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What you need to know in 2018 to manage resistant hypertension

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Speaker has no conflict of interest

Resistant vs refractory hypertension

Resistant hypertension is hypertension that does not respond to adequate doses of 3 or more antihypertensive drugs.

It represents 10-15% of the general hypertensive population.

Refractory hypertension is defined as BP that remains uncontrolled after 3 visits to a hypertension clinic within a minimum 6-month follow-up period.

Secondary causes of hypertension, obesity, diabetes, sleep disordered breathing and excess salt intake or use of AINS drugs are among some of the findings associated with resistant or refractory hypertension.

Clinical features of 8295 patients with resistant hypertension classified on the basis of ABPM

- Prevalence of resistant hypertension in the Spanish ABPM registry
- Resistance defined by BP in office ≥140/90 mmHg and ≥ 3 antihypertensive drugs

- 12.2% of 68,045
- After ABPM: 62.5% were true resistant ≥130/80 mmHg
- After ABPM :55.9% ≥135/85 mmHg

- Selected population

Table 2. Medications That Can Interfere With Blood Pressure Control

Nonnarcotic analgesics
Nonsteroidal antiinflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Calhoun DA et al. Hypertension. 2008;51:1403–1419.

Table 3. Secondary Causes of Resistant Hypertension

Common
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's disease
Hyperparathyroidism
Aortic coarctation
Intracranial tumor

Calhoun DA et al. Hypertension. 2008;51:1403–1419.

Resistant hypertension

1- Confirm BP measurement

2- Identify lifestyle characteristics

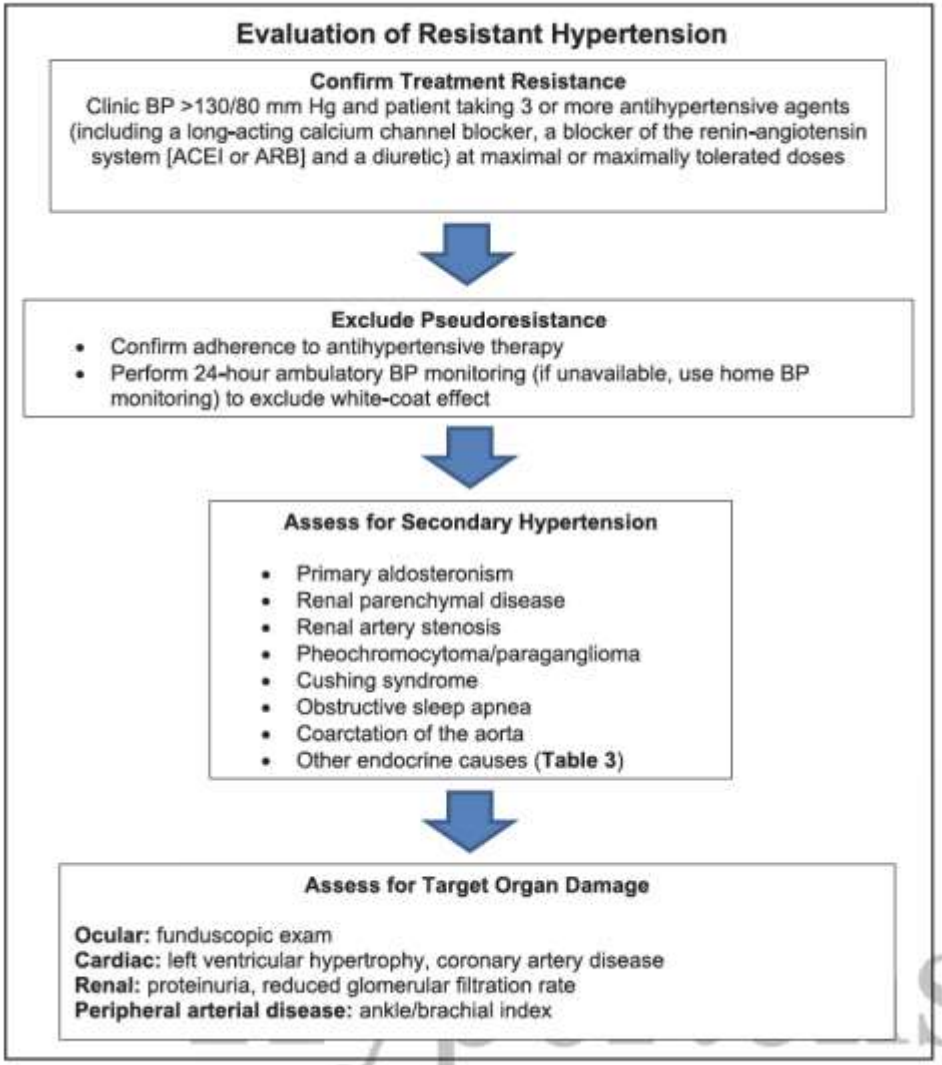
3- Identify hypertensive medications and drugs

4- Evaluate non-adherence to medications

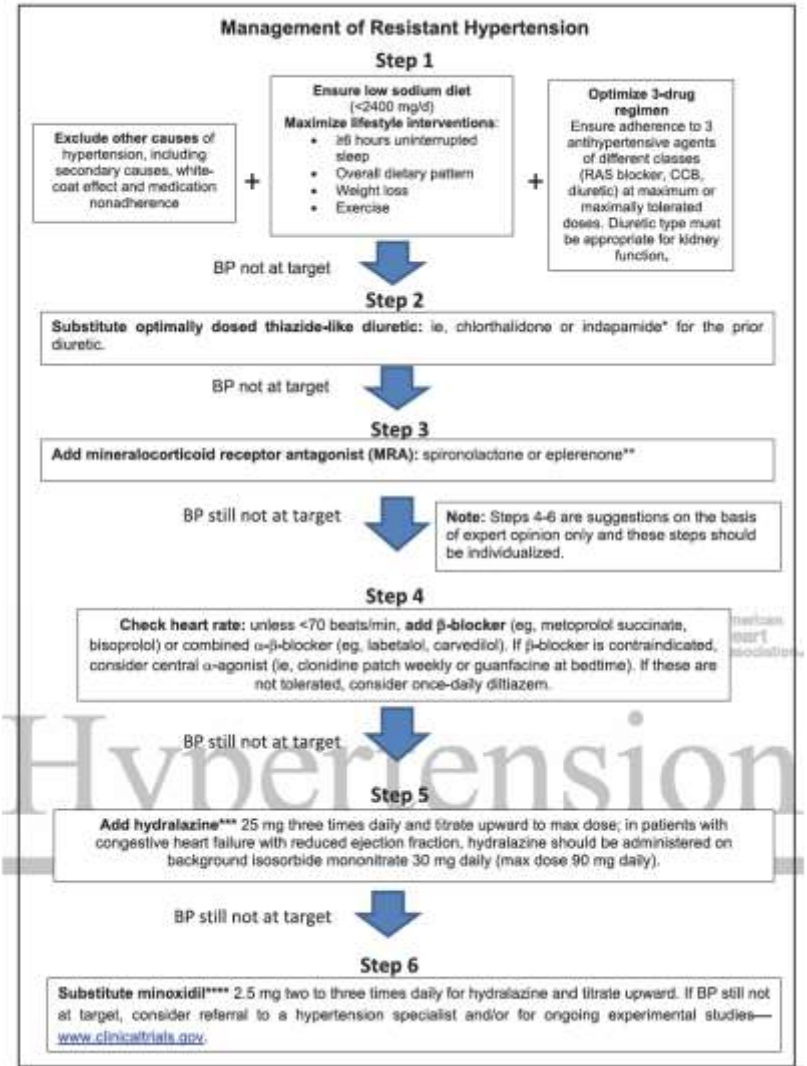
5- Screen for secondary causes of hypertension

6- Adjust anti-hypertensive medication

7- Referral to specialties



Carey RC et al. Hypertension 2018; DOI: 10.1161/HYP.0000000000000084



Carey RM et al. Hypertension 2018
DOI:
10.1161/HYP.0000000000000084

How to approach resistant hypertension

1. RAS blocker + diuretic + CCB + MR antagonist with or without a beta-blocker
2. Thiazide diuretics: chlorthalidone @ 25 mg⁄ d, preferred for most patients.
3. CKD: loop diuretic, most commonly furosemide at 20 mg to 40 mg twice daily.
4. Vasodilators, centrally acting antihypertensive agents, and alpha-adrenergic blockers added if failure to control BP.

How to approach resistant HTN

- Adherence needs to be assessed by asking the patient about medication use, perceptions about medication efficacy, and presence of adverse effects, if any.
- Patients must be seen every 4 to 8 weeks, with more frequent visits for patients with uncontrolled BP.

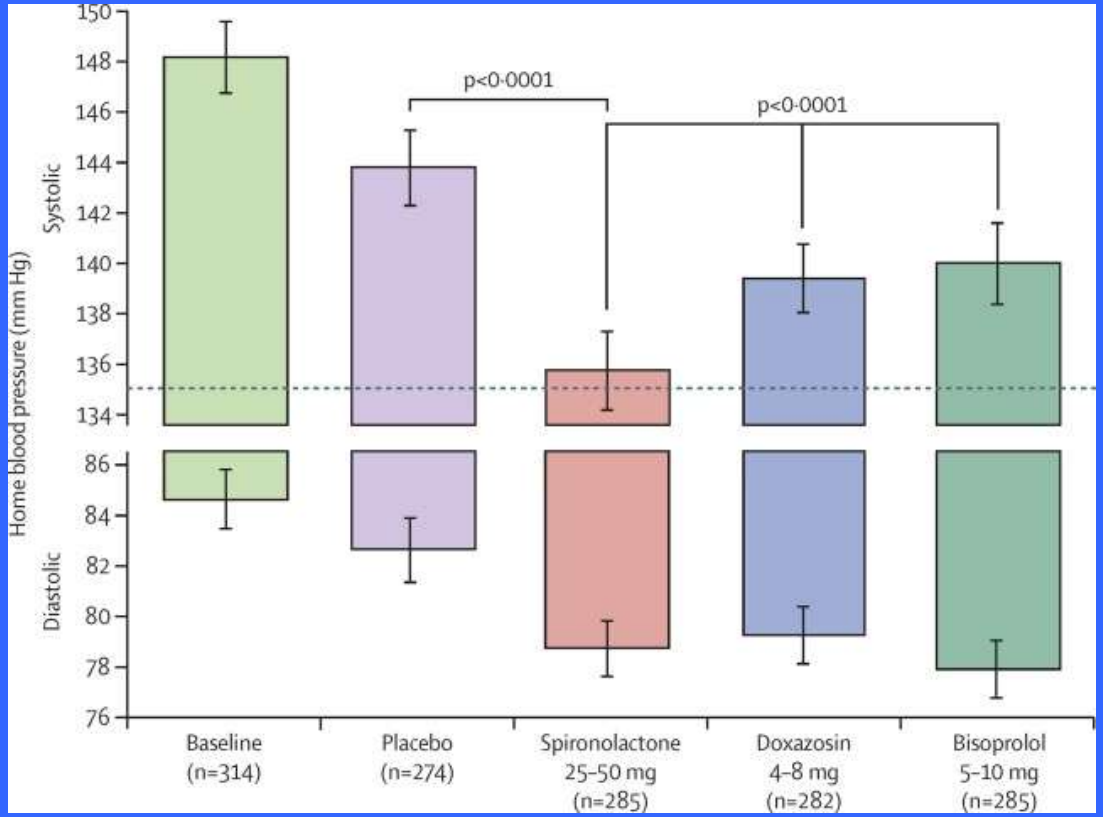
Strategies to Improve Adherence

1. Adherence to pharmacological therapy and lifestyle change should be assessed at every visit
2. Simplify medication regimens using once daily dosing of long acting medications, combination tablets and utilizing medication compliance aids
3. Tailor pill-taking to fit patients' daily habits
4. Encourage greater patient responsibility by encouraging monitoring home blood pressure
5. Adherence to an antihypertensive prescription can be improved by a interdisciplinary care team

Resistant HTN treatment

Use of a MR antagonist in addition to a diuretic, particularly chlorthalidone, in addition to a full dose of a RAS blocker and a CCB is usually associated with control rates of resistant hypertension >80%.

Spironolactone in Patients With Resistant Hypertension (Pathway-2 Trial)



Williams B et al. Lancet. 386;2059-2068, 2015

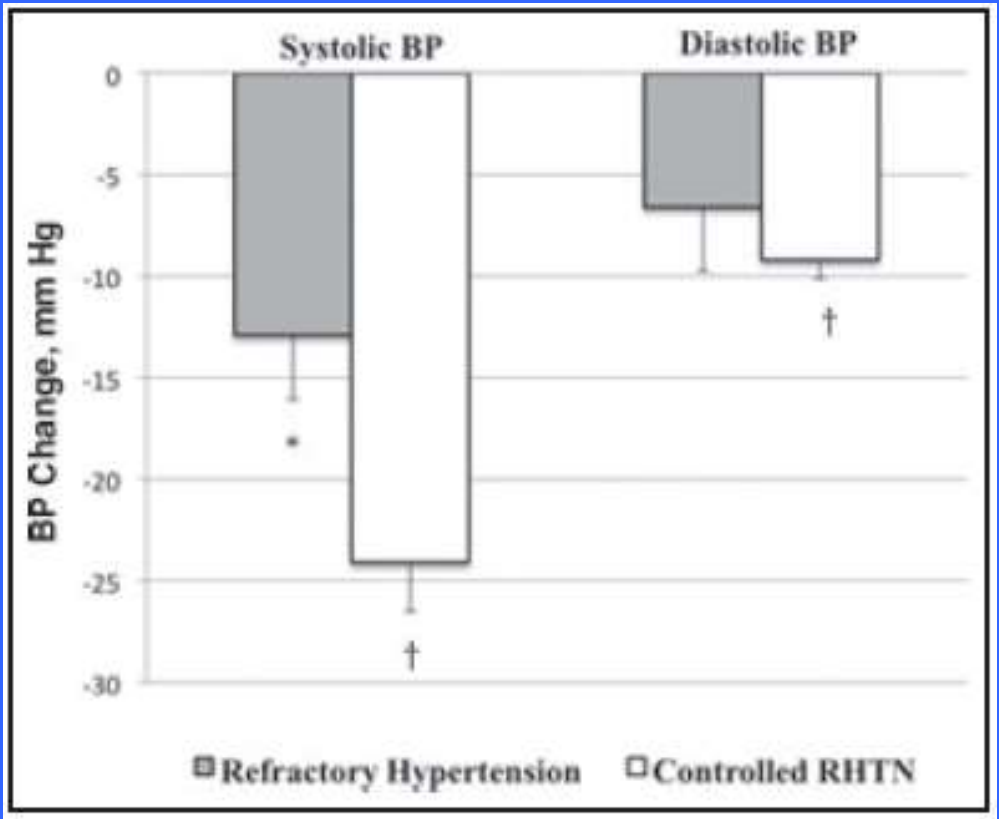
Refractory hypertension

TABLE III. Baseline Biochemical Characteristics in Patients With Refractory and Controlled Resistant Hypertension

Parameter	Refractory Hypertension (n=29)	Controlled RHTN (n=275)	*P* Value
Creatinine, mmol/L	97.2±26.5	88.4±26.5	.89
Plasma aldosterone, pmol/L	379.5±268.7	351.8±246.5	.57
PRA, pmol/L/min	53.8±230.4	49.92±120.3	.93
24-Hour urine aldosterone, nmol/d	37.9±27.4	35.7±29.1	.67
24-Hour urine sodium, mmol/d	173.1±80.9	186.5±89.5	.46

Acelajado MC et al. J Clin Hypert. 2012;14:7–12.

Response to MR antagonist



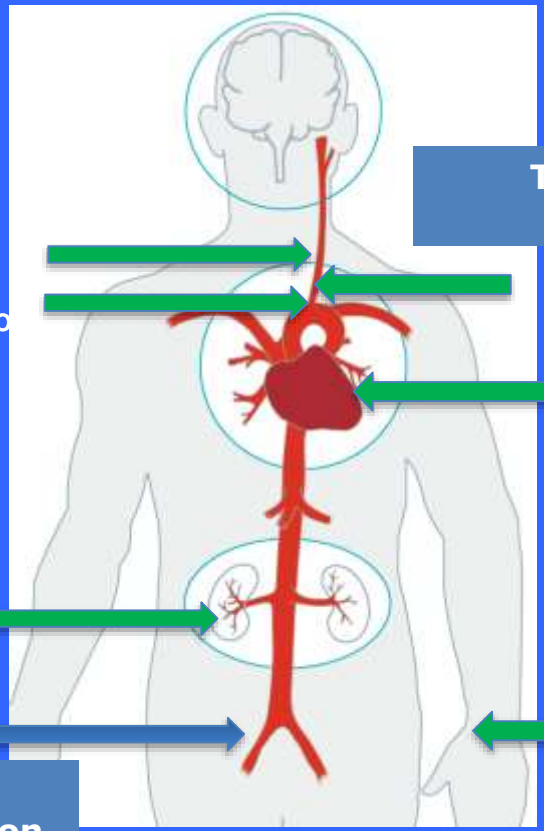
Acelajado MC et al. J Clin Hypert. 2012;14:7–12.

Refractory hypertension: mechanisms

- No evidence of greater fluid retention in refractory HTN vs controlled resistant HTN since aldosterone or PRA levels not suppressed
- Greater role of increased cardiac output and / or vascular resistance: enhanced sympathetic drive and / or increased peripheral resistance secondary to local or circulating pressor agents?

Acelajado MC et al. J Clin Hypert. 2012;14:7–12.

Device-based anti-hypertensive therapy



Target Autonomic Modulation

Carotid Bulb Expansion

Carotid Body ablatio

Baroreceptor Stimulation

Pacemaker-mediated

Renal Denervation

AV Fistula

Median Nerve stimulation

Targets mechanical aspects of the circulation

Catheter-Based Radiofrequency Ablation of Renal Sympathetic Nerves

The SYMPLICITY-HTN results showed that six months after the ablation, average office BP in the renal-denervation group was reduced by 32/12 mm Hg (average baseline 178/96 mm Hg), whereas it did not differ from baseline in the control group. Between-group differences in BP at six months were 33/11 mm Hg ($p<0.0001$).

Symplicity HTN-2 Trial

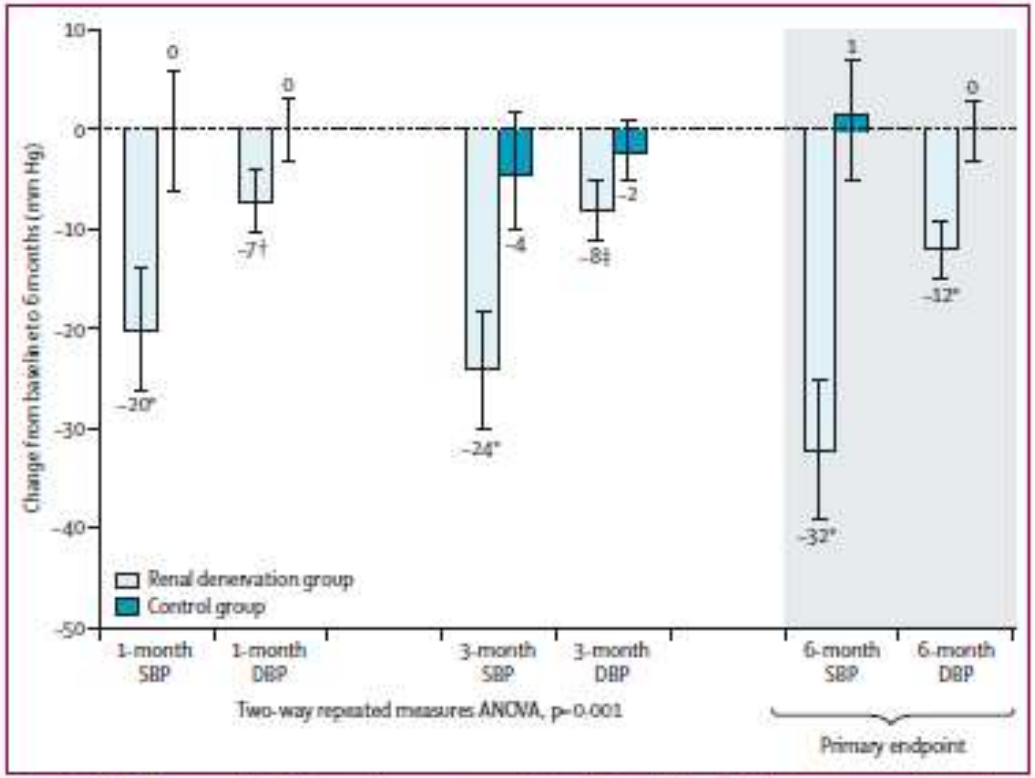


Figure 2: **Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups**

Error bars are 95% CI. Multivariable stepwise regression analysis of baseline characteristics, drugs, and treatment assignment was examined for predictors of increased 6-month systolic blood-pressure response; only variables with p<0·15 on univariate screening were entered into the model with variables with p<0·05 remaining in the final model. Multivariable analysis of baseline characteristics showed that assignment to the renal denervation group (p<0·0001), higher baseline systolic blood pressure (p<0·0001), and slower heart rate (p<0·004) predicted increased 6-month blood-pressure reduction. SBP=systolic blood pressure. DBP=diastolic blood pressure. *p<0·0001. †p=0·002. ‡p=0·005.

The Lancet 2010;376: 1903-1909.

Symplicity HTN-1 Investigators

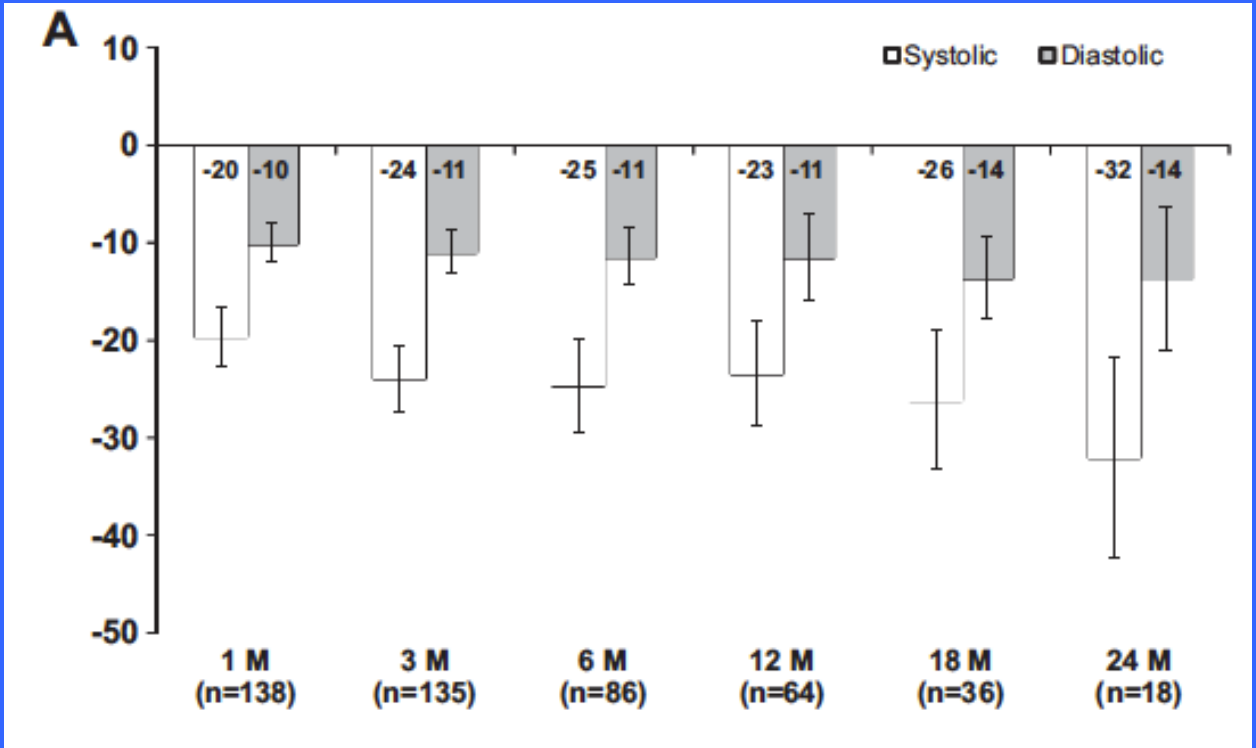
Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension:

Durability of Blood Pressure Reduction Out to 24 Months

153 patients with catheter-based renal sympathetic denervation at 19 centers

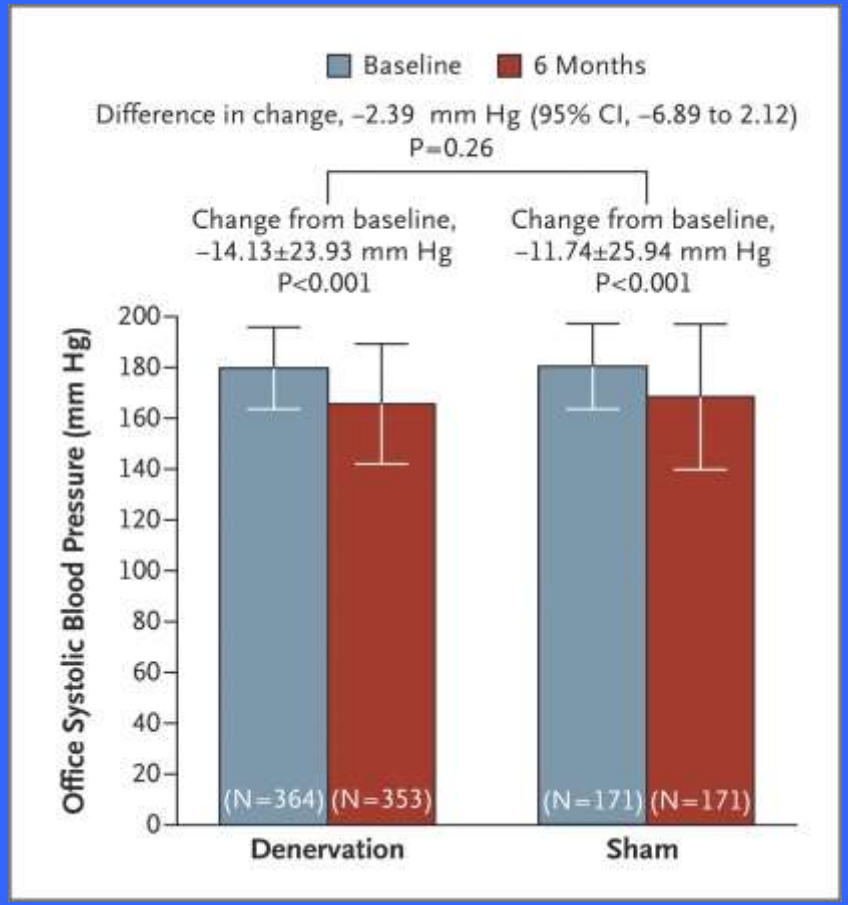
Hypertension. 2011;57:911-917.

BP changes after renal sympathetic denervation over 24-months of follow-up



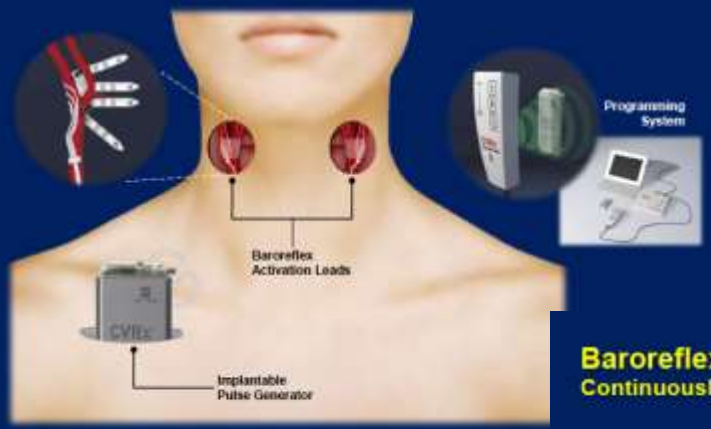
Krum H. et al. *Hypertension*. 2011;57:911-917.

Simplicity HTN-3 Trial: Primary Efficacy End Point

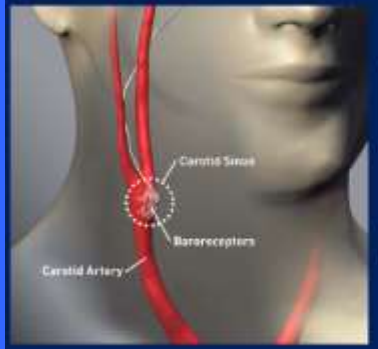


Bhatt DL et al. N Engl J Med 2014;370:1393-1401.

Baroreflex Activation Therapy (BAT)
The CVRx Rheos® System



Baroreflex Activation Therapy (BAT)
Continuously Modulates the Autonomic Nervous System



Carotid Baroreceptor Stimulation

↓

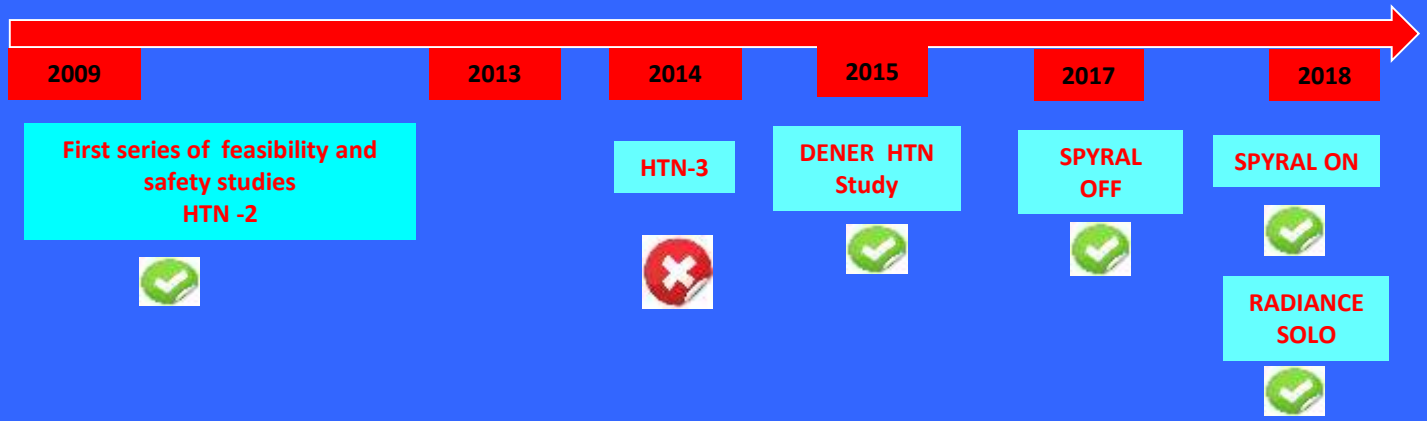
Brain

↓

Autonomic Nervous System
Inhibited **Sympathetic** Activity
Enhanced **Parasympathetic** Activity

Heart	Vessels	Kidneys
↓ HR	↑ Vasodilation ↓ Stiffness	↑ Diuresis ↓ Renin secretion

RDN: Efficacy to lower BP



RDN: No Safety Concerns

SPYRAL HTN-OFF MED

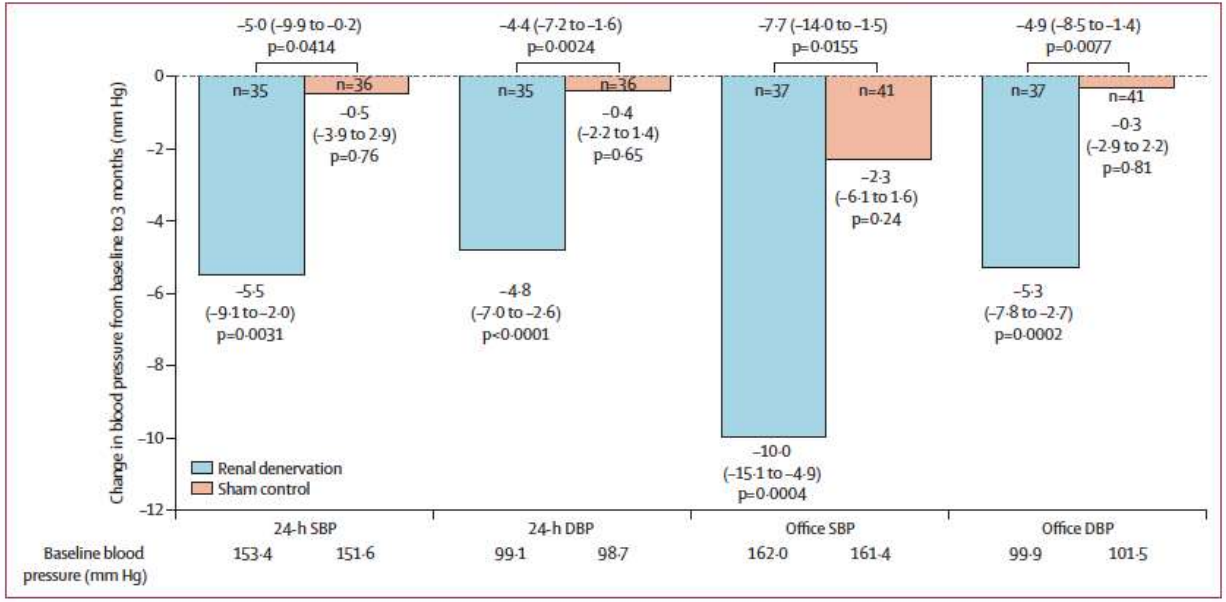


Figure 3: **Changes at 3 months in office and ambulatory SBP and DBP for renal denervation and sham control groups**
95% CIs and unadjusted p values shown. SBP=systolic blood pressure. DBP=diastolic blood pressure.

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

SPYRAL HTN-ON MED

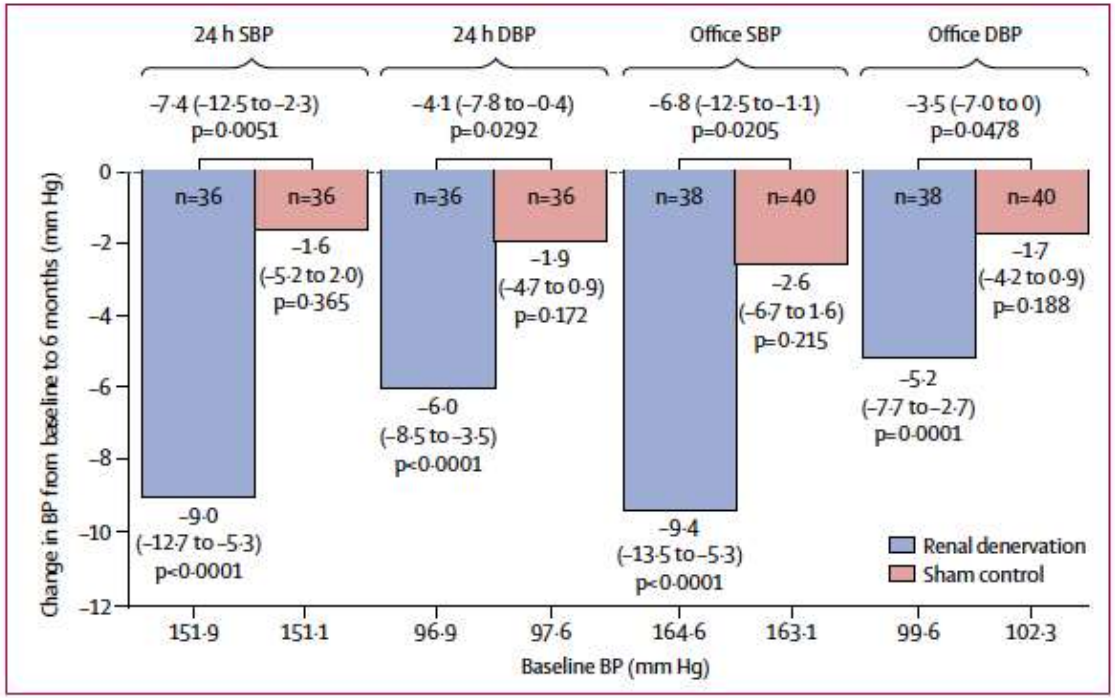


Figure 2: **Change at 6 months in office and ambulatory systolic blood pressure and diastolic blood pressure for treatment and sham control patients**

Data are mean (95% CI). SBP=systolic blood pressure. DBP=diastolic blood pressure.

Kandzari DE et al. Lancet. 2018;392:2346-2355.

RADIANCE-HTN SOLO Trial

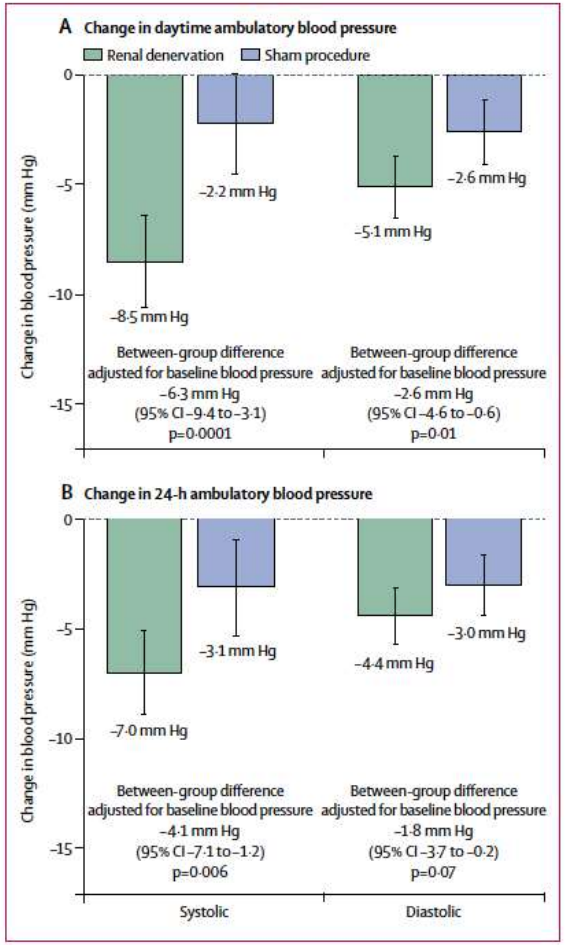


Figure 2: **Change in ambulatory blood pressure from baseline to 2 months in**

Azizi M et al. Lancet 2018 doi.org/10.1016/S0140-6736(18)31082-1.

Conclusion

- Resistant HT is common
- Manage with combination of regular patient interactions and medications
  - CCB i.e. amlodipine
  - ACEi or ARB
  - Diuretic switch to chlorthalidone
  - Add: **Spironolactone**, alpha blocker, or BB, or hydralazine
- Refractory HT is less common