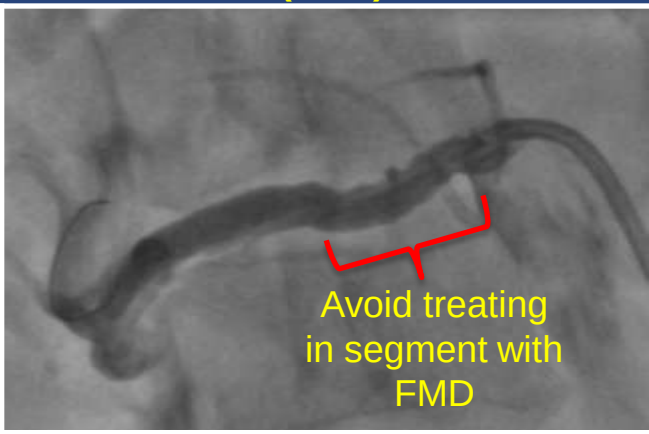
Atherosclerosis (Ostial Stenosis)



Calcification



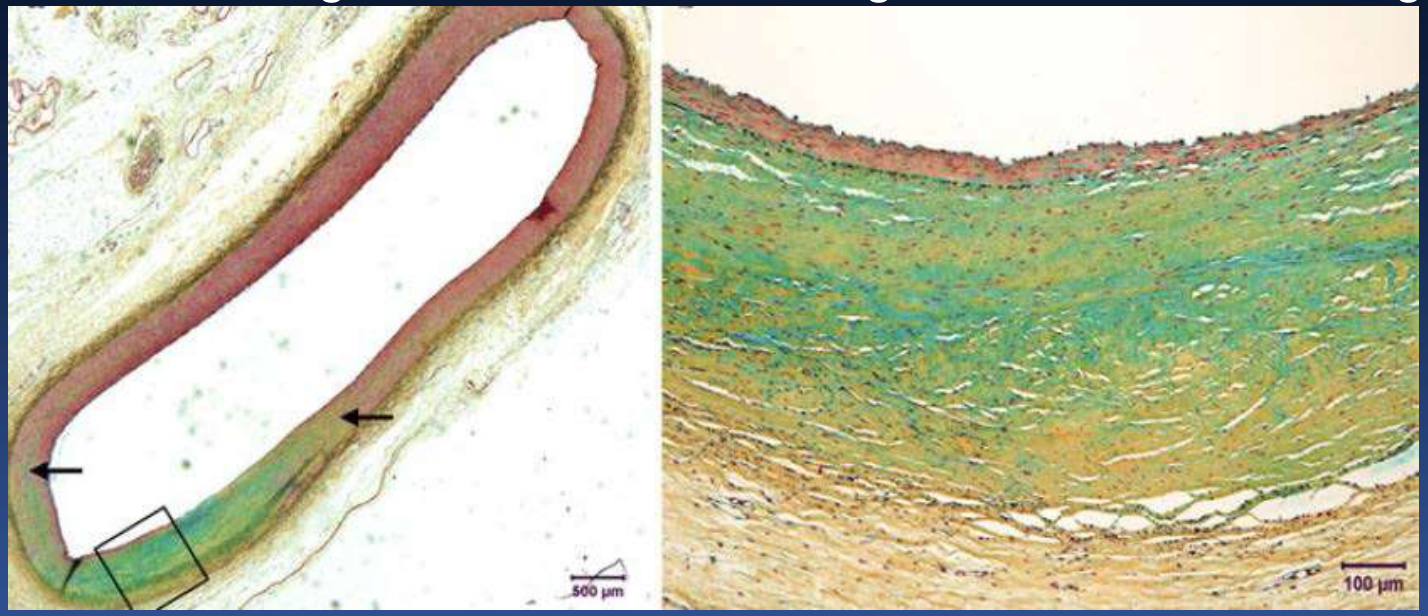
Fibromuscular Dysplasia (FMD)



Six Month Post-Procedure Histology (Porcine Model)

Movat's Pentachrome Stain

An area of medial injury (yellow) is located between the arrows on the left. An enlargement of the boxed region is shown on the right



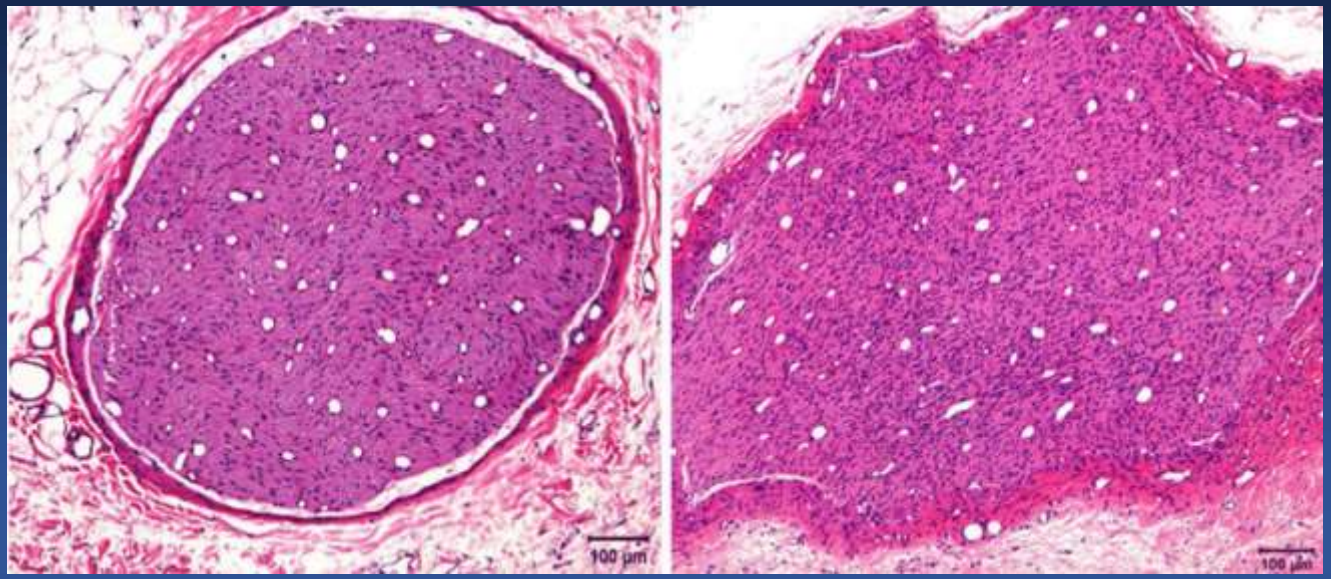
Findings: minimal intimal thickening and minimal internal elastic lamina injury overlying areas of mild full thickness medial fibrosis (yellow [fibrosis] with green [proteoglycan deposition]) and adventitial fibrosis (yellow)

Rippy MK, et. al. Clin Res Cardiol. 2011 Dec;100(12):1095-101

Six Month Post-Procedure Nerve Histology (Porcine Model)

H&E

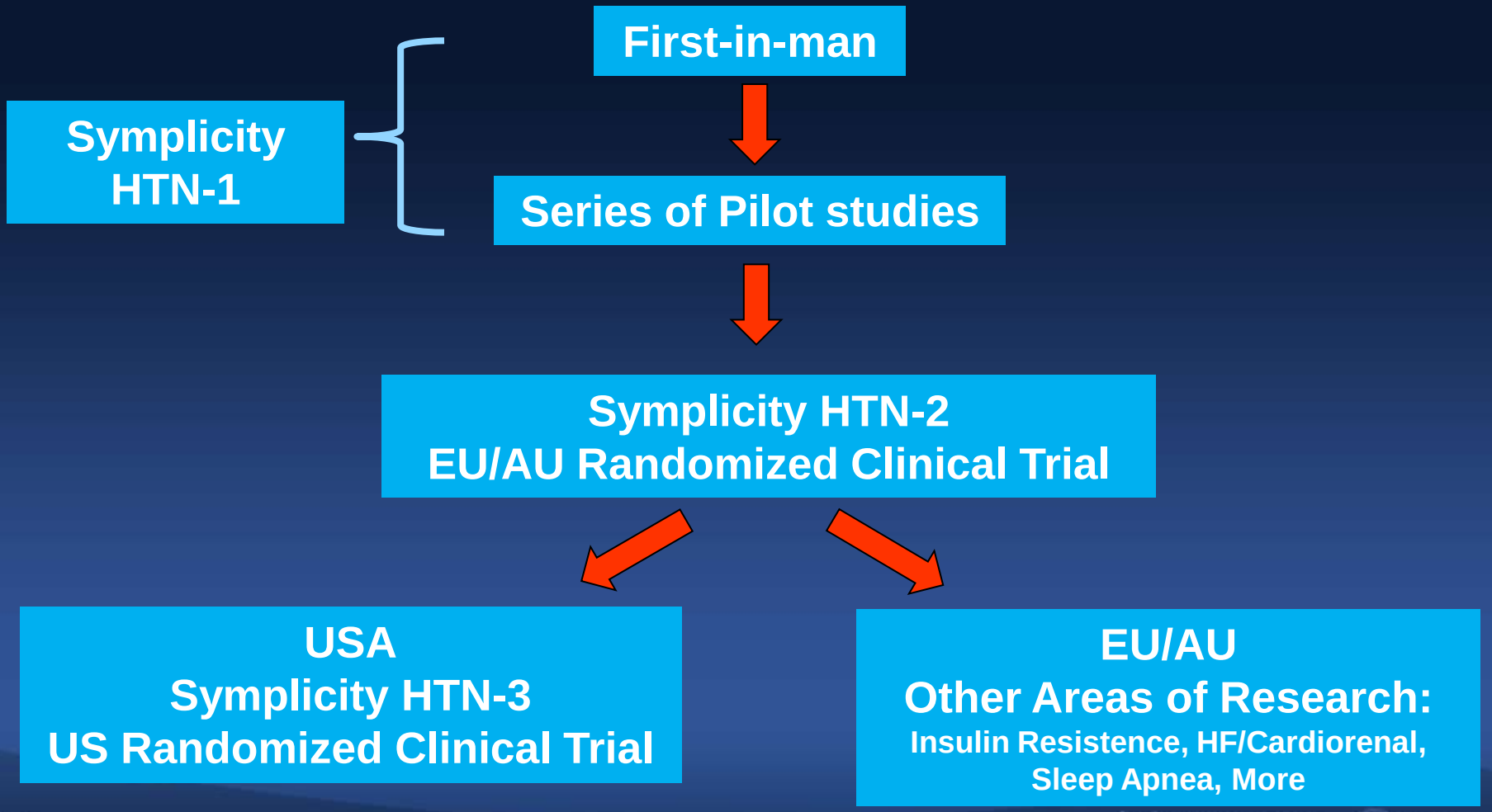
- **Nerve from untreated vessel:** Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium)
- **Nerve from treated vessel:** Periarterial nerve bundle has a hypercellular appearance and the perineurium has a thickened and fibrotic appearance.



Nerve from Untreated Vessel ***Nerve from Treated Vessel***

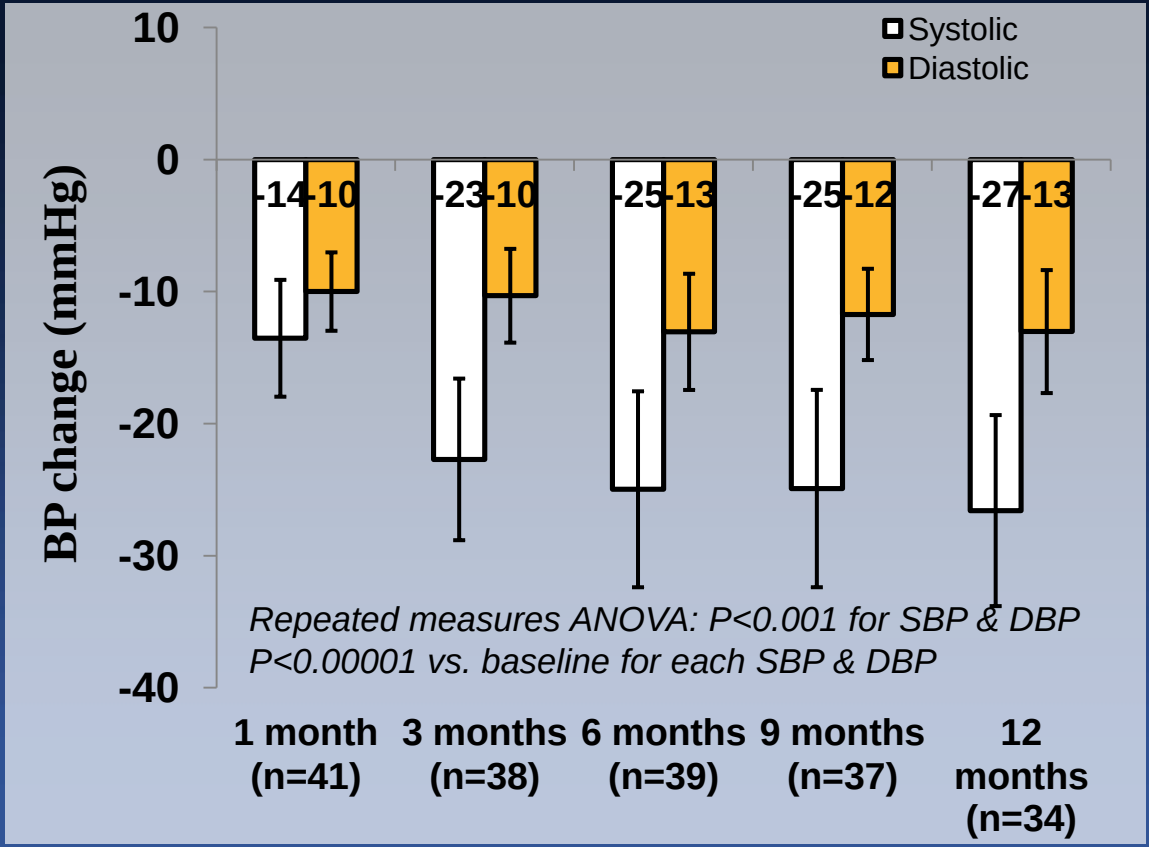
Rippy MK, et. al. Clin Res Cardiol. 2011 Dec;100(12):1095-101

Symplicity Staged Evaluation in Hypertension and Beyond



Symplicity HTN-1

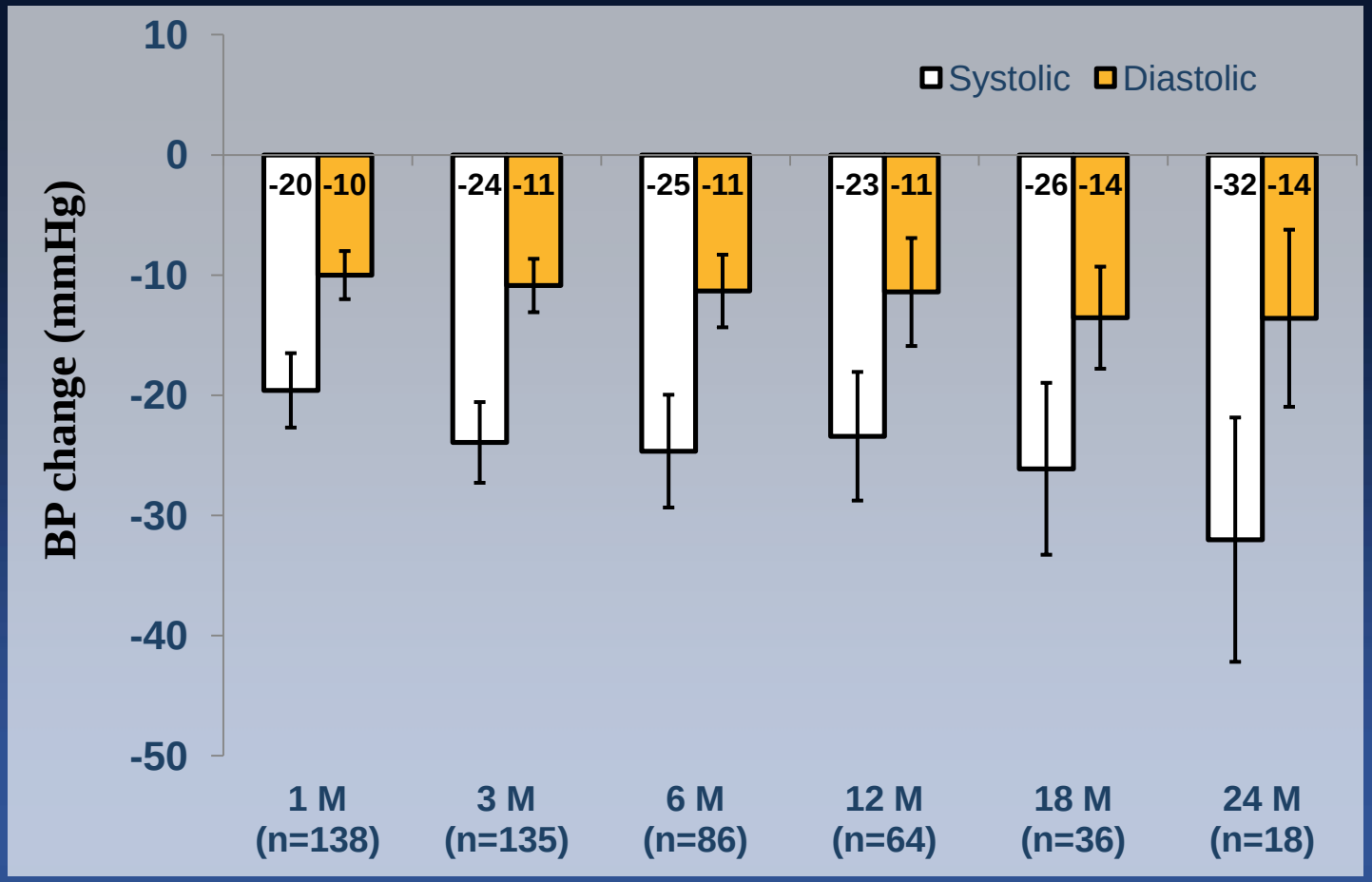
Initial cohort of 45 pts with resistant HTN
(SBP ≥160 mmHg on ≥3 anti-HTN drugs; eGFR ≥ 45 mL/min)



Krum et al. Lancet. 2009;373:1275-1281

Symplicity HTN-1 2year

Expanded cohort of 153pts

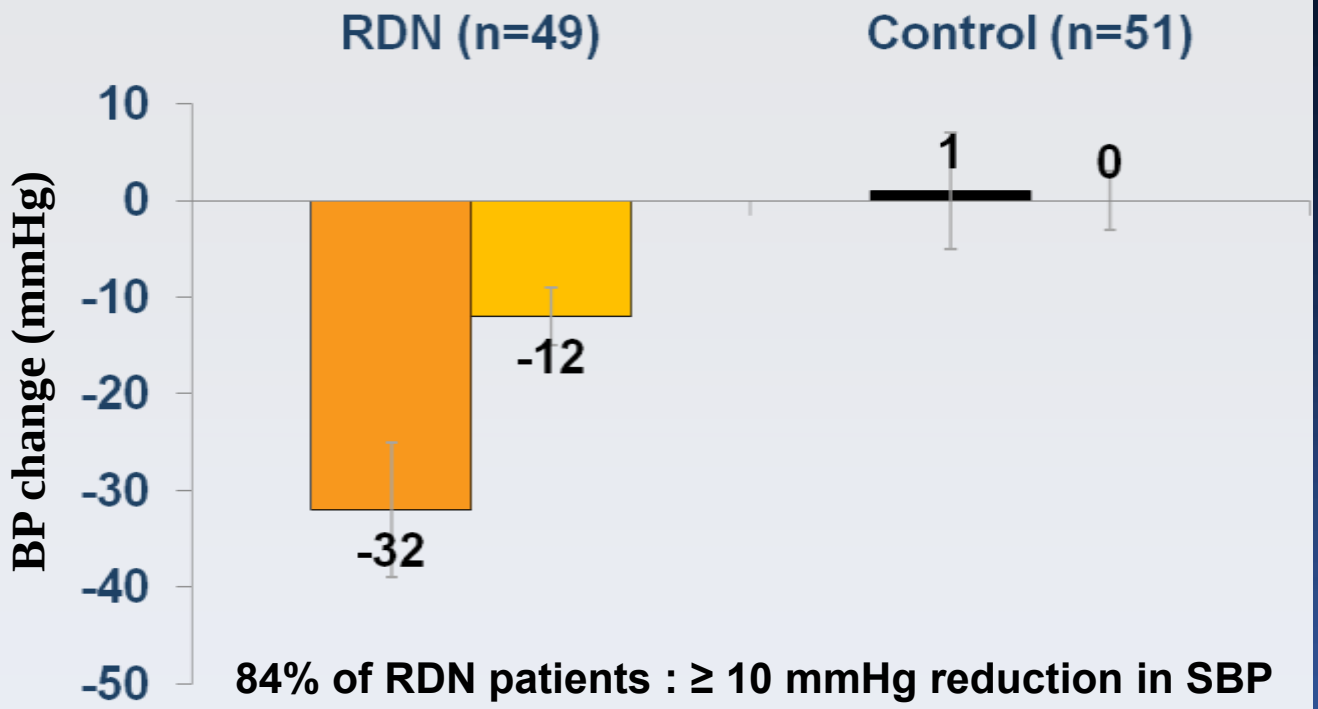


Hypertension. 2011;57:911-917

Symplicity HTN-2

Randomized, multicenter, 106pts

Primary Endpoint: 6-Month Office BP



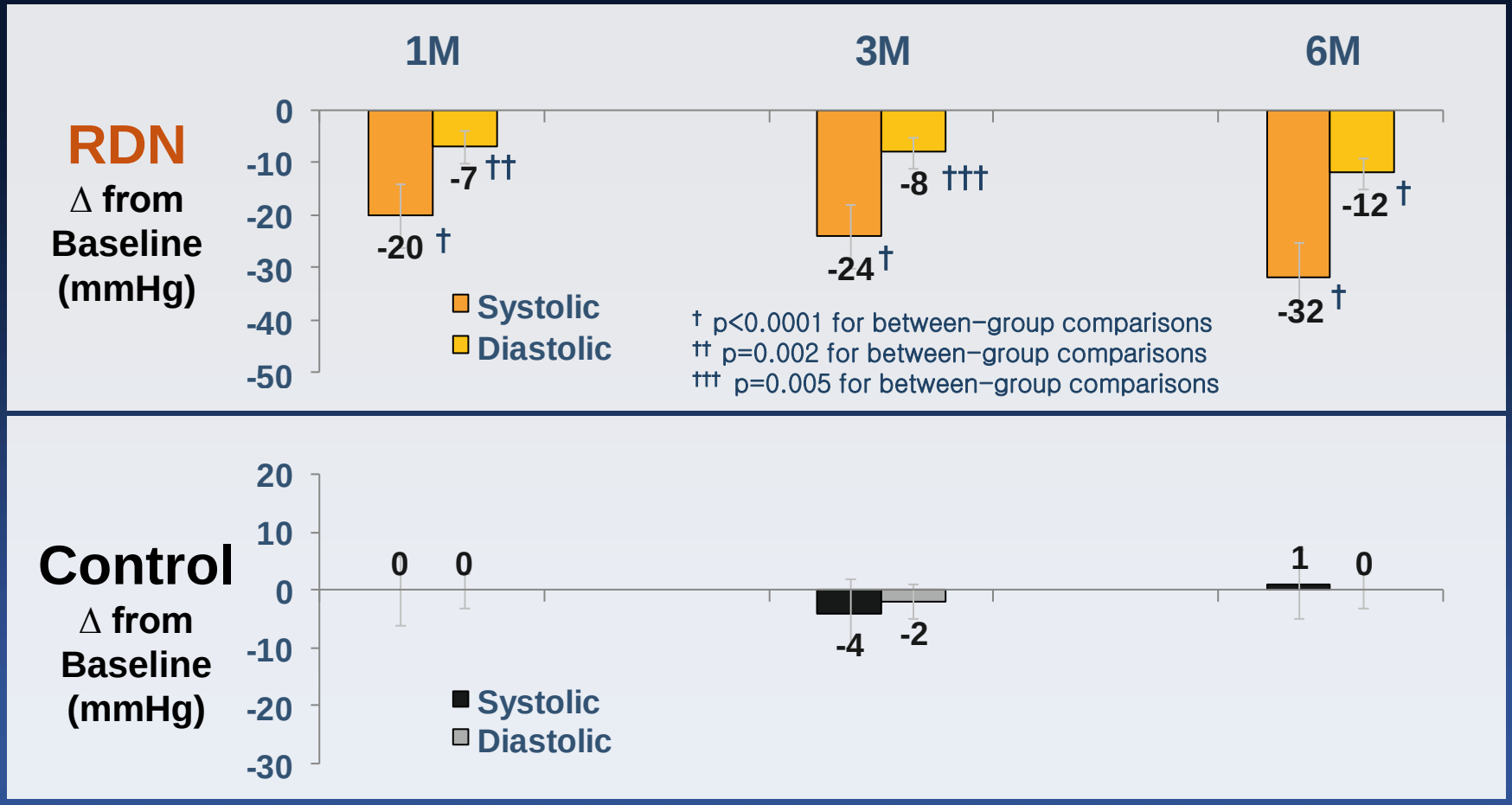
84% of RDN patients : ≥ 10 mmHg reduction in SBP
10% of RDN patients : no reduction in SBP

Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

Symplicity HTN-2

Randomized, multicenter, 106pts

Time Course of Office BP Change

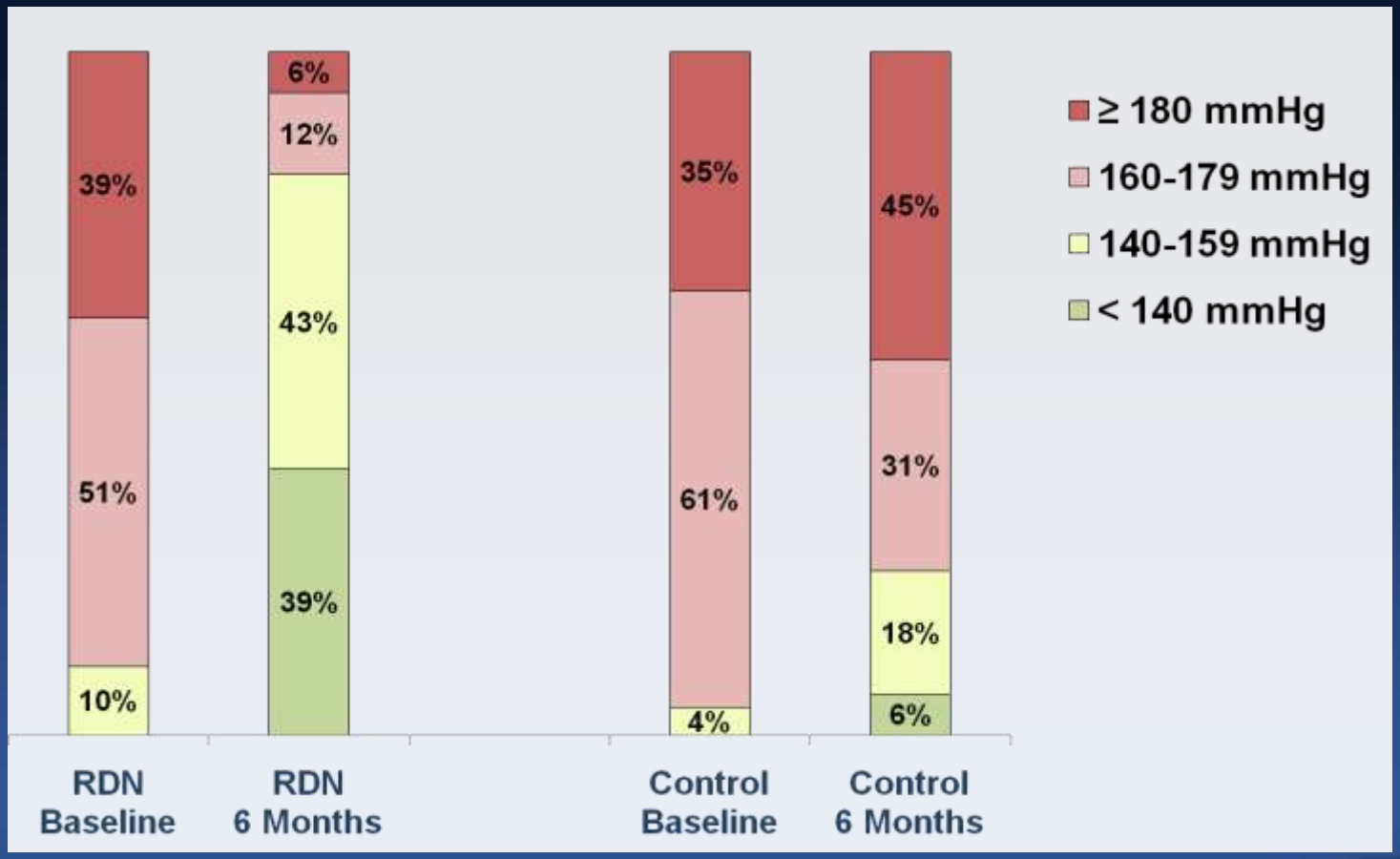


Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

Symplicity HTN-2

Randomized, multicenter, 106pts

Office Systolic BP Distribution



Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

Procedural Safety

- **No serious** device or procedure related **adverse events** (n=52)

- 6-month renal imaging (n=43)

  - No vascular abnormality at any RF treatment site

  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment

Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

Effect on Renal function

Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0, 0.1)	0.31

Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

The Symplicity HTN-3 Trial

- Design
  - Multicenter (60 sites in the United States), prospective, randomized, single-blinded, sham-controlled study
- Population
  - 535 patients with treatment-resistant hypertension
- Treatment
  - Treatment group (**endovascular catheter-based RDN** with the Symplicity® Renal Denervation System™ plus baseline antihypertensive medications)
  - Control group (**sham procedure** plus baseline antihypertensive medications)
- Primary and Secondary Efficacy End Point
  - Δ office SBP (denervation – sham control group), baseline to 6 months (superiority margin 5mmHg)
  - Δ 24hr ABPM SBP at 6 months

Symplicity HTN-3 Investigators. N Engl J Med. 2014; Epub ahead of print

Symplicity HTN-3 Trial:
Inclusion Criteria

- Average SBP ≥160mmHg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80 years

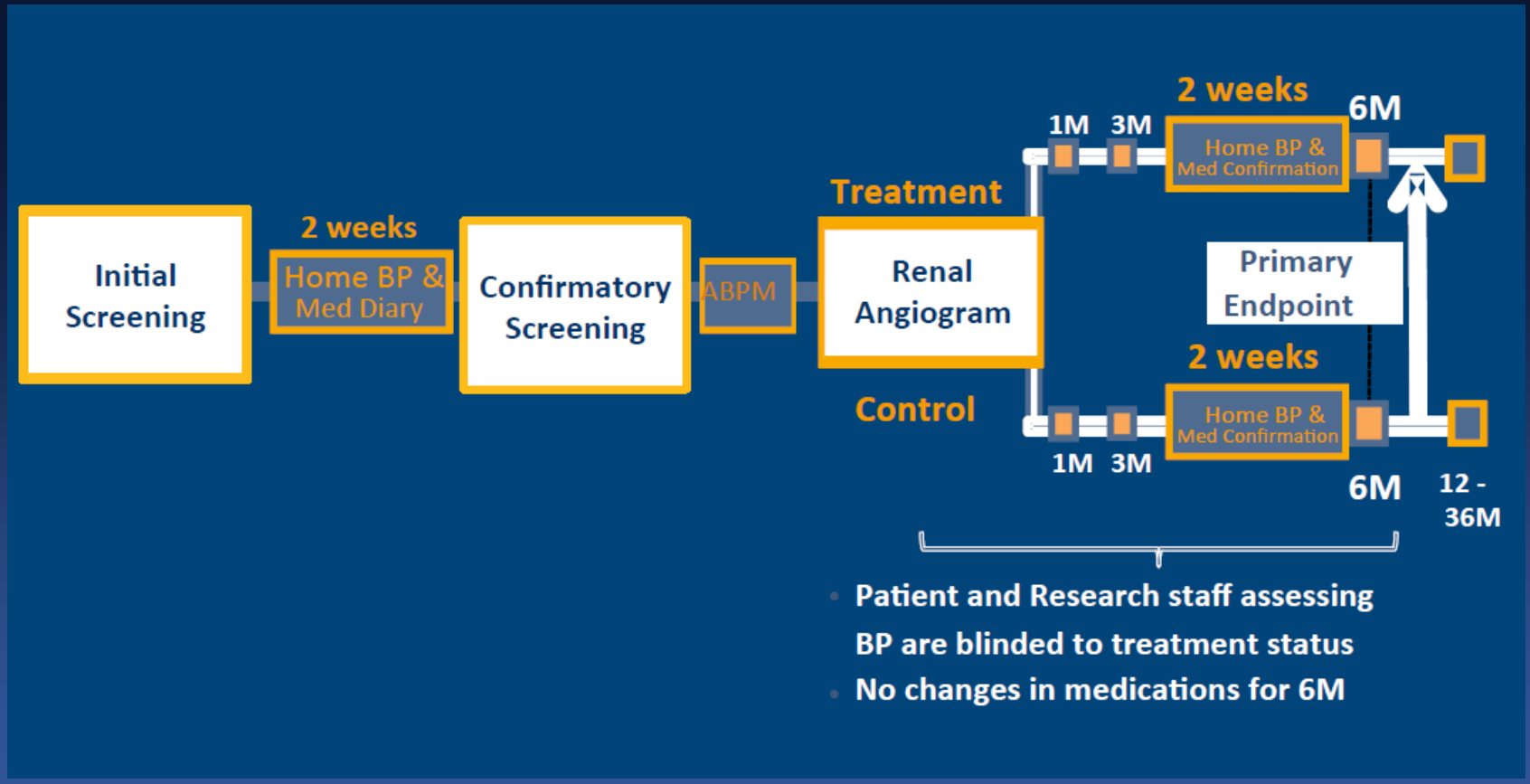
*Kandzari DE, Bhatt DL, Sobotka PA et al. Clin Cardiol. 2012; Sep;35(9):528-**35***

Symplicity HTN-3 Trial:
Exclusion Criteria

- Hemodynamically or anatomically significant renal artery abnormalities or stenosis (>50%) or prior renal artery intervention
- eGFR < 45 mL/min/1.73m2 (MDRD formula)
- In-patient hospitalization for HTN Crisis in past year
- 24 hour average ABPM SBP <135mm/Hg
- Type 1 diabetes mellitus
- Symptomatic orthostatic hypotension in past year
- Stenotic valvular heart disease for which ↓BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months
- Planned surgery or CV intervention within the next 6 months
- Known primary pulmonary HTN
- Known pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism
- Known alcohol or drug abuse

*Kandzari DE, Bhatt DL, Sobotka PA et al. Clin Cardiol. 2012; Sep;35(9):528-**35***

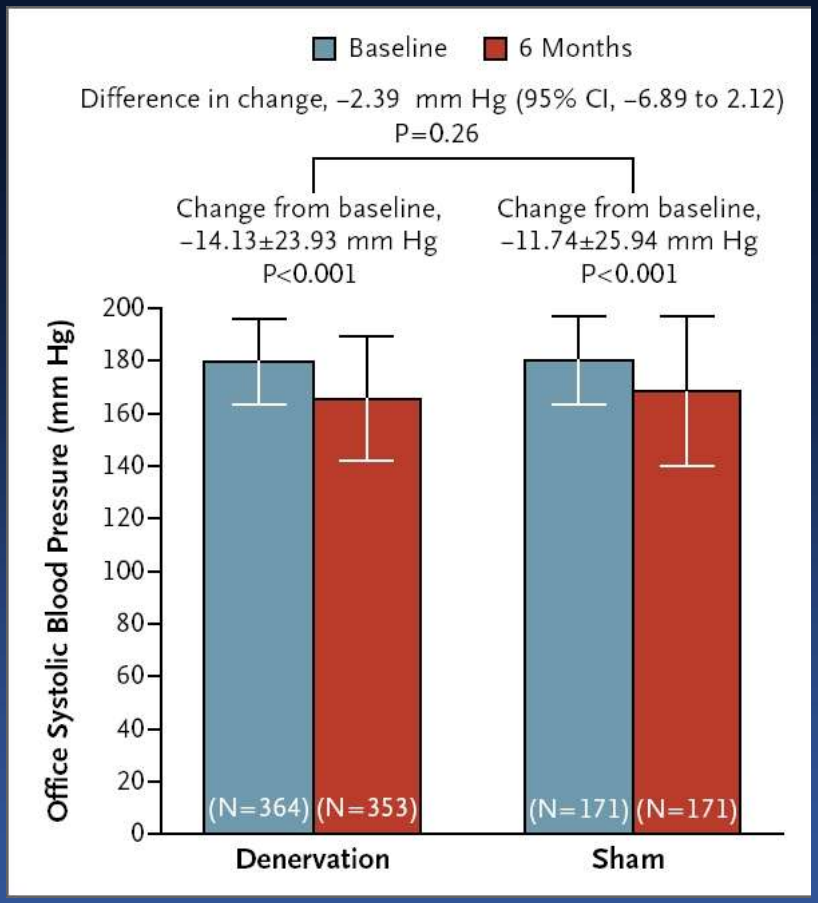
Symplicity HTN-3 Trial:
Study Design



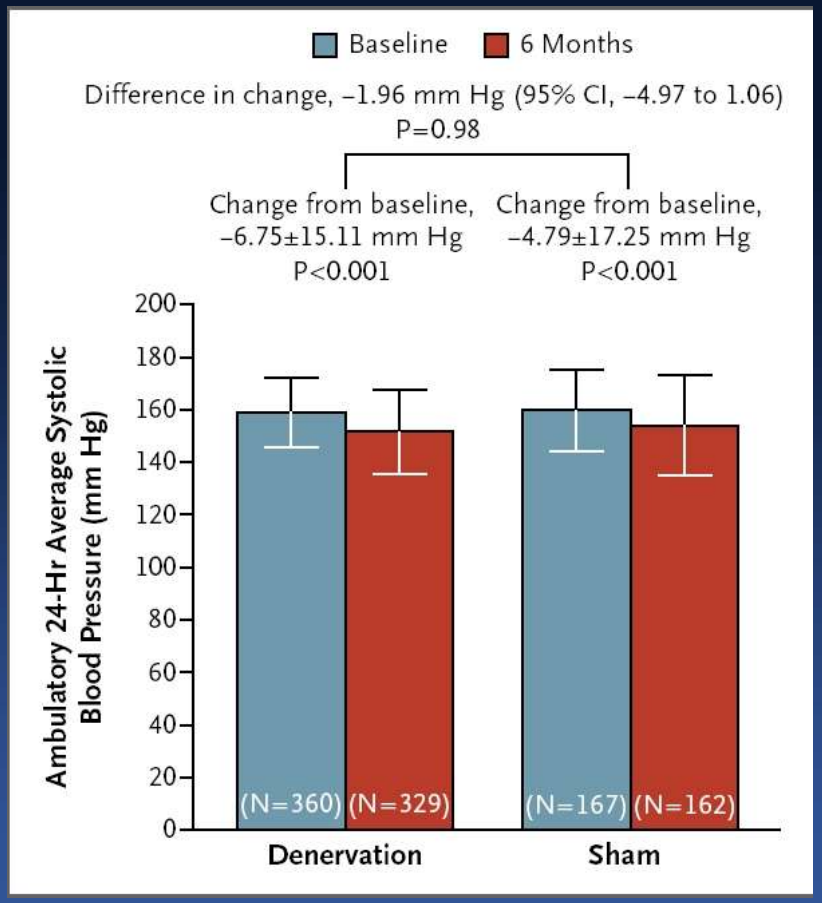
*Kandzari DE, Bhatt DL, Sobotka PA et al. Clin Cardiol. 2012; Sep;35(9):528-**35***

Symplicity HTN-3 Trial

Efficacy End Point



Primary efficacy End Point



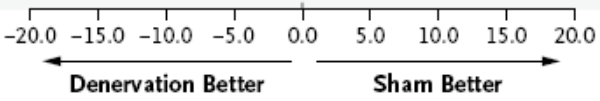
Primary efficacy End Point

Symplicity HTN-3 Investigators. N Engl J Med. 2014; Epub ahead of print

Symplicity HTN-3 Trial

Subgroup Analyses

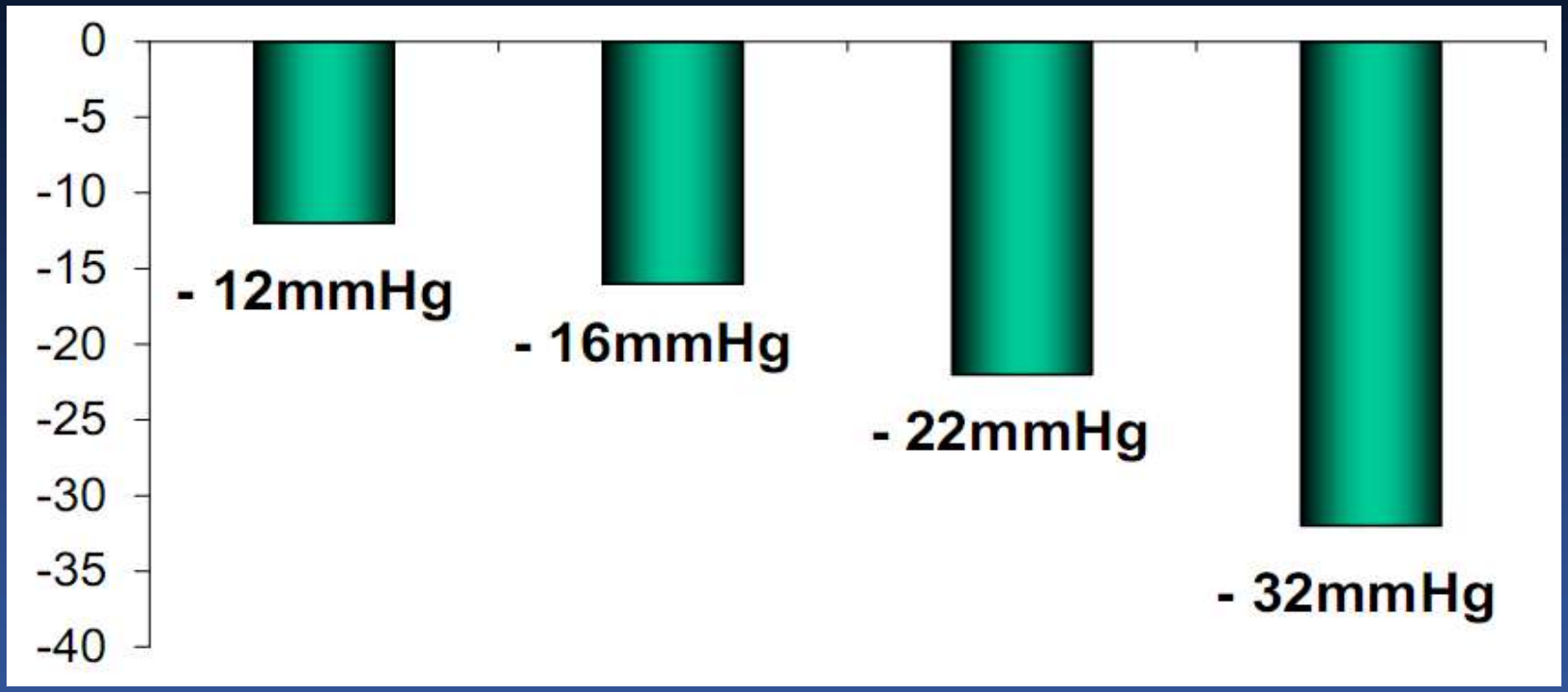
Subgroup	Denervation	Sham	Between-Group Difference in Change in Office Systolic Blood Pressure (95% CI)	P Value	P Value for Interaction
	no. of patients		*mm Hg*		
All patients	353	171	−2.39 (−6.89 to 2.12)	0.26	
Diabetes mellitus					0.82
Yes	169	68	−4.53 (−11.51 to 2.46)	0.20	
No	181	101	−3.46 (−9.55 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	



Symplicity HTN-3 Investigators. N Engl J Med. 2014; Epub ahead of print

Randomized Trials in Resistant Hypertension

Mean Reduction in Systolic BP

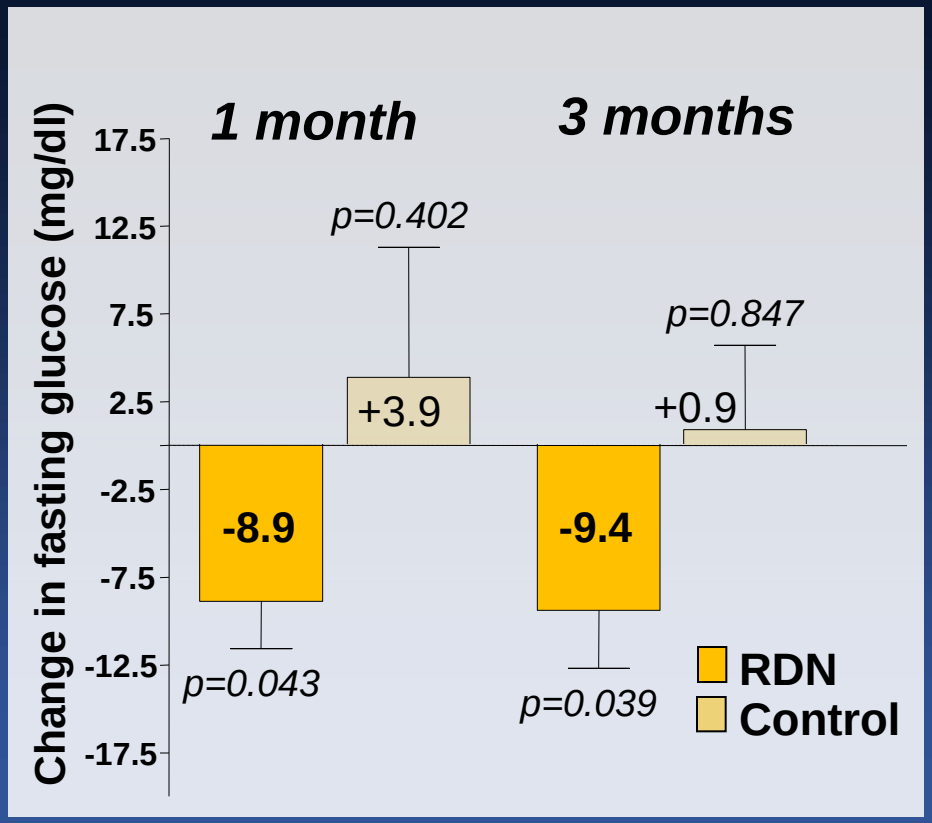


1.Curr Hypertens Rep. 2008 Dec;10(6):429-31. *2. Hypertension. 2010 Jan;55(1):147-52.*
3. Hypertension. 2010 Jul;56(1):22-3. *4. Lancet. 2010*

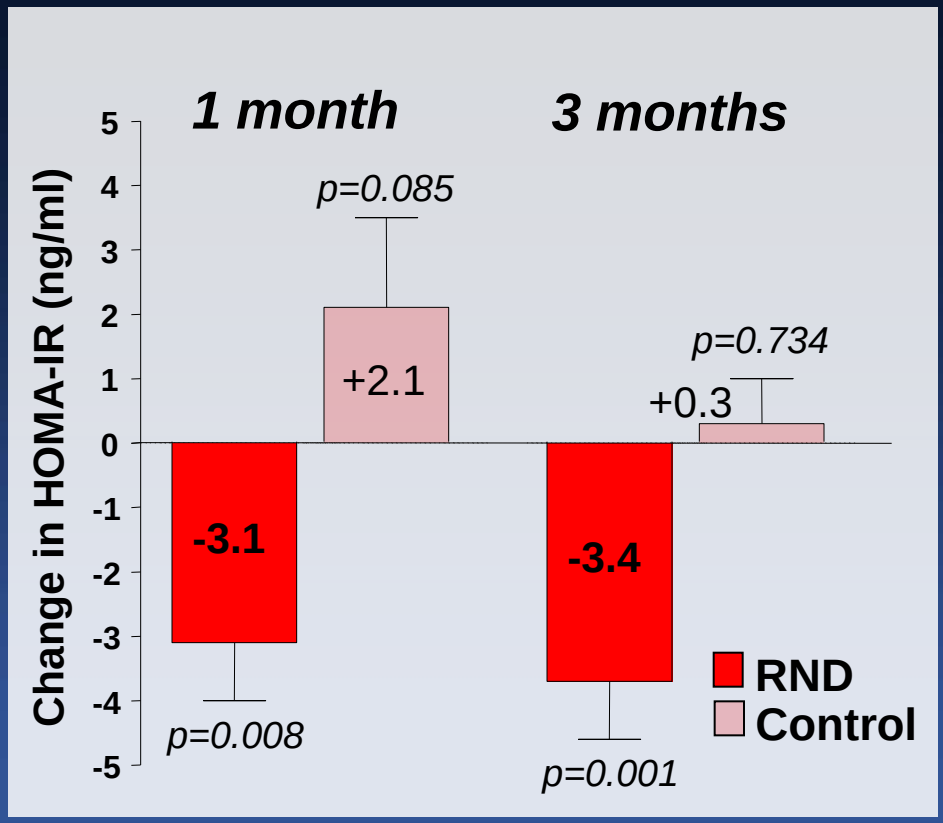
Impact on Glucose metabolism

RDN 37pts, Control 13pts, F/U (1&3month)

Reduce fasting glucose



Improve insulin sensitivity

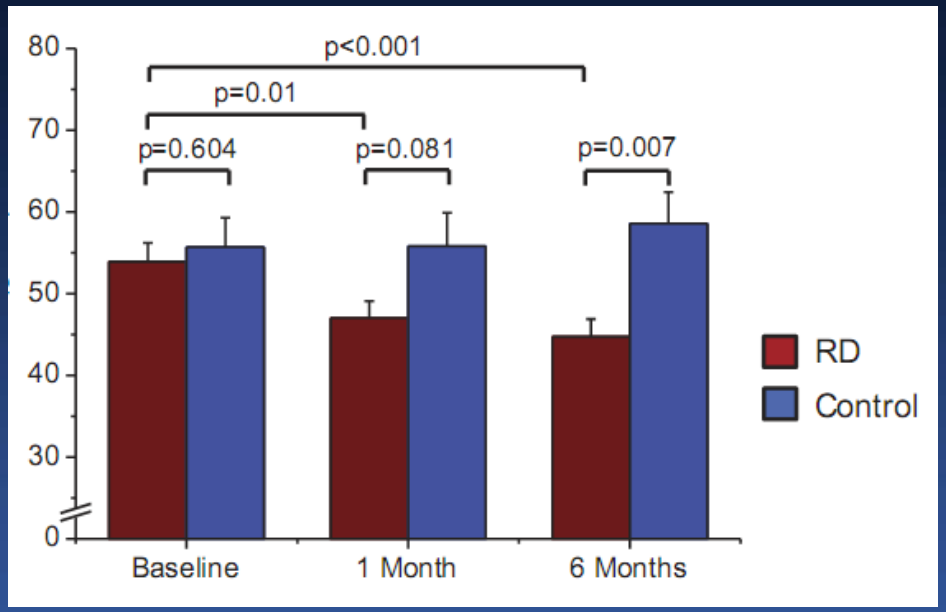


Mahfoud . Circulation. 2011; 123:1940-1946

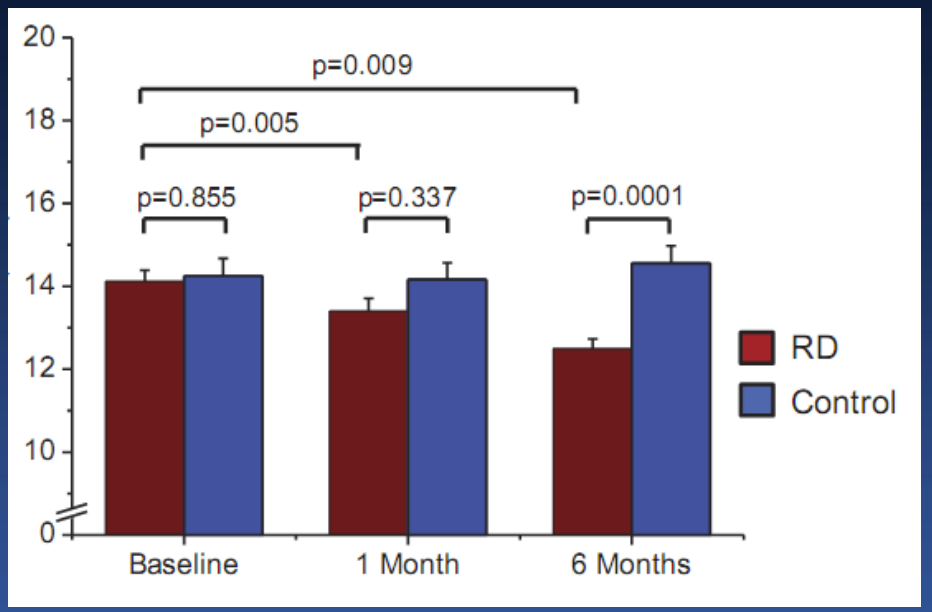
Effect on LV mass

RDN 46pts, Control 18pts, Echocardiography F/U (1&6month)

LV mass index
(LV mass/height$^{2.7}$)



End-diastolic septum thickness

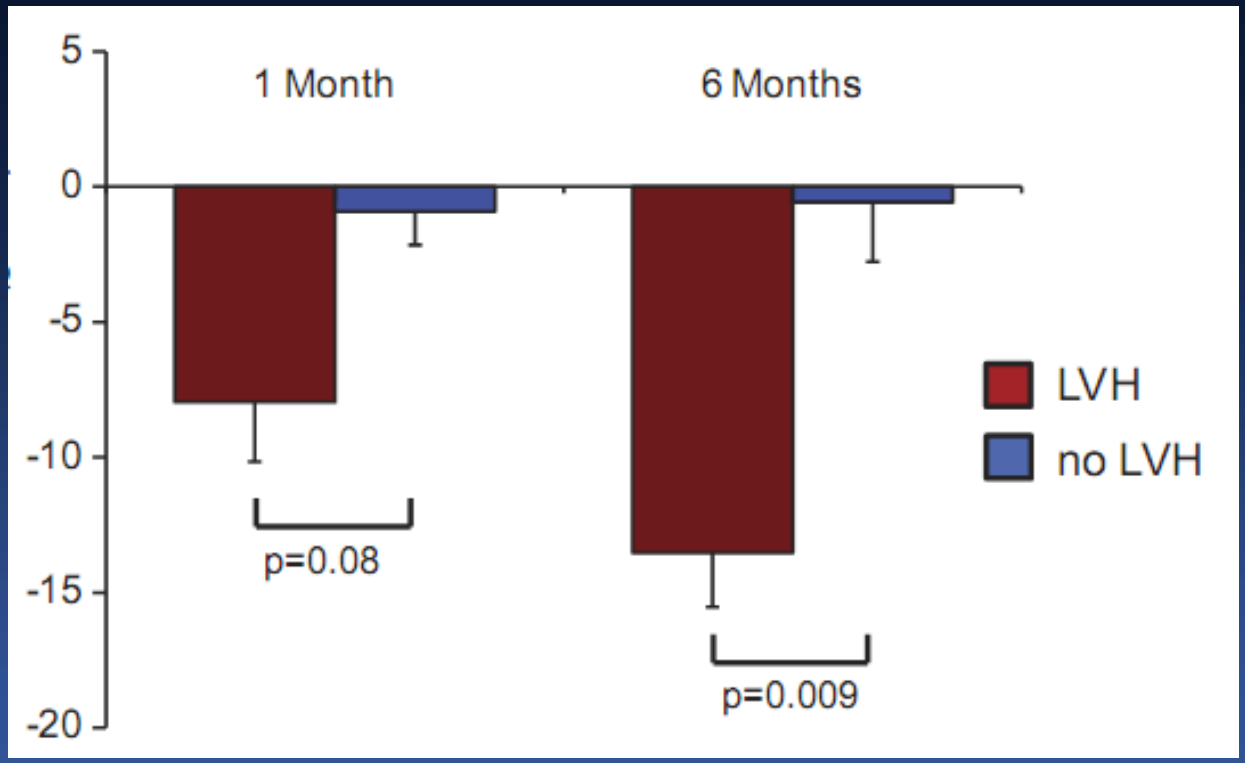


Mathias. J Am Coll Cardiol 2012;59:901–9

Effect on LV mass

RDN 46pts, Control 18pts, Echocardiography F/U (1&6month)

Differential effect on LV mass regression depends on LVH

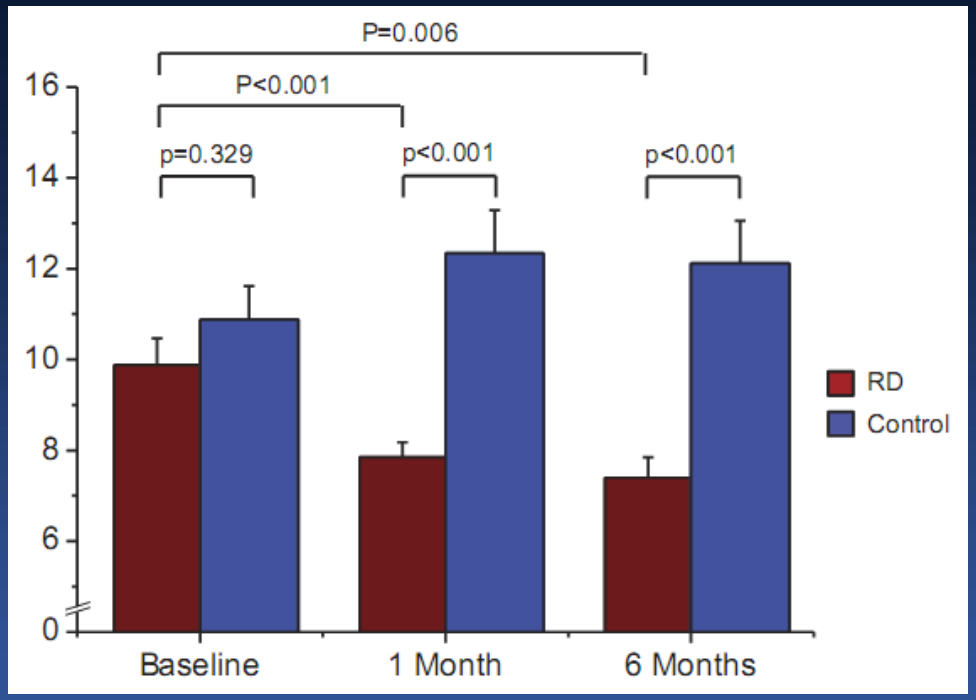


Mathias. J Am Coll Cardiol 2012;59:901–9

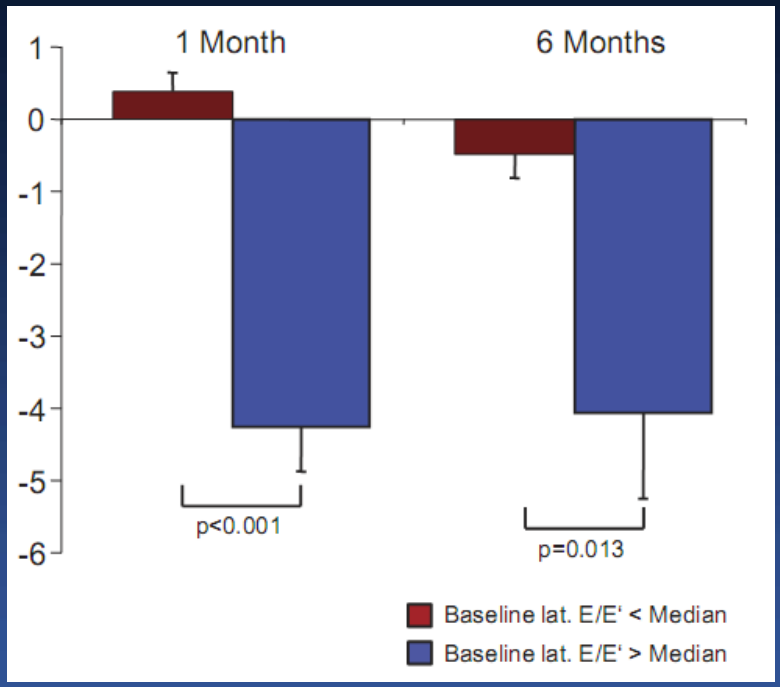
Effect on Diastolic Function

RDN 46pts, Control 18pts, Echocardiography F/U (1&6month)

Mitral valve lateral E/E’

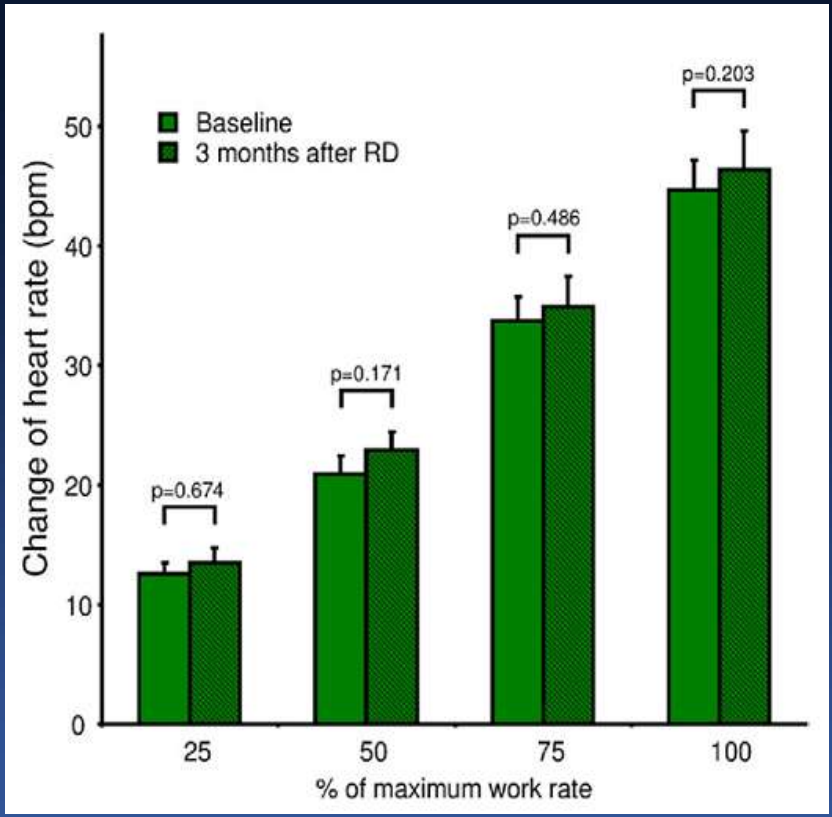


E/E’ reduction



Mathias. J Am Coll Cardiol 2012;59:901–9

Response to Exercise after Renal Denervation



Renal denervation reduces BP during Exercise without compromising chronotropic competence

Christian . J Am Coll Cardiol 2011;58:1176–82

New Devices for Renal Denervation

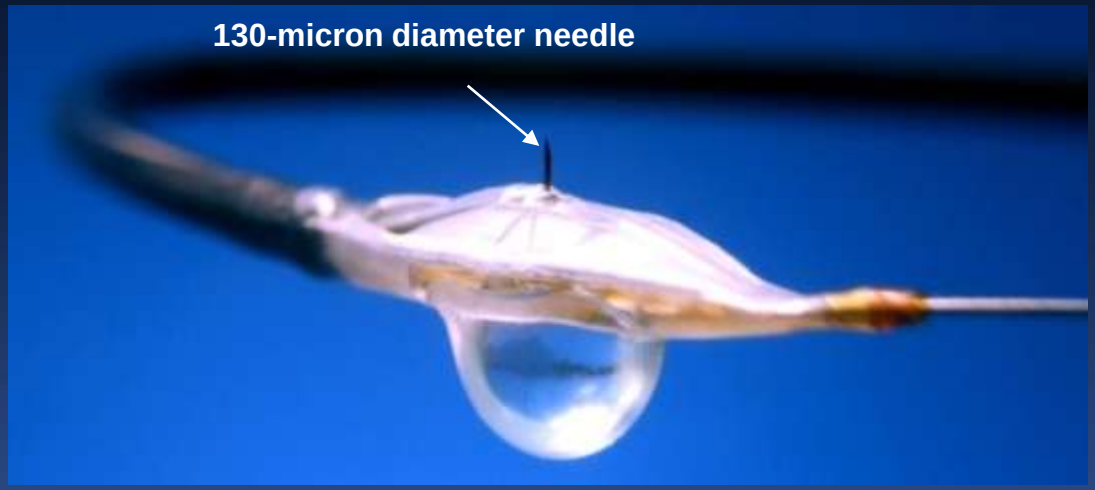
Balloon with radiofrequency

Maya Medical

Vessix Vascular

New Devices for Renal Denervation

Balloon with needle



Mercator Medsystems