

Hypertension

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OUTLINE

- DEFINITIONS
- Diagnosis
- Risk factors
- Major causes
- COMPLICATIONS
- TREATMENT
- RESISTANT

- Among nonpregnant adults in the United States, treatment of hypertension is the most common reason for office visits
- **one-half** of hypertensive individuals do not have adequate blood pressure control
- High blood pressure is a major risk factor for heart disease and stroke
- The prognostic significance of systolic and diastolic blood pressure as a cardiovascular risk factor appears to be age dependent.
- The systolic pressure and the pulse pressure are greater predictors risk in patients over the age of **50 to 60 years** .
- **Under age 50** years, diastolic blood pressure is a better predictor of mortality

DEFINITIONS

- **Normal blood pressure** – Systolic <120 mmHg and diastolic <80 mmHg
- **Elevated blood pressure** – Systolic 120 to 129 mmHg and diastolic <80 mmHg
- **Hypertension:**
 - Stage 1 – Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg
 - Stage 2 – Systolic at least 140 mmHg or diastolic at least 90 mmHg
- **Isolated systolic** hypertension is defined as a blood pressure ≥ 130 mmHg systolic and <80 mmHg diastolic
- **Isolated diastolic** hypertension is defined as a blood pressure <130 mmHg systolic and ≥ 80 mmHg diastolic.

methods to properly measure blood pressure

- Automated office blood pressure (AOBP)
- Standardized office blood pressure
- Self-measured blood pressure (ie , home blood pressure)
- 24-hour ambulatory blood pressure

Diagnosis

- ABPM records the blood pressure preset intervals (usually every 15 to 20 minutes during the day and every 30 to 60 minutes during sleep).
- A 24-hour mean of ≥ 125 mmHg systolic or ≥ 75 mmHg diastolic
- Daytime (awake) mean of ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic
- Nighttime (asleep) mean of ≥ 110 mmHg systolic or ≥ 65 mmHg diastolic
- Home blood pressure readings that average $\geq 130 / \geq 80$ mmHg
- White coat hypertension :blood pressure that is consistently elevated by office readings but does not meet diagnostic criteria for hypertension based upon out-of-office readings
- Masked hypertension :blood pressure that is consistently elevated by out-of-office measurements but does not meet the criteria for hypertension based upon office readings

Definition of hypertension based on blood pressure measurement strategy

SBP/DBP	Clinic	SMBP	Daytime ABPM	Nighttime ABPM	24-hour ABPM
ACC/AHA guidelines 2017 ^[1]	≥130/80	≥130/80	≥130/80	≥110/65	≥125/75
ESC guidelines 2024 ^[2]	≥140/90	≥135/85	≥135/85	≥120/70	≥130/80

ABPM: ambulatory blood pressure monitoring; ACC/AHA: American College of Cardiology/American Heart Association; DBP: diastolic blood pressure; ESC: European Society of Cardiology; SBP: systolic blood pressure; SMBP: self-measured blood pressure.

Proper technique

- Device is calibrated
- Support the patient's arm
- Repeated at least twice (repeated by 1 to 2 minutes)
- In both arms (at least at the initial visit)
- Higher of the two should be used for measurement at subsequent visits.
- In older individuals or those with potential orthostatic symptoms, postural measurements should also be taken
- Avoid exercise , caffeine and nicotine within 30 minutes
- Use an appropriately sized cuff (bladder is 40 percent of the circumference and covers 80 percent of the area from the elbow to the shoulder).

Home blood pressure monitoring and prepare the patient

- Quiet room
- Rest comfortably for at least five minutes(feet on floor , back support)
- Ensure patient has emptied their bladder
- Remove all clothing covering the location of cuff placement
- Seated position
- Back and arm supported
- legs uncrossed
- At least 12 to 14 measurements should be obtained, with both morning and evening measurements taken
- Over a period of one week every month

Arm circumference	Usual cuff size
22 to 26 cm	Small adult
27 to 34 cm	Adult
35 to 44 cm	Large adult
45 to 52 cm	Adult thigh

- Either unattended or attended automated office blood pressure (AOBP) measurement predict the results of awake ABPM better than traditional office blood pressure measurement and may reduce the white coat effect
- A discrepancy of more than 15 mmHg may indicate subclavian stenosis
- Postural hypotension, defined as a 20 mmHg or greater fall in systolic pressure upon rising from supine to an unassisted upright position, should be pursued in patients over age 65 years, those experiencing dizziness or weakness upon standing, or those with diabetes or Parkinson disease.
- ABPM predicts target-organ damage and cardiovascular events better than office blood pressure

ABPM indication

- Suspected episodic hypertension (eg, pheochromocytoma)
- Determining therapeutic response (ie, blood pressure control) in patients who are known to have a substantial white coat effect
- Hypotensive symptoms while taking antihypertensive medications
- Resistant hypertension
- Autonomic dysfunction
- Suspected masked hypertension

The primary factors determining the blood pressure

- Sympathetic nervous system
- Renin-angiotensin-aldosterone system
- Plasma volume (largely mediated by the kidneys)
- Blood pressure (BP) = Cardiac output (CO) x Systemic vascular resistance (SVR)

Risk factors for primary (essential) hypertension

- Age
- Obesity
- Family history (approximately twice as common in subjects who have one or two hypertensive parents)
- Race (more common, more severe, earlier in life, and be associated with greater target-organ damage in Black patients)
- Reduced nephron number
- High-sodium diet
- Excessive alcohol consumption
- Physical inactivity
- Insufficient sleep – Short sleep duration (eg, <7 hours per night)
- History of gestational hypertension or preeclampsia
- Social determinants: low socioeconomic status, lack of health insurance, food and housing insecurity, exposure to discrimination, and lack of access to safe spaces for exercise
- Noise and air pollution

Major causes of secondary hypertension

- Prescription or over-the-counter medications :

- Oral contraceptives
- Nonsteroidal anti inflammatory agents (NSAIDs)
- Acetaminophen, when given at doses of 4 grams per day for several weeks
- Antidepressants: TCA,SSRI,MAOI
- Decongestants
- Corticosteroids
- Glycyrrhizin (traditional black licorice)
- Some weight-loss medications
- Sodium-containing antacids
- Erythropoietin
- Cyclosporine or tacrolimus
- Stimulants, including methylphenidate and amphetamines
- Atypical antipsychotics, including clozapine and olanzapine
- Angiogenesis inhibitors, such as bevacizumab
- Tyrosine kinase inhibitors

Major causes of secondary hypertension

- Primary kidney disease – Both acute and chronic kidney disease
- Primary aldosteronism – should be suspected in any patient with **the triad** of hypertension, unexplained hypokalemia, and metabolic alkalosis.
- Renovascular hypertension- fibromuscular dysplasia in younger patients and to atherosclerosis in older patients.
- Pheochromocytoma - one-half of patients with pheochromocytoma have paroxysmal hypertension
- Obstructive sleep apnea
- Cushing's syndrome
- Endocrine disorders – Hypothyroidism, hyperthyroidism, and hyperparathyroidism
- Coarctation of the aorta

COMPLICATIONS OF HYPERTENSION

- Left ventricular hypertrophy (LVH)
- Heart failure, both reduced ejection fraction (systolic) and preserved ejection fraction (diastolic)
- Ischemic stroke
- Intracerebral hemorrhage
- Ischemic heart disease, including myocardial infarction and coronary artery disease

For every 20 mmHg higher systolic and 10 mmHg higher diastolic blood pressure, the risk of death from heart disease or strokes doubles.

- Chronic kidney disease and end-stage kidney disease

ASSESSMENT

- all individuals **18 years or older** should be properly evaluated, with appropriate technique, for elevated blood pressure in the office or other clinical setting
- Adults with normal blood pressure should undergo reassessment of their blood pressure **every year**
- Adults should be evaluated at least **semiannually** if they have risk factors for hypertension (eg, obesity, type 2 diabetes) or if their previously measured systolic blood pressure was elevated

DIAGNOSIS

- A patient who presents with hypertensive urgency or emergency (ie, patients with blood pressure ≥ 180 mmHg systolic or ≥ 120 mmHg diastolic)
- A patient who presents with an initial blood pressure ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic and who also has known target end-organ damage (eg, left ventricular hypertrophy [LVH], hypertensive retinopathy, ischemic cardiovascular disease)
- In all other patients who have an elevated office blood pressure, the diagnosis of hypertension should be confirmed using out-of-office blood pressure
- patients with masked hypertension should be treated the same as other patients with the diagnosis of hypertension.

DIAGNOSIS

- Hypertension is diagnosed if the mean home blood pressure, when measured with appropriate technique and with a device that has been validated in the office, is ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic.
- ABPM is an alternative to self-measured blood pressure monitoring in settings where **ABPM is readily available**, particularly if adequate home blood pressures **cannot be obtained**, if there is doubt about the validity of home readings, or if there is a large **discrepancy** between office and home readings.
- When using ABPM, hypertension is diagnosed if the mean **daytime blood pressure is ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic**.
- Occasionally, out-of-office confirmation of hypertension is not possible because of issues with availability of equipment, insurance, and cost. In these situations, a diagnosis of hypertension be confirmed by serial (**at least three**) office-based blood pressure measurements spaced over a period of weeks to months with a mean of ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic

EVALUATION

- The extent of target-organ damage, if any
 1. The presence of established cardiovascular or kidney disease
 2. The presence of other cardiovascular risk factors
- Lifestyle factors that could potentially contribute to hypertension
- Potential interfering substances (eg, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs], estrogen-containing oral contraceptives)

Important aspects of the history in the patient with hypertension

Duration of hypertension

Last known normal blood pressure

Course of the blood pressure

Prior treatment of hypertension

Drugs: types, doses, side effects

Intake of agents that may cause hypertension

Nonsteroidal antiinflammatory drugs

Estrogens

Adrenal steroids

Cocaine

Sympathomimetics

Excessive sodium

Family history

Hypertension

Premature cardiovascular disease or death

Familial diseases: pheochromocytoma, renal disease, diabetes, gout

Symptoms of secondary causes

Muscle weakness

Spells of tachycardia, sweating, tremor

Thinning of the skin

Flank pain

Symptoms of target-organ damage

Headaches

Transient weakness or blindness

Loss of visual acuity

Chest pain

Dyspnea

Claudication

Presence of other risk factors

Smoking

Diabetes

Dyslipidemia

Physical inactivity

Dietary history

Sodium

Processed foods

Alcohol

Saturated fats

Psychosocial factors

Family structure

Work status

Educational level

Sexual function

Features of sleep apnea

Early morning headaches

Daytime somnolence

Loud snoring

Erratic sleep

Important aspects of the physical examination in the hypertensive patient

Accurate measurement of blood pressure
General appearance
Distribution of body fat
Skin lesions
Muscle strength
Alertness
Fundoscopy
Hemorrhage
Papilledema
Cotton wool spots
Arteriolar narrowing and arteriovenous nicking
Neck
Palpation and auscultation of carotids
Thyroid
Heart
Size
Rhythm
Sounds

Lungs

Rhonchi

Rales

Abdomen

Renal masses

Bruits over aorta or renal arteries

Femoral pulses

Extremities

Peripheral pulses

Edema

Neurologic assessment

Visual disturbance

Focal weakness

Confusion

Laboratory testing

- Electrolytes (including potassium) and serum creatinine (to calculate the estimated glomerular filtration rate)
- Fasting glucose
- Urinalysis
- Complete blood count
- Thyroid-stimulating hormone
- Lipid profile
- Electrocardiogram
- Calculate 10-year atherosclerotic cardiovascular disease risk

Urinary albumin to creatinine ratio in all patients with diabetes or chronic kidney disease

Echocardiography is a more sensitive means of identifying the presence of left ventricular hypertrophy

Testing for secondary hypertension

- An unusual presentation of hypertension (eg, new onset at an especially young or especially old age, presentation with stage 2 hypertension, abrupt onset of hypertension in a patient with previously normal blood pressure, or significant recent elevation in blood pressure in a patient with previously well-controlled hypertension despite adherence to their antihypertensive regimen)
- Drug-resistant hypertension
- The presence of a clinical clue for a specific cause of hypertension, such as an abdominal bruit (suggestive of renovascular hypertension) or low serum potassium (suggestive of primary aldosteronism)

TREATMENT

- Nonpharmacologic therapy

Lifestyle modification should be prescribed to all patients with elevated blood pressure or hypertension

- Pharmacologic therapy: severely elevated blood pressure , high cardiovascular risk and older adults

Nonpharmacologic therapy

- Dietary **salt** restriction
- **Potassium** supplementation
- **Weight loss**: 0/5 to 2 mmHg for every 1 kg reduction in body weight
- **DASH diets** : high in vegetables, fruits, low-fat dairy products whole grains, poultry, fish, and nuts and low in sweets, sugar- sweetened beverages, and red meats. The DASH dietary pattern is consequently rich in potassium, magnesium, calcium, protein, and fiber but low in saturated fat, total fat, and cholesterol.
- **Exercise** – Aerobic, dynamic resistance and isometric resistance . least three to four sessions per week of moderate-intensity aerobic exercise lasting approximately 40 minutes for a period of 12 weeks.
- Limited **alcohol** intake: no more than two and one alcoholic drinks daily in men and women
- **Stress** management : Meditation, mindfulness, and guided breathing

Who should be treated with pharmacologic therapy?

- Patients with out-of-office daytime blood pressure ≥ 135 mmHg systolic or ≥ 85 mmHg diastolic (or an average office blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic if out-of-office readings are not available)
- Patients with an out-of-office blood pressure (mean home or daytime ambulatory) ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic (or, if out-of-office readings are unavailable, the average of appropriately measured office readings ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic) who have one or more of the following features:
 - Established clinical cardiovascular disease (eg, chronic coronary syndrome [stable ischemic heart disease], heart failure, carotid disease, previous stroke, or peripheral arterial disease)
 - Type 2 diabetes mellitus
 - Chronic kidney disease
 - Age 65 years or older
 - An estimated 10-year risk of atherosclerotic cardiovascular disease of at least 10 percent

When to initiate treatment with one drug (monotherapy)

- In patients with stage 1 hypertension (systolic pressure 130 to 139 mmHg and/or diastolic pressure 80 to 89 mmHg)
- Patients who are deemed to be at higher risk for adverse effects as
 - Those adhering to a very low salt intake
 - Those who are underweight or frail
 - Those with a known orthostatic decline in blood pressure
 - Those with a history of multiple drug allergies or intolerances

When to initiate treatment with two drugs (combination therapy)

- patients with stage 2 hypertension (systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg)
- Combination therapy lowers blood pressure more than monotherapy
- Increases the likelihood that target blood pressure will be achieved in a reasonable time period
- Reducing the risk of dose-related side effects

single pill OR free equivalents

- Patients with a history of multiple drug allergies or intolerances, starting with one drug and then adding a second agent several weeks later
- single pill reduces the risk of cardiovascular disease and mortality compared with free equivalents

single pill disadvantage

- Single-pill combinations are often more expensive
- may not be paid for by prescription drug insurance
- vary in availability by region

Avoid ineffective and/or potentially hazardous two-drug combinations

- Patients should not simultaneously be prescribed both an **ACE inhibitor and an ARB**; combining these drugs is associated with adverse cardiovascular and kidney events
- **Direct renin inhibitor** should not be combined with an ACE inhibitor or ARB
- A **beta blocker** should not be simultaneously prescribed with a **non dihydropyridine** calcium channel blocker (unless needed for blood pressure control in a patient with allergies or intolerances to other antihypertensive drugs)
- The combination of an **alpha blocker** (eg, prazosin) and a **central adrenergic** inhibitor (eg, clonidine) should be avoided, since significant orthostatic hypotension may result
- **Beta blocker** plus a **central adrenergic** inhibitor is a less effective and risky combination and should be avoided

If there are no specific indications for a particular medication based upon comorbidities, most guidelines and recommendations, including the 2017 ACC/AHA guidelines, recommend that initial therapy be chosen from among the following four classes of medications:

- Thiazide-like or thiazide-type diuretics
- Long-acting calcium channel blockers (most often a dihydropyridine such as amlodipine)
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)

Additional considerations in choice of initial therapy:

- An **ACE inhibitor or an ARB** should be used for initial monotherapy in patients who have **diabetic nephropathy** or nondiabetic **chronic kidney disease**, especially when complicated by proteinuria
- **Beta blockers** : ischemic heart disease or heart failure with decreased ejection fraction
- There are some predictable differences, such as **Black patients and older** patients generally responding better to monotherapy with a thiazide diuretic or calcium channel blocker and relatively poorly to an angiotensin-converting enzyme (ACE) inhibitor or beta blocker
- **Amount of blood pressure** reduction is the major determinant of reduction in cardiovascular risk in both younger and older patients with hypertension, not the choice of antihypertensive drug

Combination therapy

- **Initial combination** antihypertensive therapy with two first-line agents of different classes is suggested in any patient whose blood pressure is more than 20 mmHg systolic or 10 mmHg diastolic above their goal blood pressure
- Initial monotherapy is successful in many patients with mild primary hypertension.
- When more than one agent is needed to control the blood pressure, we recommend therapy with a long-acting **ACE inhibitor or ARB in concert with a long acting dihydropyridine calcium** channel blocker. Combination of an ACE inhibitor or ARB with a thiazide diuretic can also be used but may be less beneficial
- If blood pressure remains uncontrolled **despite use of two antihypertensive medications**, we recommend therapy with ACE inhibitor or ARB in conjunction with both a long-acting dihydropyridine calcium channel blocker and a thiazide-like diuretic (chlorthalidone preferred).

- If a long-acting dihydropyridine calcium channel blocker is not tolerated due to **leg swelling**, a non-dihydropyridine calcium channel blocker (ie, verapamil or diltiazem) may be used instead
- **Thiazide** diuretic is a reasonable alternative as monotherapy in patients with edema, osteoporosis, or calcium nephrolithiasis with hypercalciuria
- If a **thiazide-like diuretic is not tolerated** or is contraindicated, a mineralocorticoid receptor antagonist (ie , spironolactone or eplerenone) may be used
- In patients with advanced **chronic kidney disease** or volume retention, the addition of a loop diuretic may be helpful.

Considerations for individualizing antihypertensive therapy

Indication or contraindication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Heart failure with reduced ejection fraction	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Postmyocardial infarction	ACE inhibitor or ARB, beta blocker, aldosterone antagonist
Proteinuric chronic kidney disease	ACE inhibitor or ARB
Angina pectoris	Beta blocker, calcium channel blocker
Atrial fibrillation rate control	Beta blocker, nondihydropyridine calcium channel blocker
Atrial flutter rate control	Beta blocker, nondihydropyridine calcium channel blocker
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hyperplasia	Alpha blocker
Essential tremor	Beta blocker (noncardioselective)
Hyperthyroidism	Beta blocker
Migraine	Beta blocker, calcium channel blocker
Osteoporosis	Thiazide diuretic
Raynaud phenomenon	Dihydropyridine calcium channel blocker

Contraindications

Angioedema	Do not use an ACE inhibitor
Bronchospastic disease	Do not use a non-selective beta blocker
Liver disease	Do not use methyldopa
Pregnancy (or at risk for)	Do not use an ACE inhibitor, ARB, or renin inhibitor (eg, aliskiren)
Second- or third-degree heart block	Do not use a beta blocker, nondihydropyridine calcium channel blocker unless a functioning ventricular pacemaker

Drug classes that may have adverse effects on comorbid conditions

Depression	Generally avoid beta blocker, central alpha-2 agonist
Gout	Generally avoid loop or thiazide diuretic
Hyperkalemia	Generally avoid aldosterone antagonist, ACE inhibitor, ARB, renin inhibitor
Hyponatremia	Generally avoid thiazide diuretic
Renovascular disease	Generally avoid ACE inhibitor, ARB, or renin inhibitor

Blood pressure goals

- <130 mmHg systolic and <80 mmHg diastolic using out-of-office measurements
- <135 mmHg systolic and <85 mmHg diastolic (using out-of-office measurement) or <140 mmHg systolic and <90 mmHg diastolic (using average of appropriately measured office readings) in the following groups of hypertensive patient
 - ✓ Patients with labile blood pressure or postural hypotension
 - ✓ Patients with side effects to multiple antihypertensive medications
 - ✓ Patients 75 years or older with a high burden of comorbidity or a diastolic blood pressure <55 mmHg

Blood pressure goals

- In older adults with severe frailty, dementia, and/or a limited life expectancy, or in patients who are non ambulatory or institutionalized (eg, reside in a skilled nursing facility), we individualize goals and share decision-making with the patient, relatives, and caretakers

However, although cardiovascular events generally decrease with more intensive lowering of blood pressure, the risk of adverse effects, cost, and patient inconvenience increase as more medication is added

Inset 1

Reasons to incorporate other agents earlier in the treatment regimen include:

- A thiazide-like diuretic is useful in patients with osteoporosis, edema, calcium nephrolithiasis with hypercalciuria.
- A beta blocker should generally be used initially in patients with a history of myocardial infarction.
- A mineralocorticoid receptor antagonist is appropriate in patients with HFpEF.
- Drugs such as ARNIs, beta blockers, and mineralocorticoid receptor antagonists should be used initially in patients with HFrEF.

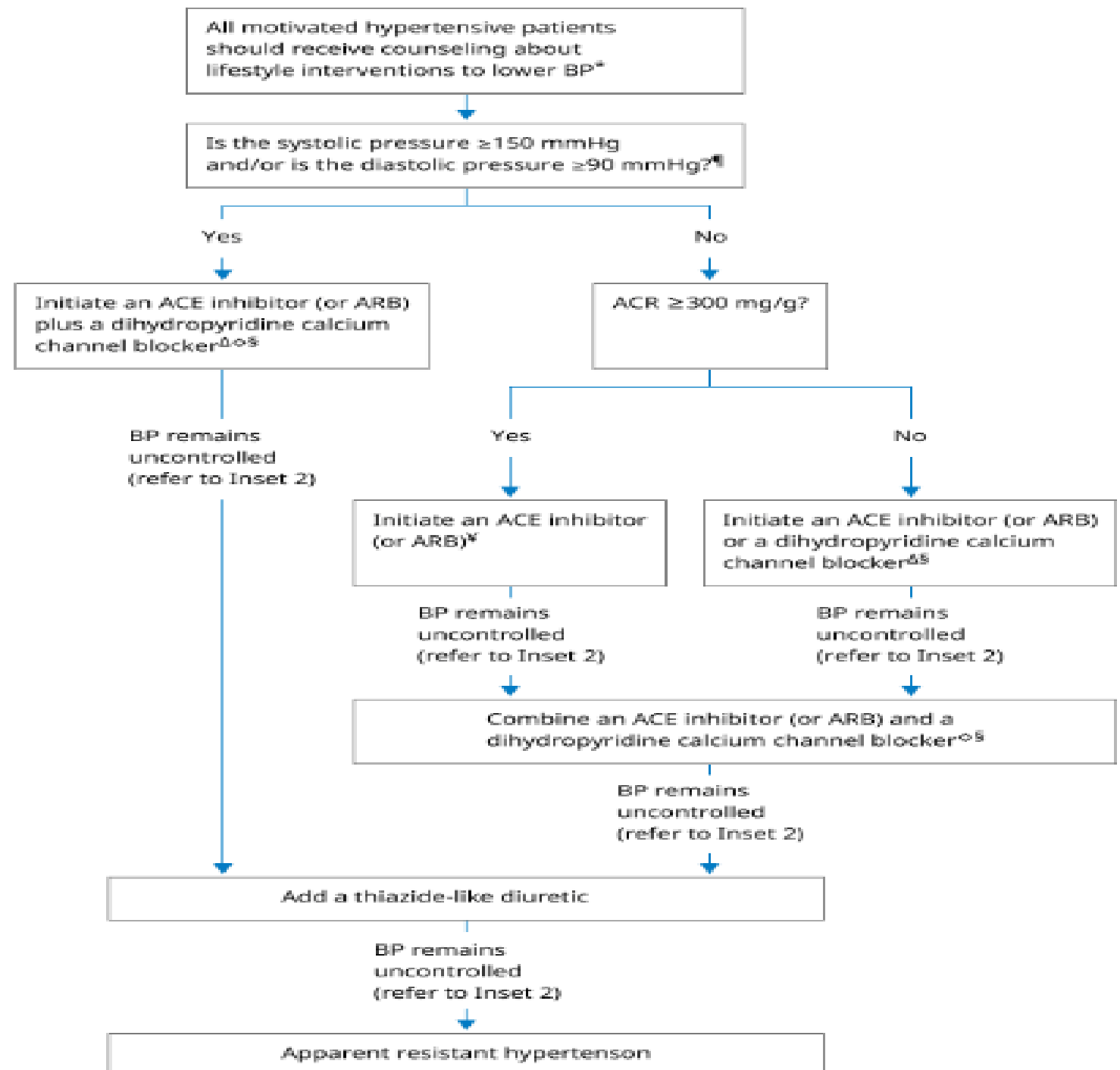
Inset 2

BP control should be reassessed approximately 2 to 4 weeks after initiation or titration of therapy.² 1 or 2 titration steps are appropriate before modifying or adding medication (because titrating drugs to their maximum dose increases the risk of adverse effects while providing diminishing benefits on BP control).

The most common causes of lack of response to antihypertensive drug therapy are:

1. Medication nonadherence
2. White coat effect
3. Improper BP measurement

Thus, when drug therapy interventions appear to be ineffective, the clinician should consider nonadherence and ensure that BP is evaluated properly.



- If the above drug classes cannot be used due to intolerance or contraindication, a **beta blocker, alpha blocker, or direct arterial vasodilators** present other options.
- Patients not controlled on a combination of three antihypertensive medications that are taken at reasonable doses and that include a diuretic are considered to have **drug-resistant hypertension** (once nonadherence and white coat effect have been eliminated as possibilities)
- **Fixed-dose, single-pill** combination medications should be used whenever feasible to reduce the pill burden on patients and improve medication adherence

Thiazide

- Metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia increase with dose
- A possibly more important difference than potency is the longer duration of action of chlorthalidone and indapamide
- Compared with thiazide-type diuretics, **thiazide-like diuretics** significantly lowered the relative risk of cardiovascular events by 12 percent and heart failure by 21 percent.

- Through the course of the study, **systolic blood pressure and LDL** cholesterol levels were also lower with chlorthalidone compared with hydrochlorothiazide
- Other observational studies suggest that chlorthalidone and hydrochlorothiazide lead to **similar rates of cardiovascular** events but that chlorthalidone **increases the risk of adverse metabolic** effects
- Concurrent use of a low-salt diet will both contribute to blood pressure lowering and reduce the risk of hypokalemia

- electrolyte complications, occurs only during the **first two weeks** of therapy before a new steady state is established
- Thus, a stable patient with a normal serum potassium concentration at three weeks is not at risk of late hypokalemia unless the diuretic dose is increased, extrarenal potassium losses increase, or dietary potassium intake is reduced

limitations associated with chlorthalidone

- There is no 12.5 mg chlorthalidone tablet. Thus, 25 mg tablets of generic chlorthalidone need to be cut in half.
- In patients who require combination therapy, fixed dose combination pills of chlorthalidone with ACE inhibitors and long-acting calcium channel blockers are not available (in contrast to hydrochlorothiazide).

Novel treatment of hypertension

- **RNA interference therapies:** Small-interfering RNA(siRNA)targeting angiotensinogen. Twice yearly . In resistant hypertension.
- **Nonsteroidal mineralocorticoid** receptor antagonist: like esaxerenone , AZD9977 and KBP-5074. Fewer side effect compared to traditional steroidal MRAs
- **Aminopeptidase A inhibitors:** inhibiting the conversion of angiotensin 2 to angiotensin 3 (main active peptide in brain RAS) by aminopeptidase A . For example firibastate
- **Endothelin receptor antagonist:** aprocitentan
- **Aldosterone synthetase inhibitors**
- **Atrial natriuretic peptide analogs**
- **Attenuators of hepatic angiotensinogen**
- **Renal denervation**
- **Electrical stimulation of the carotid** sinus baroreceptors

Table 1. Different classes of antihypertensive agents in development

PHARMACOLOGICAL CLASS	Drug/s	Mechanism of action
Non-steroidal mineralocorticoid receptor antagonists	Ocedurenone ²⁴ Esaxerenone ^{25–28}	• Decrease activation of mineralocorticoid receptor by aldosterone^{6–7} • Less sodium and water resorption in the nephron^{6–7}
Aminopeptidase A inhibitors	Firibastat ³⁰	• Decrease angiotensin III^{31–33} • Decrease systemic vasopressin effect³⁴ • Decrease sympathetic tone³⁴ • Stimulate the baroreflex³⁴
Dual endothelin antagonists	Aprocitentan ³⁵	• Vasodilation³⁶
Aldosterone synthetase inhibitors	Baxdrostat ⁴⁷	• Decrease aldosterone production⁴⁶
Atrial natriuretic peptide analogs	M-atrial natriuretic peptide (MANP) ^{51–53}	• Increase cGMP⁵¹
Attenuators of hepatic angiotensinogen	IONIS-AGT-L _{Rx} ⁵⁶ Zilebesiran ⁵⁷	• Decrease angiotensinogen activity^{55–56}
PROCEDURAL THERAPY	Device/s	Mechanism of action
Renal denervation	Spyral catheter ^{63–64}	• Decrease sympathetic activity⁵⁹
Carotid baroreflex activation therapy	Rheos ^{70–72} Neo ^{70–72}	• Increase baroreceptor stimulation^{70–71} • Decrease sympathetic tone^{70–71}
Endovascular baroreflex amplification	MobiusHD ⁷³	• Increase baroreceptor sensitivity⁷³ • Decrease sympathetic tone⁷³

Non-steroidal mineralocorticoid receptor blockers

- Renal epithelial cells, aldosterone binds to the MR, causing water and sodium reabsorption, thereby elevating blood pressure
- Spironolactone use may not be appropriate in patients with advanced renal dysfunction (estimated glomerular filtration rate [eGFR])
- Steroidal MRAs benefit patients with chronic kidney disease (CKD) by decreasing proteinuria and improving blood pressure
- NsMRAs have a higher selectivity for the MR, and stimulate various genomic reactions, thus contributing to a better overall efficacy and safety profile

Non-steroidal mineralocorticoid receptor blockers

- **Esaxerenone** was shown in preclinical studies to have a long half-life (approximately 30 hours), have high oral bioavailability, and be primarily excreted through the gastrointestinal tract
- Compared to spironolactone in hypertensive diabetic mice, showed more significant reductions in albuminuria, glomerular injury, tubulointerstitial fibrosis, inflammation and oxidative stress with similar effects on blood pressure

Aminopeptidase A inhibitors

- In the brain, a metalloprotease called aminopeptidase A (APA) is involved in the renin-angiotensin system through its role in **converting angiotensin II to angiotensin III**.
- Angiotensin III affects blood pressure by increasing central concentrations of vasopressin
- an APA inhibitor, EC33, decrease blood pressure in hypertensive rat models by reducing the levels of brain angiotensin III
- **Firibastat** is a novel prodrug that is metabolized to EC33. It has been shown to decrease blood pressure by reducing systemic vasopressin, decreasing sympathetic tone, and stimulating the baroreflex.
- Firibastat was recently shown to be effective in an 8-week, multicenter, open-label, phase 2b study of 256 patients with stage 2 primary hypertension

Dual endothelin antagonists

- **Endothelin-1** is a peptide produced by vascular endothelial cells which causes vasoconstriction, provokes endothelial dysfunction, stimulates aldosterone synthesis, and increases catecholamine release.
- There are 2 types of endothelin (ET) receptors: ETA and ETB.
- ETB receptors are present on endothelial cells and can mediate vasodilation
- ETA blockade may cause over-stimulation of ETB receptors, leading to nonselective vasodilation, increased vascular permeability, increased peripheral edema, and increased plasma vasopressin and aldosterone levels

Dual endothelin antagonists

- Aprocitentan is a nonselective ERA but has a 16-fold higher affinity for the ETB receptor.³⁵ It has a longer half life of 44 hours
- No serious adverse events were caused by aprocitentan
- There was a dose-dependent decrease in hemoglobin and a dose-dependent decrease in uric acid

Aldosterone synthetase inhibitors

- Hyperaldosteronism causes myriad changes in the heart, kidneys, and blood vessels
- Elevated aldosterone levels independently increase small- and medium-sized arterial injury and fibrosis
- Patients with PA are at an increased risk of developing metabolic syndrome via heightened insulin resistance
- Increased aldosterone levels are an independent risk factor for the development of nephropathy
- Blocking aldosterone decreases proteinuria more than ACE inhibitors or ARBs and is independent of the decrease in blood pressure

Aldosterone synthetase inhibitors

- MRAs are the current mainstay of pharmacologic treatment for patients with PA
- They can cause adverse effects such as hyperkalemia, gynecomastia, erectile dysfunction, and disturbances in menstruation
- The first ASI studied in humans was **baxdrostat**, an imidazole derivative, which showed a dose-dependent decrease in plasma and urine aldosterone levels with no change in plasma cortisol

Atrial natriuretic peptide analogs

- Activation of GC-A by ANP mediates arterial blood pressure and intravascular volume homeostasis through a variety of mechanisms, including inhibition of renin release from the kidney, inhibition of aldosterone release from the adrenal glands, prevention of angiotensin II-induced vasoconstriction, reduction of aldosterone-induced nuclear translocation of the MR, increased renal blood flow, and decreased sodium reabsorption in the renal tubules.
- Intravenous infusions of synthetic ANP have been shown to reduce blood pressure and increase natriuresis in hypertensive and normotensive subjects

Atrial natriuretic peptide analogs

- M-atrial natriuretic peptide (MANP) is a **MANP**, 40 amino acid designer natriuretic peptide that activates the GC-A receptor stimulating the generation of its second messenger, cGMP.
- After binding to GC-A in the kidney, the vasculature, and the adrenal gland, MANP mediates natriuresis, vasodilatation, and aldosterone inhibition
- Minor side effects : mild headache, lightheadedness, and orthostatic vasovagal syncope

Attenuators of hepatic angiotensinogen

- **IONIS-AGT-LRx** is an antisense oligonucleotide (ASO) that reduces plasma AGT levels by AGT mRNA knockdown in the hepatocytes
- Safety and tolerability were confirmed in phase 1 clinical trials in healthy volunteers up to a dose of 80 mg.
- No significant effect was seen on blood pressure, renin, angiotensin II, brain natriuretic peptide, or atrial natriuretic peptide
- There were no serious adverse events, hypotension, hyperkalemia, or GFR

Attenuators of hepatic angiotensinogen

- **Zilebesiran** is an investigational subcutaneous RNA interference (RNAi) therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension
- Mean reductions in 24-hour SBP of >20 mmHg were observed at a dose of 800mg at 6 months

Renal denervation

- This procedure involves catheter-based radiofrequency ablation of the renal nerve
- A meta-analysis of 7 randomized, blinded, sham-controlled renal denervation trials, which included 1,368 patients, found significant reductions in ambulatory and office blood pressures after denervation compared to the sham procedure

Carotid baroreceptor stimulation

- Baroreceptors in the carotid sinus can detect intra-arterial pressure via wall stretching and receptor deformation.
- The receptors then provide negative feedback by decreasing sympathetic and parasympathetic tone to reduce blood pressure.
- Sensitivity of the baroreceptors is hypothesized to be attenuated by various factors, including vessel wall stiffness, atherosclerosis, genetic differences, receptor damage, and changes in the coupling of the receptors and vessels.
- **Rheos** and the second-generation **Neo** are implantable pulse generators that significantly lower blood pressure through BAT
- Complications included nerve injury, dysphagia, dysphonia, hematoma, and hypotension.

Patients with CKD

- Moderately increased albuminuria – ACE inhibitor or ARB
- CKD with normal albumin excretion – different opinions, since hypertension is more difficult to treat in patients with CKD , and therefore such patients require multiple drugs
- Most patients with CKD will require diuretic therapy

Patients with orthostatic hypotension

- **Choice of pharmacologic therapy** – same as in patients without orthostatic blood pressure, diuretics may exacerbate orthostatic hypotension, Alpha blockers, central adrenergic inhibitors, and nitrates should be avoided
- **Goal blood pressure** – we use standing (rather than seated) measurements determine if the patient's blood pressure is at goal

withholding antihypertensive therapy

- Those with recurrent falls
- Dementia
- Multiple comorbidities
- Orthostatic hypotension
- Residence in a nursing home
- limited life expectancy

Patients who could become pregnant

- Initiate a **dihydropyridine calcium channel blocker** (eg , nifedipine extended release or amlodipine)
- If additional agents are needed, we use **thiazide-like diuretics** (eg , chlorthalidone) and certain **beta blockers** (eg , labetalol, carvedilol, metoprolol)
- ACE inhibitors and ARBs are avoided in this setting because of potential teratogenicity

Follow up

- After antihypertensive therapy is initiated, patients should be followed every **two to four weeks** until their blood pressure is at goal.
- If blood pressure is uncontrolled, we typically escalate doses of individual antihypertensive drugs to at least half the maximum recommended dose (ie, to a moderate or high dose) before adding additional therapy
- Once blood pressure control is achieved, patients should be reevaluated every **three to six months** to ensure maintenance of control
- Electrolyte and creatinine : **1 to 3 weeks** after ACEI, ARB AND diuretics
- Patients with white coat hypertension should undergo reevaluation with out-of-office blood pressure monitoring at least **yearly**.

Resistant hypertension

Prevalence of resistant hypertension (RH) is estimated to be 13.7%.

Resistant hypertension is defined as blood pressure that is not controlled to goal despite adherence to an appropriate regimen of **three antihypertensive drugs of different classes (including a diuretic)** in which all drugs are prescribed at suitable antihypertensive doses and after white coat effect has been excluded.

- Extracellular volume expansion
- Increased sympathetic activation
- Ingestion of substances that can elevate the blood pressure, such as nonsteroidal anti inflammatory drugs (NSAIDs) or stimulants
- Secondary or contributing causes of hypertension

- **Hypokalemia** is a more common problem in patients with resistant hypertension due at least in part to higher aldosterone levels
- Serum **brain-type natriuretic peptide** and atrial natriuretic peptide levels were significantly higher among patients with resistant hypertension compared with controls, suggesting hypervolemia
- **Diuretics should be titrated** until the blood pressure goal is attained, the maximum recommended dose of the medication has been reached, or the patient develops signs suggestive of hypovolemia (eg, fatigue, orthostatic hypotension, or decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the serum creatinine concentration).
- In patients without severe renal impairment, the thiazide-like diuretics, including chlorthalidone and indapamide, are preferred over hydrochlorothiazide for the treatment of resistant hypertension

- In patients with resistant hypertension and uncontrolled blood pressure despite potent diuretic therapy, we suggest adding a **mineralocorticoid receptor** antagonist
- We usually begin spironolactone at 12.5 mg once daily (which requires splitting of a 25 mg tablet) before titrating to 25 and, if necessary, 50 mg once daily
- We generally do not increase the spironolactone dose above 50 mg once daily unless the patient has proven primary aldosteronism.
- Eplerenone is less potent and often requires **twice-daily**

- Amiloride may be an effective alternative as the fourth-line medication in resistant hypertension
- A **vasodilating beta blocker**, such as labetalol, carvedilol, or nebivolol may provide more antihypertensive benefit with fewer side effects compared with traditional beta blockers, particularly when high doses are used
- Other medication options include **alpha-1 antagonists** such as doxazosin or direct vasodilators (hydralazine or minoxidil)
- Fluid retention and tachycardia are common side effects, and loop diuretics are often needed to control hypervolemia
- **Minoxidil** also causes hirsutism, which may be a particular problem in women

Refractory hypertension

- uncontrolled blood pressure despite prescription of five or more antihypertensive drugs
- Those have higher rates of kidney failure and cardiovascular disease

Pseudo resistance

- Inaccurate blood pressure measurement (eg, use of an inappropriately small blood pressure cuff, not allowing a patient to rest quietly before taking readings)
- Poor adherence to blood pressure medications
- Poor adherence to lifestyle and dietary approaches to lower blood pressure
- Suboptimal antihypertensive therapy, due either to inadequate doses, an inappropriate drug combination, or exclusion of a diuretic from the antihypertensive regimen
- White coat hypertension

Our strategies to prevent nonadherence

- Prescribe long-acting rather than short-acting medications and specifically those that are dosed once daily
- Prescribe single-pill combinations rather than free equivalents (ie , combination therapy as separate pills)
- Synchronize prescriptions so as to minimize the need for repeated trips to the pharmacy for refill
- Counsel patients that, as their blood pressure falls, they may have symptoms of fatigue, but that these symptoms are typically transient and that the medications should be continued

Hypertensive emergency and urgency

- Severe hypertension (usually a diastolic blood pressure above 120 mmHg) with evidence of acute end-organ damage is defined as a hypertensive emergency
- Hypertensive emergencies can be life-threatening and require immediate treatment, usually with parenteral medications in a monitored setting
- Severe hypertension (usually a diastolic blood pressure above 120 mmHg) in asymptomatic patients who are not experiencing acute end-organ damage is referred to as hypertensive urgency
- There is no proven benefit from rapid reduction in blood pressure in such patients

Discontinuation of treatment

- After discontinuation of treatment, a substantial proportion of patients remain normotensive for at least one to two years ; a larger fraction of patients do well with a decrease in the number and/or dose of medications taken
- More gradual tapering of drug dose is indicated in well-controlled patients taking multiple drugs
- Abrupt cessation of some antihypertensive drugs, especially higher doses of short-acting beta blockers (such as **propranolol**) or the short-acting alpha-2 agonist (**clonidine**) can lead to a potentially fatal withdrawal syndrome

When to refer

- If a specific secondary cause of hypertension is suspected
- If the blood pressure remains elevated despite six months of intensive treatment with at least three drugs from those described above

