Review Article

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Hypertension Diagnosis and Management: New findings from the recent guidelines

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Abstract

Hypertension is a common disorder around the world which is mainly asymptomatic and in this regard, it is known as a silent killer disease. Hypertension can induce various complications including cardiovascular disorders i.e. heart failure, angina, and acute coronary syndrome, renal failure, cerebrovascular disease, and retinopathies, in this regard, regular screening, early diagnosis and management of hypertension is crucial. In general, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), β-blockers, and thiazide diuretics are considered as first-line agents for hypertension management. However, selection of a suitable antihypertensive regimen is mainly affected by the patients' specific conditions and also their comorbidities. In this review, the latest versions of different hypertension guidelines including "2023 European Society of Heart (ESH) Guidelines for the Management of Arterial Hypertension", "2020 International Society of Hypertension Global Hypertension Practice Guidelines" and "2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" and also recently related publications have been reviewed. Moreover, pharmacotherapy in special groups of patients and those with comorbidities have been summarized according to the latest guidelines that are currently available for each predisposing disease. Finally, hypertension crises diagnosis and management are discussed.

Keywords: Hypertension, Diagnosis, Pharmacotherapy, Guideline-Directed Medical Therapy (GDMT), Comorbidities, Hypertension Crises.

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1. Introduction

Hypertension, also known as high blood pressure, is a common disorder and today more than 1.28 billion adults have a type of hypertension worldwide. Unfortunately, hypertension is an asymptomatic disease and about half of the patients are unaware of their high blood pressure. Therefore, it has been reported that only about 42% of the patients with hypertension are diagnosed and receive anti-hypertensive agents and among these individuals, about 80% have uncontrolled blood pressure in spite of medical therapy (1). Hypertension has been considered as "silent killer" disease which can enhance the risk of cardiovascular disease including heart failure, angina, and myocardial infarction, cerebrovascular disease including stroke, renal disease, and retinopathies. Therefore, early diagnosis and treatment of hypertension is

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essential to avoid the occurrence of these complications (2).

According to 2021 World Health Organization (WHO) guideline, hypertension is considered as a serious medical condition that can be associated with various cardiovascular, renal, and brain disorders. Therefore, initiation of pharmacologic treatments in a timely manner would be essential. In addition, blood pressure threshold for treatment initiation should be individualized based on the patients' conditions and their comorbidities including cardiovascular disorders, diabetes mellitus, and chronic kidney disease (CKD). Moreover, WHO has recommended that after pharmacological treatment initiation, patients should be screened for numerous comorbidities, major cardiovascular disease risk factors, and potential secondary hypertension. Pharmacologic treatment can be started with any of first-line therapeutic agents based on patient's condition. Moreover, in adult patients, combination therapy using single-pill combination can be considered as an initial treatment. Target blood pressure following administration of antihypertensive agents should also be individualized based on the patients' specific condition and their predisposing disorders. A monthly follow-up would be crucial after treatment initiation or after application of any changes to the therapeutic regimen, while in those with under control blood pressure, follow-up frequencies can be reduced to every 3 to 6 months (3).

2. Blood pressure monitoring

There are numerous approaches for blood pressure monitoring including office blood pressure monitoring which is mainly perform through the auscultatory technique and out of office blood pressure monitoring methods including ambulatory blood pressure monitoring and home blood pressure monitoring which is commonly perform through the oscillometric machines (4). Among the mentioned methods for blood pressure assessment, office blood pressure monitoring is the most accurate one. Therefore, based on the method of blood pressure monitoring, criteria for hypertension definition and also targeted blood pressure values after pharmacotherapy initiation can be different (5).

3. Blood pressure definition and diagnosis

According to "2017 American Academy of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults", hypertension has been defined as systolic blood pressure (SBP) of ≥130 mmHg or diastolic blood pressure (DBP) of ≥80 mmHg assessed through the office blood pressure monitoring method (6). According to this guideline, individuals can be divided in to 4 categories based on their blood pressure as it is summarized in Table 1 that should be confirmed by ≥2 careful measurement on ≥2 occasions (6). While according to "2023 European Society of Heart (ESH) Guidelines for the management of arterial hypertension", hypertension has been defined as SBP of ≥140 mmHg or DBP of ≥90 mmHg assessed through the office blood pressure monitoring method (5). According to 2023 ESH guideline, individuals can be divided in to 8 categories based on their blood pressure as shown in Table 2 that should be confirmed by at least 2 to 3 visits. Since the criteria for hypertension definition and diagnosis is highly dependent on the method of blood pressure monitoring, in this regard, according to "2020 International Society of Hypertension Global Hypertension Practice Guidelines" (7), criteria for hypertension diagnosis based on the method of monitoring is summa-

Table 1. Blood pressure categories according to 2017 ACC/AHA Guideline for Hypertension (confirmed by ≥2 careful measurement on ≥2 occasions)

Categories	SBP[1] (mmHg)		DBP[2] (mmHg)
Normal BP[3]	<120	AND	<80
Elevated BP	120-129	AND	<80
Stage 1 Hypertension	130-139	OR	80-89
Stage 2 Hypertension	≥140	OR	≥90

[1]Systolic blood pressure
[2]Diastolic blood pressure
[3]Blood pressure

Table 2. Blood pressure categories according to 2023 ESH Guideline for Hypertension (confirmed by at least 2 to 3 visits).

Categories	SBP[1] (mmHg)		DBP[2] (mmHg)
Optimal	<120	and	<80
Normal	120-129	and	80-84
High-Normal	130-139	and/or	85-89
Grade 1 Hypertension	140-159	and/or	90-99
Grade 2 Hypertension	160-179	and/or	100-109
Grade 3 Hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90
Isolated diastolic hypertension	<140	and	≥90

[1]Systolic blood pressure
[2]Diastolic blood pressure

Table 3. Criteria for hypertension diagnosis based on the blood pressure monitoring method.

BP[1] monitoring method		SBP[2] (mmHg)		DBP[3] (mmHg)
Office BP monitoring		≥140	and/or	≥90
Out-of-office BP monitoring	Home BP monitoring	≥135	and/or	≥85
	Ambulatory BP monitoring			
	Average (24-hour)	≥130	and/or	≥80
	Day	≥135	and/or	≥85
	Night	≥120	and/or	≥70

[1]Blood pressure
[2]Systolic blood pressure
[3]Diastolic blood pressure

rized in Table 3.

4. Blood pressure management

Since uncontrolled hypertension can result in numerous complications (8), therefore, early diagnosis and treatment of hypertension would be essential. Life style modifications including weight loss, reduced sodium intake, enhanced potassium intake, increased physical activity, reduced alcohol intake, smoking cessation, using dietary approaches to stop hypertension (DASH) diet are among the primary treatment approaches in patients with hypertension (4). The blood pressure threshold for hypertension management using antihypertensive agents along with life style modification is completely dependent on the level of cardiovascular disease risk. 2023 ESH Guideline for management of arterial hypertension has been reported that in all patients with grade 2 and grade 3 hypertension, pharmacotherapy with antihypertensive agents should be initiated along with life style modification. However, in those with grade 1 hypertension who involve with low risk cardiovascular disease and have no hypertension-mediated organ damage (HMOD) and have blood pressure of <150/95, life style modification alone can be initiated for 3 to 6 months based on the patients' response. While in those with grade 1 hypertension and high risk of cardiovascular disease (with 10-year Atherosclerosis Cardiovascular Disease (ASCVD) risk of ≥10%) or any HMOD, immediate pharmacotherapy should be initiated along with life style modification at the early stages of diagnosis. Some differences in various guidelines regarding the threshold for pharmacotherapy initiation and also targeted blood pressure values after treatment initiation are summarized in Table 4. It should be mentioned that SBP of <120 mmHg and DBP of <70 mmHg should be avoided in all patients due to risk of adverse drug reactions and orthostatic hypotension occurrence (5). In addition, it should be mentioned that the recent 2023 ESH guideline has recommended that in elderly patients who are ≥80 years old, the threshold for pharma-

Table 4. Systolic and diastolic blood pressure thresholds for pharmacotherapy initiation and targeted blood pressure values after treatment initiation.

Guideline	Threshold for pharmacotherapy initiation			Target blood pressure		
	Positive history of CVD, CKD, Diabetes mellitus, or any HMOD (mmHg)	High risk of CVD (mmHg)	Low risk of CVD (mmHg)	18-64 years old (mmHg)	65-79 years old (mmHg)	≥80 years old (mmHg)
2023 ESH Guidelines	≥130/80	≥140/90	≥150/95	<130/80	<140/80 If tolerated: < 130/80	140-150/<80
2017 ACC/AHA Guideline	≥130/80	≥130/80	≥140/90	<130/80	<130/80	<130/80

CVD: Cardiovascular disease, CKD: Chronic kidney disease, HMOD: Hypertension-mediated organ damage, ESH: European Society of Heart, ACC/AHA: American College of Cardiology/American Heart Association

cotherapy initiation is SBP ≥160 mmHg (5). In addition, this guideline has been specially justified the targeted blood pressure after pharmacotherapy initiation based on the patients age (5) as shown in Table 4.

5. Pharmacological treatment

First-line medicines for hypertension treatment are angiotensin conversing enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide diuretics (4, 9). According to 2017 ACC/AHA guideline, β-blockers can be considered as first-line options only in patients that have hypertension along with cardiovascular disorders including heart failure or coronary artery disease such as myocardial infarction. While the recent 2023 ESH guideline recommended that β-blockers can be considered as first-line agent for hypertension management regardless of the presence of cardiac diseases or not (5). Other antihypertensive agents are steroidal mineralocorticoid receptor antagonists (MRAs) including spironolactone and eplerenone, α1-blockers including terazosin, prazosin, and doxazosin, central α2-agonists including methyldopa and clonidine, and arterial vasodilators including minoxidil and hydralazine (4). Recently it has been reported that sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors), which are approved for type 2 diabetes and heart failure treatment, can also be used in hypertension management. The possible mechanism of SGLT-2 inhibitors in blood pressure lowering can be attributed to their natriuretic effect, renin-angiotensin-aldosterone system (RAAS) regulation, and sympathetic nervous system inhibition (10). Moreover, non-steroidal MRAs i.e. finerenone has also been considered as an anti-hypertensive agent with blood pressure lowering potential, especially in patients with chronic kidney disease (CKD) associated with type 2 diabetes (11).

Besides antihypertensive agents, according to the United States Preventive Services Taskforce (USPSTF), primary prevention of cardiovascular disease with low-dose aspirin (81 mg/day) has been recommended in adult patients between 50 and 59 years old with hypertension who have 10-year ASCVD risk of ≥10%, have life-expectancy of at least 10 years, have no enhanced risk of bleeding, and have good compliance to take aspirin for at least 10 years (4).

5.1. Angiotensin converting enzyme inhibitors (ACEIs)

Angiotensin converting enzyme inhibitors (ACEIs) are among the first-line antihypertensive agents commonly used in patients with hypertension. ACEIs modulate the RAAS and block the conversion of angiotensin I to angiotensin II through the inhibition of angiotensin converting enzyme (ACE). In this regard, reduction in angiotensin II levels, diminishes angiotensin II-induced vasoconstriction and aldosterone secretion which in turn can result in a reduction in blood pressure (4). A complete list of ACEIs, their dosing, advantages, possible adverse drug reactions, and contraindications are summarized in Table 5 (4-6).

5.2. Angiotensin receptor blockers (ARBs)

Angiotensin receptor blockers (ARBs) are among the first-line antihypertensive agents. ARBs act through the RAAS and directly block

Table 5. Angiotensin converting enzyme inhibitors (ACEIs) as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Captopril	50-100 mg/day BID or TID	Favorable in patients with low to normal potassium level, patients with high fasting plasma glucose (FPG), and patients with microalbuminuria and CKD diseases	Hyperkalemia, increase in serum creatinine level, orthostatic hypotension (in elderly), non-productive cough, and angioedema	Pregnancy, bilateral renal artery stenosis (unilateral in patients with single kidney), history of angioedema or hypersensitivity reactions to an ACEI, renal function deterioration like acute kidney injury, concomitant use with aliskiren in patients with diabetes mellitus	Not reported
Enalapril	10-40 mg/day QD or BID				
Lisinopril	20-40 mg/day QD				
Benazepril	20-40 mg/day QD or BID				
Fosinopril	20-40 mg/day QD				
Moexipril	7.5-30 mg/day QD or BID				
Perindopril	4-16 mg/day QD				
Quinapril	20-80 mg/day QD or BID				
Ramipril	2.5-20 mg/day QD or BID				
Trandolapril	2-4 mg/day QD				

QD: Once daily, BID: Twice daily, TID: Three times daily, CKD: Chronic kidney disease

the angiotensin II receptor. Therefore, ARBs block the angiotensin II-induced vasoconstriction and aldosterone secretion which can in turn reduce the blood pressure (4). Overall, ARBs are considered as the best tolerated first-line antihypertensive agents and it is possible to switch from ACEIs to ARBs when dry cough or angioedema occur following ACEIs administration. A list of these agents, their dosing, advantages, possible adverse drug reactions, and contraindications are summarized in Table 6 (4-6).

5.3. Calcium channel blockers (CCBs)

Calcium channel blockers (CCBs) are among the first-line antihypertensive agents, especially in elderly patients and black ethnicities who are poor-responsive to ACEIs, ARBs, and β-blockers. CCBs are categorized into two main class of dihydropyridines and non-dihydropyridines. CCBs can induce coronary and peripheral vasodilation through the inhibition of calcium entry into the smooth muscles. Dihydropyridine CCBs including amlodipine, felodipine, nicardipine, nifedipine, nislodipine, and isradipine are primary vasodilators which can induce reflex tachycardia (except for amlodipine and felodipine). While non-dihydropyridine CCBs including verapamil and diltiazem directly inhibit atrioventricular (AV) node that can result in reduced heart rate and cardiac contractility, along with vasodilation

Table 6. Angiotensin receptor blockers (ARBs) as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Valsartan	80-320 mg/day QD	Favorable in patients with low to normal potassium level, patients with high fasting plasma glucose (FPG), and patients with microalbuminuria and CKD diseases	Hyperkalemia, increase in serum creatinine level, and orthostatic hypotension (in elderly).	Pregnancy, bilateral renal artery stenosis, (unilateral in patients with single kidney), history of angioedema or hypersensitivity reactions to an ARB, renal function deterioration like acute kidney injury, concomitant use with aliskiren in patients with diabetes mellitus	Not reported
Telmisartan	20-80 mg/day QD				
Losartan	25-100 mg/day QD or BID				
Irbesartan	75-300 mg/day QD				
Olmesartan	20-40 mg/day QD				
Eprosartan	600-800 mg/day QD or BID				
Candesartan	8-32 mg/day QD or BID				
Azilsartan	80 mg/day QD				

QD: Once daily, BID: Twice daily, CKD: Chronic kidney disease

Table 7. Calcium channel blockers (CCBs) as antihypertensive agents

	Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Dihydropyridine	Amlodipine	2.5-10 mg/day QD	Favorable in elderly patients, those with isolated systolic hypertension, patients with cyclosporine-induced hypertension, and those with Raynaud phenomenon.Preferred first-line agents in elderly and black patients.	Peripheral edema, headache, dizziness, flushing, and tachycardia (except for amlodipine and felodipine)	Left ventricular dysfunction (except for amlodipine and felodipine)	Risk of angina occurrence
	Felodipine; ER tablets	2.5-10 mg/day QD				
	Nicardipine; ER capsules	60-120 mg/day BID				
	Nifedipine; ER tablets	30-90 mg/day QD				
	Nislodipine; ER tablets	17-34 mg/day QD				
	Isradipine; ER tablets	5-20 mg/day QD				
Non dihydropyridine	Verapamil	180-480 mg/day Qhs	Favorable in patients with tachycardia, patients with Raynaud phenomenon, those with migraine headache, and those with supraventricular arrhythmia	Constipation, headache, dizziness, bradycardia, and heart block	2nd and 3rd degree atrioventricular (AV) block, sick sinus syndrome, and left ventricular dysfunction (LVD)	Risk of angina occurrence
	Diltiazem	120-540 mg/day QD				

QD: Once daily, BID: Twice daily, Qhs: Every night at bedtime

(4). A list of dihydropyridine and non-dihydripyridine CCBs, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 7 (4-6).

5.4. Thiazide and thiazide-like diuretics

Thiazides or thiazide-like diuretics are among the first-line antihypertensive agents especially used in black ethnicity and elderly patients poor-responsive to ACEIs, ARBs, and β-blockers. Thiazide and thiazide-like diuretics act through the induction of natriuresis which can result in diuresis, decrease in plasma volume, and decreases in

Table 8. Thiazides or thiazide-like diuretics as antihypertensive agents.

Drugs	**Usual dosing**	**Advantages**	**Main adverse drug reactions**	**Contraindications**	**Effect of abrupt discontinuation**
Hydrochlorthiazide	12.5-25 mg/day QD	Favorable in patients with high-normal potassium levels, patients who have osteoporosis, and also in elderly patients. Thiazides can prevent calcium-related kidney stones. Preferred first-line agents in elderly and black patients	Hyponatremia, hypokalemia, hypovolemia, hypercalcemia, hyperglycemia, hyperuricemia, hypercholesterolemia, hypertriglyceridemia, orthostatic hypotension (in elderly), azotemia, and skin rash.	Anuria, severe kidney dysfunction	Fluid retention, edema, and risk of heart failure decompensation
Chlorthalidone	12.5-25 mg/day QD				
Indapamide	1.25-5 mg/day QD				
Metholazone	2.5-10 mg/day QD				

QD: Once daily

Table 9. β-blockers as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Bisoprolol	5-20 mg/day QD	Suitable in patients with heart failure and coronary artery disease. Carvedilol is preferred in patients with type 2 diabetes mellitus. Carvedilol and labetalol are mixed α1 and β-blockers.	Bradycardia, hyperglycemia, masking hypoglycemia symptoms, hypertriglyceridemia, bronchospasm in patients with asthma (with non-selective β-blockers)	Severe asthma, 2nd or 3rd degree atrioventricular (AV) block, severe sinus bradycardia, acute left ventricular dysfunction exacerbation, severe peripheral vascular disease, Prinzmetal variant angina, pheochromocytoma	Rebound hypertension, risk of angina occurrence, especially in patients with coronary artery disease
Carvedilol	12.5-50 mg/day BID				
Labetaol	200-800 mg/day BID				
Metoprolol succinate	25-400 mg/day QD				
Metoprolol tartrate	100-400 mg/day BID				
Atenolol	25-100 mg/day QD or BID				
Propranolol	40-180 mg/day QD or BID				

QD: Once daily, BID: Twice daily.

cardiac output. Following chronic use, tolerance may occur to the natriuresis effect of thiazides, however, an extended reduction in peripheral vascular resistance (PVR) would be responsible for their long-term antihypertensive effects (4). Thiazide and thiazide-like diuretics should be avoided in patients with GFR values less than 30 ml/min and 10 ml/min, respectively and also those with anuria. A list of thiazides and thiazide-like diuretics, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 8 (4-6).

5.5. β-blockers

According to 2017 ACC/AHA guideline, β-blockers are second-line antihypertensive medicines or first-line in patients with cardiovascular comorbidities including heart failure or coronary artery disease. While based on the recent 2023 ESH guideline, β-blockers can be considered as first-line agents for hypertension management, even in patients without cardiovascular disorders. β-blockers are divided into selective β1-blockers and non-selective β-blockers. Also, mixed α/β-blockers including carvedilol and labetalol are commonly used as antihypertensive agents can act through a dual mechanism. A list of β-blockers, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 9 (4-6).

5.6. Mineralocorticoid receptor antagonists (MRAs)

Mineralocorticoid receptor antagonists (MRAs) are second-line antihypertensive agents. They are divided into 2 classes of steroidal MRAs including spironolactone and eplerenone and non-steroidal MRAs including finerenone. The main advantage of finerenone over spironolactone and eplerenone would be attributed to the lower risk

Table 10. Mineralocorticoid receptor antagonists (MRAs) as antihypertensive agents.

Drugs	**Usual dosing**	**Advantages**	**Main adverse drug reactions**	**Contraindications**	**Effect of abrupt discontinuation**
Spironolactone	12.5-50 mg/day QD or BID	Suitable in resistant hypertension and patients with severe CKD.	Hyperkalemia, hyponatremia, gynecomastia (spironolactone only), menstrual irregularities (spironolactone only)	Hypokalemia, hyponatremia, severe CKD, and Addison disease (only finerenone)	Not reported
Eplerenone	50-100 mg/day QD or BID				
Finerenone	20 mg/day QD				

QD: Once daily, BID: Twice daily, CKD: Chronic kidney disease.

Table 11. Loop diuretics as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Furosemide Torsemide Bumetanide	20-80 mg/day BID 2.5-10 mg/day QD 0.5-4 mg/day BID	Suitable in patients with severe CKD (eGFR <30 ml/min), severe edema, and heart failure (left ventricular dysfunction)	Hypokalemia, hyponatremia, hypocalcemia, hypovolemia, hyperuricemia, azotemia, skin rash, hearing loss, orthostatic hypotension (in elderly),	Anuria and complete kidney shutdown, hepatic cirrhosis	Fluid retention, edema, and risk of heart failure decompensation

QD: Once daily, BID: Twice daily, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate.

of hyperkalemia occurrence following finerenone administration since it has a milder effect on renal electrolyte exchange (12, 13). MRAs should be preserved for patients with resistant hypertension or those with other comorbidities including heart failure or type 2 diabetes mellitus. MRAs should be administered as an add-on therapy regimen in combination with first-line antihypertensive agents. A list of steroidal and non-steroidal MRAs, their dosing, advantages, possible adverse drug reactions, and contraindications are summarized in Table 10 (4-6).

5.7. Loop diuretics

Loop diuretics are alternative antihypertensive agents that can be preserved for patients with resistant hypertension, severe CKD with reduced eGFR values (up to 10 ml/min), and severe edema as add-on therapy agents. Among loop diuretics, furosemide and bumetanide are short-acting agents and should be administered twice daily, while torsemide is long-acting loop diuretic and can be administered once daily. A list of loop diuretics, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 11 (4-6).

5.8. Direct renin inhibitors

Direct renin inhibitors are alternative antihypertensive agents that act through blocking RAAS and have a similar pattern of adverse drugs reactions to ACEIs and ARBs. Therefore, the main adverse drug reactions of aliskiren as a renin inhibitor are increased serum creatinine, hyperkalemia, and angioedema. According to its long half-life (about 24 hours), aliskiren is dosed once daily. Notably, the exact role of aliskiren in the treatment of hypertension in clinical practice is currently unclear. Dosing, advantages, possible adverse drug reactions, and contraindications of aliskiren are summarized in Table 12 (4-6).

5.9. Potassium-sparing diuretics

Potassium-sparing diuretics are mainly administered in combination with thiazide diuretics to compensate their hypokalemia effect. They inhibit the epithelial sodium channels located on the luminal side at the late distal convoluted tubule and collecting tubule. Administration of these agents at the beginning of thiazide administration is not recommended and they should be initiated when hypokalemia occurs following thiazide diuretics administration. A list of potassium-sparing

Table 12. Direct renin inhibitors as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Aliskiren	150-300 mg/day QD	Suitable in patients with resistant hypertension	Hyperkalemia, rise in serum creatinine, and angioedema	Pregnancy, history of angioedema, concomitant administration with ACEIs or ARBs in patients with diabetes mellitus or CKD (eGFR <60 ml/min)	Not reported

QD: Once daily, ACEI: Angiotensin converting enzyme inhibitor, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate.

Table 13. Potassium-sparing diuretics as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Triamterene	50-100 mg/day QD or BID	Suitable add-on therapy in patients experienced thiazide-induced hypokalemia	Hyperkalemia, dizziness, headache, hyponatremia, and hyperchloremic metabolic acidosis	Hyperkalemia (K level of >5.5 mEq/L). In CKD patients with BUN >30 mg/dL or serum creatinine >1.5 mg/dL) or in patients with diabetes mellitus can only be administered with close monitoring of electrolyte levels and kidney function.	Not reported
Amiloride	5-10 mg/day QD or BID				

QD: Once daily, BID: Twice daily, CKD: Chronic kidney disease, BUN: Blood urea nitrogen.

diuretics, their dosing, advantages, possible adverse drug reactions, and contraindications are summarized in Table 13 (4-6).

5.10. α1-blockers

α1-blockers are alternative antihypertensive agents that should be preserved for patients with resistant hypertension as an add-on therapy regimen. They exert their anti-hypertensive effects by inhibiting the uptake of catecholamines in smooth muscle cells of peripheral vasculature, resulting in vasodilation. Caution is required due to the risk of postural orthostatic hypotension, especially in elderly patients. In addition, abrupt withdrawal of α1-blockers can be associated with rebound hypertension. These agents have also been approved for benign prosthetic hyperplasia (BPH) management. A list of α1-blockers, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 14 (4-6).

Table 14. α1-blockers as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Prazosin	2-10 mg/day BID or TID	Suitable in patients with resistant hypertension. Suitable in patients with benign prosthetic hyperplasia (BPH) and hypertension	Orthostatic hypotension, drowsiness, dizziness, reflex tachycardia, headache, and nausea.	None except for hypersensitivity reactions to ingredients.	Rebound hypertension
Terazosin	1-20 mg/day QD or BID				
Doxazosin	1-8 mg/day QD				

QD: Once daily, BID: Twice daily, TID: Three times daily.

5.11. Central α2-agonists

Central α2-agonists including clonidine and methyldopa are alternative antihypertensive agents that are suitable for resistant hypertension treatment. By stimulating α2-adrenergic receptors in the brain, they reduce sympathetic outflow and increase vagal tone. The main adverse drug

Table 15. Central α2-agonists as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Clonidine	0.1-0.8 mg/day BID	Suitable for patients with resistant hypertension. Methyldopa is considered as the first-line agent during pregnancy.	Dizziness, sedation, orthostatic hypotension, headache, mental depression, edema, sexual dysfunction, dry mouth, hemolytic anemia (only methyldopa), and hepatitis (only methyldopa).	Severe bradyarrhythmia in patients with 2nd or 3rd degree AV block (only clonidine) and active hepatic disorders (only methyldopa)	Rebound hypertension, risk of angina, especially in patients with coronary artery disease, over activation of sympathetic nervous system that can present with tachycardia, nervousness, headache, and agitation
Methyldopa	250-1000 mg/day BID				

BID: Twice daily, AV block: Atrioventricular block.

Table 16. Arterial vasodilators as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Hydralazine Minoxidil	25-100 mg/day BID or TID 2.5-80 mg/day QD or BID	Suitable in patients with resistant hypertension and severe CKD	Reflex tachycardia, fluid retention, drug-induced lupus (only hydralazine with dose more than 200 mg per day), hypertrichosis (only minoxidil)	Idiopathic systemic lupus (only hydralazine), coronary artery disease	Not reported

QD: Once daily, BID: Twice daily, TID: Three times daily, CKD: Chronic kidney disease.

reaction is sedation and orthostatic hypotension. Abrupt withdrawal of these agents can result in rebound hypertension. Methyldopa is considered as first-line antihypertensive agent for gestational hypertension that is first diagnosed during pregnancy. A list of α2-agonists, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 15 (4-6).

5.12. Arterial vasodilators

Arterial vasodilators are alternative antihypertensive medicines that are mainly preserved for resistant hypertension and patients with severe CKD. Hydralazine and minoxidil belong to this category. Hydralazine induces arteriolar smooth muscle relaxation that can result in a reduction in blood pressure. Minoxidil is another potent arterial vasodilator that can be used in resistant hypertension management. Hydralazine can be replaced by minoxidil when maximal doses of the former are not effective or in hypertensive CKD patients, who do not respond well to hydralazine. These agents should be administered as an add-on therapy regimen in combination with first-line antihypertensive medications. Due to the risk of reflex tachycardia, fluid retention, and increased cardiac output, hydralazine or minoxidil should be administered in combination with β-blockers and diuretics in hypertension management (4). A list of direct vasodilators, their dosing, advantages, possible adverse drug reactions, contraindications, and effect of abrupt withdrawal are summarized in Table 16 (4-6).

5.13. Sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors)

Sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors) are oral antihyperglycemic agents that are approved for type 2 diabetes mellitus management. SGLT-2 inhibitors can also result in the reduction of both systolic (about 3 to 4 mm Hg) and diastolic (about 1 to 2 mm Hg) blood pressure and diminish the progression of CKD. Since SGLT-2 inhibitors block the simultaneous reabsorption of sodium and glucose from the proximal tubules of the nephrons, they can result in enhanced renal excretion of sodium and glucose

Table 17. Sodium glucose co-transporter 2 inhibitors (SGLT-2 inhibitors) as antihypertensive agents.

Drugs	Usual dosing	Advantages	Main adverse drug reactions	Contraindications	Effect of abrupt discontinuation
Empagliflozin Dapagliflozin Canagliflozin Bexagliflozin Luseogliflozin	10-25 mg/day QD 5-10 mg/day QD 100 mg/day QD 5 mg/day QD 2.5 mg/day QD	Reduction in the risk of major cardiovascular events, reduction in the risk of heart failure occurrence. Suitable in patients with resistant hypertension. Suitable in patients with type 2 diabetes mellitus and hypertension.	Genitourinary tract infection, dyslipidemia, and nausea, transient increase in serum creatinine	Severe CKD (eGFR <20 ml/min), ESRD patients, and those on dialysis	Not reported

QD: Once daily, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, ESRD: End stage renal disease.

which in turn reduce blood pressure and blood glucose, respectively (14). Moreover, SGLT-2 inhibitors including empagliflozin and dapagliflozin can reduce the risk of cardiovascular disorders (15). Despite having anti-hypertensive effects, this class of medication has not been approved for the treatment of only essential hypertension in patients without diabetes, CKD, or heart failure (HF). A list of SGLT-2 inhibitors, their dosing, advantages, possible adverse drug reactions, and contraindications are summarized in Table 17.

5.14. Angiotensin receptor-neprilysin inhibitor (ARNI)

Angiotensin receptor-neprilysin inhibitor (ARNI) is a fixed dose combinational drugs consisting of valsartan as an ARB and sacubitril as a neprilysin inhibitor that can result in the inhibition of natriuretic peptide degradation and therefore, inducing peripheral vasodilation (5). Although the blood pressure lowering effects of valsartan-sacubitril has been proved in numerous studies, to date it has not been approved by the United States Food and Drug Administration (FDA) or European Medical Center (EMC) for hypertension treatment. On the other hand, ARNI has been approved for the management of HF (16). Therefore, valsartan-sacubitril as an ARNI would be a promising therapeutic agents in patients with concomitant hypertension and heart failure diseases.

6. Hypertension pharmacotherapy in special groups of patients

Pharmacotherapy considerations in special groups of patients are discussed as follows with a focus on preferred regimen selection in each group.

6.1. Black patients

In the absence of a compelling indication like diabetes, CKD, and HF, drug of choice for hypertension management in black patients are CCBs and thiazide diuretics since these patients are poor responsive to ACEIs, ARBs, and β-blockers, especially as monotherapy regimens, mostly secondary to their low-renin activity (4, 17). Also, the risk of angioedema following ACEIs administration is higher in black patients (up to five times greater). Moreover, since the pattern of hypertension pathophysiology in black patients is mainly volume retention and volume overload, therefore, administration of thiazide diuretics would be helpful. In those with eGFR <30 ml/min, thiazide diuretics can be replaced with loop diuretics including furosemide, torsemide, and bumetanide. Notably, loop diuretics have only transient antihypertensive effects and they are not considered/classified as antihypertensive agents. In addition, it has been recommended that black patients older than 40 years old should be screened for glaucoma following hypertension diagnosis (5).

6.2. Elderly patients

Similar to black patients, drug of choice for hypertension management in elderly subjects over 65 years old without any compelling indication are CCBs and thiazide diuretics since these patients are poor responsive to ACEIs, ARBs, and β-blockers (4). In old and frail patients, initial monotherapy should be considered and also due to the risk of orthostatic hypotension and adverse drug reactions, pharmacotherapy should be initiated at low doses and then gradually titrated based on the patients' tolerance. Moreover, patients with 65 years old or more should be screened for glaucoma occurrence following hypertension diagnosis (5).

6.3. Pregnant women

Since the rate of white-coat hypertension is higher among pregnant women, therefore, using ambulatory blood pressure monitoring approach would be useful to avoid unnecessary treatment of hypertension in pregnant women with high blood pressure values. Also, these patients should be closely monitored due to the high risk of preeclampsia occurrence. In pregnant women with hypertension, life style modification including aerobic exercise (if not contraindicated), low-salt diet, and calcium supplementation (about 1000 mg/day) can be considered to avoid or at least reduce the risk of preeclampsia occurrence (5). According to the American College of Obstetricians and Gynecologists (ACOG), in pregnant women with mild gestational hypertension or preeclampsia with SBP of <160 mmHg or DBP of <110 mmHg, pharmacotherapy initiation is not recommended, while in those with preeclampsia and blood pressure of ≥160/110 mmHg, pharmacotherapy should be initiated using safe therapeutic agents. Recom-

mended therapeutic options in pregnant women are methyldopa and labetalol as first-line agents and long-acting nifedipine, verapamil, and clonidine as second line agents (18). Moreover, hydrochlorthiazide in low doses seems to be safe and can be an alternative anti-hypertensive agent in pregnant women. It should be mentioned that administration of ACEIs, ARBs, direct renin inhibitors, and spironolactone are contraindicated in pregnancy due to their teratogenic effects (18). According to 2023 ESH guideline, the first-line antihypertensive agent in pregnancy is oral long-acting nefidipine. While pregnant women with persistent severe hypertension, recurrent severe hypertension, and preeclampsia should be hospitalized as soon as possible and intravenous labetalol or urapidil should be administered to achieve targeted blood pressure of <160/105 mmHg (5). The 2017 ACC/AHA guideline has recommended long-acting nifedipine, methyldopa, and labetalol as first-line treatment agents in pregnancy, as well (6). Besides labetalol, other beta blockers, especially metoprolol and bisoprolol, are generally safe in pregnancy without teratogenic effects and they can be considered as potential alternatives for labetalol.

6.4. Children and adolescents

Hypertension diagnosis in children and adolescents has been considered as blood pressure of ≥95th percentile in comparison to the normal blood pressure distribution percentile at the same age, sex, and height. Accurate blood pressure monitoring through validated auscultatory and also out-of-office methods with appropriate cuff sizes is essential to diagnose hypertension in these patients. There is a significant association between body weight and hypertension occurrence in adolescents; therefore, life style modification including weight loss and physical activity should be considered in these patients (5). ACEIs, ARBs, and dihydropyridine calcium channel blockers are the most commonly used agents for hypertension management in children and adolescents and considered as the first-line drugs of choice for this age category. While, thiazide diuretics and β-blockers are taken into account as the second-line agents in those who are non-responsive to the monotherapy with first-line agents. The targeted blood pressure after treatment initiation in children and adolescents is to reduce the blood pressure to less than 95th percentile in those without comorbidities and to less than 90th percentile in those with either of CKD, diabetes mellitus, or any hypertension-mediated organ damage (19). In adolescents aged 13 years and older, the goal of blood pressure is less than <130/80 mmHg. Among ACEIs, enalapril has FDA approval for infants ≥1 month(s) and lisinopril, benazepril, and fosinopril are approved for children ≥6 years old if they have eGFR value of ≥30 ml/min (20).

6.5. Patients with isolated systolic hypertension

According to 2023 ESH guideline, isolated systolic hypertension, defined as SBP of ≥140 mmHg and DBP of <90 mmHg (5), is highly associated with obesity, overweight, high-salt diet, and smoking. It is more common in older adults and also in very young individuals, especially in the male gender. The possible mechanisms of isolated systolic hypertension might be enhanced cardiac output, stroke volume, and heart rate; therefore, its prevalence is significantly higher in athletes (5). In patients with isolated systolic hypertension, white-coat hypertension should be ruled out through the out-of-office blood pressure monitoring or central blood pressure assessment. After confirmation of isolated systolic hypertension, pharmacotherapy should be initiated, especially in those with cardiovascular risk factors or hypertension-mediated organ damage (5). Therefore, the administration of antihypertensive agents in isolated systolic hypertension can be associated with reduced risk of cardiovascular events, stroke, and all-cause mortality (6). Thiazide-like diuretics (including chlorthalidne and indapamide) and dihydropyridine CCBs (including amlodipine, nifedipine, and nitrendipine) are considered as the first-line drugs of choice for isolated systolic hypertension management (21).

6.6. Patients with isolated diastolic hypertension

According to 2023 ESH guideline, isolated diastolic hypertension, which is defined as SBP of <140 mmHg and DBP of ≥90 mmHg, is more common in male gender and is highly associated with obesity, overweight, and metabolic syndrome. In addition, it has been reported that the prevalence of isolated diastolic hypertension is more common in young adults (usually less than 50 years old), patients with diabetes, smokers,

and alcohol abusers. Therefore, isolated diastolic hypertension can be considered as a risk factor of cardiovascular disease in younger adults. There is controversial regarding pharmacotherapy initiation in these patients, however, treatment can be considered in those who are younger than 50 years old and have risk factors for cardiovascular events (5). CCBs are the commonly administered antihypertensive agents in isolated diastolic hypertension management, followed by ACEIs, ARBs, and diuretics (22).

7. Hypertension pharmacotherapy in patients with other comorbidities

Pharmacotherapy considerations in patients with hypertension and also other comorbidities are discussed as follow with a focus on preferred regimen selection to reduce their complications.

7.1. Hypertension with diabetes mellitus

According to the JNC8 guideline for hypertension management in adults, in patients with hypertension and diabetes mellitus, pharmacotherapy should be initiated in blood pressure of >140/90 mmHg, regardless of their age. Moreover, the target blood pressure after treatment initiation is also the same as other hypertensive patients with targeted SBP of <140 mmHg and DBP of <90 mmHg (23). On the other hand, based on the 2024 American Diabetes Association (ADA) guideline, targeted blood pressure in patients with diabetes and hypertension should be individualized based on the risk of cardiovascular diseases and adverse drug reactions. Therefore, according to 2024 ADA guideline, a target blood pressure of <130/80 mmHg would be promising if well tolerated by patients (24). Also, 2023 ESH guideline and 2017 ACC/AHA guideline have reported the same data and recommended a target blood pressure of <130/80 mmHg in patients with diabetes mellitus and hypertension. While the blood pressure thresholds for antihypertensive agent initiation in patients with diabetes mellitus and hypertension are ≥140/90 mmHg and ≥130/80 mmHg based on 2023 ESH guideline and 2017 ACC/AHA guideline, respectively (5, 6). In addition, it has been mentioned that in pregnant women with concomitant diabetes and hypertension, pharmacotherapy initiation at blood pressure threshold of ≥140/90 mmHg would be associated with better outcome in comparison to medication treatment at severe hypertension levels of ≥160/110 mmHg. Targeted blood pressure in pregnant women with diabetes mellitus is considered as SBP range of 110-130 mmHg and DBP of ≤85 mmHg (24).

ACEIs and ARBs, at their maximum well-tolerated doses, are first-line antihypertensive agents in patients with hypertension and diabetes. If targeted blood pressure is not achieved or the initial blood pressure on diagnosis is ≥150/90 mmHg, a combination of an ACEI or an ARB with a dihydropyridine CCB or a thiazide-like diuretic (including chlorthalidone or indapamide) can be administered. If further blood pressure lowering effect is required, despite combination therapy of the aforementioned major antihypertensive agents, a MRA can also be used as an add-on therapy to achieve targeted blood pressure. In any stages of hypertension management, the co-administration of ACEIs and ARBs or ACEIs/ARBs and ARNI is highly discouraged because of safety issues (24).

7.2. Hypertension with chronic kidney disease (CKD)

Hypertension and diabetes mellitus are the two most common causes of CKD occurrence (25). According to the JNC8 guideline, in patients with hypertension and CKD, pharmacotherapy should be initiated in blood pressure of >140/90 mmHg, regardless of their age. In addition, targeted blood pressure after treatment initiation is blood pressure of <140/90 mmHg assessed through the office-based monitoring approach. Since ACEIs or ARBs can be associated with improved kidney-related outcomes, therefore, in patients with hypertension and CKD, either an ACEI or an ARB should be administered as a first-line or add-on therapy agent (23).

`According to 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline, in patients with hypertension and CKD who present with albuminuria, ACEIs or ARBs in combination with either a thiazide diuretic or CCBs are first-line therapeutic agents; however, if albuminuria is not present, then dihydropyridine CCBs and thiazide diuretics can also be considered as first-line agents. If further blood pressure lowering effect is required, a dual or triple combination of first-line agents can be administered. Finally, in those with

resistant hypertension or type 2 diabetes mellitus, a MRAs can also be used as add-on therapy in patients with eGFR values of ≥45 ml/min. On the other hand, 2024 KDIGO guideline recommended a targeted SBP of <120 mmHg in CKD patients with hypertension. In those who are receiving a MRA in combination with an ACEIs or an ARBs, close patient monitoring for the possible development of hyperkalemia is essential. Moreover, SGLT2 inhibitors are first-line agents in CKD patients that should be administered in combination with ACEIs or ARBs as initial treatment in CKD patients and should be continued until developing to end stage renal disease (ESRD) stage i.e. dialysis or kidney transplantation (25).

7.3. Hypertension with coronary artery disease (CAD)

Hypertension is a major risk factor for CAD and all first-line antihypertensive agents can prevent CAD due to hypertension. In order to treat individuals with concomitant hypertension and CAD, combined dual therapy consisting of an ACEI or ARB plus a β-blocker should be initiated. If further antihypertensive effect is required, a dihydropyridine CCB can be added in patients with angina and a dihydropyridine CCB or a thiazide diuretic can be added in patients without angina. Moreover, according to 2023 ESH guideline, in patients with concomitant CAD, pharmacotherapy should be started at high-normal blood pressure threshold which is defined as SBP of ≥130 mmHg or DBP of ≥85 mmHg. While the target blood pressure after treatment initiation is the same as general population without CAD using an age-based threshold (5). According to "2023 ACC/AHA Guideline for the Management of Patients with Chronic CAD", targeted blood pressure in patients with hypertension and chronic CAD is <130/80 mmHg to reduce the risk of cardiovascular disease and all-cause mortality rates. It has been mentioned that the threshold for pharmacotherapy initiation in these patients is SBP of ≥130 mmHg and DBP of ≥80 mmHg. The first-line antihypertensive drugs of choice in patients with hypertension and chronic CAD are ACEIs, ARBs, and β-blockers. ACEIs and ARBs can reduce the risk of cardiovascular events in patients with chronic coronary disease who have other comorbidities including hypertension, diabetes mellitus, or CKD. If further blood pressure lowering effects is required in these patients, dihydropyridine CCBs, MRAs, and long acting thiazide diuretics including chlorthalidone can be used as add-on therapy regimens to achieve targeted blood pressure of <130/80 mmHg (26).

7.4. Hypertension with heart failure

Hypertension management with any of first-line antihypertensive agents including ACEIs, ARBs, CCBs, thiazide diuretics, and β-blockers can be associated with at least 50% reduction in the risk of heart failure development as a complication of hypertension. In addition, in patients with hypertension and type 2 diabetes mellitus, the administration of SGLT2 inhibitors can prevent heart failure occurrence (5).

In patients with hypertension and heart failure with reduced ejection fraction (HFrEF), first-line antihypertensive agents are ACEIs (or ARBs or ARNIs), β-blockers, steroidal MRAs (either spironolactone or eplerenone), and SGLT2 inhibitors. If fluid retention detected, thiazide or loop diuretics can also be added based on the patient's eGFR values. Moreover, if further blood pressure lowering effects is still required to achieve targeted blood pressure, dihydropyridine CCBs including amlodipine or felodipine can also be added to the treatment regimen. According to "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure", antihypertensive administration at the maximum tolerated doses is recommended in patients with concomitant hypertension and HFrEF (27, 28).

In patients with hypertension and heart failure with preserved ejection fraction (HFpEF), a dual combination of an ACEIs or an ARBs plus a CCB or a thiazide diuretic can be initiated. Then, β-blockers and SGLT-2 inhibitors can be added at any stage regardless of type 2 diabetes mellitus occurrence or not (5). Moreover, the administration of an steroidal MRAs (spironolactone or eplerenone) can be useful to avoid the progression of heart failure even in those with no evidence of resistant hypertension (27). Furthermore, ACEIs or ARBs can be replaced with ARNI (e.g., valsartan-sacubitril) to improve the heart failure outcome and also reduce cardiovascular death in these patients (29).

8. Response to treatment evaluation

After pharmacotherapy initiation in patients with hypertension, follow-up evaluation should be performed in monthly intervals to assess the patients' response to medication, their compliance, and to monitor possible adverse drug reactions. In patients who are on monotherapy antihypertensive regimen, if targeted blood pressure is not achieved after 1 month of pharmacotherapy, the dose of the administered drug can be titrated or maximized as tolerated or the 2nd drug from the first-line agents can be added to the previous one. If target blood pressure is not achieved after 1 month of dual combination therapy with first-line agents, then, the 3rd drug from major first-line antihypertensive agents should be added and then titrated as tolerated. Finally, if targeted blood pressure is still not achieved after a triple combination of major first-line antihypertensive agents with maximal tolerated doses and one of these medications is thiazide diuretic, then, patient can be labeled as resistant hypertension. In patients with resistant hypertension, diuretic therapy should be enhanced by either switching from a short-acting thiazide to a long-acting thiazide/thiazide-like diuretic or switching to a loop diuretic based on the patients' conditions and comorbidities like the presence of edema (4). The best method for diagnosis of resistant hypertension would be ambulatory blood pressure monitoring after exclusion of the risk of secondary hypertension. Since resistant hypertension can be associated with cardiovascular diseases, renal diseases, and all-cause mortality, therefore, early diagnosis and management of resistant hypertension would be crucial. The cornerstone for resistant hypertension management would be administration of an optimized pharmacotherapy regimen. While non-pharmacologic options including renal denervation, baroreflex activation therapy, or arterial anastomosis are not recommended for resistant hypertension management (30). In order to achieve an optimized pharmacologic treatment, first of all, a combination of antihypertensive agents with different mechanism of actions should be administered. Second, long-acting antihypertensive agents should be administered in order to manage resistant hypertension. Third, the dosing of each drug in selected therapeutic regimen can be enhanced to the maximum tolerated dose with no serious adverse drug reaction. Forth, addition of a diuretic agent to the selected therapeutic regimen or maximizing it would be essential for resistant hypertension management. Fifth, after achieving the right combinations of antihypertensive agents, physicians can switch to single-pill combination medications in order to enhance patients' compliance. Sixth, aldosterone receptor antagonists and β-blockers should be administered in resistant hypertension if there is no evidence of contraindication to these agents (30). The most commonly used antihypertensive combinations for resistant hypertension management are ACEIs/ARBs, CCBs, long acting thiazide-like diuretics, and mineralocorticoid receptor antagonists (31).

9. Hypertension crises

According to 2017 ACC/AHA guideline, hypertension crises has been defined as SBP of >180 mmHg and/or DBP of >120 mmHg (6). While, 2023 ESH guideline has defined hypertension crises as grade 3 hypertension (severe hypertension) with SBP of ≥180 mmHg and/or DBP of ≥110 mmHg (5). Hypertension crises can be presented with 2 forms of hypertensive emergencies and hypertensive urgencies. Hypertensive emergencies are mainly presented with new symptomatic/progressive organ damage or worsening of a previous hypertension-mediated organ damage (HMOD). Since hypertension emergencies can be life threatening, therefore, immediate administration of intravenous antihypertensive agents is crucial to lower the blood pressure within hours. While hypertensive urgencies are presented with no evidence of acute organ damage and can be treated with oral antihypertensive agents over several hours or days (32).

9.1. Hypertensive emergencies

Patients presented with hypertensive emergencies should be hospitalized urgently in intensive care unit and monitor closely for blood pressure and also for organ damage. Parenteral antihypertensive agents should be initiated as soon as possible. According to 2017 ACC/AHA guideline, in adult patients with aortic dissection and hypertensive emergency, SBP should be reduced to <120 mmHg within the first hour. For those presented with either severe preeclampsia, eclampsia, or pheochromocytoma and hypertensive emergency, SBP should be reduced to <140 mmHg within the

first hour. In patients without the aforementioned high-risk conditions, only about 25% reduction in SBP is allowed within the first hour, then blood pressure can be reduced to 160/100 mmHg in stable conditions within the next 2 to 6 hours, and then it can be reduced to targeted blood pressure within 24 to 48 hours (6).

Based on 2023 ESH guideline, in those hypertensive emergencies that present with acute coronary events and acute cardiogenic pulmonary edema, SBP should be immediately reduced to <140 mmHg. In those presented with acute aortic dissection, immediate reduction of SBP to <120 mmHg and pulse rate to <60 beats/min is essential. In patients with severe preeclampsia or eclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, immediate reduction of blood pressure to <160/105 mmHg is required. In those with hypertensive encephalopathy, immediate 20-25% reduction in mean arterial pressure (MAP) is needed. While in patients presented with malignant hypertension, only 20-25% reduction in

Table 18. The dosing, indications, precautions, and contraindications of parenteral antihypertensive agents for hypertensive emergencies management.

Medication	Dosing	Indication(s)	Precautions/Contraindications
Nicardipine	5 mg/h IV infusion Doses can be increased by incremental dose of 2.5 mg/h every 15-30 min up to a max dose of 15 mg/h	First-line agent for malignant hypertension, hypertensive encephalopathy, acute aortic dissection, eclampsia and severe preeclampsia/ HELLP	Nicardipine is contraindicated in advanced aortic stenosis and liver failure.
Clevidipine	1-2 mg/h continuous IV infusion Dose can be increased by incremental dose of 2 mg/h every 2 min up to targeted blood pressure achievement	Hypertensive emergency caused by acute pulmonary edema, acute kidney injury, preoperative hypertension, acute sympathetic discharge, and catecholamine excess states including pheochromocytoma	Clevidipine is contraindicated in patients with history of allergy to soybean and egg products. Also, it is contraindicated in patients with defective lipid metabolism.
Sodium nitroprusside	0.3-0.5 µg/kg/min continuous IV infusion Can be increased by incremental doses of 0.5 µg/kg/min every 5 min up to the max dose of 10 µg/kg/min	First-line agent for acute cardiogenic pulmonary edema, and acute aortic dissection. Alternative agent for malignant hypertension and hypertensive encephalopathy	Prolonged administration of sodium nitroprusside can result in cyanide toxicity (neurological changes and cardiac arrest). It has relative contraindication in patients with liver/kidney failure. Sodium nitroprusside adjustment to the lower doses is required in elderly patients.
Nitroglycerin	5-200 µg/min continuous IV infusion Doses can be increases by incremental doses of 5 µg/min every 5 min	First-line agent for acute coronary event, acute cardiogenic pulmonary edema, and acute aortic dissection	Nitroglycerin should not be administered in volume-depleted patients.
Hydralazine	10-20 mg slow IV infusion Can be repeated Q4-6h as needed	Acute coronary syndrome, acute pulmonary edema	Hydralazine has an unpredicted response to emergency hypertension and also, it has prolong duration of action, therefore, it should not be considered as first-line agent.
Esmolol	0.5-1 mg/kg IV bolus Followed by 50-300 µg/kg/min continuous IV infusion	First-line agent for acute aortic dissection	Esmolol is contraindicated in patients with 2nd or 3rd degree atrioventricular (AV) block, bradycardia, decompensated heart failure (HF), systolic HF, asthma, and in those with concurrent β-blocker therapy.

Continued Table 18.

Labetalol	10-20 mg IV bolus (over 1 min); incremental doses ≥20 mg can be administered every 10 min up to a max dose of 80 mg Or 1-3 mg/min continuous IV infusion	First-line agent for malignant hypertension, hypertensive encephalopathy, acute coronary event, and Eclampsia and severe preeclampsia/HELLP Alternative agent for acute aortic dissection	Labetalol is contraindicated in patients with 2nd or 3rd degree AV block, bradycardia, systolic HF, asthma, and chronic obstructive pulmonary disease (COPD) or reactive airways disease.
Phentolamine	1-5 mg IV bolus Or 0.5-20 µg/kg/min continuous IV infusion	Hypertensive emergency caused by catecholamine excess including pheochromocytoma, cocaine or amphetamine toxicity, clonidine withdrawal, MAO inhibitors drug & food interactions	-
Fenoldopam	1-5 mg IV bolus Or 0.5-20 µg/kg/min continuous IV infusion	Hypertensive emergency caused by catecholamine excess including pheochromocytoma, cocaine or amphetamine toxicity, clonidine withdrawal, MAO inhibitors drug & food interactions	-
Fenoldopam	0.1-0.3 µg/kg/min continuous IV infusion Can be increased by increments of 0.1 µg/kg/min every 15 min up to targeted blood pressure achievement	Hypertensive emergencies caused by/associated with acute kidney injury	Fenoldopam is contraindicated in patients who are at risk of glaucoma or intracranial pressure and also in those with sulfite allergy.
Enalaprilat	0.62-1.25 mg IV bolus (over 5 min) Q6h	Hypertensive emergencies caused by high plasma renin activity like acute left ventricular heart failure	Enalaprilat is contraindicated in pregnancy, patients with acute myocardial infarction (MI), those with bilateral renal artery stenosis, and patients with history of angioedema
Metoprolol	2.5-5 mg IV bolus (over 2 min) Can be repeated every 5 min up to a max dose of 15 mg	Alternative agent for acute aortic dissection	Metoprolol is contraindicated in 2nd or 3rd degree AV block, systolic HF, bradycardia, and asthma.
Urapidil	12.5-25 mg IV bolus Followed by 5-40 mg/h continuous IV infusion	Alternative agent for malignant hypertension, acute coronary event, and acute cardiogenic pulmonary edema	-
Clonidine	0.2-0.5 µg/kg/min continuous IV infusion		-
Magnesium sulfate	Initial dose of 4-6 g IV infusion over 15-30 min at onset of labor Followed by 1-2 g/h continuous IV infusion for at least 24 hours after labor	First-line agent for eclampsia and severe preeclampsia/HELLP	-

HELLP: Hemolysis. elevated liver enzymes, and low platelets.

MAP within several hours is allowed (5).

Various intravenous antihypertensive agents have been considered in hypertensive emergencies management including nicardipine and clevidipine as CCBs, sodium nitroprusside and nitroglycerin as vasodilators, hydralazine as an arterial vasodilator, esmolol as a selective β1-blockers, labetalol as a mixed α/β-blockers, phentolamine as a non-selective α-blocker, fenoldopam as a selective dopamine1-receptor agonist, and enalaprilat as an ACEI . Selection among these parenteral medications should be performed based on the patients special conditions (6). In addition to the aforementioned intravenous medications, 2023 ESH guideline has also recommended metoprolol as a selective β1-blocker, urapidil as an α1-blockers, and clonidine as a central α2-agonist, for hypertensive emergencies management (5). A summary of intravenous antihypertensive agents that are commonly used in hypertensive emergencies with their dosing and indications are listed in Table 18 (4-6).

9.2. Hypertensive urgencies

Hypertensive urgencies can be treated by either maximizing the previously administered oral antihypertensive agents in each patient or by starting new ones. These interventions can be accompanied with implementing non-pharmacological approaches (e.g., sodium restriction, removing medications/other substances that can increase blood pressure). The most commonly used oral antihypertensive agents in hypertensive urgency conditions are captopril as an ACEI, clonidine as a central α2-agonist, labetalol as a mixed α/β-blocker, and minoxidil as an arterial vasodilator (32). The administration of immediate-release nifedipine capsules or other rapidly acting calcium-channel blockers sublingually, by either the bite and chew method or by swallowing intact, is not recommended today because of the potential risk of life-threatening ischemic adverse events such as myocardial infarction and stroke.

10. Potential novel and investigational antihypertensive agents

In general, there are 6 main novel categories of investigational antihypertensive agents that can be potentially useful in hypertension management: (1) Non-steroidal mineralocorticoid receptor antagonists, (2) Aminopeptidase A inhibitors with central effect on vasopressin, (3) dual endothelin A and B receptor antagonists, (4) Aldosterone synthase inhibitors without glucocorticoid activity, (5) Atrial natriuretic peptide inhibitors, and (6) Hepatic angiotensinogen attenuators. These potential antihypertensive agents are still in phase II or phase III clinical trials. Another novel therapeutic agent, that is in phase II clinical trial, acts through the antisense blockade that can result in inhibition of angiotensinogen synthesis in the liver (33, 34). In addition to the mentioned novel antihypertensive agents, some procedural interventions including renal denervation and devices with enhanced carotid baroreceptor activity potential have also been considered and currently are under investigation for the possible management of uncontrolled essential hypertension or resistant hypertension (34).

11. Conclusion

In conclusion, since hypertension can be associated with various major complications including cardiovascular disorders, cerebrovascular disorders, renal failure, and retinopathies, early diagnosis and management of hypertension through the life style modifications and pharmacological treatments based on the patients' conditions and levels of baseline blood pressure are crucial. Selection of a suitable antihypertensive regimen to achieve a targeted blood pressure should be performed according to the guideline-directed medical therapy recommendations which is highly influenced by various patients' populations, comorbidities, and ethnicities. In general, initial monotherapy or combinational therapy of ACEIs/ARBs, CCBs, β-blockers, and thiazide diuretics are considered as first-line agents for hypertension management according to different guidelines, but pharmacotherapy regimen should be individualized based on the patients' conditions.

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Conflict of Interest

The authors declare no conflict of interest.

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