Evaluation and Management of Resistant Hypertension: Core Curriculum 2024

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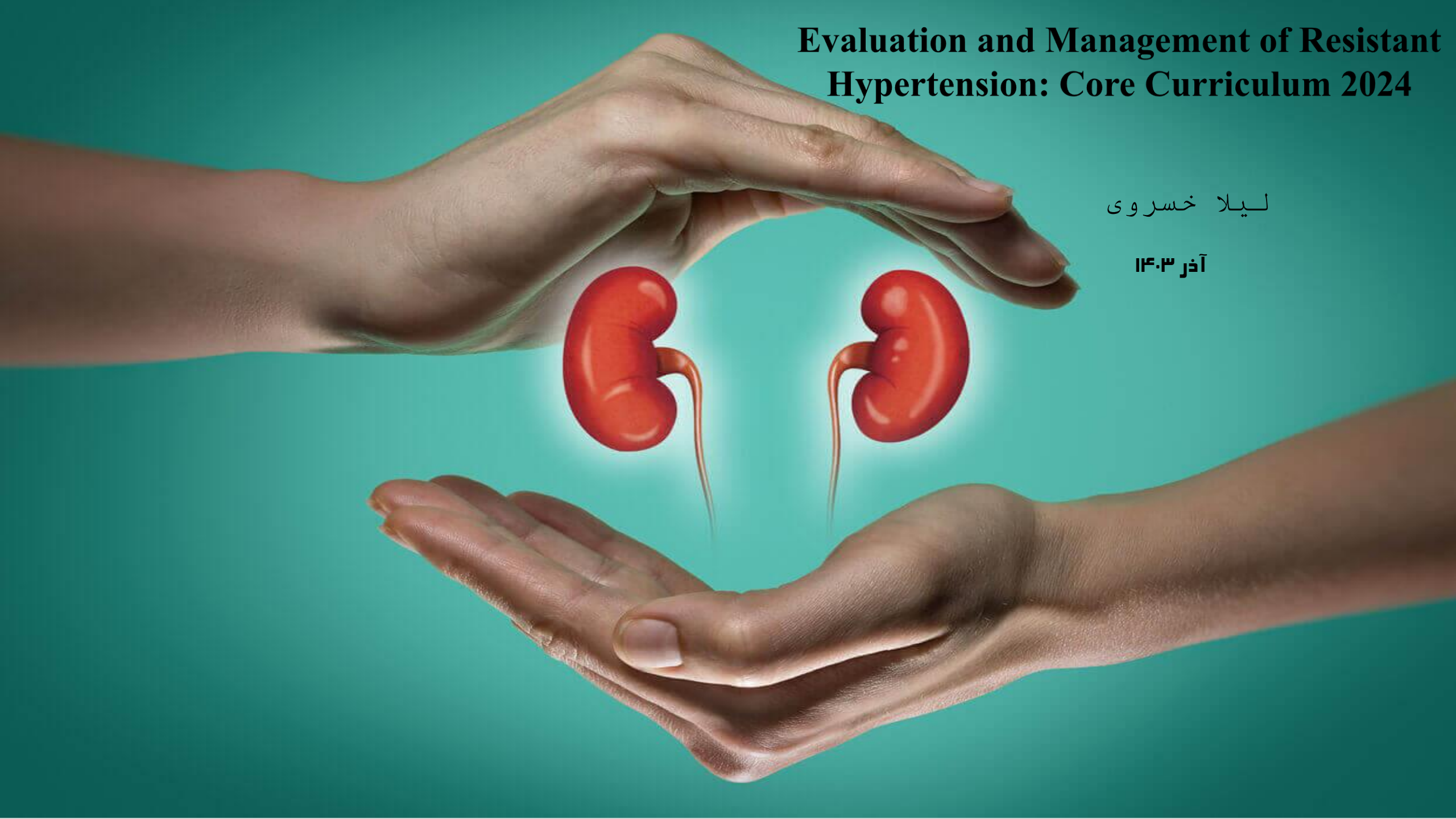


Introduction

Hypertension is the most common modifiable cardiovascular risk factor and is both a cause and a consequence of chronic kidney disease

Nearly half of adults in the United States have hypertension as defined as a systolic blood pressure (BP) ≥ 130 mm Hg and/or a diastolic BP ≥ 80 mm Hg.

Patients whose BP is not at goal despite the use of 3 different classes of antihypertensive medications at the highest (or highest tolerated) doses are considered to have **resistant hypertension (RHTN)**

patients who require 4 or more BP medications to achieve BP control are categorized as having **“controlled RHTN.”**

The true prevalence of RHTN is difficult to ascertain because many patients with uncontrolled hypertension are on suboptimal treatment regimens, have intermittent adherence, or have white coat effects

Introduction

Patients with RHTN are nearly 50% more likely to have a cardiovascular event and 25% more likely to develop kidney failure than those with HTN that is not resistant.

Table 1. 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.

Introduction

Figure 1. Framework and strategies for resistant hypertension clinic visit.

Factors to Consider at Every Visit

Case 1: *A 56-year-old woman is referred for uncontrolled BP. Her other past medical history includes hyperlipidemia and obesity. Her antihypertension regimen includes amlodipine 10 mg once daily, valsartan 320 mg once daily, and chlorthalidone 25 mg once daily. Her physical examination is notable for a BP of 151/76 mm Hg and a body mass index (BMI) of 34.8 kg/m².*

Question 1: Which of the following options could be used to evaluate for white coat effects *and* guide ongoing medication titration?

(a) Repeated auscultatory BP measurement by a physician at the end of a visit

(b) Automated office blood pressure monitoring (AOBP) performed in a quiet room

(c) 24-hour ambulatory blood pressure monitoring (ABPM)

(d) Self-measured blood pressure (SMBP) readings taken at home with proper technique

Factors to Consider at Every Visit

Then, if needed, white coat effect should be excluded by obtaining out-of-office BP readings either through SMBP readings or, where available, 24-hour ABPM.

The term **“white coat effect”** applies to individuals on pharmacologic treatment for hypertension whose in-office BP readings average above 130/80 mm Hg while their out-of-office readings are consistently below 130/80.

Optimal Office-based BP Measurement

The accuracy of BP measurements relies on both adequate patient preparation and proper technique.

It is important to note that most of the potential errors in preparation will result in a BP reading that is higher rather than lower; the exception to this rule is using a BP cuff that is too large for the patient's arm size.

Auscultatory Versus Oscillometric BP Measurement

Starting in 1998, mercury-based devices have been phased out of all US hospitals and clinics, replaced by aneroid devices which, although safer from an environmental and toxicology perspective, are delicate devices that are highly susceptible to error and require frequent calibration to ensure accuracy.

There are multiple sources of potential inaccuracy with **auscultatory** BP measurement including terminal digit bias and cuff-deflation errors, which can occur if the cuff pressure is released too quickly or too slowly.

Automated Office BP Measurement (AOBP)

AOBP refers to the use of a fully automated oscillometric BP device that can be programmed to take multiple BP readings after varying periods of rest with a single activation.

It has the advantage of being able to be performed while the patient rests quietly and undisturbed, and can eliminate some important sources of operator bias and error.

AOBP can be considered a reasonable surrogate for the average awake BP as measured with 24-hour ABPM and mitigates some, though not all, of the white coat effects seen when measuring BP in medical office settings

If the BP is still above goal on AOBP, an out-of-office BP strategy should be used next to confirm the diagnosis of RHTN.

Out-of-Office BP Measurement: 24-Hour ABPM and SMBP

The 24-hour ABPM has long been considered the gold standard for BP measurement

ABPM has a stronger association with cardiovascular outcomes than other methods of BP assessment.

ABPM also allows for the identification of different nocturnal BP patterns such as "nondipping," in which BP fails to drop by the expected 10%-20% while sleeping, or "reverse dipping," in which BP increases while sleeping.

Table 3. Summary of Common Features Among Guidelines for Home BP Monitoring

Element	Comments
Frequency of BP readings	At least 2, measured 30-60 seconds apart
Time of day	AM before medications and eating PM before medications, either before dinner or before bedtime
Minimum readings if BP uncontrolled	At least 12 readings over 3-7 days Some suggest discarding first day
Goal	Average BP <130/<80
Type of device	Validated upper arm oscillometric device preferred Wrist devices only in settings of large arm circumferences

Abbreviation: BP, blood pressure.

Medication and Other Substance-related Hypertension

Case 2: *A 73-year-old woman with hypertension, hyperlipidemia, obesity, obstructive sleep apnea (OSA), and gastroesophageal reflux presents to her primary care physician for routine follow-up evaluation. She has been seeing an orthopedic surgeon and plans to have a total knee replacement in the next 2 months. She is currently taking losartan 50 mg twice daily, amlodipine 5 mg daily, hydrochlorothiazide 12.5 mg daily, carvedilol 6.25 mg twice daily, and rosuvastatin 5 mg. In addition, she has been using over-the-counter naproxen 220 mg twice daily for her knee pain. On examination, her BP is 148/91 mm Hg and BMI is 33.6 kg/m². At the most recent visit 6 months ago, her BP was 131/76 mm Hg.*

Question 2: Which of the following pharmacologic strategies is the most appropriate next step?

(a) Increase losartan from 50 mg twice daily to 100 mg twice daily.
(b) Change amlodipine from 5 mg once daily to verapamil extended release 180 mg once daily.
(c) Switch naproxen 220 mg to topical diclofenac gel.
(d) Add spironolactone 25 mg once daily.

Many medications, both prescribed and over the counter, can cause increased BP. Examples include calcineurin inhibitors, methylphenidate, vascular endothelial growth factor (VEGF) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Other non-medication substances such as alcohol, cocaine, caffeine, tobacco, amphetamines, herbal supplements, or even licorice are frequently cited as contributors to elevated BP.

NSAIDs, can antagonize prescribed antihypertensive medications, making their impact on BP particularly problematic.

Adherence to Antihypertensive Medications

Case 3: *A 43-year-old woman with a past medical history of pre-eclampsia and postpartum hypertension is seen in a follow-up visit. Two years after delivery, her BP has remained elevated. Her current regimen is labetalol 200 mg twice daily, and hydrochlorothiazide 25 mg once daily. Lisinopril 10 mg once daily in the evening was added a few months ago. Her BP in the office is 148/91 mm Hg, as determined by AOBP. She acknowledges that she often forgets to take her evening doses of labetalol and lisinopril.*

Question 3: Which of the following strategies would be the most effective way to improve medication adherence?

(a) Ask her to bring all of her pill bottles to each visit for review.

(b) Change medications to long-acting medications dosed once daily where possible.

(c) Check urine or serum metabolites of prescribed antihypertensives.

(d) Instruct the medical assistant to perform a medication reconciliation at the start of each visit.

Many side effects from antihypertensive medications are dose-related, such as the lower extremity edema often seen with higher doses of dihydropyridine calcium channel blockers (CCB) that can be reduced or eliminated by using a lower dose.

Adherence to Antihypertensive Medications

Table 4. Strategies to Minimize or Address Common Barriers to Medication Adherence

Barriers to Medication Adherence	Strategies to Minimize/Address
Cost	• Choose low-cost generic medications where feasible • Reduce copays with combination tablets (if generic)
Complexity of regimen/ too many pills	• Convert to once daily formulations where available • Convert to combination tablets to minimize pill burden • Use blister packs/pill boxes • Minimize trips to pharmacy for refills • Use 90-day refills instead of 30-day refills • Ensure all medications (not just BP medications) are eligible to be refilled at the same time • Use mail order if available/cost effective
Adverse effects of medications	• Use lowest effective doses of BP medications to minimize side effects • ARB/ACE inhibitors can counteract edema from CCBs • ARB/ACE inhibitors can counteract hypokalemia from thiazides
Patient motivation/ insight	• Multidisciplinary team-based care • Patient education and motivational interviewing • Text messaging reminders • Home BP monitoring with ongoing feedback through electronic health record and ability to modify medications and doses

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

Lifestyle Interventions

Case 4: *A 68-year-old woman with obesity and osteoarthritis presents with worsening BP control. She is discouraged because she has gained 12 pounds over the past year. Her husband passed away 6 months ago, and, as a result, she is cooking less at home as she adjusts to living alone. Fresh fruits and vegetables tend to go bad before she can finish them, so she is relying on canned soups, frozen dinners, and take-out meals. Previously, they had been going to the local senior center to take group exercise classes together at least 4 days a week, but she stopped going and has not found any suitable alternatives. In the past, she had been drinking alcohol only on weekends but is now having a glass of wine each night. Her BP in the office today (taken by AOBP) is 143/92 mm Hg. A year ago, her BP was measured at 127/78 mm Hg.*

Question 4: Which of the following nonpharmacologic strategies is likely to have the greatest impact on her BP?

(a) Counseling on reduced sodium options that fit her current life circumstances

(b) Referring to physical therapy for dynamic resistance training for 20 minutes twice a week

(c) Advising her to stop drinking alcohol

(d) Recommending losing 10 pounds over the next 2 months

Sustained weight loss can improve diabetes, reduce pain from osteoarthritis, and lessen the severity of OSA. Lastly, making healthier lifestyle choices has independent benefits on overall cardiovascular risk.

Increased physical activity, healthy diet changes, sodium reduction, alcohol moderation, and weight loss for all patients with hypertension, though not all of these have been studied specifically in patients with RHTN.

Lifestyle Interventions

Pharmacologic treatment with renin-angiotensinaldosterone– blocking medications and can offset the hypokalemic effects of thiazide diuretics.

Independent of sodium reduction, increasing dietary potassium intake can also lower BP

The consumption of high potassium foods rather than through supplements, though even substituting regular table salt with a salt substitute containing 75% sodium chloride and 25% potassium chloride was found to both reduce BP and decrease cardiovascular events.

The Dietary Approaches to Stop Hypertension (DASH) diet is a generic diet pattern with a focus on vegetables and fruits, whole grains, lean protein sources, and low-fat dairy products that can be adapted to suit a variety of different ethnic or cultural backgrounds and food preferences.

Lifestyle Interventions

Newer glucagon-like peptide 1 (GLP-1) receptor agonists (liraglutide, dulaglutide, and semaglutide) and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (tirzepatide)

Protective effects on the cardiovascular and kidney systems independent of hemoglobin A1c reduction and weight loss.

Using strategies such as motivational interviewing, helping patients set SMART (specific, measurable, achievable, relevant, and time-bound) goals,

Evaluating for Secondary Causes of Hypertension

Case 5: *A 75-year-old man with longstanding hypertension, hyperlipidemia, coronary artery disease (CAD), OSA, osteoarthritis, and stage 4 CKD describes worsening BP control over the last few months. He had previously been able to keep his BP readings below 120/80 mm Hg on olmesartan 40 mg once daily, felodipine 10 mg once daily, and carvedilol 12.5 mg twice daily. However, his readings are now consistently above 150/90 mm Hg using his validated home BP cuff, which is confirmed with AOBP in the clinic. He is using his continuous positive airway pressure (CPAP) machine on a nightly basis. Laboratory testing reveals a baseline creatinine of 1.5 mg/dL, potassium of 3.2 mEq/L, and bicarbonate of 28 mEq/L. His plasma aldosterone concentration is measured at 12 ng/dL (reference range, <21, measured between 4 and 6 PM) and plasma renin activity is 0.15 ng/mL/hour (reference range, 0.25-5.82).*

Question 5: Which of the following is the next best step?

(a) Check 24-hour urine collection for aldosterone and sodium with high sodium intake.

(b) Stop olmesartan and carvedilol for 2-4 weeks and recheck serum aldosterone and renin.

(c) Refer for repeat polysomnography and CPAP mask refitting.

(d) Refer for adrenal venous sampling.

Primary aldosteronism is an increasingly common and underrecognized cause of RHTN

Independent of plasma renin concentrations, leading to volume expansion primarily from sodium reabsorption and enhanced sympathetic nervous system activity.

Important clues to primary aldosteronism include hypokalemia and metabolic alkalosis early on, with cardiovascular and kidney disease presenting as later findings

Evaluating for Secondary Causes of Hypertension

Individuals with primary aldosteronism have been observed to have increased risk of atrial fibrillation, myocardial infarction, heart failure, and stroke.

Given the high prevalence and significant risks, all individuals with RHTN should be screened with an aldosterone/ renin ratio (ARR),

Consisting of plasma aldosterone concentration and plasma renin activity, ideally drawn from a patient in a seated position in the morning hours after potassium repletion if hypokalemic

Some would suggest that any degree of renin suppression (<1.0 ng/mL/hour) from a routine blood draw should raise suspicion for primary aldosteronism

An ARR of >30, or >20 with plasma aldosterone of >15 ng/dL almost certainly represents primary aldosteronism.

Evaluating for Secondary Causes of Hypertension

It is often helpful to evaluate the plasma renin activity (PRA) and plasma aldosterone concentration (PAC) separately

Pa unlikely If the PAC is less than 5-10 ng/mL. False negatives related to MRAs (and occasionally ACE inhibitors and ARBs) are more common

If the ARR is positive and pretest probability is high, confirmatory testing is recommended in most cases

For those with ongoing hypokalemia, a highly suppressed PRA of <1 ng/nL/hour, and PAC of ≥20 ng/dL, confirmatory testing may not be necessary.

The simplest confirmatory test is the saline suppression/infusion test. This protocol typically involves the infusion of 2 liters of 0.9% saline over 4 hours in the seated position from 8 AM to 12 PM, with aldosterone, renin, and potassium levels checked before and after infusion.

Evaluating for Secondary Causes of Hypertension

If serum aldosterone production is sustained at >10 ng/dL, this is a positive confirmatory test.

An **oral salt-loading test** is less resource intensive but requires a 3-day consumption of 5 grams of sodium per day. This is often achieved with a combination of food intake and sodium chloride tablets, with subsequent measurement of serum electrolytes and a 24-hour urine collection for sodium and creatinine

If a urine sodium of >200 mEq per 24 hours is achieved, then an elevated urine aldosterone excretion of >12 µg would confirm primary aldosteronism.

Additional confirmatory testing options include the **captopril challenge test** and **the fludrocortisone suppression test**, both of which are cumbersome and less commonly done.

An **abdominal computed tomography (CT) scan with an adrenal protocol** can distinguish between a unilateral aldosterone-producing adenoma and bilateral hyperplasia as well as rule out an adrenal carcinoma (rare).

Evaluating for Secondary Causes of Hypertension

If surgery is considered, **adrenal venous sampling**, performed at an experienced center, will help to determine if there is sufficient laterality for unilateral laparoscopic adrenalectomy.

In patients **younger than 35 years with overt primary aldosteronism and a unilateral adrenal nodule > 1 cm**, adrenal venous sampling may not be necessary before proceeding to adrenalectomy

Patient with bilateral adrenal hyperplasia require lifelong medical therapy with MRAs, titrated as tolerated to achieve a **serum potassium level of 4.5 mEq/L and a target BP of <130/<80.**

New data have suggested that targeting renin > 1 ng/nL/hour may also decrease cardiovascular events and improve renal outcomes (i.e., a slower decline in estimated glomerular filtration rate).

Evaluating for Secondary Causes of Hypertension

Table 5. Effect of Antihypertensive Medication Classes on the Plasma Aldosterone Concentration to Plasma Renin Activity Ratio

Medication Class	Effect on PAC	Effect on PRA	Overall Effect on ARR	Interpretation of ARR if Medication Continued During Testing
β_1-Receptor antagonists	↓	↓↓	↑	Low PAC (<5 ng/dL) argues against PA even if renin activity is suppressed.
Central α_2-agonists	↓	↓↓	↑	
ACE inhibitors	↓	↑ ↔	↓	Low renin activity would be highly suggestive of PA. High renin activity would not rule out PA.
ARBs	↓	↑ ↔	↓	
Diuretics (loop and thiazide)	↔ ↑	↑↑	↓	Similar to ACE inhibitors/ARBs
MRA	↔ ↑	↑↑	↓	If renin not suppressed, MRA should be held for testing. Diagnosis of PA can be made if PAC is high and PRC is suppressed.
DHP calcium channel blockers	↔ ↓	↔ ↑	↓	Data are mixed, but may produce excess false-negative results.
α_1-Receptor antagonists	↔	↔	↔	Does not interfere with testing.
Direct arterial vasodilators	↔	↔	↔	
Non-DHP calcium channel blockers	↔	↔	↔	

Based on information in Jędrusik P, Symonides B, Lewandowski J, Gaciong Z. The effect of antihypertensive medications on testing for primary aldosteronism. *Front. Pharmacol.* 2021;12:684111. doi:10.3389/fphar.2021.684111. Abbreviations: ACE, angiotensin converting enzyme; ARR; aldosterone to renin ratio; ARB, angiotensin receptor blockers; DHP, dihydropyridine; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

Evaluating for Secondary Causes of Hypertension

Case 6: *A 45-year-old woman with hypothyroidism presents to the clinic with hypertension that has been difficult to control. She is currently taking chlorthalidone 25 mg once daily, verapamil extended release 240 mg once daily, carvedilol 25 mg twice daily, and valsartan, which was recently increased from 160 mg once daily to twice daily. Her baseline creatinine level is around 1.1 mg/dL, but it has recently been elevated to 1.8 mg/dL over the last 2-3 months, as confirmed on recheck a few weeks later. Her electrolyte panel is notable for potassium of 4.9 mEq/L and bicarbonate of 22 mEq/L.*

Question 6: Which of the following studies should be done first?

(a) Abdominal CT scan with an adrenal protocol
(b) Polysomnography
(c) Renal angiography
(d) Renal duplex ultrasound of renal arteries

Renal artery stenosis (RAS) is quite common among those with RHTN, especially among older individuals with known vascular disease, atherosclerosis, smoking history, diabetes mellitus, and CKD.

Although most individuals will tolerate ACE inhibitor or ARB therapy, a small fraction may develop acute kidney injury, especially if concurrently on diuretics.

Peak systolic velocity (PSV) is the most important direct evaluation of a stenotic area, and elevated PSV is among the most sensitive and specific ultrasound criterion for a RAS diagnosis.

Evaluating for Secondary Causes of Hypertension

The PSVs of the renal artery and aorta (renal/aortic ratio) for a more reliable measure, where an elevated renal/aortic ratio is highly suggestive of RAS.

The most common abnormality seen in RAS is the "tardus-parvus" waveform, where the distal flow of the renal artery shows a slow rise (tardus) to a lower systolic peak (parvus).

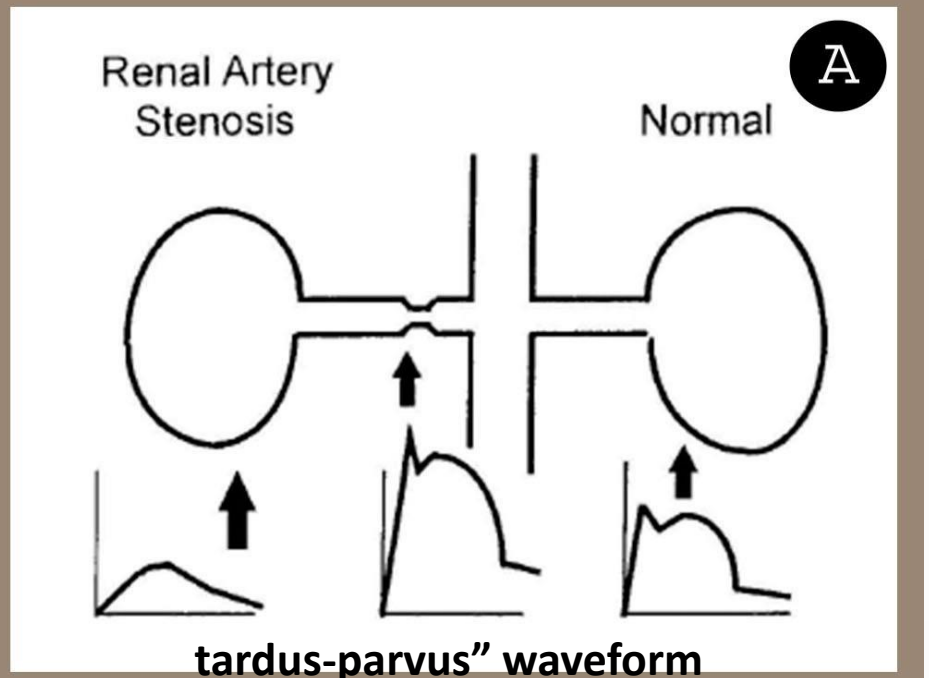
In cases with ambiguous or contradictory results, confirmation by CT or magnetic resonance angiography (with consideration of the safety of iodinated or gadolinium contrast exposure if kidney function is decreased) is necessary.

Additionally, although plasma renin activity may be elevated in RAS, this measurement is not helpful in establishing a diagnosis because it can be suppressed by a high-sodium diet and influenced by multiple medications

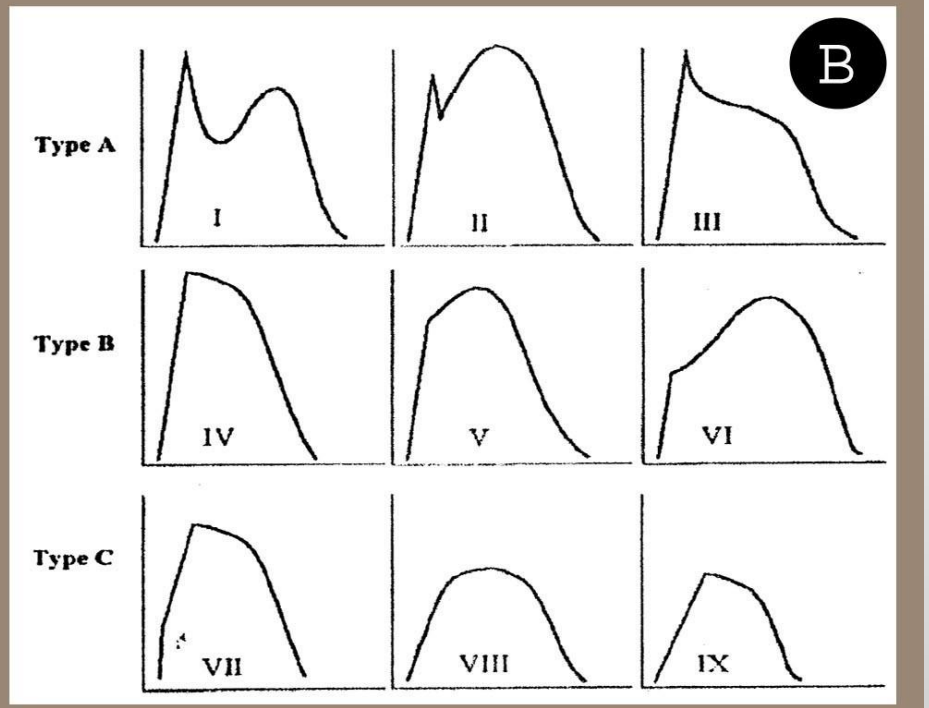
Duplex Assessment of RAS

Duplex Criteria	Stenosis
RAR<3.5 and PSV<200 cm/sec	0-59%
RAR >3.5 and PSV>200 cm/sec	60-99%
RAR>3.5 and EDV > 150 cm/sec	80-99%
Absence of flow and low amplitude parenchymal signal	Occluded

NEIAMS



tardus-parvus” waveform



Evaluating for Secondary Causes of Hypertension

It is also important to consider which individuals are the most likely to benefit from invasive intervention of a discovered stenotic lesion, including those with a solitary kidney or severe bilateral disease with rapidly rising creatinine, significant acute kidney injury in the presence of an ACE inhibitor/ARB and a diuretic, documented fibromuscular dysplasia (especially common among younger women), or known RAS with flash pulmonary edema.

Aspirin and statin initiation along with smoking cessation should be considered for any individual with suspected RAS who develops refractory hypertension despite optimal medical therapy

Evaluating for Secondary Causes of Hypertension

Case 7: *A 36-year-old woman with obesity (BMI > 40 kg/m²), type 2 diabetes mellitus, and hyperlipidemia presents with a new diagnosis of hypertension. Despite successfully losing 30 pounds over the summer, she has been unable to keep the weight off in the subsequent winter months. She joined a gym, but chronic back and knee pain have prevented her from a regular exercise routine. With these efforts, discontinuation of all NSAIDs for her pain control, and initiation of lisinopril at 20 mg daily, her BP is mildly improved to 145/83 mm Hg on AOBP in the clinic. She is provided with a 24-hour ABPM before referral for polysomnography testing.*

Question 7: Which of the following findings on 24-hour ABPM would be most suggestive of a diagnosis of OSA?

(a) Elevated BP readings between 3 PM and 5 PM.
(b) Elevated BP readings between 12 AM and 5 AM.
(c) Low BP readings between 6 PM and 9 PM.
(d) Low BP readings upon awakening at 7 AM.

OSA remains highly prevalent in individuals with RHTN, characterized by intermittent hypoxia episodes that track with nighttime increases in BP ("nondipping")

Increased fluid retention along with supine positioning may increase upper airway edema in those at highest risk, which may improve with diuretic therapy.

Although CPAP treatment for at least 4 hours per night can result in a 2- 5 mm Hg drop in systolic BP (though even more in those with superior adherence or RHTN), adjunctive pharmacologic agents targeting these systems, including longacting ARBs, α-β blockers, and central α2-agonists given at bedtime, remain essential.

Chronic Kidney Disease

Hypertension is highly prevalent among those with CKD.

Increased activity of both the renin-angiotensinaldosterone system and sympathetic nervous system due to decreased overall glomerular filtration rate leads to sodium avidity and subsequent volume expansion.

Along with the direct deleterious effects of sodium on the vasculature itself, leading to accelerated arteriosclerosis, the ongoing sodium and water reabsorption complicate the treatment of hypertension in the CKD population.

The CLICK trial showed that thiazide diuretics can be used safely and effectively alongside loop diuretics in this population to help counteract the volume overload that leads to hypertension.

Dietary sodium restriction remains the cornerstone of treatment, increasing the efficacy of antihypertensive medications and potentially slowing CKD progression.

Optimizing Pharmacologic Therapies

Case 8: *A 72-year-old man with heart failure with reduced ejection fraction, stage 4 CKD, and a diagnosis of hypertension since his early 30s, presents to the clinic 3 months after a non-ST elevation myocardial infarction. His BP has remained uncontrolled, with an AOBP reading of 164/63 mm Hg, despite lisinopril 40 mg once daily, amlodipine 5 mg twice daily, and metoprolol 100 mg twice daily. Recent laboratory testing shows acute kidney injury, with creatinine elevated to 3.4 mg/dL (baseline 2.5 mg/dL), as well as potassium (K^+) of 5.4 mEq/L.*

Question 8: Which of the following medication adjustments is indicated at this time?

(a) Addition of daily eplerenone at 25 mg
(b) Substitution of twice daily metoprolol at 100 mg with daily bisoprolol at 10 mg
(c) Decrease of daily lisinopril to 20 mg and addition of daily chlorthalidone at 12.5 mg
(d) Discontinuation of lisinopril with replacement of daily spironolactone at 25 mg

Thiazide-like diuretics, such as chlorthalidone and indapamide, have longer half-lives than hydrochlorothiazide and tend to be more effective antihypertensive agents within this class.

Hyperkalemia, especially in the setting of ongoing ACE inhibitors or ARB therapy and CKD, is the most common adverse effect of MRAs

Longer-acting options with high oral bioavailability such as torsemide are preferred over shorter-acting agents such as furosemide that have less predictable bioavailability and require multiple daily doses.

Optimizing Pharmacologic Therapies

Table 6. Less Common Endocrinologic Etiologies of Secondary Hypertension

Condition	Clinical Clues to Diagnosis	Screening Tests	Additional Evaluation or Confirmatory Testing
Pheochromocytoma / paraganglioma	• Paroxysmal hypertension + headache, palpitations, pallor and "cold sweat" • Family history of diagnosis	Levels typically >4 times the upper limit of normal in: • Plasma free metanephrines (preferred initial test, with high sensitivity and specificity) • 24-Hour urinary fractionated metanephrines (highest sensitivity, but prone to collection error) Note that false-positive results may occur in the setting of tricyclic antidepressants, other medications interfering with adrenergic receptors, and physical stress/illness (ie, during hospitalization).	CT or MRI of abdomen and pelvis (95% of tumors). Imaging characteristics include: • >3 cm • increased vascularity • >20 HU on noncontrast CT • high signal intensity of T2-weighted MRI Note that 40% of these tumors are due to germline variant, for which genetic testing for VHL, MEN2, NF1, and SDH variants should be performed in all patients with a confirmed diagnosis.
Cushing syndrome	• Changes in mood • Altered menstruation patterns • Proximal muscle weakness or atrophy • Easy bruising • Weight gain along with abdominal striae • Hirsutism • Dorsal and/or supraclavicular fat • Difficulties with glucose control	First-line testing includes (initial testing varies by center, often repeated for those with higher suspicion): • Bedtime salivary cortisol • 24-Hour urinary free cortisol excretion • Overnight dexamethasone suppression testing	• Rule out physiologic hypercortisolism (physical or psychological stress, alcohol withdrawal, morbid obesity, pregnancy). • Endocrinology referral
Hypothyroidism	• Constipation • Cold intolerance • Dry/cold skin • Weight gain	TSH (high) and low/normal free T_4	Not applicable
Hyperthyroidism	• Diarrhea • Heat intolerance • Moist/warm skin • Weight loss • Tremulousness • Proximal muscle weakness	TSH (low) and high/normal free T_4 and T_3	Radioactive iodine uptake and scan
Apparent mineralocorticoid excess	• Hypokalemia and metabolic alkalosis • Arrhythmias • Licorice ingestion • Triazole antifungal medications (ie, posaconazole)	Low aldosterone and low renin levels	• Urinary free cortisol/cortisone ratio (defective 11-β HSD2 enzyme leads to very low cortisone and high ratio) • Deoxycortisone levels • Genetic testing for Liddle's syndrome (milder phenotypes can present later in life)

Chronic Kidney Disease

Although non-dihydropyridine CCBs may have mild antiproteinuric effects in combination with reninangiotensin-aldosterone system inhibitors, their BP-lowering effects have not been compared with newer agents of particular utility in the setting of proteinuria (i.e., sodium/glucose cotransporter 2 [SGLT2] inhibitors or GLP-1 receptor agonists).

Anyone who requires 5 or more medications for BP management, regardless of whether the BP has reached the target, should be considered to have **refractory hypertension, a subtype of RHTN**.

Many clinicians may find that their patients are already taking sympatholytic agents such as β-blockade (typically with α activity for vasodilatory effect) due to comorbidities such as heart failure, atrial fibrillation, or recent myocardial infarction, given their overall mortality benefit in these patient populations.

Additional sympatholytic agents with antihypertensive action include central α2-agonists (clonidine, guanfacine), α1 antagonists (doxazosin), and direct arterial vasodilators (hydralazine, minoxidil), all of which can be quite effective when utilized in this context but can also lead to significant adverse effects,

Renal Denervation

Case 9: *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 α-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).*

Question 9: Which of the following is true regarding RDN?

(a) Beneficial effects of RDN have been limited to patients with RHTN.
(b) RDN may be recommended in patients with multiple medication intolerances.
(c) Second-generation sham-controlled trials showed an increased risk of RAS.
(d) RDN can be expected to lower systolic BP by 10-12 mm Hg.

RDN is a novel nonpharmacologic treatment that can lower BP by targeted catheter-based treatments to ablate the renal sympathetic nerves.

Pharmacologic management of resistant hypertension

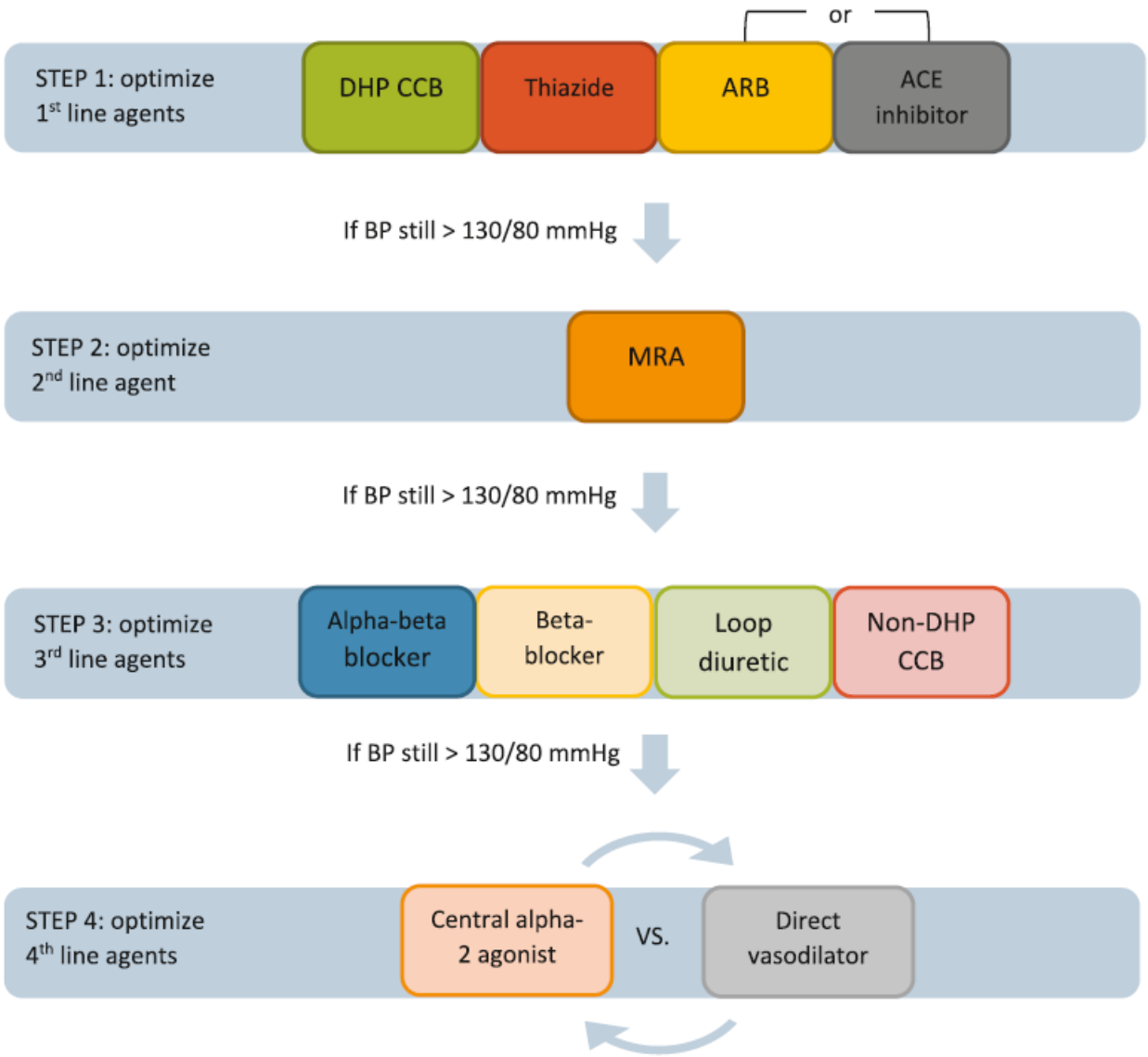


Figure 2. Pharmacologic management of resistant hypertension. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DHP CCB, dihydropyridine calcium channel blocker; MRA, mineralocorticoid receptor antagonist.

با سپاس و قدردانی از اساتید گرانقدر و حضار محترم.