Novel Approach to Management of Hypertension in People with CKD

Dr Reyhane Motamedi Fard
Assistant Professor of Nephrology
Isfahan University Of Medical Sciences

Introduction

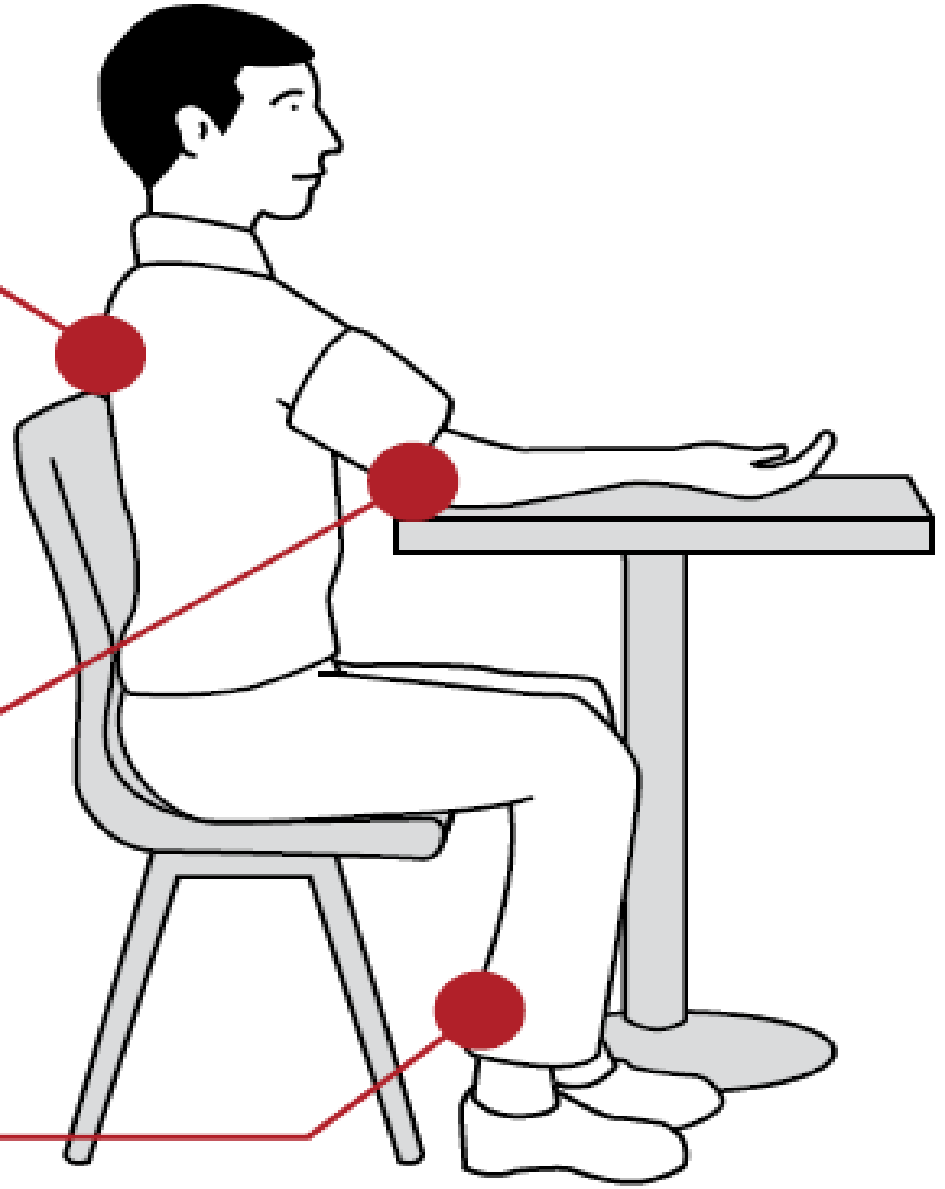
- Hypertension is a major contributing factor for CVD and renal diseases, that can increase the risks of comorbidities such as myocardial infarction, stroke and heart failure
- Classical antihypertensive drugs include renin inhibitor, ACE inhibitors, angiotensin II receptor blockers ,β-adrenoreceptor blockers ,aldosterone-related blocker

Introduction

- Blood pressure control through the administration of first-line classes of antihypertensive drugs has been proven to significantly improve the clinical outcome of hypertension in the overall population and in the subgroups of patients with different degrees of severity of the disease

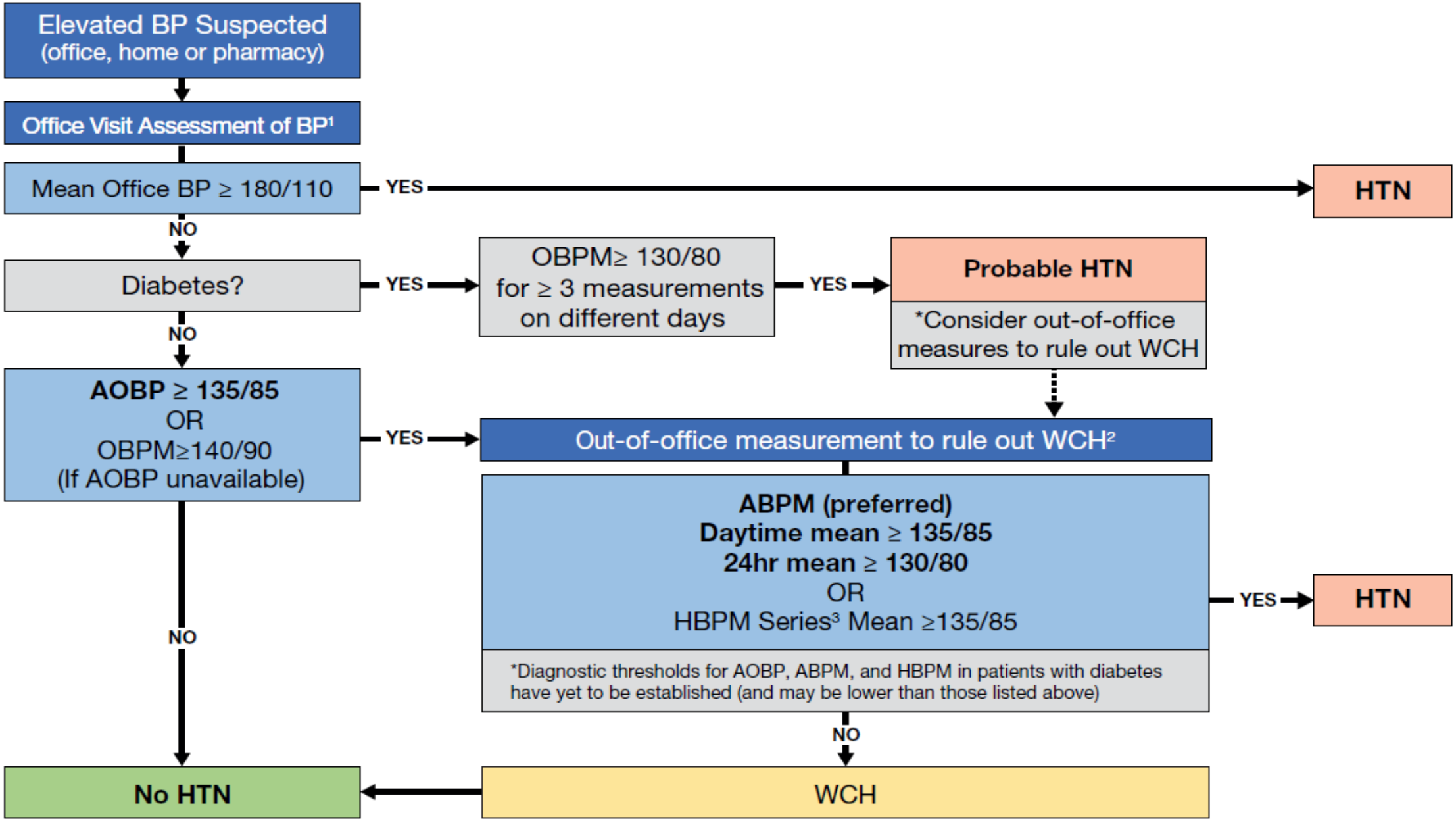
Positions

- ✓ Sitting position
- ✓ Back supported
- ✓ Arm bare and supported
- ✓ Use a cuff size appropriate for your arm
- ✓ Middle of the cuff at heart level
- ✓ Lower edge of cuff 3 cm above elbow crease
- ✓ Do not talk or move before or during the measurement
- ✓ Legs uncrossed
- ✓ Feet flat on the floor



The use of standardized measurement techniques and validated equipment is recommended for all blood pressure (BP) methods.

Acronym	Definition	
AOBP	Automated Office Blood Pressure is performed using an automated device that can take a series of oscillometric measurements without the provider or others present. The patient is left unattended in a private area while 3-6 oscillometric, consecutive readings are taken.	Preferred method of in-office measurement.
OBPM	Office Blood Pressure Measurement is performed using an upper arm device with the provider in the room. Oscillometric or electronic devices are preferred when using this method. Auscultatory – mercury or aneroid – devices are an alternative if an electronic device is not available.	
ABPM	Ambulatory Blood Pressure Monitoring requires the use of a validated oscillometric device which must be worn by the patient for a 24-hour period, with measurements taken at 20- to 30-minute intervals.	Preferred out-of-office method for diagnosis
HBPM	Home Blood Pressure Monitoring is a self-monitoring method which requires the patient to measure their blood pressure twice in the morning and evening for 7 days.	


Elevated BP Suspected
(office, home or pharmacy)
Office Visit Assessment of BP1
Mean Office BP ≥ 180/110
YES
HTN
NO
Diabetes?
YES
OBPM≥ 130/80
for ≥ 3 measurements
on different days
YES
Probable HTN
*Consider out-of-office
measures to rule out WCH
NO
AOBP ≥ 135/85
OR
OBPM≥140/90
(If AOBP unavailable)
YES
Out-of-office measurement to rule out WCH2
ABPM (preferred)
Daytime mean ≥ 135/85
24hr mean ≥ 130/80
OR
HBPM Series3 Mean ≥135/85
YES
HTN
*Diagnostic thresholds for AOBP, ABPM, and HBPM in patients with diabetes
have yet to be established (and may be lower than those listed above)
NO
NO
No HTN
WCH

Health Behaviour Recommendations

Objective	Recommendation	Application
Being More Physically Active	An accumulation of 30-60 minutes of dynamic exercise of moderate intensity (such as walking, cycling, swimming) 4-7 days per week in addition to the routine activities of daily living. Higher intensities of exercise are no more effective at BP lowering. For non-hypertensive or hypertensive individuals with SBP/DBP of 140-159/90-99 mmHg, the use of resistance or weight training exercise (such as free weight lifting, fixed weight lifting, or hand grip exercise) does not adversely influence BP.	Prescribe to both normotensive and hypertensive individuals for prevention and management of hypertension, respectively.
Weight Reduction	A healthy BMI (18.5 – 24.9 kg/m^2) and waist circumference (<102 cm for men and <88 cm for women) is recommended for non-hypertensive individuals to prevent hypertension and for hypertensive patients to reduce BP.	Encourage multidisciplinary approach to weight loss, including dietary education, increased physical activity, and behaviour modification.

Moderation in Alcohol Intake	To prevent hypertension, abstain, as there is no safe limit for alcohol consumption. Patients with hypertension should abstain from, or limit alcohol consumption to <2 drinks per day to lower blood pressure.	Prescribe to normotensive and hypertensive individuals for prevention and management of hypertension, respectively.
Eating Healthier	DASH-like diet: • High in fresh fruits, vegetables, dietary fibre, non-animal protein (e.g., soy) and low-fat dairy products. Low in saturated fat and cholesterol. • To decrease BP in hypertensive patients, consider increasing dietary potassium.	Prescribe to both normotensive and hypertensive individuals for the prevention and management of hypertension, respectively.
Relaxation Therapies	Individualized cognitive behaviour interventions are more likely to be effective when relaxation techniques are employed.	Prescribe for selected patients in whom stress plays a role in elevating BP.
Smoking Cessation	Advise smokers to quit and offer them specific pharmacotherapy to help them quit. Abstinence from smoking. A smoke-free environment.	Global cardiovascular risk reduction strategy.

Populations and Stratification

Hypertension Canada stratifies patients by cardiovascular risk and, based on that risk, there are different thresholds and targets for treatment.

Hypertension Canada *High-Risk* Patient*

Diabetes Mellitus

Moderate-to-high Risk
(multiple cardiovascular risk factors & 10-year global risk 10-14%)

Low Risk
(no TOD or cardiovascular risk factors & 10-year global risk < 10%)

*** Hypertension Canada *High-Risk* Patient**

Individuals ≥50y **AND** with SBP 130-180 mmHg **AND** with one or more of the following CV risk factors should be considered for intensive BP management:

- ✓ Clinical or sub-clinical cardiovascular disease

OR

- ✓ Chronic kidney disease (non-diabetic nephropathy, proteinuria <1g/d, *estimated glomerular filtration rate 20-59 mL/min/1.73m²)

OR

- ✓ Estimated 10-year global cardiovascular risk ≥15%

OR

- ✓ Age ≥75 years

Four variable Modification of Diet in Renal Disease (MDRD) equation

± Framingham Risk Score

Blood pressure thresholds for initiation of antihypertensive therapy and treatment targets in adults:

Patient population	BP threshold for initiation of antihypertensive therapy		BP treatment target	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
Hypertension Canada High-Risk Patient*	≥ 130	N/A	< 120	N/A
Diabetes mellitus**	≥ 130	≥ 80	< 130	< 80
Moderate-to-high Risk (TOD or CV risk factors)**	≥ 140	≥ 90	< 140	< 90
Low Risk (No TOD or CV risk factors)**	≥ 160	≥ 100	< 140	< 90

Criteria for Hypertension Based on Office , ABPM , HBPM

	SBP/DBP, mm Hg
Office BP	≥140 and/or ≥90
ABPM	
24-h average	≥130 and/or ≥80
Day time (or awake) average	≥135 and/or ≥85
Night time (or asleep) average	≥120 and/or ≥70
HBPM	≥135 and/or ≥85

BP targets for individuals with preexisting CKD

1.6.1: In people with CKD aim to keep the systolic BP below 140 mmHg (target range 120–139 mmHg) and the diastolic BP below 90 mmHg [NICE, 2014].

1.6.2: In people with CKD and diabetes, and also in people with an ACR of 70 mg/mmol or more, aim to keep the systolic BP below 130 mmHg (target range 120–129 mmHg) and the diastolic BP below 80 mmHg [NICE, 2014].

The 2017 American Guidelines[2] recommend a lower BP target for all adults with CKD:

9.3: Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mmHg.

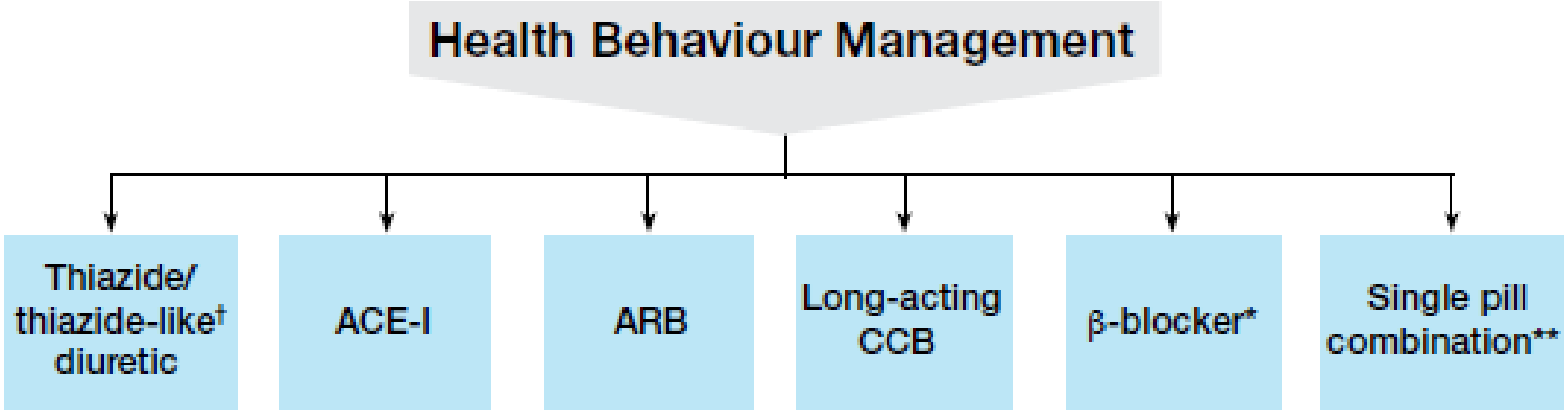
The 2018 European Hypertension guidelines[3] offer a third alternative to the NICE and American recommendations:

8.12: In patients with diabetic or non-diabetic CKD it is recommended to lower SBP to a range of 130–139 mmHg. Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.

Preliminary investigations of patients with hypertension

1. Urinalysis
2. Blood chemistry (potassium, sodium and creatinine)
3. Fasting blood glucose and/or glycated hemoglobin (A1c)
4. Serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), non-HDL cholesterol, and triglycerides; lipids may be drawn fasting or non-fasting
5. Standard 12-lead ECG

First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications



† Long-acting diuretics like indapamide and chlorthalidone are preferred over shorter acting diuretics like hydrochlorothiazide.

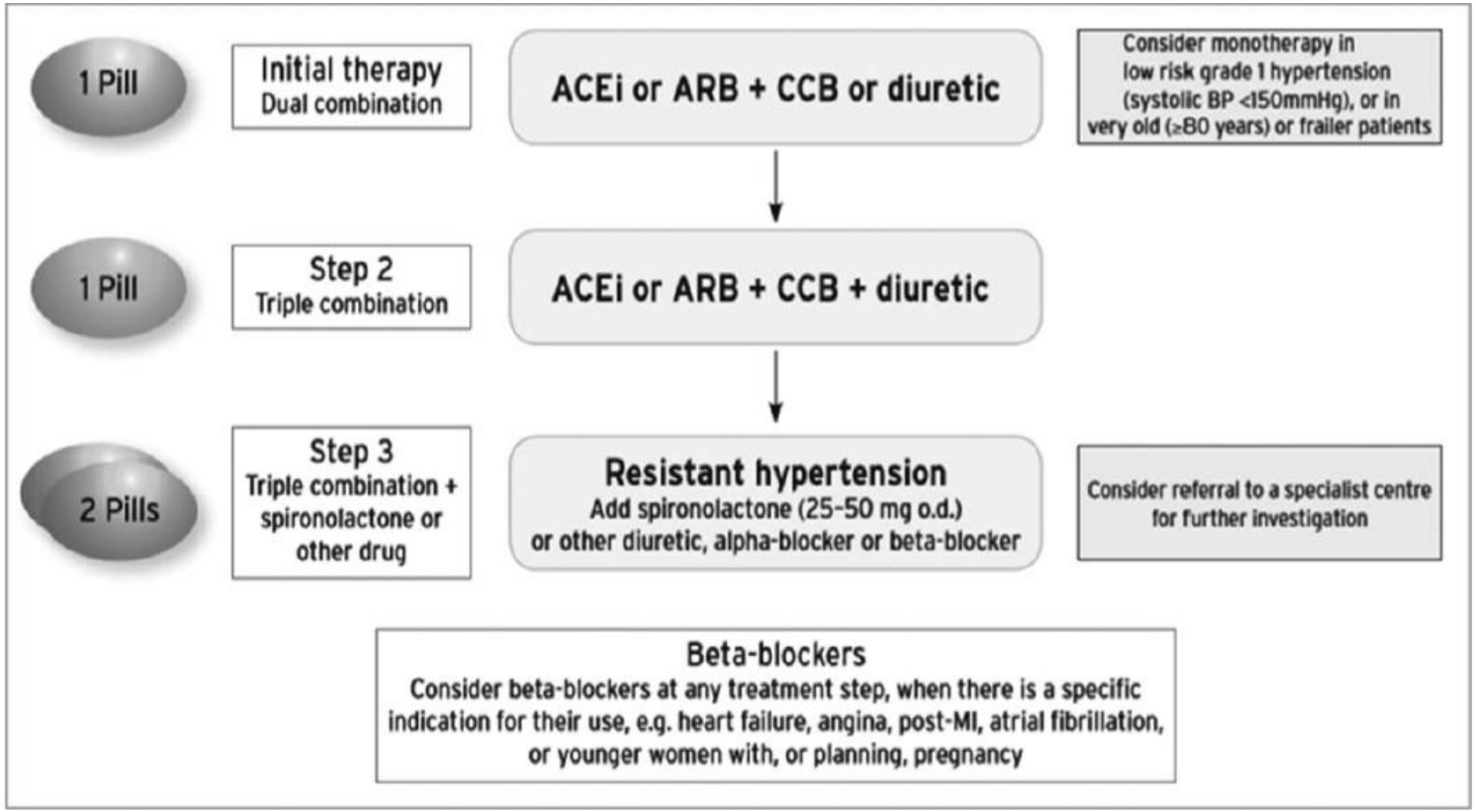
* β-blockers are not indicated as first-line therapy for age 60 and above.

Short-acting nifedipine should not be used for management of hypertension.

First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

** Recommended SPC choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or an ACE-I or ARB with a diuretic

Renin angiotensin system (RAS) inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential


1 Pill
Initial therapy
Dual combination
ACEi or ARB + CCB or diuretic
Consider monotherapy in low risk grade 1 hypertension (systolic BP <150mmHg), or in very old (≥80 years) or frailer patients
1 Pill
Step 2
Triple combination
ACEi or ARB + CCB + diuretic
2 Pills
Step 3
Triple combination + spironolactone or other drug
Resistant hypertension
Add spironolactone (25–50 mg o.d.) or other diuretic, alpha-blocker or beta-blocker
Consider referral to a specialist centre for further investigation
Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

Combination Therapy

- Single pill combinations or monotherapy should be considered for initial antihypertensive therapy
- Low doses of multiple drugs may be more effective and better tolerated than higher doses of fewer drugs

Combination Therapy

- Reassess patients with uncontrolled BP at least every two months.
- The combination of ACE inhibitors and ARBs should not be used
- In patients in whom combination therapy is being considered, an ACE inhibitor plus a long-acting dihydropyridine CCB is preferable to an ACE inhibitor plus a thiazide or thiazide-like diuretic

Antihypertensive medication

- Patients on antihypertensive drug treatment should be seen every 1-2 months, depending on the level of BP, until readings on 2 consecutive visits are below their target
- When the target BP has been reached, patients should be seen at 3- to 6-month intervals

Possible reasons for poor response to antihypertensive therapy

- Inaccurate measurement
- Suboptimal treatment regimens
- Poor adherence
- Associated conditions
- Drug interactions
- Volume overload
- Secondary hypertension

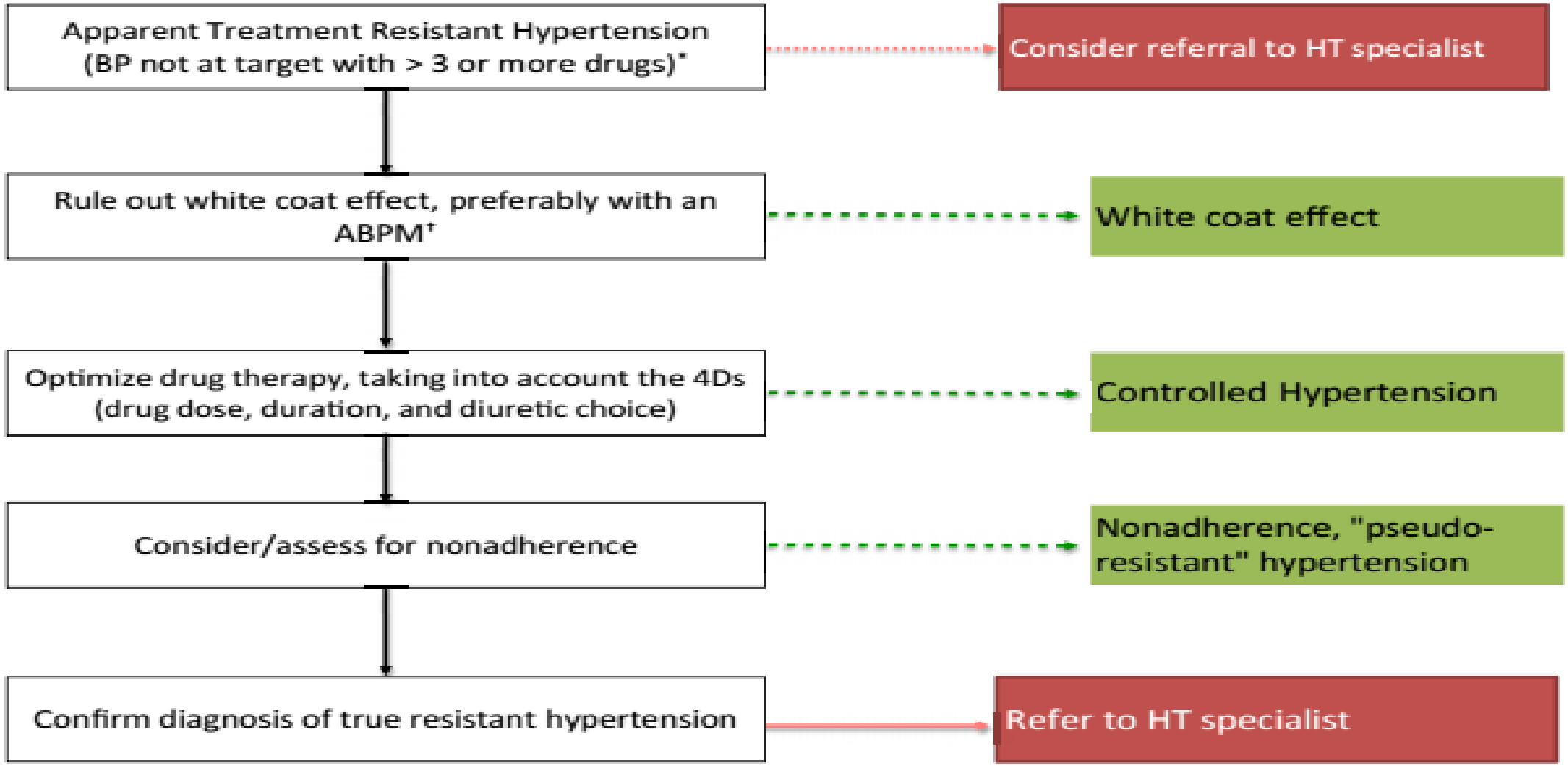
Is it resistant hypertension

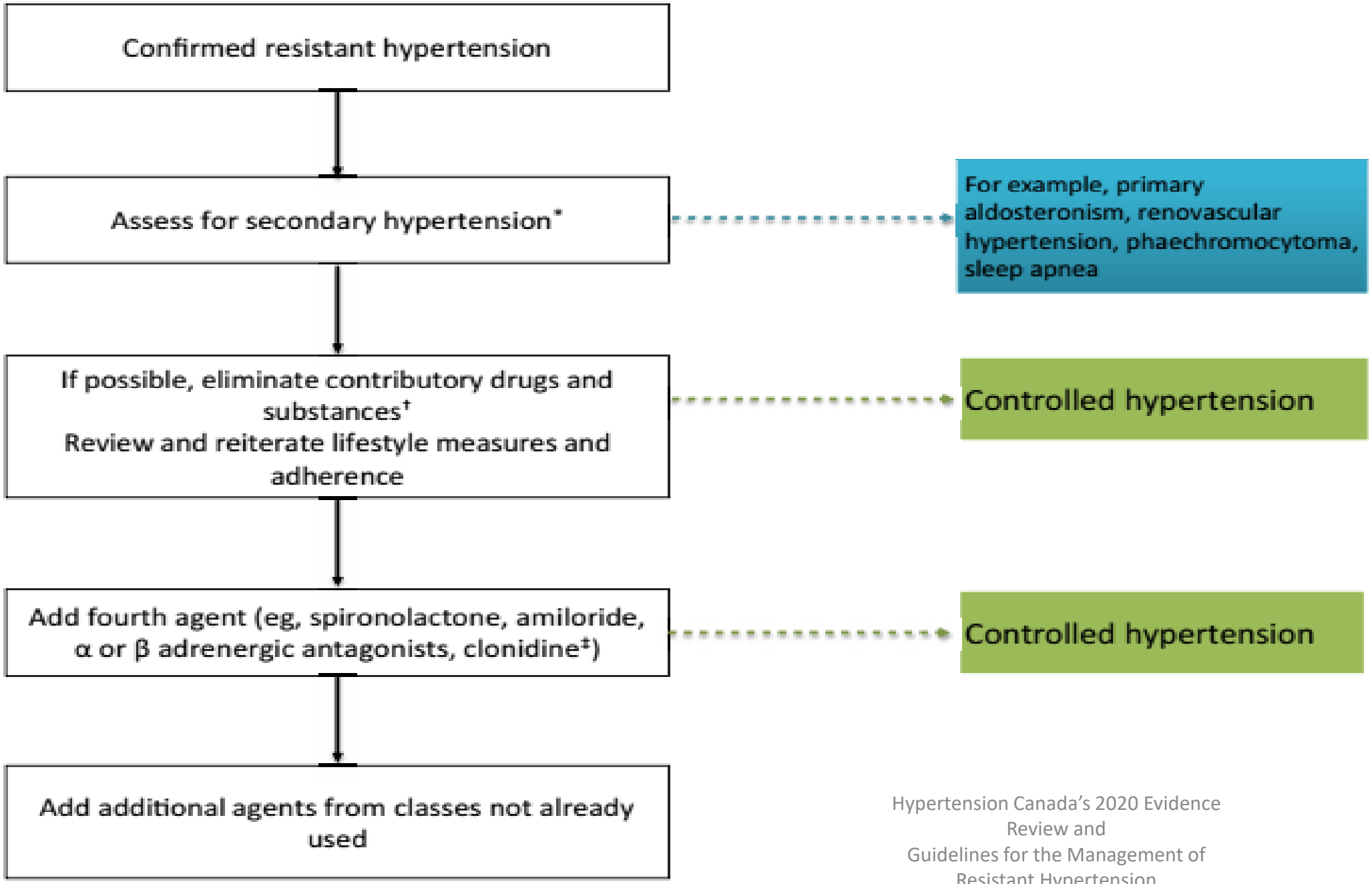
Causes of apparent resistant hypertension

1. nonadherence
2. secondary hypertension
3. white coat effect

These should be ruled out before true resistant hypertension is diagnosed

Management of Resistant Hypertension





Hypertension Canada's 2020 Evidence Review and Guidelines for the Management of Resistant Hypertension

Evaluation of Secondary Hypertension

Disorder	Suggestive Clinical Features	Screening Tests	Confirmatory Tests
Primary aldosteronism	Hypokalemia; metabolic alkalosis; adrenal incidentaloma; HTN onset at young age	PRA, PAC	24-h urine aldosterone or saline suppression testing; if positive proceed with AVS
Renal artery stenosis	Scr increase >50% on ACEi/ARB; diffuse atherosclerotic disease; flash pulmonary edema; females <50 y with recent-onset RH	Renal artery duplex ultrasonography	CTA (preferred initial study when suspecting FMD) or MRA
Pheochromocytoma	Paroxysmal HTN; triad of headache, palpitations, and diaphoresis	Fractionated plasma metanephrines	Adrenal/abdominal MRI or CT
Hyperthyroidism	Heat intolerance; nervousness; insomnia; diarrhea; weight loss	TSH, T_3, fT_4	Radioactive iodine uptake and scan
Hypothyroidism	Dry skin; cold intolerance; constipation; weight gain	TSH, fT_4	
Cushing syndrome	Obesity; facial plethora; proximal myopathy; purple striae; easy bruising; diabetes	Late-night salivary cortisol, 24-h urinary free cortisol, overnight DST	
Mineralocorticoid excess syndromes	Early-onset HTN; hypokalemia	PRA, PAC	DOC; urinary cortisol metabolites; genetic testing

Management of Resistant Hypertension

- Optimize drug therapy, using longer-duration medications and a diuretic, preferably thiazidelike (ie, chlorthalidone or indapamide)
- Increase the doses to the highest tolerated level
- Review adherence and consider obstructive sleep apnea in patients with suspected RHT

Management of Resistant Hypertension

- Health behaviour modification, including a reduction in dietary sodium intake, might still be beneficial in patients with suspected RHT.
- Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone

Classical targets in hypertension

- AngII-AT1R/AT2R axis
- ACE2/Ang1–7/Mas receptor axis
- Aldosterone
- Aldosterone receptor (AR)

New targets in hypertension

- Aminopeptidase of the brain renin-Ang system (RAS)
- Vasoactive intestinal peptide (VIP) receptor
- Intestinal NHE3
- Endothelin receptor (ETR)
- Drugs targeting the NO pathway
- Vaccines
- Gastrointestinal microbiota
- Leptin

Aminopeptidase of the brain RAS

- The activation of RAS in the brain can improve sympathetic tone and consequently increase vascular resistance and the release of arginine vasopressin which lead to elevated BP level

Aminopeptidase of the brain RAS

- Aminopeptidase A (APA) is a membrane-bound zinc metalloprotease. It is responsible for the N-terminal cleavage of Ang II and it can convert Ang II to Ang III
- EC33 [(S)-3-amino-4-mercaptobutyl sulfonic acid] is a specific APA inhibitor
- RB150 [4,40-dithio[bis(3-aminobutyl sulfonic acid)]] is a systemically active prodrug of EC33

Aminopeptidase of the brain RAS

- RB150 may be the prototype of a new class of centrally active anti-hypertensive agents
- phase I clinical trials were conducted to evaluate the safety, pharmacokinetics and pharmacodynamic effects of RB150 in humans

Vasoactive intestinal peptide receptor

- VIP is a neuropeptide that exerts positive inotropic, chronotropic and vasodilatory effects by activating the G protein-coupled receptors VPAC1 and VPA 2
- VIP is associated with several CVDs and cardiopulmonary diseases

Vasoactive intestinal peptide receptor

- Vasomera (PB1046) was developed by fusing an analog of VIP with an elastin-like polypeptide
- This drug exerts its effects through selectively binding VPAC2, thereby avoiding the gastrointestinal side effects associated with VPAC1 activation
- PB1046 has a longer half-life than native VIP

Intestinal NHE3

- The imbalance of sodium intake and excretion plays an important role in the pathogenesis of hypertension and its complications
- NHE3 expressed on enterocytes throughout the intestinal lumen plays a dominant role in intestinal sodium absorption

Intestinal NHE3

- Inhibition of NHE3 has been considered a potential strategy for controlling hypertension and its complications
- SAR218034 (SAR) is an orally nonabsorbable specific NHE3 inhibitor

Intestinal NHE3

- SAR (1 mg/kg per day in chow) increased fecal sodium excretion and reduced urine sodium excretion
- Drug increased feces water content and reduced SB
- the hypotensive effect of SAR can be significantly enhanced when combined with the ACE inhibitor ramipril

Endothelin receptor (ETR)

- Endothelin-1 (ET-1) is an endothelium-derived contractile factor released by vascular endothelial cells
- It is the most potent vasoconstrictor and an important factor for maintaining vascular tension

Endothelin receptor (ETR)

- ET-1 can bind with its specific receptors ETRs including ETAR and ETBR which are G-protein coupled receptors
- The binding of ET-1 to ETAR can promote vasoconstriction, cell proliferation, tissue fibrosis and vascular endothelial injury
- The binding of ET-1 to ETBR can activate endothelial cells to produce NO, thereby relaxing vascular smooth muscle and inhibiting vasoconstriction and cell proliferation
- Therefore, inhibition of ETAR may be a strategy for the treatment of hypertension.

ETR antagonists

- Selective ETAR antagonists such as darusentan and ambrisentan
- Nonselective ETRAs such as bosentan and macitentan
- Selective ETBR antagonists

Drugs targeting the NO pathway

- NO is a vasodilation factor that plays an important role in BP regulation
- Asymmetric and symmetric dimethylarginine (ADMA and SDMA, respectively) are endogenous NOS inhibitors that can inhibit the production of NO

Drugs targeting the NO pathway

- Increasing NO levels in the body may reduce BP
- NOS substrates and drugs that reduce ADMA and ADMA levels and NO donors may be useful for reducing BP

Drugs targeting the NO pathway

- Sphingosine-1-phosphate, the bioactive lipid mediator is a potent activator of endothelial nitric oxide synthase through G protein-coupled receptors
- The autocrine/paracrine activation of Sphingosine-1-phosphate receptors (SIPR) plays an important role in the regulation of BP level

Drugs targeting the NO pathway

- Drugs that reduce ADMA and SDMA levels such as resveratrol, melatonin, and N-acetylcysteine (NAC) can also play an important role in regulating BP
- NO donors such as sodium nitrate and pentaerythritol tetranitrate can also lower BP

Vaccines

- Vaccines targeting the RAS for the treatment of hypertension have been reported since the 1950s
- The antihypertensive effect of vaccines must be verified in a broader population with hypertension

Gastrointestinal microbiota

- The metabolites of the gastrointestinal microbiota play an important role in BP regulation
- Microbial abundance and diversity were dramatically reduced in the pre-hypertension and hypertension group

Gastrointestinal microbiota

- High intake of fruit and vegetables, which are considered as sources of SCFAs, can reduce BP
- Lactobacilli can play a protective role against the development of hypertension

Leptin

- Obesity is the most common cause of primary HTN and is directly proportional to increases BMI
- The relationship of leptin and hypertension is mutual
- Whether the selective leptin antagonists have the property of antihypertensive drugs remains unclear

Sodium-glucose cotransporter 2

- The mechanisms of SGLT2 inhibitors lowering BP level may be via natriuresis and osmotic diuresis
- SGLT2 inhibitors seem to reduce nighttime BP compared with daytime

New drug target for hypertension

Target	Drug	Mode of action	Status
Aminopeptidase A	Firibastat (RB150)	APA inhibitor	Phase I/II
Vasoactive intestinal peptide	Vasomera (PB1046)	VIP receptor agonists	Phase I
Na+/H+ exchanger 3	Tenapanor	NHE3 inhibitor	
	SAR218034	NHE3 inhibitor	
Endothelin-1	Bosentan	Nonselective ETR antagonists	Approved
	Macitentan	Dual ETAR/ETBR antagonist	Approved
	Darusentan	Selective ETR antagonists	Approved
	Aprocitentan	Dual ETAR/ETBR antagonist	Approved

New drug target for hypertension

Nitric oxide	NG-nitro-L-arginine methyl ester hydrochloride	NO synthase inhibitor	Preclinical
	L-arginine or L-citrulline	NO synthase	Preclinical
	Pentaerythritol tetranitrate	NO	Preclinical
Sphingosine-1-phosphate	FTY702	S1PR1 antagonist	Approved
Ang I and Ang II	CYT006-AngQβ	ANGII antibody	Phase II
	PMD3117	ANGI antibody	Phase I/II
	ATRQβ-001	ANGII type 1 receptor antibody	Preclinical
Sodium-glucose cotransporter 2	Canagliflozin	SGLT2 inhibitor	Approved
	Dapagliflozin	SGLT2 inhibitor	Approved

با تشکر فراوان از حسن توجه شما عزیزان