

IN THE NAME OF GOD

# Resistant Hypertension

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# Resistant hypertension

## Definition

Elevated blood pressure *despite* taking three optimally dosed medications, typically

- a diuretic
- a calcium-channel blocker
- an ACE inhibitor or ARB

Maximum doses.....

Resistant



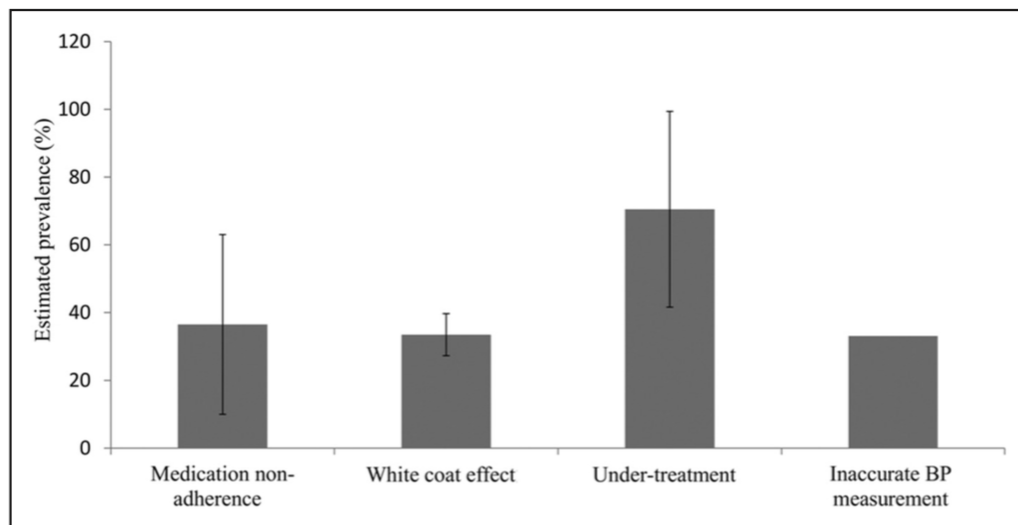
...include pts that has been named as  
**controlled RHTN**

RHTN is a high-risk phenotype, leading to increased  
all-cause mortality and cardiovascular disease  
outcomes



# Compendium on the Pathophysiology and Treatment of Hypertension

## Treatment of Resistant and Refractory Hypertension



pseudoresistance

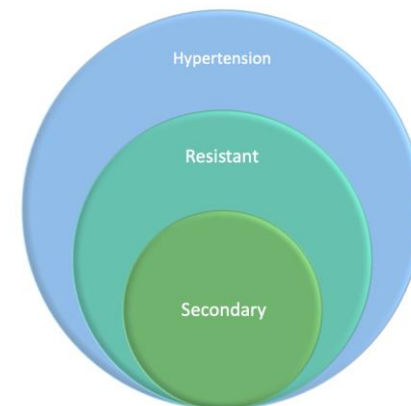
Estimated prevalence of common causes of pseudotreatment resistance

*Circulation Research March 29, 2019*

## Diagnosis of resistant hypertension

- In-office blood pressure  $\geq 140/\geq 90$  mmHg on optimized treatment with three or more drugs, including a diuretic

- Ambulatory blood pressure  $\geq 135/\geq 85$  mmHg during the daytime or  $\geq 130/\geq 80$  mmHg over 24 h.



- **Exclude secondary hypertension**
- primary aldosteronism
- obstructive sleep apnoea
- Cushing syndrome
- renal artery stenosis
- aortic coarctation,
- consumption of glycyrrhizin-rich foods
- illicit drugs that increase blood pressure

NATURE Reviews | **NePhRology** 2018

Don't trust office BP!

method of choice

*condicio  
sine qua  
non.*

## ABPM

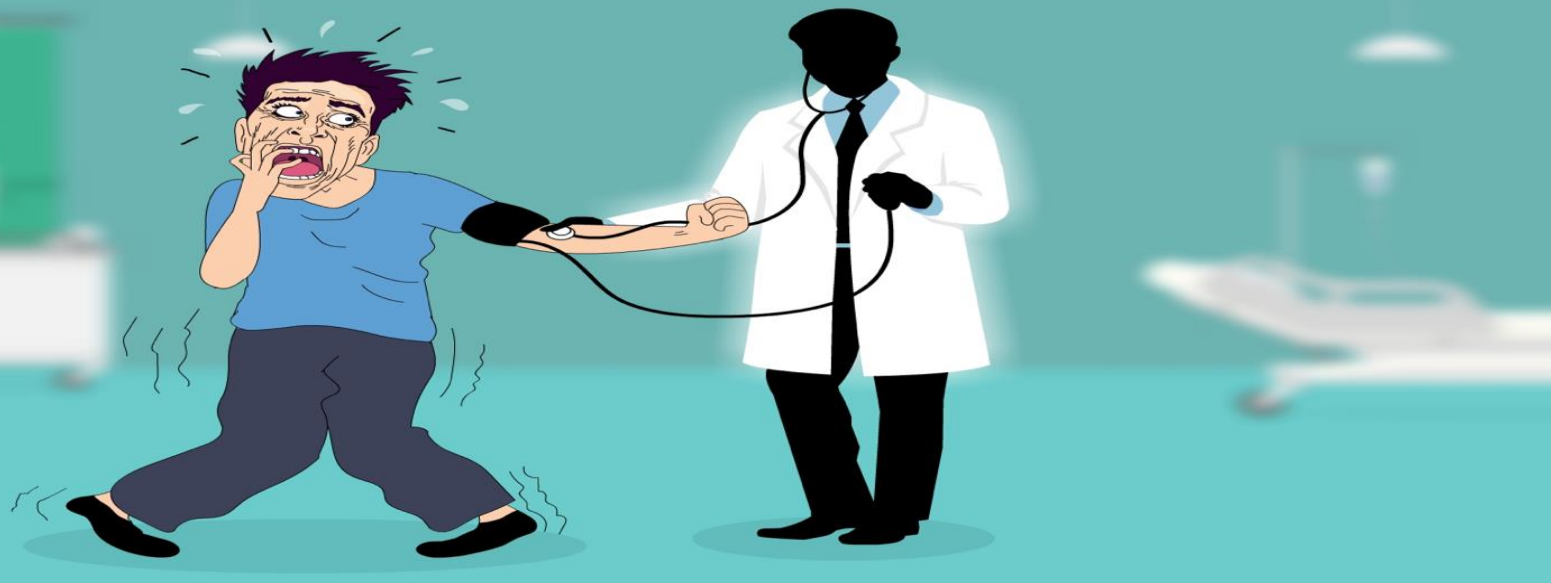
gold standard

cornerstone

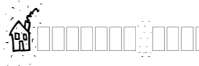
- ABPM is a very important tool not only for diagnosis but also for treatment and follow up.
- Office BP has a poor prognostic value than ABPM

- Ambulatory blood pressure monitoring is the gold standard for diagnosis of resistant hypertension; this method enables the identification of patients with isolated nocturnal hypertension, sustained hypertension or white-coat hypertension.



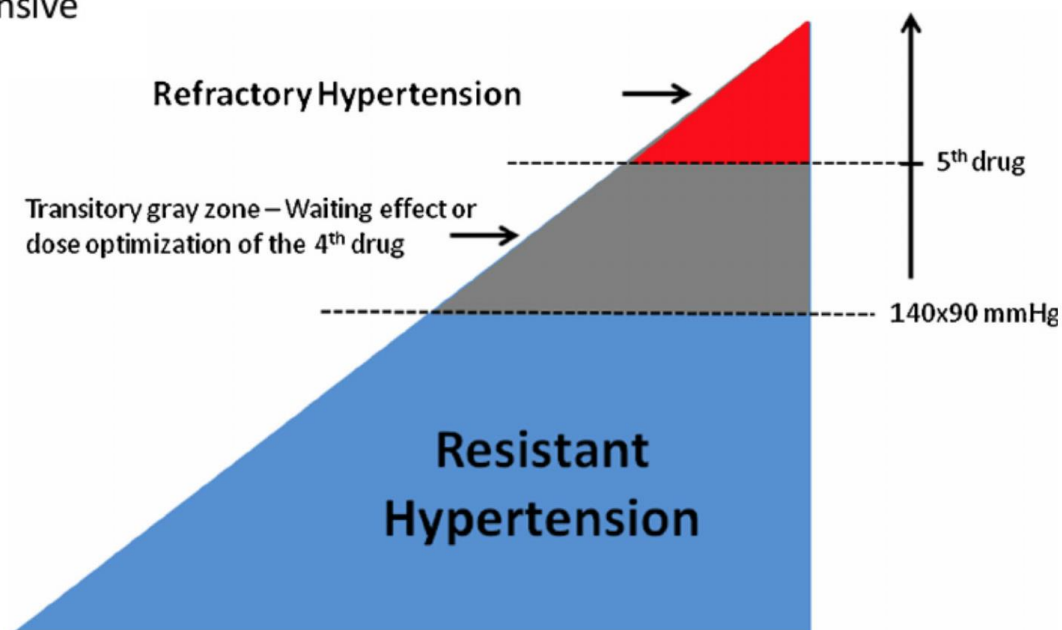


more than 37% of those with a diagnosis of RH  
had normal BPs on ambulatory monitoring



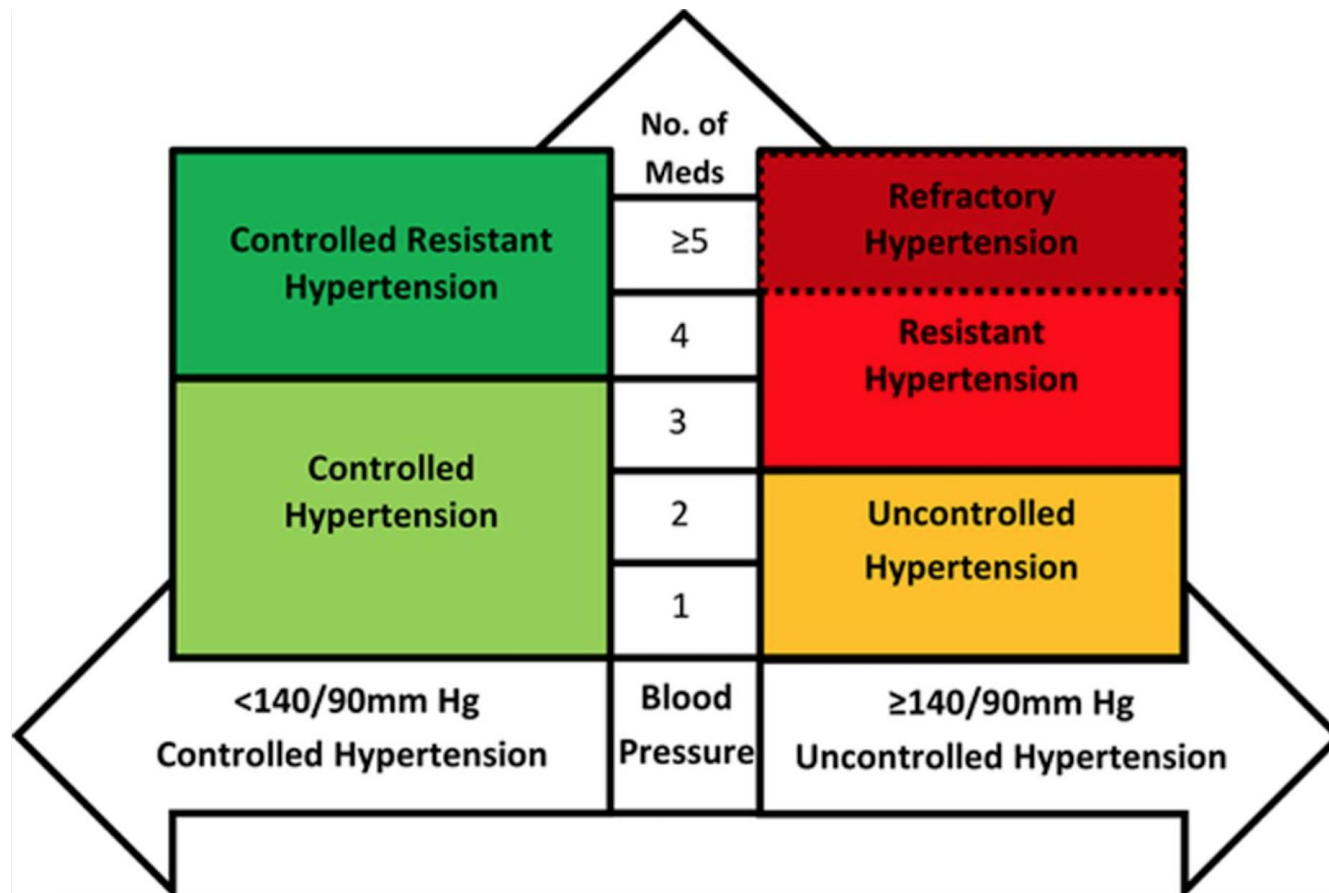
## “Refractory” hypertension

**Refractory hypertension** was defined as **failure to achieve blood pressure control** with treatment prescribed by **hypertension experts** at minimum of **3 follow-up visits** during **at least 6 months** of care, receiving a **5 or more** different antihypertensive medications.



Graphic demonstration of the current definition of refractory hypertension





## Resistant and Refractory Hypertension: Antihypertensive Treatment Resistance vs Treatment Failure

### prevalence

Multiple studies indicate that the prevalence of resistant hypertension is approximately 10%–15% of treated hypertensive patients

The prevalence of refractory hypertension was 3.6% of patients with resistant hypertension (uncontrolled blood pressure with 3 or more medications or controlled blood pressure with 4 or more) and 0.5% of all hypertensive participants included in the cohort.

# Resistant vs Refractory HTN

## Resistant HTN

- Fluid dependent
- Low renin
- BNP high

## Refractory HTN

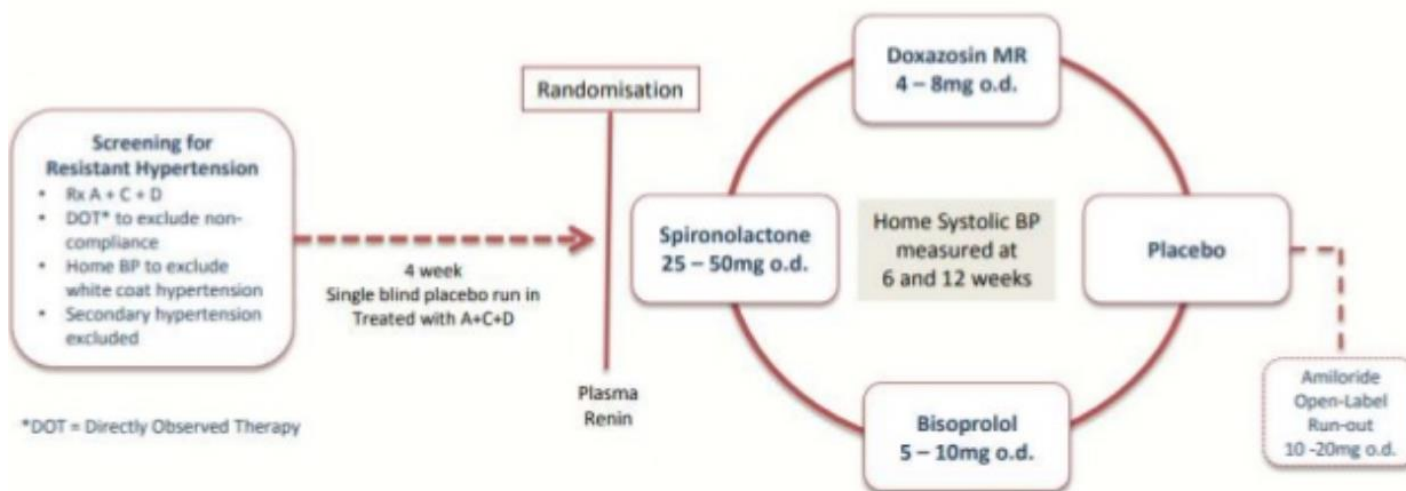
- Not fluid dependent
- High sympathetic tone
- BNP low

Experts speculate that a significant proportion of patients with resistant hypertension have inappropriate aldosterone excess due to aldosterone producing **microadenomas** that are **poorly detected by conventional imaging**, explaining the quadratic relationship between aldosterone and renin levels

*Dudenbostel et al. J Nat Sci 2017*

# PATHWAY 2

Double blind, Randomised, Placebo-Controlled, Cross-over Study



\*DOT = Directly Observed Therapy

**Home monitoring to exclude white coat HTN**  
**Directly observed therapy to ensure adherence**

- 12 weeks per treatment cycle
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles

**Patients with eGFR <45 mL/min were excluded**  
**Included predominantly white Caucasians**

*Williams et al, PATHWAY 2, Lancet 2015*

# PATHWAY-2 uncovers main cause of drug-resistant hypertension, finds old drugs work best

28 Aug 2017

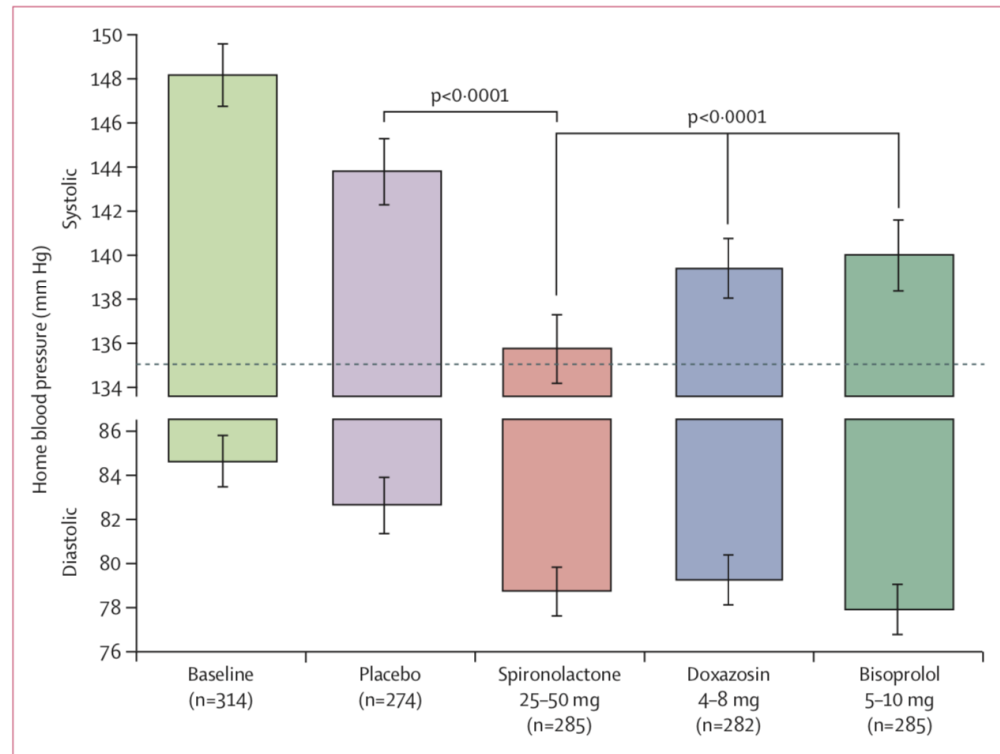
- PATHWAY-2 is the **first study** to use **home blood pressure averages** rather than **clinic blood pressure** to assess the primary outcome of blood pressure response in patients with resistant hypertension.

# Spirolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank,

2015

Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles



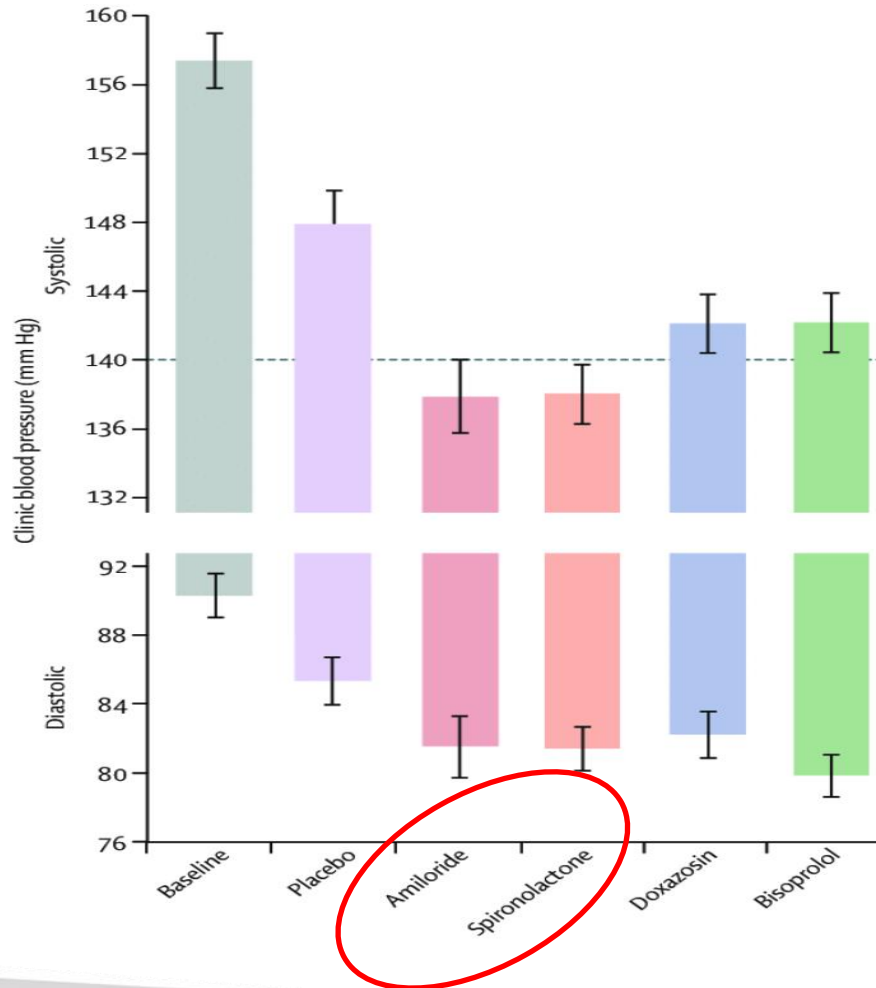


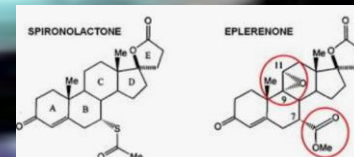
# CAVEATS

**Pathway 2 study excluded  
patients with an eGFR less  
than 45 mL/min**

*Lancet.2015 Nov*

## Effects of amiloride versus spironolactone on clinic systolic BP in resistant hypertension





With prolonged use at higher doses, gynecomastia and erectile dysfunction in men and menstrual irregularities in women may limit the use of spironolactone.  
In such cases, eplerenone may be used successfully.

Because of its shorter half-life compared with spironolactone, eplerenone should be administered twice daily for optimal effect.

The risk of resistant hypertension is increased in patients with high sympathetic drive owing to obesity, diabetes mellitus, renal dysfunction or obstructive sleep apnoea

In obesity, the excessive synthesis of aldosterone contributes to the development and progression of metabolic and cardiovascular dysfunctions

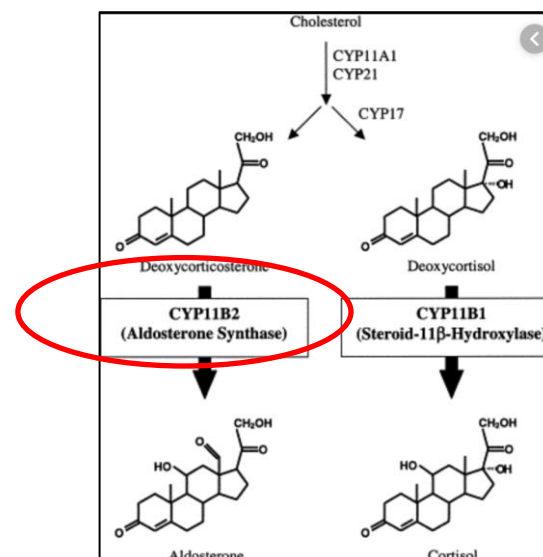
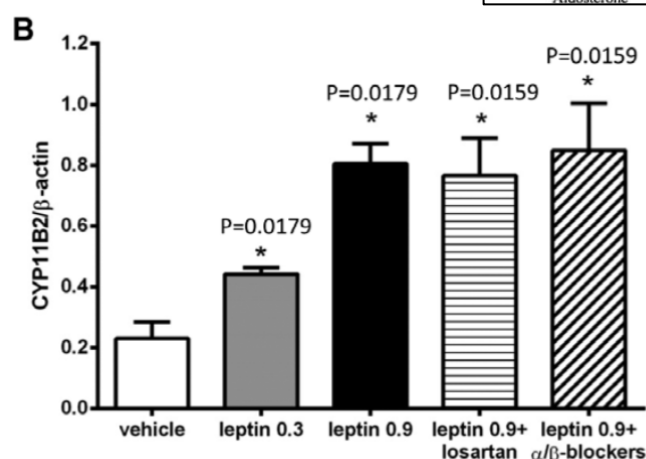
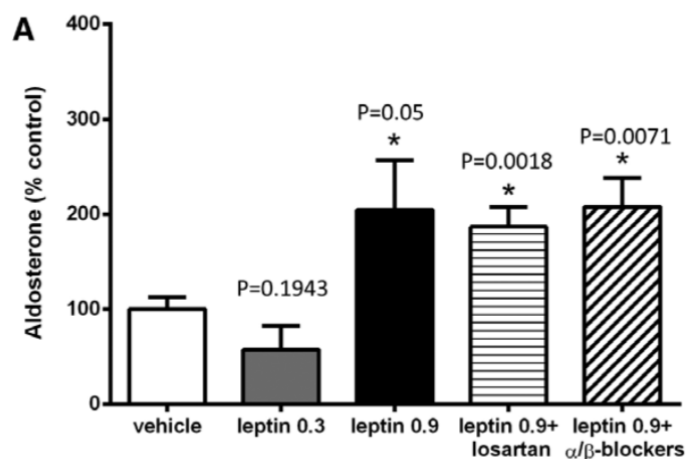


# Circulation

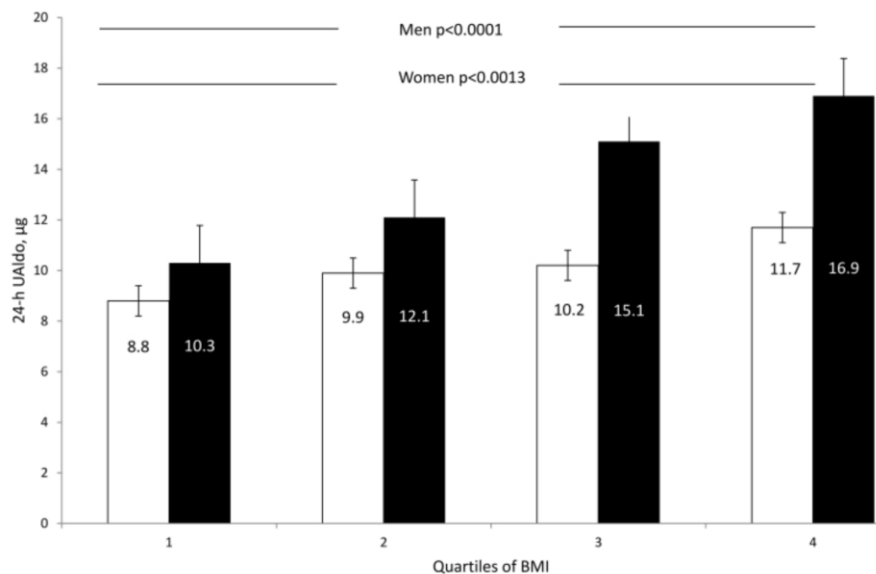
AHA Journals Journal Information All Issues Subjects

## Adipocyte-Derived Hormone Leptin Is a Direct Regulator of Aldosterone Secretion, Which Promotes Endothelial Dysfunction and Cardiac Fibrosis

2015;132:2134–2145



## Body Mass Index predicts 24-hr Urinary Aldosterone Levels in Patients with Resistant Hypertension



Mean 24-hr urinary aldosterone (UAldo) levels to quartiles of body mass index (BMI) in men versus women. White columns represent women and black columns represent men. Figure shows Bonferroni corrected p values.

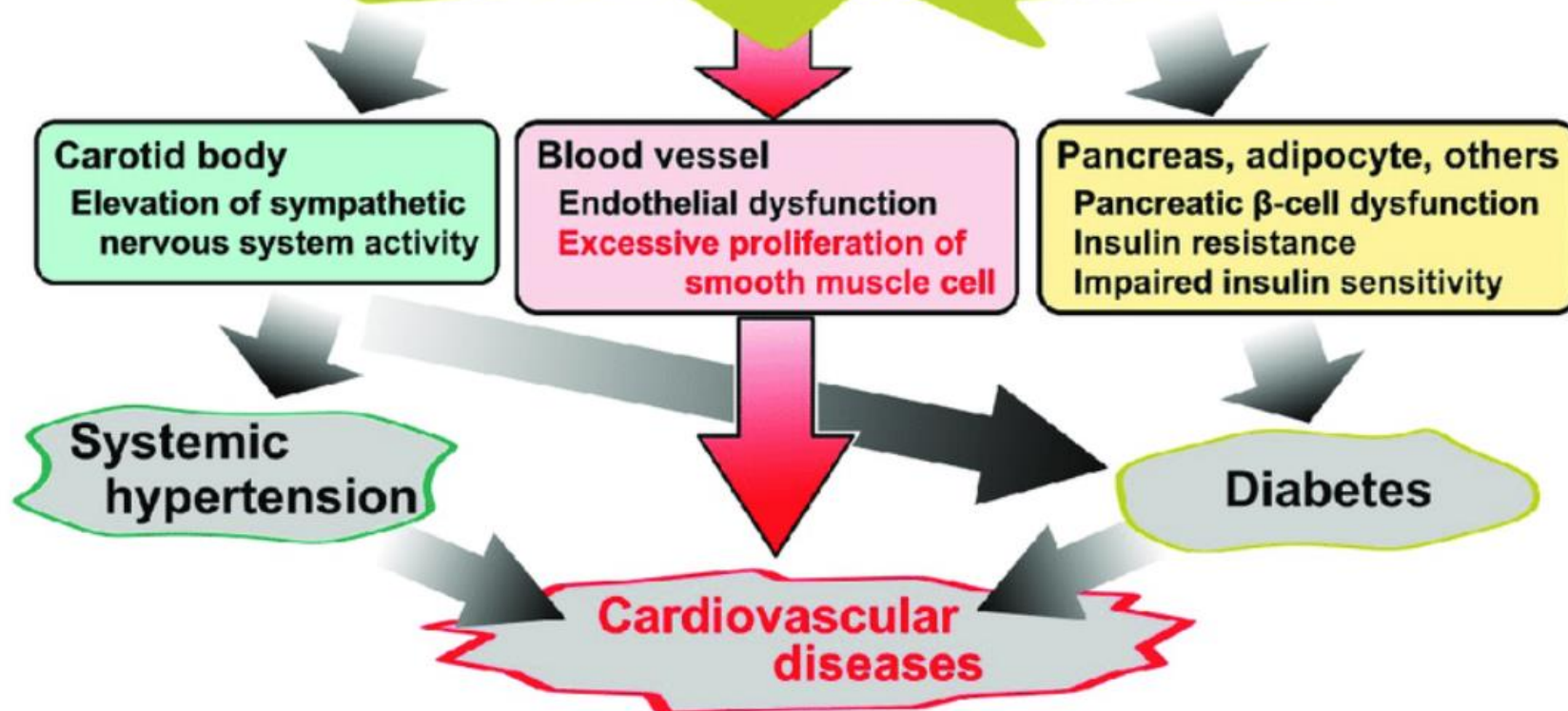
### Summary

In a large cohort of AA and Caucasian patients with RHTN, there was a consistent and significant correlation between 24-hr UAldo levels and BMI in obese compared to non-obese individuals. The correlation of aldosterone and BMI was stronger in men than women, independent of race and renin, suggesting that factors other than the renin-angiotensin system and more related to visceral obesity, typical of men, might be causative. Confirmation of identification of these hypothesized factors that stimulate aldosterone release in obese patients will provide important insight into the growing problem of obesity-related hypertension, and especially, resistant hypertension.



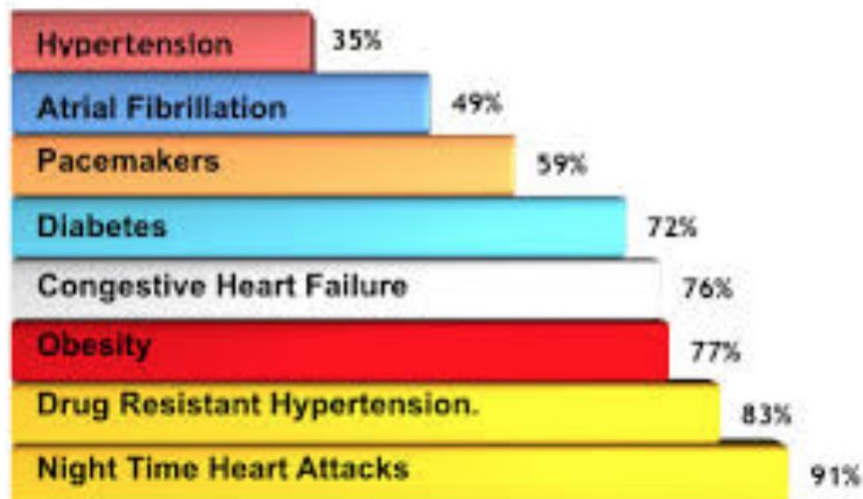
OSA

# Intermittent Hypoxia (patients with obstructive sleep apnea)



# OSA is highly prevalent in patients with resistant hypertension

Diseases Associated with OSA



## • MECHANISM

- INCREASED SYMPATHETIC ACTIVITY
- INCREASED ALDOSTERONE LEVELS
- INCREASE IN REACTIVE OXYGEN SPECIES WITH CONCOMITANT REDUCTIONS IN NITRIC OXIDE

The other mechanisms might be partly attributed to intermittent hypoxemia-induced renin-angiotensin-aldosterone system activation

# SCIENTIFIC REPORTS

**OPEN** Association of aldosterone excess and apnea-hypopnea index in patients with resistant hypertension

Received: 21 December 2016

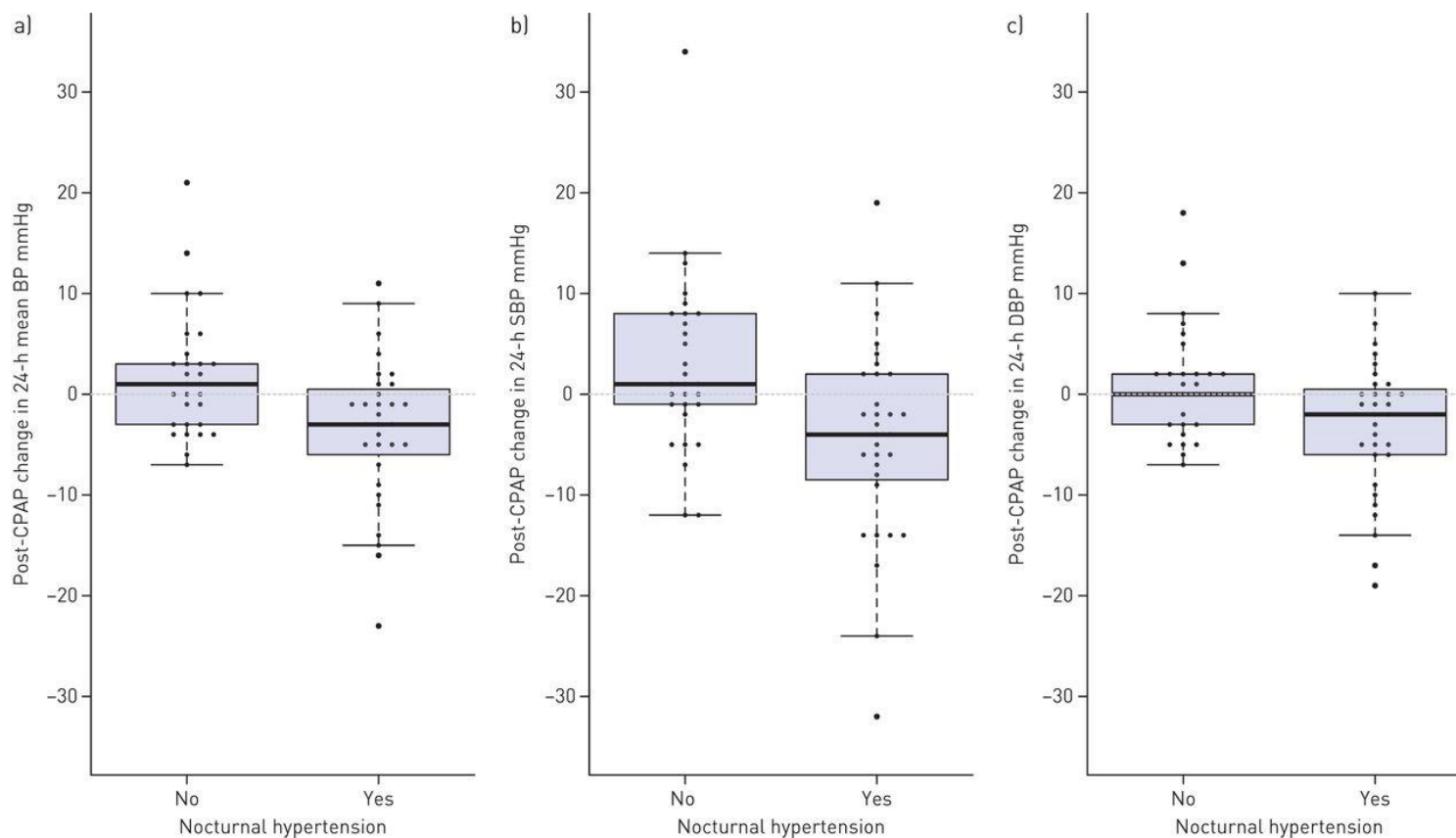
Accepted: 20 February 2017

OSA is highly prevalent in patients with resistant hypertension and both **Plasma Aldosterone Concentration** and **24 h-urine aldosterone level** are significantly associated with AHI(**apnea hypopnea index** )

AHI is calculated by the total number of apnea and hypopnea events per sleep hour, with AHI of 5–14 were defined as mild, 15–29 moderate, and 30 or more severe OSA, respectively



## Change in blood pressure after continuous positive airway pressure (CPAP) treatment in patients with and without nocturnal hypertension.



*Anabel L. Castro-Grattoni et al. Eur Respir J 2017*



## Management of hypertension in obstructive sleep apnoea: predicting blood pressure reduction under continuous positive airway pressure

Renaud Tamisier, Patrick Lévy

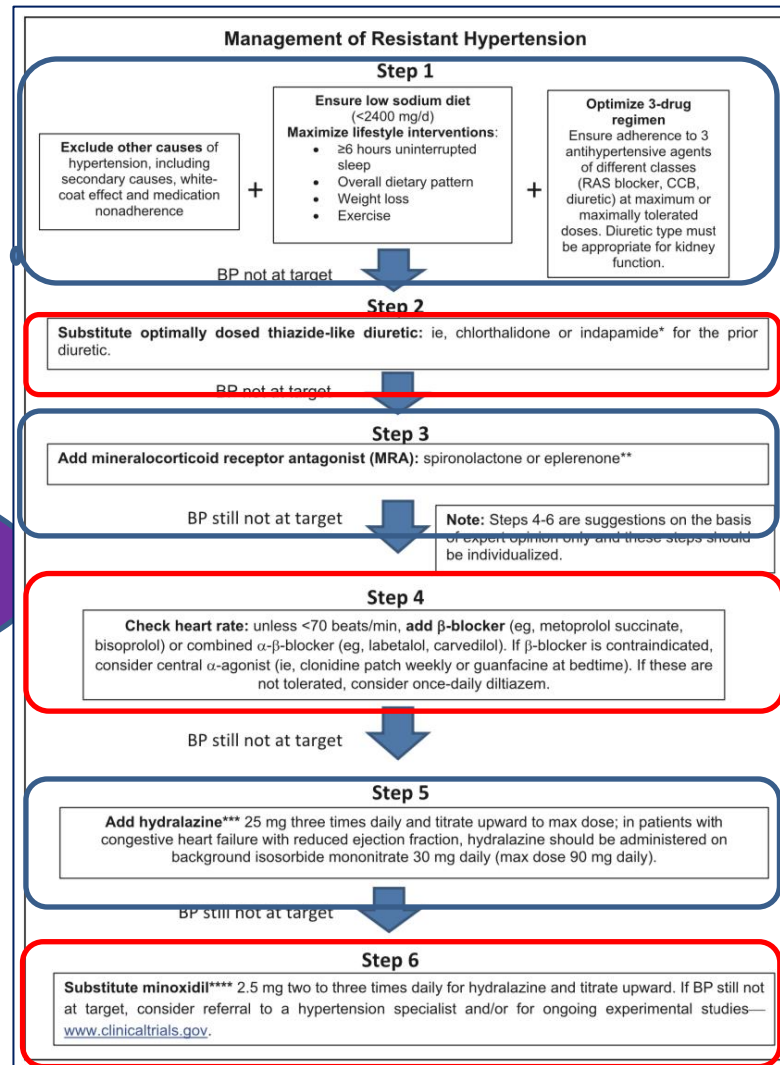
it has been evidenced that a reduction in BP as well as a reduced incidence of hypertension cannot be obtained until **a minimum of 4 to 6 h of CPAP** is realised .

BP response to CPAP also appears to be dependent on **sleep apnoea severity** and is very limited in patients who are minimally symptomatic



# Management of RH

Hypertension November 2018



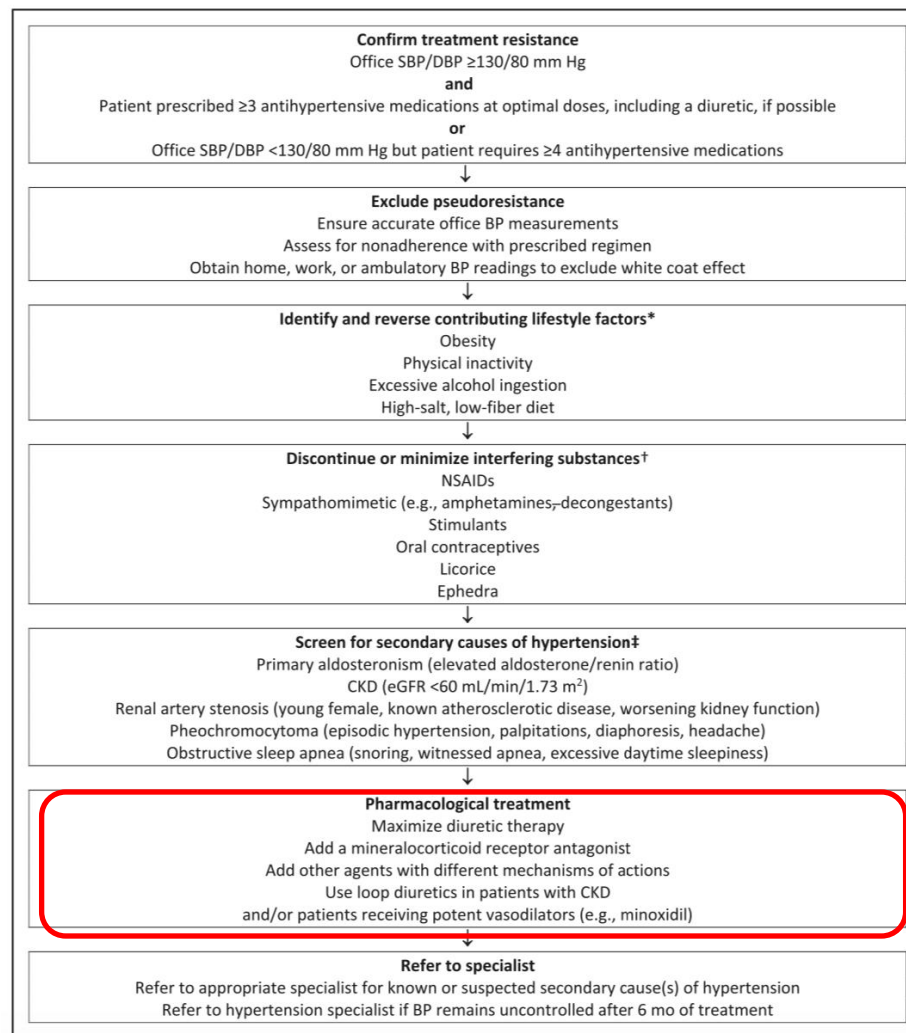


## Circulation

### CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

*Circulation. 2018;*



# AHA Scientific Statement

## Resistant Hypertension: Detection, Evaluation, and Management A Scientific Statement From the American Heart Association

*Hypertension*      November 2018

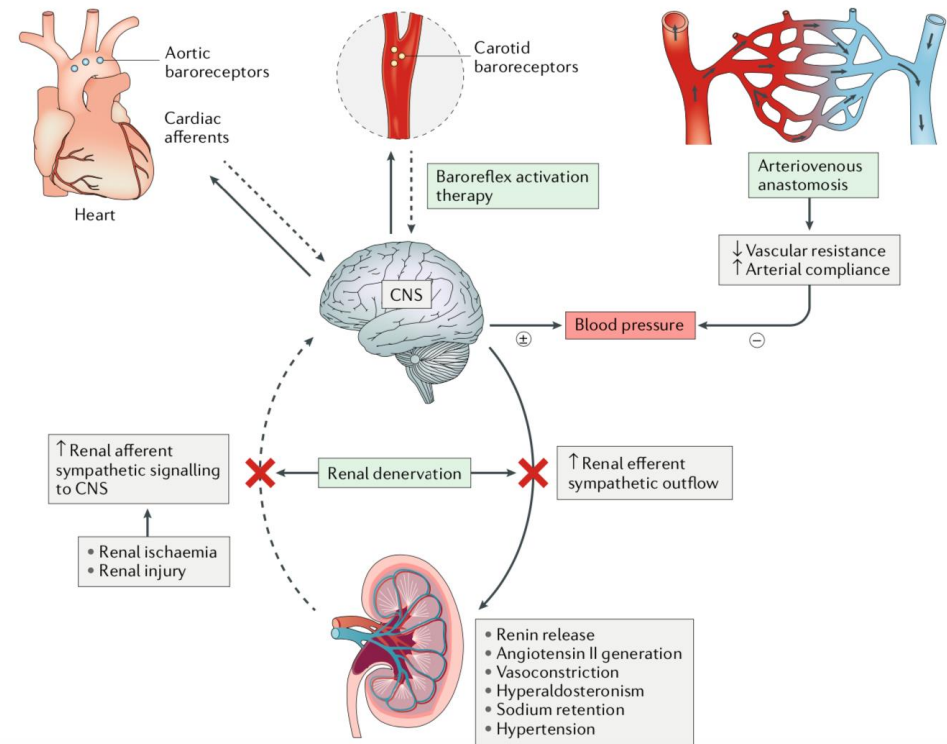
The choice of ARB may also be important. Studies comparing various ARBs demonstrate clear advantages of certain agents in BP reduction over others.

Specifically, 24-hour ABPM studies demonstrate that

**azilsartan medoximil** provides on average an additional 4 to 8 mm Hg further SBP reduction over other ARBs (eg, valsartan and olmesartan) or the ACE inhibitor ramipril

# Modulation of Sympathetic Overactivity to Treat Resistant Hypertension

- Renal denervation
- Baroreflex activation therapy
- *Arteriovenous anastomosis*
- Carotid body ablation.



# Renal denervation studies

Simplicity HTN – 1

SYMPPLICITY HTN-2:



INSPIRED pilot trial

OsloRDN trial

RADIANCE-HTN randomized trial

SPYRAL HTN-ON MED

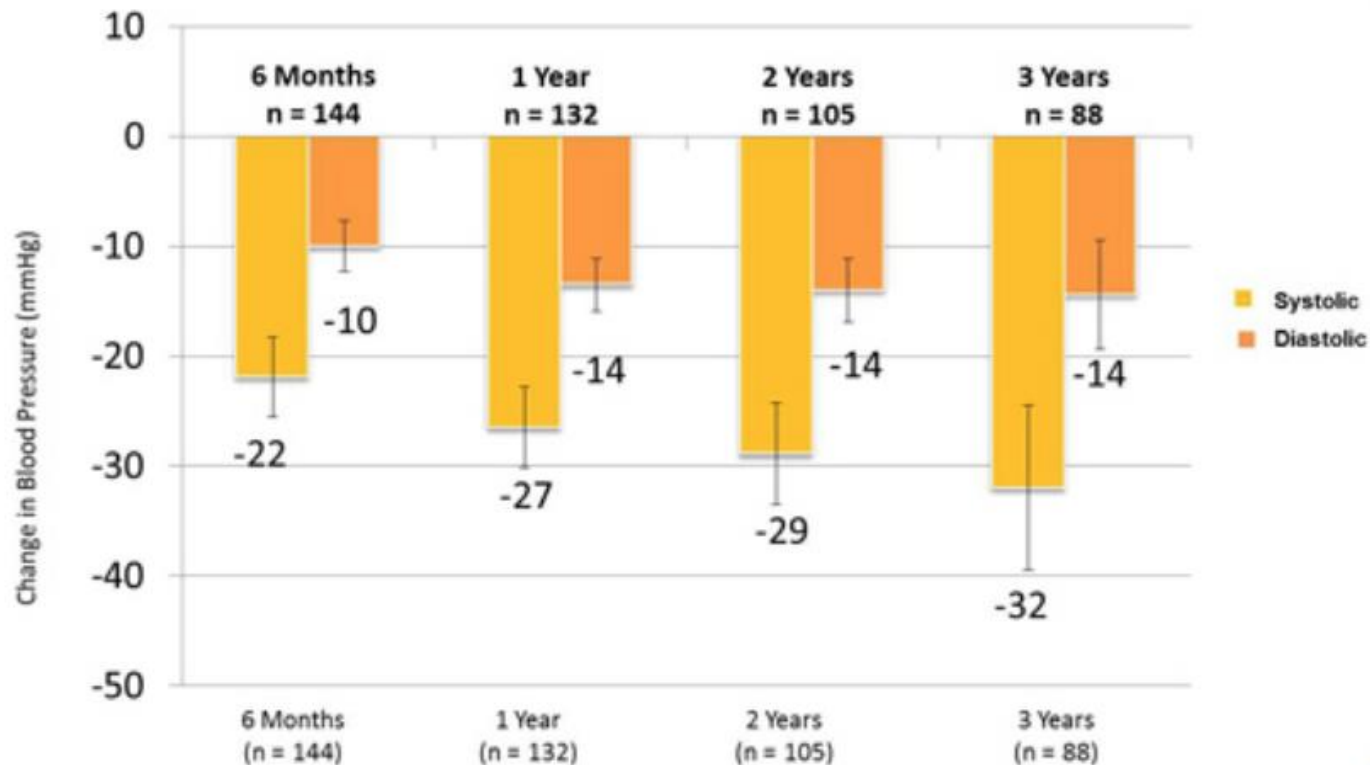
SYMPPLICITY HTN-1

DENERHTN study

SPYRAL HTN-OFF MED

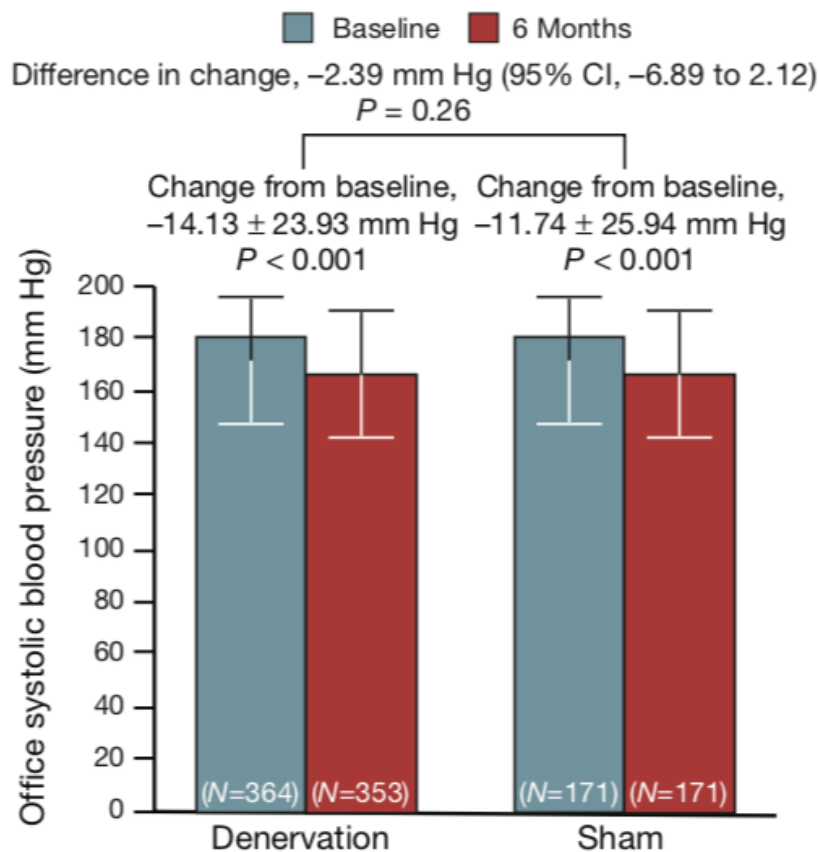
# First-in-human study

## nonrandomized **SYMPPLICITY HTN-1**



# SYMPPLICITY HTN-3 trial

The end result was a minimal non-significant difference between study patients and controls.



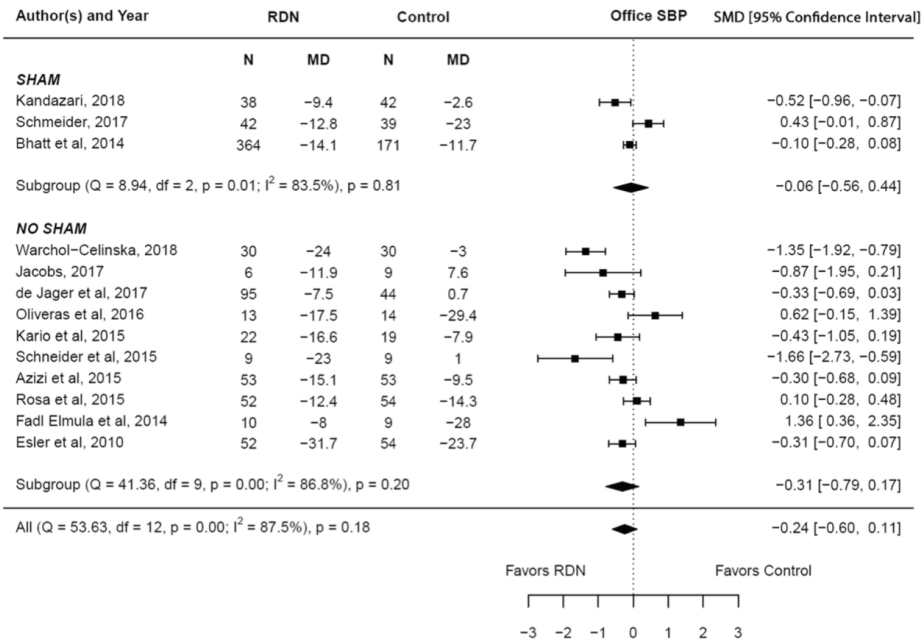


# Renal Denervation for Resistant Hypertension in the contemporary era: A Systematic Review and Meta-analysis

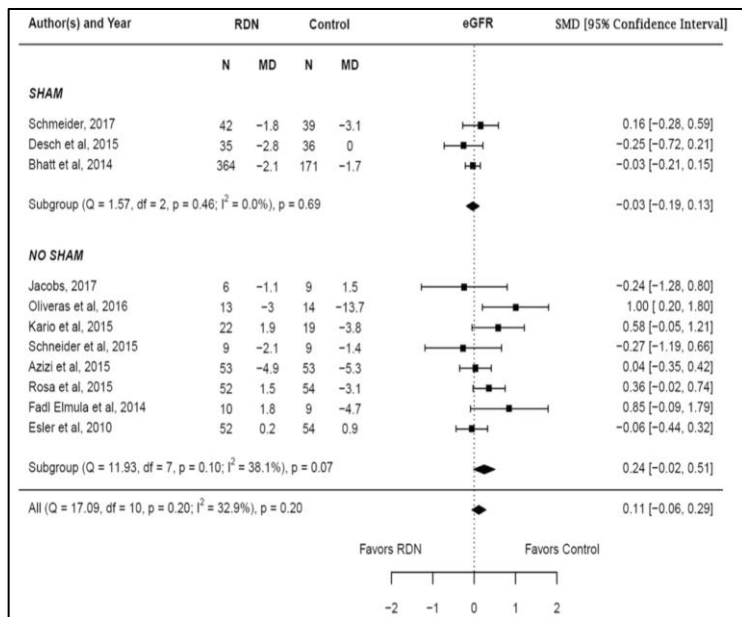
Pradyumna Agasthi<sup>1</sup>, Justin Shipman<sup>1</sup>, Reza Arsanjani<sup>1</sup>, Moses Ashukem<sup>2</sup>,

[www.nature.com/scientificreports](http://www.nature.com/scientificreports)

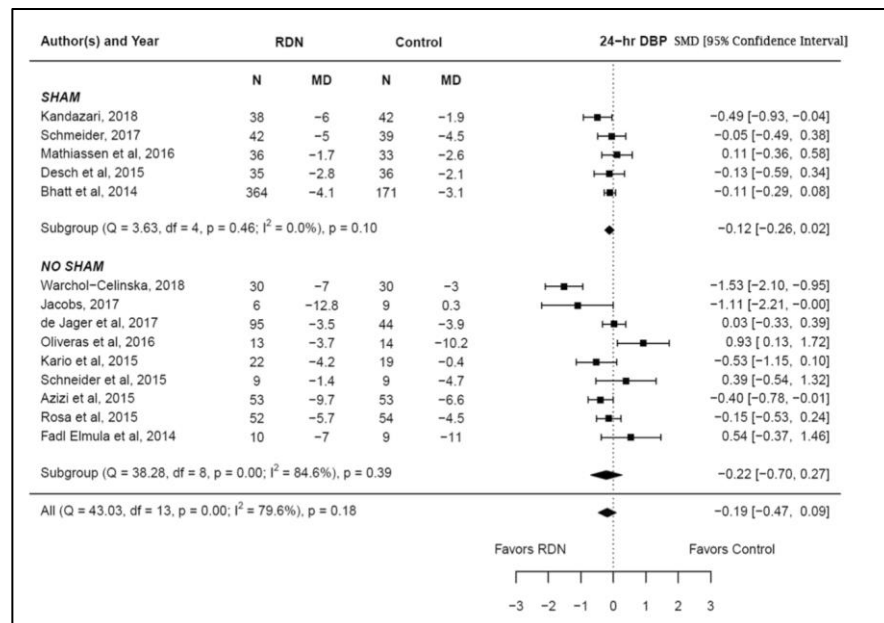
2019



Adjusted standardized mean difference in office systolic blood pressure after renal denervation.



Adjusted standardized mean difference in estimated glomerular filtration rate after renal denervation.



Adjusted standardized mean difference in 24 diastolic blood pressure after renal denervation.

[www.nature.com/scientificreports](http://www.nature.com/scientificreports)

# *Renal denervation studies:*

## conclusion



For now, device treatment should remain the last resort in adherent and truly resistant patients with severe hypertension in whom all other efforts to reduce blood pressure have failed and should be offered to patients only within the context of clinical research in highly skilled tertiary referral centres.

## Pharmacological strategies...

- Change in dosing times (eg, to include a nocturnal dose)
- Using divided doses of drugs with half-lives of <12 to 15 hours may also improve BP control even when the drug theoretically has a pharmacodynamic effect of up to 24 hours in duration

*D. Cimmaruta et al February 2018*

Although rates of nonadherence appear to be lower in RH than in the general population with HTN, steps should be taken to maximize patient adherence through simplification of treatment regimens, education, and behavioral strategies

simplification of treatment regimens and administration of polypills is one of the best way to maximize patient adherence



***Thank you***