IN THE NAME OF GOD

Resistant Hypertension

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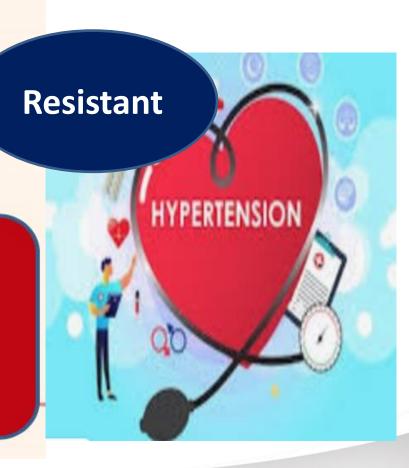
Resistant hypertension

Definition

Elevated blood pressure despite taking three optimally dosed medications, typically

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

Maximum doses.....



















...include pts that has been named as controlled RTHTN

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









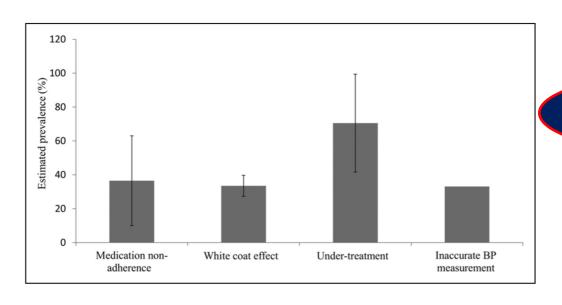






Compendium on the Pathophysiology and Treatment of Hypertension

Treatment of Resistant and Refractory Hypertension



pseudoresistance

Estimated prevalence of common causes of pseudotreatment resistance

Circulation Research March 29, 2019







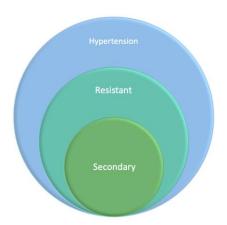








Diagnosis of resistant hypertension



- •In-office blood pressure ≥140/≥90 mmHg on optimized treatment with three or more drugs, including a diuretic
- •Ambulatory blood pressure ≥135/≥85 mmHg during the daytime or ≥130/≥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



- 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









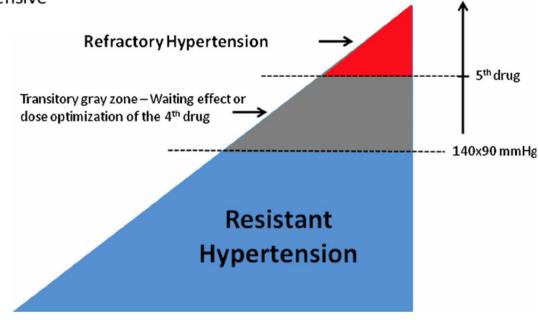






"Refractory" hypertension

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



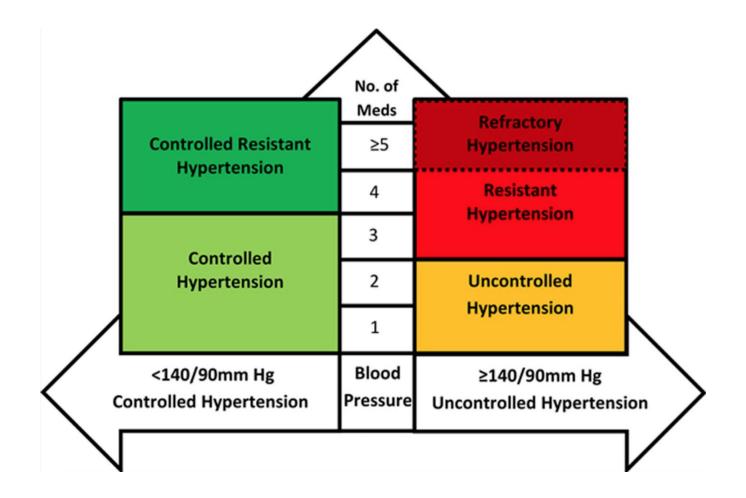






















Resistant and Refractory Hypertension: Antihypertensive Treatment Resistance vs Treatment Failure

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







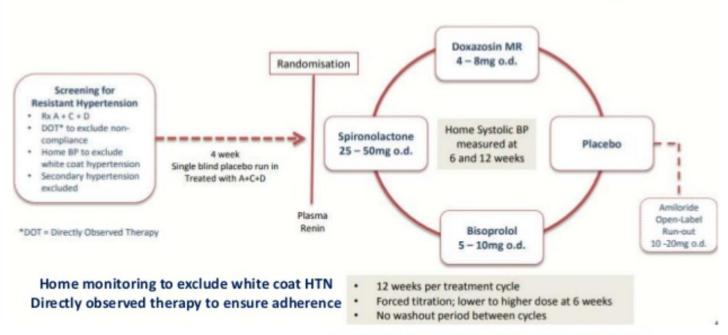






PATHWAY 2

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



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.









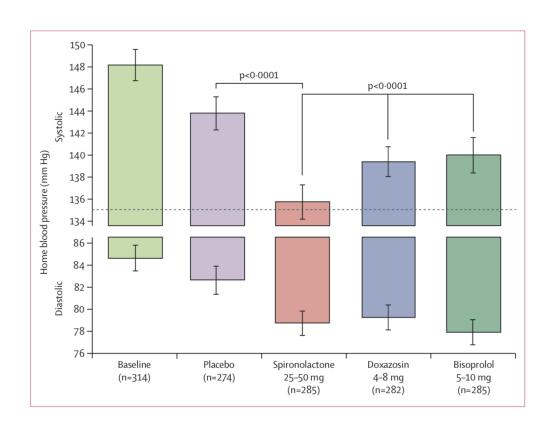


Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

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



















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

Lancet.2015 Nov







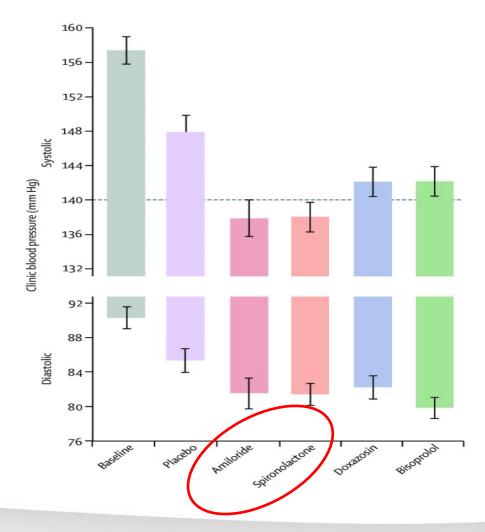








Effects of amiloride versus spironolactone on clinic systolic BP in resistant hypertension









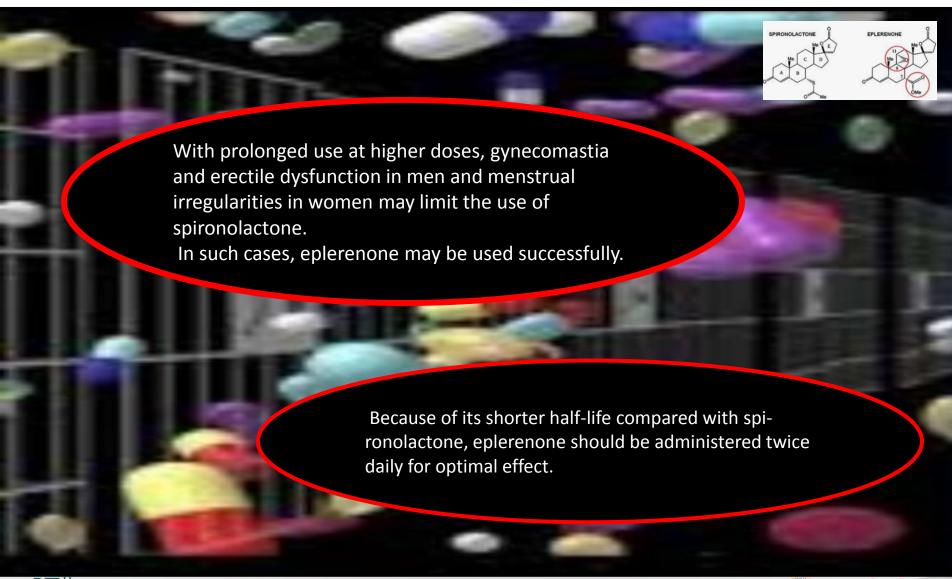
























The risk of resistant hypertension is increased in patients with high sympathetic drive owing to obesity, diabetes mellitus, renal dysfunction or obstructive sleep apnoea

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

















Circulation

AHA Journals

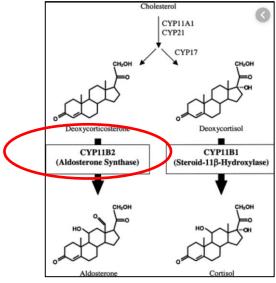
Journal Information

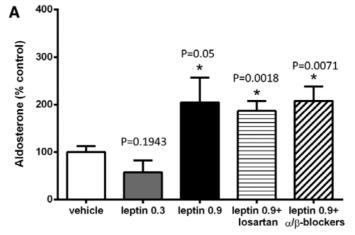
All Issues

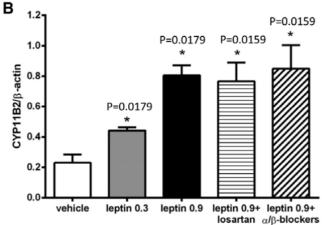
Subjects

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

2015;132:2134-2145













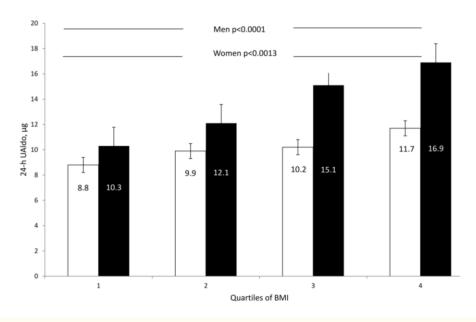








Body Mass Index predicts 24-hr Urinary Aldosterone Levels in **Patients with Resistant Hypertension**



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.

















Intermittent Hypoxia

(patients with obstructive sleep apnea)

Carotid body Elevation of sympathetic nervous system activity **Blood vessel**

Endothelial dysfunction Excessive proliferation of smooth muscle cell Pancreas, adipocyte, others Pancreatic β-cell dysfunction Insulin resistance

Impaired insulin sensitivity

Systemic hypertension

> Cardiovascular diseases

Diabetes







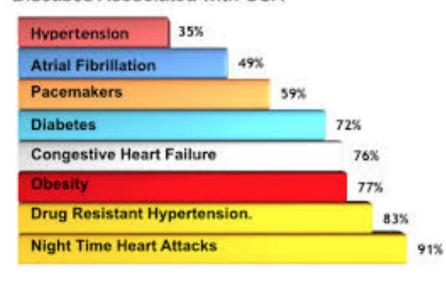






OSA is highly prevalent in patients with resistant hypertension

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















Accepted: 20 February 2017

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

> OSA is highly prevalent in patients with resistant hypertension and both Plasma Aldosteron Consentration 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







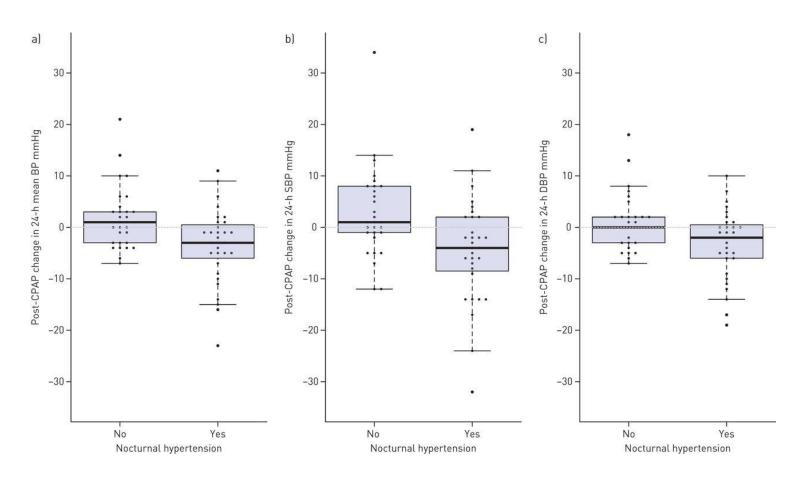








Change in blood pressure after continuous positive airway pressure (CPAP) treatment in patients with and without nocturnal hypertension.



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













EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

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













Maximize lifestyle interventions: Ensure adherence to 3 Exclude other causes of ≥6 hours uninterrupted antihypertensive agents hypertension, including sleep of different classes secondary causes, white-Overall dietary pattern (RAS blocker, CCB, coat effect and medication Weight loss diuretic) at maximum or nonadherence Exercise maximally tolerated doses. Diuretic type must be appropriate for kidney function. BP not at target Step 2 Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior Step 3 Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone** Management of BP still not at target Note: Steps 4-6 are suggestions on the basis be individualized. Step 4 Check heart rate: unless <70 beats/min, add β-blocker (eg, metoprolol succinate, bisoprolol) or combined α - β -blocker (eg, labetalol, carvedilol). If β -blocker is contraindicated, consider central α -agonist (ie, clonidine patch weekly or quanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem. November 2018 BP still not at target Step 5 Add hydralazine*** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily). BP Still not at target Step 6

www.clinicaltrials.gov

Management of Resistant Hypertension Step 1 Ensure low sodium diet

(<2400 mg/d)

Optimize 3-drug

regimen





Substitute minoxidil**** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies-











Hypertension

RH

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

Confirm treatment resistance

Office SBP/DBP ≥130/80 mm Hg

and

Patient prescribed ≥3 antihypertensive medications at optimal doses, including a diuretic, if possible

or

Office SBP/DBP <130/80 mm Hg but patient requires ≥4 antihypertensive medications

4

Exclude pseudoresistance

Ensure accurate office BP measurements

Assess for nonadherence with prescribed regimen

Obtain home, work, or ambulatory BP readings to exclude white coat effect

1

Identify and reverse contributing lifestyle factors*

Obesity Physical inactivity

Excessive alcohol ingestion

High-salt, low-fiber diet

 \downarrow

Discontinue or minimize interfering substances†

NSAIDs

Sympathomimetic (e.g., amphetamines, decongestants)

Stimulants

Oral contraceptives

Licorice

Ephedra

1

Screen for secondary causes of hypertension‡

Primary aldosteronism (elevated aldosterone/renin ratio)

CKD (eGFR <60 mL/min/1.73 m²)

Renal artery stenosis (young female, known atherosclerotic disease, worsening kidney function)

Pheochromocytoma (episodic hypertension, palpitations, diaphoresis, headache) Obstructive sleep apnea (snoring, witnessed apnea, excessive daytime sleepiness)

 \downarrow

Pharmacological treatment

Maximize diuretic therapy

Add a mineralocorticoid receptor antagonist

Add other agents with different mechanisms of actions

Use loop diuretics in patients with CKD

and/or patients receiving potent vasodilators (e.g., minoxidil)

+

Refer to specialist

Refer to appropriate specialist for known or suspected secondary cause(s) of hypertension Refer to hypertension specialist if BP remains uncontrolled after 6 mo of treatment















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 coparing 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





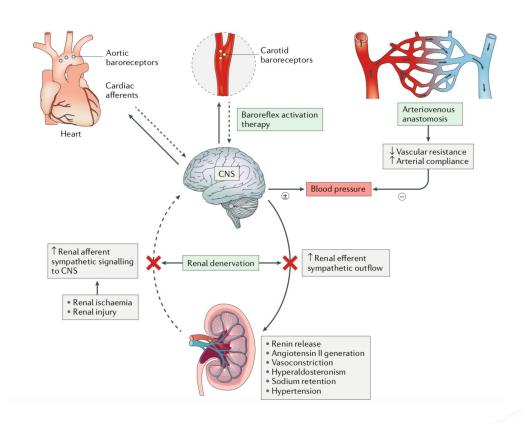






Modulation of Sympathetic Overactivity to Treat Resistant Hypertension

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





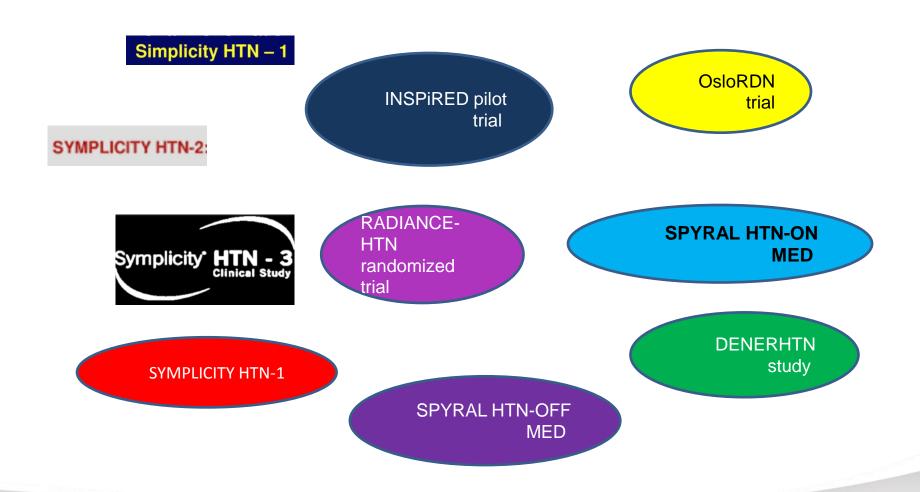








Renal denervation studies







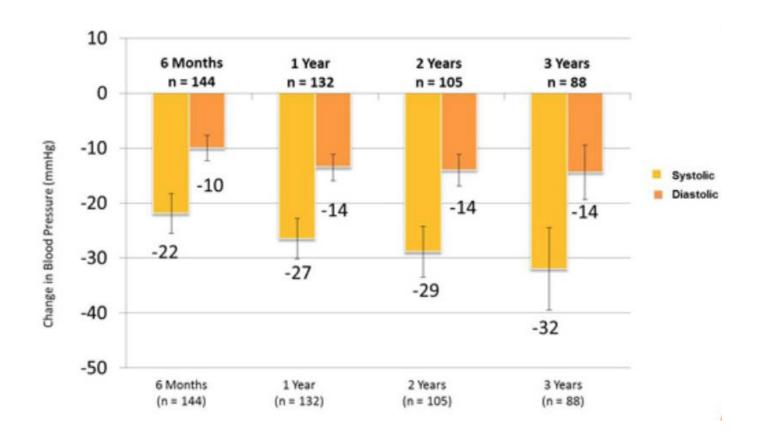








First-in-human study nonrandomized **SYMPLICITY HTN-1**









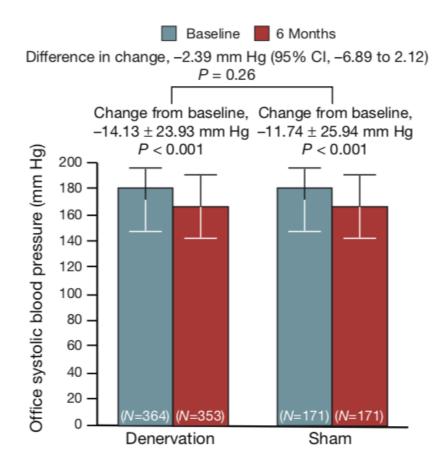


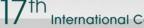




SYMPLICITY HTN-3 trial

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















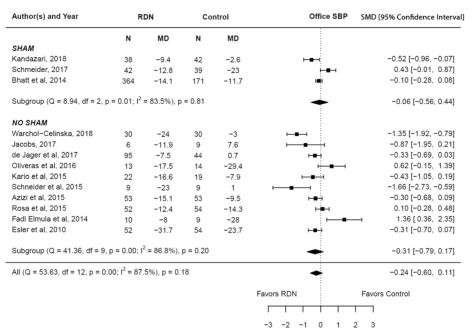


Renal Denervation for Resistant Hypertension in the contemporary era: A Systematic Review and Meta-analysis

Pradyumna Agasthi 61, Justin Shipman1, Reza Arsanjani 61, Moses Ashukem2,

www.nature.com/scientificreports

2019



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







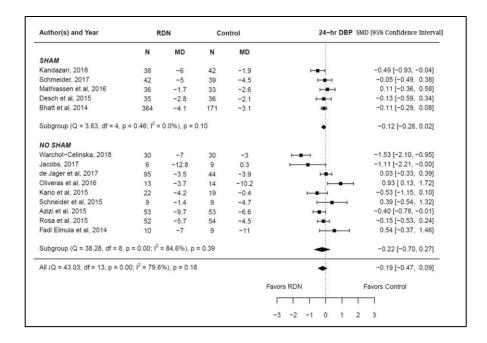








Author(s) and Year	RDN		Control		eGFR		SMD [95% Confidence Interval]
	N	MD	N	MD			
SHAM							
Schmeider, 2017	42	-1.8	39	-3.1	-	•	0.16 [-0.28, 0.59]
Desch et al, 2015	35	-2.8	36	0	⊢-	÷	-0.25 [-0.72, 0.21]
Bhatt et al, 2014	364	-2.1	171	-1.7	+	÷	-0.03 [-0.21, 0.15]
Subgroup (Q = 1.57, df = 2, p = 0.46; I^2 = 0.0%), p = 0.69						•	-0.03 [-0.19, 0.13]
NO SHAM							
Jacobs, 2017	6	-1.1	9	1.5	·		-0.24 [-1.28, 0.80]
Oliveras et al, 2016	13	-3	14	-13.7		-	1.00 [0.20, 1.80]
Kario et al, 2015	22	1.9	19	-3.8		-	0.58 [-0.05, 1.21]
Schneider et al, 2015	9	-2.1	9	-1.4			-0.27 [-1.19, 0.66]
Azizi et al, 2015	53	-4.9	53	-5.3	-	•	0.04 [-0.35, 0.42]
Rosa et al, 2015	52	1.5	54	-3.1		-	0.36 [-0.02, 0.74]
Fadl Elmula et al, 2014	10	1.8	9	-4.7		-	0.85 [-0.09, 1.79]
Esler et al, 2010	52	0.2	54	0.9	-	•	-0.06 [-0.44, 0.32]
Subgroup (Q = 11.93, df = 7, p = 0.10; 1 ² = 38.1%), p = 0.07							0.24 [-0.02, 0.51]
All (Q = 17.09, df = 10, p = 0.2	20; I ² = 32.99	%), p = 0	20			•	0.11 [-0.06, 0.29]
				Favors	RDN	Fe	avors Control
				Г	- 1	i i	
				-2	-1	0 1	2



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













Renal denervation studies:



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 adminstration of polypills is one of the best way to maximize patient adherence



























