IN THE NAME OF GOD

RESISTANT HYPERTENSION

JALAL ETEMADI KHIAVI, MD

TABRIZ UNIVERSITY OF MEDICAL SCIENCE

DEFINITIONS

- **Resistant hypertension** is defined as blood pressure that remains above goal in spite of concurrent use of three antihypertensive agents of different classes . If tolerated, one of the three agents should be a diuretic, and all agents should be prescribed at maximum recommended (or maximally tolerated) antihypertensive doses .
- Patients whose blood pressure is controlled with four or more medications should also be considered to have resistant hypertension.

DEFINITIONS

- **Apparent resistant hypertension** – Patients with apparent resistant hypertension have uncontrolled clinic blood pressure despite being prescribed three or more antihypertensive medications or require prescriptions of four or more drugs to control their blood pressure . However, such patients may have pseudoresistant hypertension.
- **True resistant hypertension** – Patients with true resistant hypertension are those who have 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 who also have uncontrolled blood pressure confirmed by 24-hour ambulatory blood pressure monitoring.

DEFINITIONS

- **Refractory hypertension** was defined as the inability to achieve blood pressure control (by office or ambulatory blood pressure monitoring) despite maximum tolerated doses of at least five antihypertensive medications, including chlorthalidone and spironolactone.

DEFINITIONS
Pseudoresistant hypertension

Pseudoresistance refers to poorly-controlled hypertension that appears resistant to treatment but is actually attributable to other factors.

- Inaccurate measurement of blood pressure (eg, use of an inappropriately small blood pressure cuff
- Poor adherence to antihypertensive therapy.
- Suboptimal antihypertensive therapy.
- Poor adherence to lifestyle and dietary approaches to lower blood pressure, such as a reduced sodium intake
- White coat hypertension

TREATMENT GOAL

The goal blood pressure for patients with resistant hypertension is the same as that in patients with hypertension without treatment resistance

	Casual/conventional office blood pressure (manual or oscillometric measurement without proper patient preparation or technique)*	AOBPM, standardized office blood pressure, daytime ABPM, or self-measured blood pressure¶
Higher-risk populationΔ		
▪ Known ASCVD◊ ▪ Heart failure ▪ Diabetes mellitus ▪ Chronic kidney disease ▪ Age ≥65 years§ ▪ Calculated 10-year risk of ASCVD event ≥10% ¥	125 to 130/<80	120 to 125/<80
Lower-risk‡		
▪ None of the above risk factors	130 to 139/<90	125 to 135/<90

TREATMENT GOAL

Summary of Blood Pressure Target Recommendations

		Recommended BP Targets					
		2017 ACC/AHA	2020 ISH	2021 KDIGO	2021 AHA/ASA	2023 ESH	2024 ADA
Age	<65		120/70-130/80			<130/80	
	65-79		<140/90			<140/80	
	≥80		<140/90			140-150 SBP	
ASCVD risk	ASCVD risk <10%	<140/90					
	Clinical CVD/ASCVD risk ≥10%	<130/80					
Comorbidities	Diabetes						<130/80
	CKD (nondialysis)	<130/80		<120 SBP		<140/90	
	Kidney transplant recipient			<130/80			
	Stroke/TIA				<130/80		

Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESH, European Society of Hypertension; ISH, International Society of Hypertension; KDIGO, Kidney Disease Improving Global Outcomes; SBP, systolic blood pressure; TIA, transient ischemic attack.

MANAGEMENT
Identify and treat secondary causes

- An essential component of the management of resistant hypertension is identification and subsequent treatment of potentially reversible causes of secondary hypertension .
- While the actual prevalence of secondary causes in resistant hypertension is not well described, it is likely higher than in the general population of patients with hypertension .
- The most common secondary causes are obstructive sleep apnea, primary aldosteronism, and renal artery stenosis.

MANAGEMENT

Stop medications that raise blood pressure

Nonsteroidal antiinflammatory drugs (NSAIDs)
Oral contraceptives
Antidepressants (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors)
Corticosteroids (including glucocorticoids and mineralocorticoids)
Decongestants (eg, phenylephrine, pseudoephedrine)
Some weight loss medications (eg, phentermine, diethylpropion)
Sodium-containing antacids
Erythropoietin
Cyclosporine or tacrolimus
Cocaine or methamphetamine
Stimulants (eg, methylphenidate, amphetamines)
Atypical antipsychotics (eg, clozapine, olanzapine)
Angiogenesis inhibitors (eg, bevacizumab)
Tyrosine kinase inhibitors (eg, sunitinib, sorafenib)

MANAGEMENT

Prescribe lifestyle modification

- Following the Dietary Approaches to Stop Hypertension (DASH) diet
- Reducing sodium intake and increasing potassium intake
- Losing weight (in obese and overweight patients)
- Exercising
- Moderating alcohol intake (if excessive)

MANAGEMENT

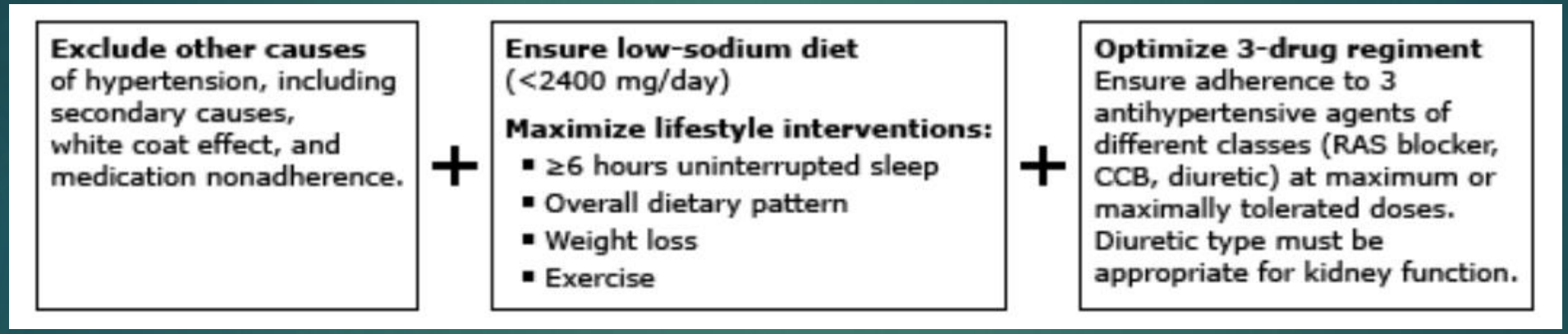
Address nonadherence to antihypertensive therapy

- Nonadherence to antihypertensive therapy is a major contributor to inadequate blood pressure control and is a common problem in patients who have apparent treatment resistance.
- As an example, in a systematic review of studies that performed objective assessments of drug adherence (ie, with urine or blood testing), approximately 40 percent of patients with apparent resistant hypertension were either partially or completely nonadherent to antihypertensive therapy.
- Regimens should be simplified, and long-acting combination agents should be used as much as possible in order to reduce the number of prescribed pills and to permit once-daily dosing.

Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 1



Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

Switch to a more potent diuretic (if necessary)

In patients who are taking a thiazide-type diuretic and who have an eGFR ≥30 mL/min/1.73 m_2, we suggest switching to a thiazide-like diuretic (either chlorthalidone or indapamide). In patients with an eGFR ≥30 mL/min/1.73 m_2 who are already treated with a thiazide-like diuretic, and who have persistent signs of hypervolemia (ie, edema), we suggest adding a loop diuretic to the thiazide-like diuretic (ie, sequential nephron blockade).

In patients with an eGFR <30 mL/min/1.73 m2, we suggest using a thiazidelike diuretic (ie, chlorthalidone or indapamide) or switching to a loop diuretic, if such patients are already taking a loop diuretic, then we intensify the loop diuretic dose, unless the patient develops signs of hypovolemia.

Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 3

Add MRA: spironolactone or eplerenone.¶

In patients with resistant hypertension and uncontrolled blood pressure despite potent diuretic therapy, we suggest adding a mineralocorticoid receptor antagonist (spironolactone or eplerenone). A potassium-sparing diuretic (eg, amiloride, triamterene) is an alternative if a mineralocorticoid receptor antagonist cannot be used.

The more specific aldosterone blocker, eplerenone, does not induce the side effects see with spironolactone. However, eplerenone is less potent and often requires twicedaily dosing (ie, 50 mg twice daily) to be as effective for blood pressure lowering.

Williams B, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drugresistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015; 386:2059.

Aldosterone-Driven RH

- **Mechanistic biomarker advance(*Hypertension. 2024)*:** ENaCγ (the cleaved form of the epithelial Na+ channel γ) protein in urinary extracellular vesicles (uEVs) rises with renal MR signaling—an emerging human readout of aldosterone activity that may help phenotype "**aldosterone-driven**" RH.

- **What Is Relevant**? Aldosterone/MR (mineralocorticoid receptor) is involved in the pathogenesis of a wide range of diseases, such as treatment-resistant hypertension, chronic heart failure, and chronic kidney disease. However, there is no established marker for tissue aldosterone/MR signaling. Our study **(Yuto Hayama, *Hypertension. 2024)*** revealed that cleaved ENaCγ in urinary extracellular vesicles can serve as a valuable, noninvasive marker of MR signaling in the kidney.

Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 4

Check heart rate: unless <70 beats/minute, **add beta blocker** (eg, metoprolol succinate, bisoprolol) or combined alpha-beta blocker (eg, labetalol, carvedilol). If beta blocker is contraindicated, consider central alpha agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 5

Add hydralazine$^{\Delta}$ 25 mg 3-times daily and titrate upward to maximum dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (maximum dose 90 mg daily).

Overall management approach of resistant hypertension in adults

Stepwise approach to pharmacologic therapy

Step 6

Substitute minoxidil◇ 2.5 mg 2- to 3-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.

Device-based Therapies for RHT
Renal denervation and Baroreceptor Stimulation

- Denervation of the renal sympathetic nerves, either by catheter-based radiofrequency ablation or by catheter-based ultrasound ablation, reduces blood pressure in patients without resistant hypertension as well as in patients with resistant hypertension.
- Initial enthusiasm for this technology was subsequently lessened by the results of SYMPLICITY HTN-3(NEJM 2014), a sham-controlled trial that failed to show significant benefit.
- Most of these trials have shown a modest average systolic BP reduction when compared with the sham-controlled group, ranging from 4-7 mm Hg.
- RDN was approved by the United States Food and Drug Administration in late 2023 for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of antihypertensive medications or in patients who have documented intolerance to antihypertensive medications

Device-based Therapies for RHT
Renal denervation and Baroreceptor Stimulation

- **RADIANCE-HTN TRIO** (ultrasound RDN)(THE LANCET, 2021) showed greater daytime ambulatory SBP reduction at 2 months vs sham (**median between-group −4.5 mmHg**; −5.8 mmHg in complete ABPM set) on a standardized triple pill.

- **Guideline posture (ESC 2024):** RDN **may be considered** for *true* RH after multidisciplinary review (Class IIb), **not first-line**.

Device-based Therapies for RHT
Renal denervation and Baroreceptor Stimulation

- **Sympathetic nervous system overactivity ("neural RH"):** Direct microneurography (muscle sympathetic nerve traffic) shows **>40% higher muscle sympathetic nerve activity** in RH vs non-resistant HTN; renal norepinephrine spillover is likewise elevated—defining a *neurogenic* phenotype that sustains resistance and predicts response to device therapy (e.g., RDN).
- **Prominent clue:** sympathetic overdrive is *not* seen in pseudoresistance, supporting its causal role in *true* RH.

Current Hypertension Reports (2023) 25:263–270

Renal denervation CASE:

- A 67-year-old woman with a past medical history of type 2 diabetes and gout presents for follow-up evaluation of her hypertension. She is taking valsartan 320 mg once daily. In the past, she developed severe hyponatremia on thiazide diuretics and spironolactone. She has been unable to take β-blockers or a-agonists due to bradycardia. She experienced a lupus-like syndrome while taking hydralazine and had gingival hyperplasia on amlodipine. AOBP in the office is 151/93 mm Hg. Her 24-hour ABPM shows a daytime average BP 149/91 mm Hg. She is worried about high BP because her younger sister recently had a stroke. She asks whether she is a candidate for renal denervation (RDN).

New Pharmacologic Options
Dual endothelin antagonists

- **Endothelin pathway finally lands in practice (aprocitentan/Tryvio).**
- **PRECISION** (2022, LANCET) showed clinically meaningful, *sustained* BP reductions in true RH when the dual ETA/ETB blocker **aprocitentan** was added to standardized background therapy.
- In the 4-week, placebo-controlled phase, unattended office SBP fell ~15 mmHg on aprocitentan vs ~12 mmHg on placebo (between-group −3.8 to −3.6 mmHg), with larger effects in ambulatory BP and durable control over 48 weeks; edema/headache were the main AEs.
- **Regulatory milestone:** FDA approval (brand **Tryvio**) for RH (Dec 2024; labeling updated May 2025). This gives us a *non-RAAS, non-diuretic* add-on option when MRAs are limited by hyperkalemia or intolerance. (FDA Access Data)

EXPERIMENTAL THERAPIES

Novel medications : zilebesiran

- **Interfering RNA** – In a trial of 84 patients with elevated blood pressure on no antihypertensive medications, a single subcutaneous injection of **zilebesiran**, a long-acting interfering RNA **that inhibits angiotensinogen production by the liver**, reduced 24-hour systolic blood pressure at 12 weeks by 13 to 16 mmHg compared with placebo, depending upon the dose. Blood pressure reductions persisted at six months.
- In a separate group of 28 patients, zilebesiran blunted both the increase in blood pressure induced by a high-salt diet and decrease in blood pressure induced by taking an angiotensin receptor blocker.