

Resistant Hypertension

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Disclosure

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Objectives

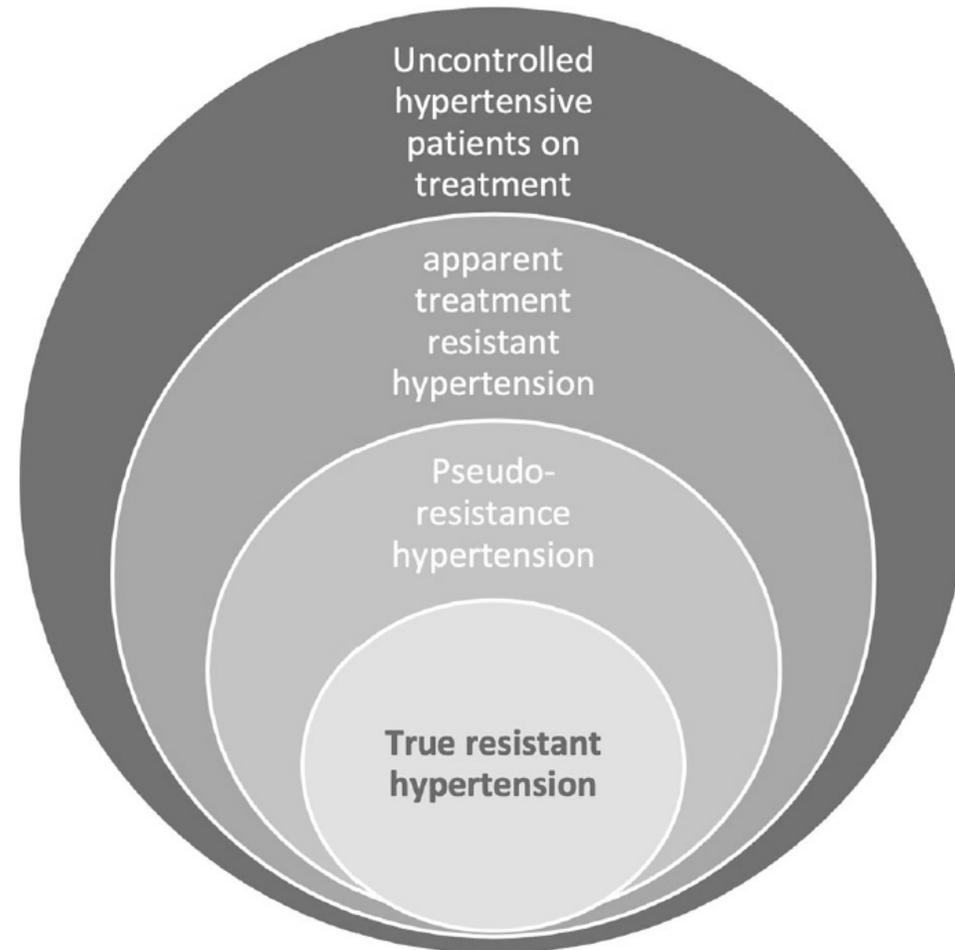
- Understand different terms used to describe resistant hypertension
- Identify true resistant hypertension
- Common causes of apparent resistant hypertension
- A brief overview of secondary causes of hypertension
- Management of resistant hypertension

What is resistant hypertension (RH) ?

Resistant hypertension is above-goal elevated blood pressure in a patient despite the concurrent use of 3 antihypertensive drug classes

- One of the three agents should be a [diuretic](#).
- Other agents commonly are a [long-acting calcium channel blocker](#) and [blocker of the renin-angiotensin system](#)
- All agents should be prescribed at [maximum recommended](#) (or maximally tolerated) antihypertensive doses
- RH also includes patients whose BP achieves target values on ≥ 4 antihypertensive medications.

True resistant hypertension and pseudo resistant hypertension



Pseudo resistant hypertension

Apparent resistant hypertension caused by other factors

- Inaccurate office BP measurement technique
- White coat hypertension
- Nonadherence to antihypertensive therapy
- Lifestyle and dietary factors

True resistant hypertension

Uncontrolled clinic blood pressure despite being adherent to an antihypertensive regimen that includes three or more drugs (including a diuretic, and each at optimal doses)

and

- Correct BP technique
- Confirm out of office elevated BP readings
- Appropriate antihypertensive therapy
- Optimal lifestyle and dietary status

How common is resistant hypertension ?

Population Based	Time Period	n	Uncontrolled With ≥ 3 BP Medications, %	Controlled With ≥ 4 BP Medications, %	aTRH, %
NHANES ¹³	1988–1994	2755	8.3	1.1	9.4
NHANES ¹³	1999–2004	3031	8.8	2.9	11.7
NHANES ¹⁴	2003–2008	3710	12.8
NHANES ¹³	2005–2008	2586	9.7	4.8	14.5
REGARDS ¹⁵	2003–2007	14 731	9.1	5.0	14.1
REGARDS ¹⁶ (CKD)*	2003–2007	3134	28.1
Clinic based					
EURIKA ¹⁷ (diabetes mellitus)	2009–2010	5220	13.0†	3.1	16.1
Spanish ABPM ¹⁸	2004–2009	68 045	12.2	2.6	14.8
CRIC (CKD) ^{19‡}	2003–2008	3939	21.2	19.2	40.4
South Carolina ^{20§}	2007–2010	468 877	9.5	8.4	17.9
Clinical trials					
ALLHAT ²¹	1994–2002	14 684	11.5	1.2	12.7
ASCOT ²²	1998–2005	19 527	48.5
ACCOMPLISH ²⁵	2003–2006	10 704	39
INVEST ²⁶	1997–2003#	17 190	25.1	12.6	37.8

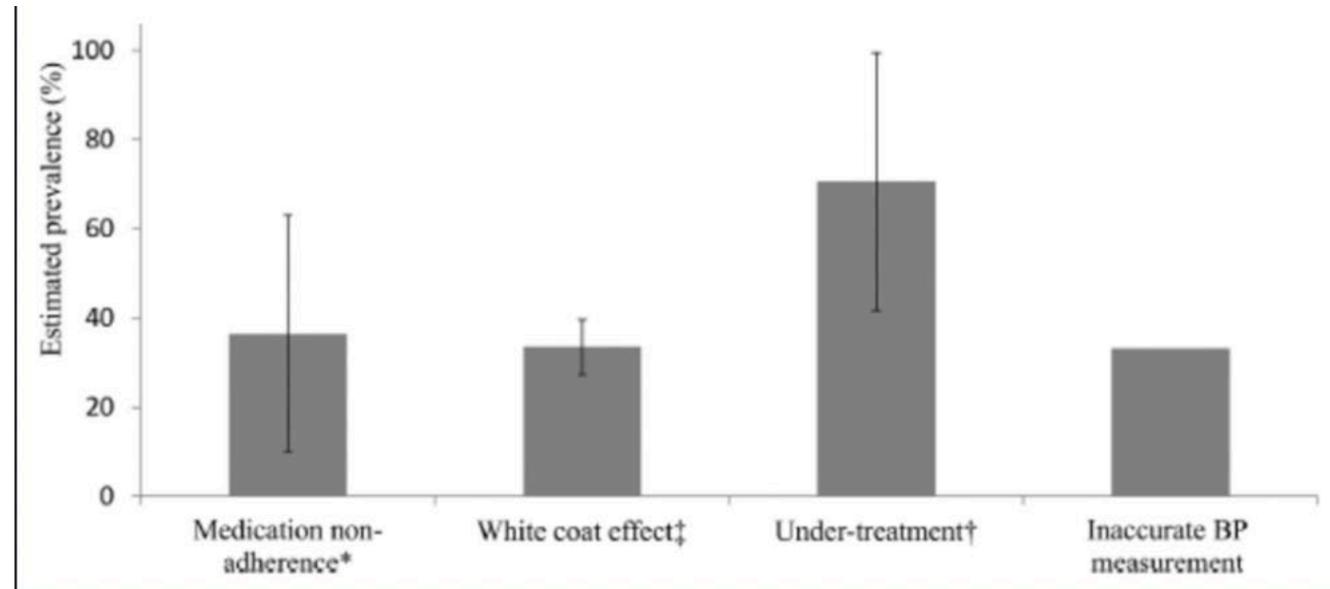
Uncontrolled aTRH is defined as BP ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic on ≥ 3 BP medications. Controlled aTRH is defined as BP < 140 mm Hg systolic and < 90 mm Hg diastolic on ≥ 4 BP medications unless otherwise specified.

Patient characteristic with RH

- Demographics . Old age , black race and male gender
- Obesity
- Left ventricular hypertrophy
- Albuminuria
- Diabetes mellitus
- CKD
- Higher Framingham 10-year risk score
- Obstructive sleep apnea (OSA) . 60%–84% of individuals with RH have OSA
- The normal nocturnal decline in BP is attenuated in up to 65% of individuals with RH

Diagnosis of resistant hypertension

- Identify and address nonadherence to medical therapy
- BP measurement technique
- White coat effect
- Under treatment
- Lifestyle and diet
- Concomitant medication
- Secondary causes of hypertension



Suboptimal treatment

Suboptimal antihypertensive therapy accounts for a large subset of patients not achieving BP targets

- Approximately **1 in 7** of all uncontrolled hypertensives and **1 in 2** with uncontrolled RH are prescribed ≥ 3 BP medications in optimal regimens.¹
- BP medications were administered at <50% of their maximally recommended dose in 42.1% of patients with RH.¹

Examples of drug regimen

55 years old AA male with stage III CKD and albuminuria (GFR 48ml/min) hyperlipidemia and asthma was seen for RH

Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Hydralazine 100 mg TID	Lisinopril 20 mg daily	Lisinopril 20 mg daily	Valsartan 320 mg daily	Valsartan 320 mg daily	Amlodipine 10/ Valsartan 320/HCTZ 25mg daily
Metoprolol 50 mg BID	metoprolol 50 mg BID	metoprolol 10 mg BID	HCTZ 25 mg daily	HCTZ 25 mg daily	spironolactone 25 mg daily
Clonidine 0.1 mg TID	Hydralazine 100 mg BID	Hydralazine 100 mg TID	Amlodipine 10 mg daily	Amlodipine 10 mg daily	
Terazosin 5 mg daily	Clonidine 0.1 mg TID	Clonidine 0.1 mg TID		Hydralazine 100 mg TID	
		Terazosin 5 mg daily			



Treatment Nonadherence

- Assessment of adherence

- Communication strategy
- Self reporting medication adherence (Morisky Medication Adherence Scale)
- Pharmacy and refill database
- Urine and blood drug metabolites measurement

- Identify barriers

- Related to patient
- Prescribers
- Health care system

- Interventions

- Patient engagement and self management
- Use once daily antihypertensive agents
- Use combination agents
- Discussion and education about side effects
- Cost effectiveness

1/3 of RH patients have white coat syndrome

- Spanish Ambulatory Blood Pressure Monitoring Registry with > 8000 patients with RH . After ambulatory BP monitoring:¹
 - 62.5% of patients were classified as true resistant
 - 37.5% had white-coat resistance.
- 24 hours ambulatory BP monitoring is reliable and preferred way to rule out white coat syndrome
- Self-measured home BP with oscillometric digital devices correlate with average daytime BPs measured by 24-hour ABPM.²

1-Hypertension. 2011;57:898–902 Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

2-Hypertension. 2008;52:10–29. doi: 10.1161/HYPERTENSIONAHA.107.189010

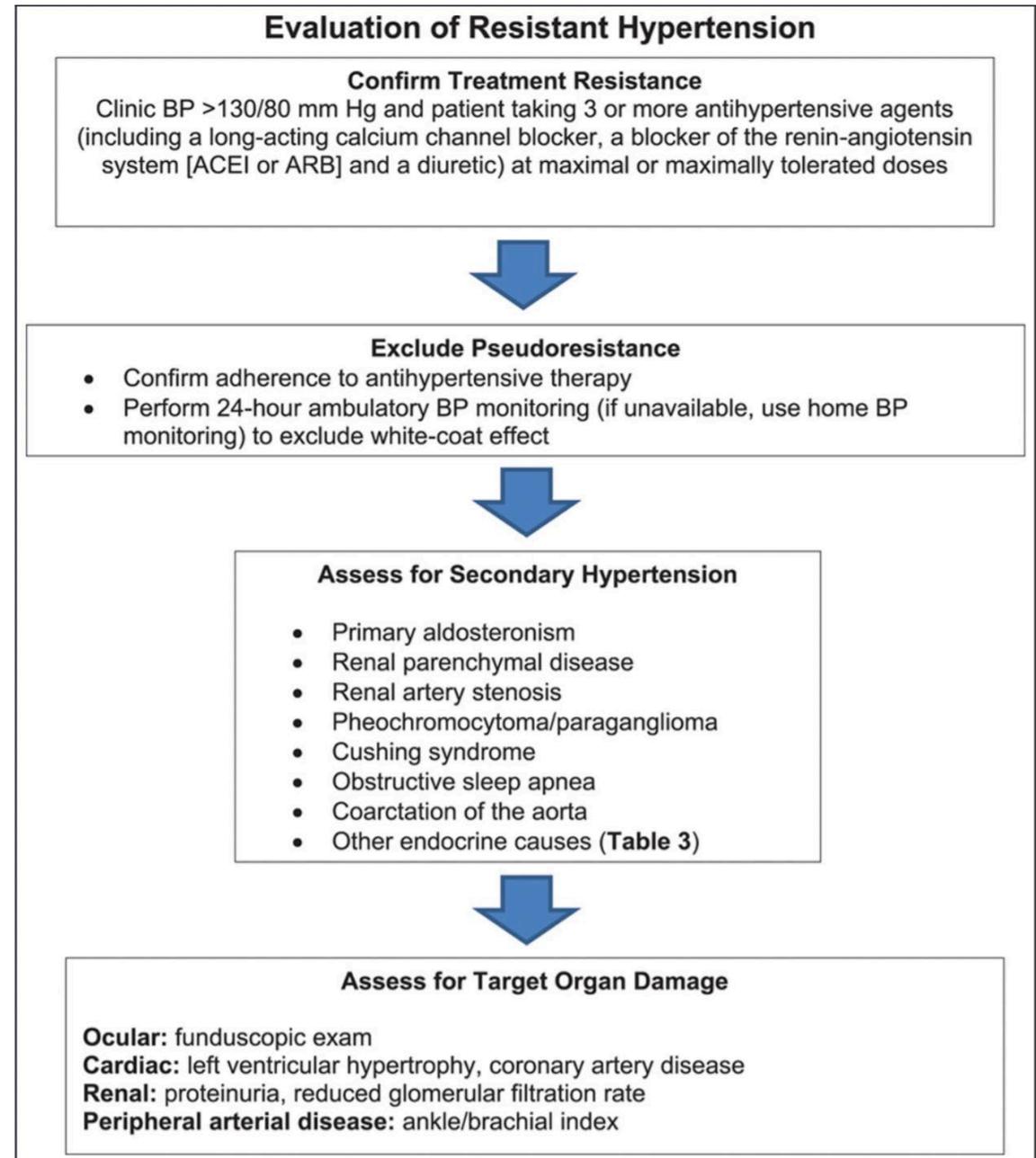
Optimizing lifestyle factors is part of RH management

- Obesity
 - Spanish Ambulatory Blood Pressure Monitoring Registry, a BMI ≥ 30 kg was an independent risk factor for RH
 - Obesity causes enhanced salt sensitivity , sympathetic activity and RAAS activation
- Dietary sodium
- Alcohol intake
- Physical activity

Medication affecting RH

- NSAID's
- Calcineurin inhibitors (tacrolimus , cyclosporine)
- VEGF inhibitors
- Glucocorticoids
- Erythropoietin
- Oral contraceptive

Evaluation of RH



Secondary hypertension – Primary aldosteronism

- Aldosterone secretion is *inappropriately high, autonomous, independent of renin* and not *suppressed by salt loading*.
- Prevalence of primary aldosteronism is high (20%) and **all patients with RH should be screened**
- More than 50% of patients with primary aldosteronism have **normal potassium**

Primary aldosteronism- Diagnosis

- Screening test – Ratio between morning blood plasma aldosterone concentration and plasma renin activity .
- Patient must be off spironolactone, eplerenone, and high-dose amiloride for at least 4 weeks before testing
- Positive screening tests needs to be **confirmed** by and confirmatory test.
- Refer to nephrology or endocrinology for further management .

Renovascular hypertension

- Two most common causes
 - Atherosclerotic renal vascular disease
 - Fibromuscular dysplasia
- Who to test ?
 - *Feature of secondary hypertension and other causes ruled out*
 - *Intervention will be considered if significant lesion found*
 - *A short duration of blood pressure elevation prior to the diagnosis*
 - *Failure or intolerance to optimal medical management*
 - *Recurrent flash pulmonary edema*
 - *Suspected fibromuscular dysplasia*

Renovascular hypertension

- Diagnostic test
 - Doppler ultrasonography
 - CT Angiogram
 - Magnetic resonance angiography
- Treatment options
 - Medical Therapy
 - Percutaneous revascularization
 - Surgical revascularization

Revascularization versus medical therapy

- CORAL trial – 947 patients with unilateral or bilateral atherosclerotic renal artery stenosis + high BP on 2 or more agents and/or GFR < 60

Results

- No benefit of revascularization on primary outcome
- 2 mmHg lower BP in revascularization arm
- Due to selection bias in CORAL and other trials, benefit of revascularization in selected patients should be considered.

Treatment of renovascular hypertension

- Patients with **fibromuscular dysplasia** should be referred for **revascularization**
- All patients with atherosclerotic renovascular hypertension must be treated with **appropriate and maximally tolerated medical regimen** including **RAAS blockers**.
- Likely benefit of revascularization in patients with
 - Short duration of hypertension prior to renovascular disease diagnosis
 - Failure of optimal medical therapy or intolerance to optimal medical therapy
 - Recurrent flash pulmonary edema or refractory heart failure

Sleep disorders and RH

- Prevalence of OSA in patients with RH is as high as 70-85% .¹
- Sympathetic activation and increase in plasma aldosterone is implicated.
- Treatment of patients with OSA and RH with CPAP induces modest reductions in BP
 - The HIPARCO Randomized Clinical Trial – 3.1 mmHg decrease in 24 hrs mean BP.²
 - Therapy with CPAP plus usual care did not prevent cardiovascular events in patients established cardiovascular disease.³

1-Obstructive sleep apnoea and 24-h blood pressure in patients with resistant hypertension. J Sleep Res. 2010;19:597–602. doi: 10.1111/j.1365-2869.2010.00839. 2-Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension JAMA. 2013;310(22):2407-2415.3-N Engl J Med 2016; 375:919-931

OSA screening

- Routine evaluation by polysomnography is not indicated for all patients with RH
- However, given the high prevalence of often severe OSA in patients with RH and the potential benefit of CPAP to enhance BP control, clinicians should screen such patients for symptoms of OSA

Pharmacological approach to treatment of RH

Switching to an appropriate diuretic (chlorthalidone or indapamide)

Add a mineralocorticoid receptor antagonist (spironolactone ,
eplerenone)

Diuretic of choice in RH

- Chlorthalidone and indapamide are diuretic of choice in patients with RH
 - Chlorthalidone 12.5 – 25 mg daily
 - Indapamide 1.25 – 5 mg daily
- In patients with an eGFR <30 switch to a loop diuretic
 - Prefer long-acting loop diuretic such as torsemide
 - Furosemide and bumetanide should be used BID
- Studies show SBP reduction of 7 to 8 mmHg simply by switching from hydrochlorothiazide to chlorthalidone. ^{1,2}

Benefit of adding a mineralocorticoid antagonist

- PATHWAY-2 trial . 285 pt with RH. Addition of spironolactone 25-50 mg resulted in 9 mmHg improvement as compared with placebo .¹
- ASCOT trial – 1411 patients with aRH . Addition of 25 mg spironolactone resulted in mean 22/10 mmHg reduction in BP.²
- In PATHWAY-2 study amiloride 10 mg daily was as effective as spironolactone.¹

Other therapeutic considerations

- Some ARB (azilsartan medoximil) may be more effective, but cost and formulary considerations are important.
- Amlodipine and extended release nifedipine are the most studied in the setting of hypertension. Evidence for Non dihydropyridine CCBs such as verapamil is limited.
- Bedtime administration of BP agents may be beneficial

Additional agents, 5th drug ?

- There is little evidence to support choice of additional drugs
- In post hoc analyses from large outcome trials, patients with heart rates >80 bpm had higher mortality.^{1,2}
- Thus, agents such as [β-blockers](#) or, if medically contraindicated, central α-2 agonists such as [transdermal clonidine](#) should be considered
- A vasodilating beta blocker, such as [labetalol](#), [carvedilol](#), or [nebivolol](#) may provide more antihypertensive benefit
- Other vasodilators agents such as hydralazine and minoxidil to be considered if other interventions fails.

Experimental therapies- No benefit of renal denervation

- SYMPLICITY HTN-3. In 535 patients with RH assigned to renal nerve denervation or a sham procedure; blood pressure decreased to a similar degree in both groups at six months. ¹
- SYMPATHY trial randomly assigned 139 patients with resistant hypertension routine care plus renal nerve denervation. 24 hrs ABPM decreased more in control (non statistical)²

Experimental therapies- Carotid sinus baroreceptor stimulation

- Rheos pivotal trial . 265 participants with RH. Failed to meet the primary end point of the trial.¹ Nonsignificant decrease in BP and more likelihood of having BP < 140 mmHg.
- 35% of patients had a serious procedure-related adverse event
- Rheos Pivotal Trial failed two of its five primary endpoints and not approved by the FDA
- CALM-FIM-EUR study . Open labelled non sham controlled showed BP reduction and acceptable safety profile.²

Management of Resistant Hypertension

Step 1

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence

+

Ensure low sodium diet (<2400 mg/d)
Maximize lifestyle interventions:

- ≥6 hours uninterrupted sleep
- Overall dietary pattern
- Weight loss
- Exercise

+

Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or 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 diuretic.

BP not at target



Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target



Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should 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 guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

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

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—www.clinicaltrials.gov.

Take home points

- Pseudo resistance is very common and should be aggressively ruled out
 - Accurate BP measurement
 - Home BP monitoring for white coat
 - Optimal medical regimen
 - Compliance with medical treatment
- Lifestyle modification can be challenging but crucial for BP control
- Optimized antihypertensive regimen. One of the three agents should be a [diuretic](#) and other if feasible [long-acting calcium channel blocker](#) and [blocker of the renin-angiotensin system](#)

Take home points

- Rule out secondary causes of hypertension and focus on common causes like [hyperaldosteronism](#) and [CKD](#)
- In patients with RH switch thiazide diuretics to [chlorthalidone](#) and [indapamide](#)
- Add mineralocorticoid receptors antagonist such as [spironolactone](#) or [eplerenone](#)