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# Review Article

## A Broad Review of Hypertension Pharmacology

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### Abstract

Most patients who develop primary hypertension are treated with medications despite lifestyle changes. For providers, determining when to start medications can be confusing as guidelines frequently change and determining which medication to start can also be challenging. In general, medication is initiated after assessing a patient's risk for developing atherosclerotic cardiovascular disease using risk calculators as well as their medical comorbidities. Target blood pressure, time for follow-up, and initial medication(s) vary among patients. First-line agents include thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Second-line agents include beta-blockers, diuretics, alpha-1 antagonists, alpha-2 agonists, and direct-acting vasodilators. It is important to note that not all classes of blood pressure-lowering medications are considered equal and each patient's unique medical comorbidities should always be taken into account before initiating treatment. These medications have their own respective side effects and contraindications that providers should be aware of so that they can monitor for adverse reactions as well as counsel their patients.

**Key words:** Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, atherosclerotic cardiovascular risk score, calcium channel blockers, hypertension, thiazide diuretics

Hypertension affects approximately 1.13 billion people worldwide, and these numbers continue to rise as the population gets older and the definition of hypertension continues to change. It has been shown repeatedly that controlling high blood pressure (BP) helps prevent developing cardiovascular (CV) disease, especially in the older population.<sup>[1,2]</sup> Every patient with hypertension should pursue lifestyle changes and non-pharmacological approaches to lower their blood pressure. These lifestyle changes generally include a healthy diet, regular exercise, minimal alcohol intake, and working toward a healthy weight.<sup>[3]</sup> However, when non-pharmacological approaches fail to achieve target blood pressure goals, antihypertensive medications can help patients to achieve the recommended targets. In this article, we will offer a broad review of the pharmacology of blood pressure-lowering drugs with their common indications, as well as common side effects.

### When to Start Medication and What is Our Target?

Before beginning a discussion on the hypertension pharmacological agents available, it is important to mention how

target blood pressure goals continue to evolve, as evidenced by the 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.<sup>[4]</sup> The current recommendations favor an individualized approach based on one's personal CV risk factors. Once these CV risk factors and consequent target blood pressure goals are identified, pharmacological agents should be tailored toward a person's specific risk factors. For example, an individual with diabetes may benefit from one class of antihypertensives, while an individual who has known coronary atherosclerotic disease might do better with a different class. One tool that has been valuable in guiding blood pressure management is the atherosclerotic cardiovascular (ASCVD) risk score, which is available as an online calculator.<sup>[5]</sup> The ASCVD risk score helps determine an individual's 10-year and lifetime risk of developing atherosclerotic CV disease (including coronary death or non-fatal myocardial infarction [MI] and fatal or non-fatal stroke). It is used for primary prevention of developing atherosclerotic disease, and in recent guidelines, to establish goals in treating hypertension.<sup>[6]</sup>

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Patients with an elevated ASCVD risk score > 10% or with known CV disease with Stage 1 hypertension (defined as a systolic blood pressure (SBP)  $\geq$ 130 mmHg or a diastolic blood pressure (DBP)  $\geq$ 80 mmHg) should initiate a BP-lowering medication, as well as continue non-pharmacological methods in reducing BP. Patients who have Stage 2 hypertension (defined as an SBP  $\geq$  140 mmHg or a DBP  $\geq$  90 mmHg) without a known history of CV disease and with an estimated ASCVD risk score of <10% should use BP-lowering medications for the primary prevention of CV disease.<sup>[4]</sup> Patients who have Stage 2 hypertension will generally require at least two antihypertensive medications of different classes, in addition to following non-pharmacological approaches to lower BP. Furthermore, patients who have a systolic pressure 20 mmHg above target goal or a diastolic pressure 10 mmHg above goal will likely require at least two antihypertensive agents.<sup>[7]</sup>

Patients with an estimated ASCVD risk score of <10% with an elevated BP or Stage 1 hypertension should be managed with non-pharmacological methods and should have their BP rechecked in 3–6 months. Patients with normal BP of <120/80 mmHg should have yearly follow-up for BP checks and continue with lifestyle modifications.

Blood pressure reducing medications are also recommended for the prevention of recurrent CV events in patients with known CV disease with a goal SBP < 130 mmHg and a goal DBP < 80 mmHg. Ultimately, a goal BP of <130/80 mmHg should be obtained for patients with an ASCVD risk score >10% over 10 years, as well as those patients who have diabetes, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD), prior MI, or prior stroke.<sup>[4, 8-10]</sup>

Typically, clinicians should first follow standard treatment guidelines for patients with a history of known CV disease, HFrEF, prior MI, stable angina, and titrate the indicated medications to achieve a goal BP < 130/80 mmHg. For sole hypertension in the absence of other CV comorbidities, clinicians should increase the dose of one first-line antihypertensive medication until the goal BP is reached. If goal BP cannot be reached with maximal dosing, then a second first-line agent is added to the medication regimen. Patients should have monthly follow-ups if a medication is increased or if a new medication is added to their regimen to ensure adherence and to allow for monitoring of adverse events.<sup>[4,11]</sup> One major side effect of all antihypertensives is the potential to cause hypotension, which is why close monitoring is necessary when making changes.

## First-line Agents for Stage 1 Hypertension

### Thiazide diuretics

Thiazides are the most commonly used diuretics and are typically a first-line agent for treating hypertension.<sup>[12,13]</sup> These diuretics work by inhibiting the sodium chloride transporter in the distal convoluted tubule of the nephron, thus resulting in inhibition of sodium reabsorption and promoting water excretion.<sup>[14]</sup>

### Side effects

Side effects are predominantly electrolyte disturbances, which include hyponatremia, hypomagnesemia, hypokalemia, hyperuricemia, hyperglycemia, hypercalcemia, and metabolic alkalosis. Side effects are typically dose dependent.<sup>[15,16]</sup>

### Comments

Chlorthalidone is typically the preferred thiazide with its long half-life. It also has a well-established CV disease risk reduction in clinical trials. When starting a thiazide diuretic, clinicians should monitor for electrolyte disturbances with laboratories.<sup>[13]</sup>

### Calcium channel blockers

Calcium channel blockers (CCBs) reduce calcium flux into cells by binding to voltage-gated calcium channels located in vascular smooth muscle cells and cardiac myocytes, including the sinoatrial (SA) and atrioventricular (AV) nodes. In cardiac tissue (including the SA and AV nodes), these channels play an important role in cardiac inotropy and chronotropy.<sup>[17,18]</sup> These medications are offered in two different classes: Dihydropyridine CCBs and non-dihydropyridine CCBs. Dihydropyridine CCBs usually exhibit more vasodilation, causing a decrease in systemic vascular resistance (SVR) and are useful in decreasing blood pressure. Non-dihydropyridine CCBs work primarily by reducing chronotropy and inotropy in the SA/AV nodes and are useful in the management of supraventricular tachycardias.<sup>[19]</sup>

### Side effects

Side effects include peripheral edema, flushing, headache, and constipation.<sup>[20]</sup>

### Comments

A CCB from either class should generally be avoided in patients with HFrEF.<sup>[19,21]</sup> Non-dihydropyridine CCBs should be used with caution when combined with beta-blockers, as their concurrent use can increase the risk of heart block and symptomatic bradycardia.<sup>[4,22]</sup>

### Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers

Angiotensin is a peptide hormone important in regulating vasoconstriction. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) both work effectively in the same way on the angiotensin system. Both of these medications limit the systemic effects of angiotensin II; ACE inhibitors decrease the amount of angiotensin II, and ARBs block the binding of angiotensin II to its respected receptors, thereby decreasing vasoconstriction.<sup>[23-25]</sup>

### Side effects

Hyperkalemia is the most common side effect. Dry cough, which usually begins 1–2 weeks after starting therapy, however, can develop up to 6 months after starting treatment and is much more common in ACE inhibitors than in ARBs. Angioedema is

a rare but potentially fatal complication that is associated with ACE inhibitors and is less likely to develop with ARBs.<sup>[25,26]</sup> If angioedema does occur, an ARB can be used for BP control only after discontinuation of the ACE inhibitor for 6 weeks. Furthermore, hypotension is seen more often in ARBs than in ACE inhibitors.<sup>[27]</sup>

#### Comments

ACE inhibitors and ARBs should never be used in conjunction with each other or in combination with a direct renin inhibitor. Both of these agents should be avoided in pregnancy and in patients with bilateral renal artery stenosis.<sup>[4,28-30]</sup> There is an increased risk of hyperkalemia in patients with CKD or when they are used in combination with potassium-sparing diuretics. These agents are typically the first-line antihypertensive agent in patients with CKD, HFrEF, and diabetics with albuminuria.<sup>[11,23,31]</sup>

#### Secondary agents

Common secondary medications used for treating hypertension include beta-blockers, loop diuretics, potassium-sparing diuretics, aldosterone antagonists, and alpha-blockers. In specific medical comorbidities, some of these agents are used as first-line treatment for hypertension. For the most part though, they are used in adjunct with primary agents to control blood pressure.

**Beta-blockers:** Beta-blockers include a large class of medications that have variable affinities for beta and alpha receptors throughout the body, thus giving them diverse roles in treating different conditions. Depending on their target beta-receptor ( $\beta$ -1 or  $\beta$ -2), certain beta-blockers have a significant role in metabolic activity and smooth muscle relaxation.<sup>[32]</sup> Beta-blockers are rarely used as initial therapy for hypertension list, a patient has a history of prior MI, coronary artery disease (CAD), or heart failure (HF).<sup>[33]</sup> In the case of CAD or HF, cardioselective beta-blockers are first-line agents in treating hypertension as they block the  $\beta$ -1 receptors in cardiomyocytes, leading to decreased chronotropy/inotropy and therefore cardiac oxygen demand.<sup>[34-36]</sup> Non-cardioselective beta-blockers should be avoided in patients with reactive airway disease. In general, practitioners should avoid abrupt cessation of beta-blockers as patients can exhibit beta-blocker withdrawal including symptoms of tachycardia, anxiety, and hypertension. Side effects of beta-blockers include fatigue, sexual dysfunction, impaired glucose tolerance, increased airway resistance (non-cardioselective), and bradycardia.<sup>[37]</sup>

#### Diuretics

##### Loop diuretics

Loop diuretics work by inhibiting the Na-K-2Cl transporter in the thick ascending loop of Henle. They can lead to the excretion of up to 20–25% of filtered sodium and thus decrease BP.<sup>[38]</sup> Loop diuretics are preferred in patients with moderate-to-severe CKD (GFR < 30 mL/min) over thiazide diuretics and

are used in patients with symptomatic heart failure. Side effects include hypokalemia, metabolic alkalosis, hyperuricemia, and hyponatremia.<sup>[38-40]</sup>

##### Potassium-sparing diuretics

Potassium-sparing diuretics act in the collecting tubule by blocking sodium channels, thereby decreasing the reabsorption of sodium and thus decreasing the excretion of potassium. These agents are minimally effective at lowering blood pressure; however, they can be used in patients with hypokalemia on thiazide monotherapy. Side effects include hyperkalemia and metabolic acidosis and should be avoided in patients with GFR < 45 mL/min.<sup>[4,38]</sup>

**Aldosterone antagonists:** Aldosterone antagonists include eplerenone and spironolactone. These medications act by directly inhibiting the mineralocorticoid receptor, thus limiting the effects of aldosterone. This leads to a decrease in sodium reabsorption and potassium excretion in the collecting tubule. Eplerenone has a higher affinity for the mineralocorticoid receptor than spironolactone, therefore causing fewer endocrine side effects. These are primary agents when treating hyperaldosteronism and are also useful add-on therapies when treating resistant hypertension.<sup>[41]</sup> It has been proven that these agents reduce mortality in patients with HFrEF and an ejection fraction of <35%.<sup>[42]</sup> Side effects include hyperkalemia, gynecomastia, menstrual abnormalities, impotence, and decreased libido.<sup>[41]</sup>

##### Alpha-1 blockers

These medications work by inhibiting the activation of alpha-1 receptors (located on the peripheral vasculature) by norepinephrine, thus leading to a decrease in BP.<sup>[43]</sup> They are often used in patients with benign prostate hypertrophy (BPH) and are typically considered second-line BP agents, often used in combination with other agents. They are associated with orthostatic hypotension and should be used with caution in the elderly.<sup>[4,44]</sup>

##### Alpha-2 agonists

These agents work by stimulating alpha-2 receptors in the central nervous system (CNS), which reduces sympathetic outflow and causes a decrease in peripheral resistance, heart rate, and blood pressure. These agents are generally used as last line efforts to control blood pressure. Abrupt cessations of drugs like clonidine can lead to rebound hypertension and should, therefore, be tapered. Additional adverse reactions include sedation orthostatic hypotension, dry mouth, and sedation.<sup>[4,45]</sup>

##### Direct-acting vasodilators

These agents include hydralazine, minoxidil, and nitrates. They work by relaxing the peripheral smooth muscles, causing vasodilation and a decrease in blood pressure. They are typically used in patients with angina to help control symptoms and blood pressure.<sup>[4,46]</sup> The combination of hydralazine and long-acting nitrates has been shown to decrease mortality in patients with

HFrEF and can be considered if patients cannot tolerate ACE inhibitor/ARB therapy.<sup>[4,47]</sup>

## Conclusion

Hypertension is a disease that affects a large portion of the world's population, and achieving target blood pressure goals is instrumental in preventing the development or recurrence of CV disease. Achieving these blood pressure goals can be both an art and a science, and hypertension guidelines recommend an individualized approach, taking a person's CV risk factors into account. There are a multitude of medications that can be used, but we generally recommend initiating therapy with a CCB, thiazide diuretic, or an ACE inhibitor/ARB as first-line therapy. A patient's medical comorbidities should help guide a clinician's choice of antihypertensive medication, and in some instances, secondary agents may be the preferred medication to initiate therapy.

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