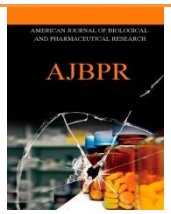
e- ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr



A REVIEW OF CARDIOVASCULAR DRUG PHARMACOLOGY: ANTIHYPERTENSIVE AND VASODILATOR AGENTS

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Article Info

Received 25/02/2026
Revised 26/02/2026
Accepted 13/03/2026

Key words: -
Antihypertensive agents, Vasodilators, Cardiovascular pharmacology, Neprsilysin inhibitors.

ABSTRACT

This literature review is a detailed discussion of cardiovascular drug pharmacology with emphasis being on antihypertensive and vasodilator drugs. The problem of hypertension is a significant risk factor of cardiovascular diseases, and polypharmacological therapy is necessary to manage it. The antihypertensive medications, such as diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs), have a key role in reducing blood pressure and avoiding certain complications, including stroke, heart failure and kidney damage. Nitrates and hydralazine and the newer neprilysin inhibitor drugs are a part of the hypertension and heart failure management because they induce a vasodilatory effect and decrease vascular resistance. The review provides an understanding of the mechanism of action, clinical signs, side effects, the changing therapy approaches, which are intended to improve the effectiveness and safety of such agents. The paper further talks about the current new developments in drug delivery systems and personalized therapy and how the developments can enhance patient outcomes when they are used to treat hypertension and cardiovascular diseases.

INTRODUCTION

Hypertension is a major risk factor for cardiovascular diseases (CVD), including heart attack, stroke, and heart failure. Globally, its prevalence is increasing due to aging populations, sedentary lifestyles, and unhealthy dietary patterns. [1] According to the World Health Organization (WHO), nearly 1.13 billion people worldwide suffer from hypertension, with less than half of them having their condition controlled. The burden of hypertension is particularly significant in low- and middle-income countries, where limited access to healthcare exacerbates the situation. [2, 3] Early detection, prevention, and treatment strategies are crucial in mitigating the growing global burden of cardiovascular disease linked to hypertension.

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The causes of hypertension are a complex combination of genetic factors, environmental factors and physiological factors. The mechanism of pathophysiology includes changes in vascular tone, renal activity, renin-angiotensin-aldosterone system (RAAS). Heightened sympathetic nervous system activity, unregulated sodium absorption by the kidneys and dysfunction of the endothelium are factors that cause high blood pressure. [4,5]The chronicity of the hypertension causes the remodeling of the vessels, damaging the walls of the arteries and expediting the formation of atherosclerosis. This amplifies the cardiovascular risk in turn. These mechanisms need to be understood so that specific therapies are developed to control hypertension. The key pharmacological objective of combating hypertension and cardiovascular diseases is to lower blood pressure and avoid prolonged effects of stroke, heart failure, and kidney injuries. The usual agents to bring about the blood pressure control are the

antihypertensive agents that are the ACE inhibitors, calcium channel blockers, beta blockers, and diuretics.[6,7] The goals of these therapies include the decrease of systemic vascular resistance and enhancement of the endothelial functions and prevention of cardiac remodeling. Pharmacological interventions should also be applied to reduce the risk factors in addition to reducing blood pressure which include dyslipidemia, diabetes and thromboembolic event. This is aimed at personalizing the treatments according to the profile of the individual patient to maximize cardiovascular outcomes.

Classification of Antihypertensive Drugs

The site of action classification of antihypertensive agents is the particular systems or physiological locations in the body where the antihypertensive agents have their effects in reducing blood pressure. The location of action will determine the interaction of the drugs with the vascular, renal or central nervous systems in the body to produce blood pressure control. The location of action is vital in determining the relevant therapies that should be used depending on the underlying health conditions, comorbidities, and response to treatment that the patient has. [8,9]Antihypertensive drugs have their main action in the central nervous system, peripheral vasculature, and kidneys, which have a unique role in blood pressure regulation.

Central Acting Agents

Central acting agents act by reducing the sympathetic outflow by targeting the central nervous system thereby decreasing peripheral resistance to vascularity. The drugs mainly work on the brainstem which activates sympathetic tone-inhibitory receptors. Popular central acting agents are alpha-2 adrenergic receptors such as clonidine and methyldopa. These drugs decrease blood pressure by decreasing the amount of norepinephrine released into the body. They come in handy especially when dealing with patients who have resistant hypertension although are linked with side effects like sedation and dry mouth, which need close monitoring.[10,11]

Renal Modulators

Renal modulators impact on the capacity of kidneys to manage the blood volume and electrolyte balance, thus regulating the blood pressure. Angiotensin-converting enzyme (ACE) and angiotensin receptor blocker (ARB) are drugs that control the renin-angiotensin-aldosterone system (RAAS) which is an important blood pressure regulator. These medications prevent the secretion of aldosterone, thereby encouraging sodium and water loss, thereby decreasing the blood volume and lowering blood pressure. Renal modulators are believed to be used first line to hypertension particularly by patients with other underlying renal disease or diabetes.[12]

Based on Mechanism of Action

The agents of antihypertension may also be categorized according to their mechanisms of action that are the biochemical processes that are affected by the agents in order to lower blood pressure. These actions activate different physiologic systems that deal with the vascular tone, the heart output, blood volume and the systemic resistance. With this knowledge of the mechanism of action, the clinicians are able to customize treatments in order to target the unique pathophysiological activities that lead to hypertension in various individuals.[13,14]

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

ACE inhibitors, ARBs, and direct renin inhibitors such as aliskiren block the RAAS pathway that is important in the maintenance of blood pressure and fluid balance. The ACE inhibitors inhibit the angiotensin I to angiotensin II conversion, and the ARBs inhibit the receptors of angiotensin II. The two methods lower vasoconstriction and aldosterone release, which stimulate vasodilation, less fluid retention, and low blood pressure. RAAS inhibitors are also most useful in patients having chronic kidney diseases, diabetes, or heart failures [11,15].

Diuretics

Diuretics decrease the blood pressure by facilitating the production of sodium and water by the kidney, a process that decreases the blood volume and consequently the blood pressure. Hydrochlorothiazide can be used as a first-line treatment of mild to moderate hypertension. More serious cases are treated with loop diuretics such as furosemide especially in those who have heart failure or renal failure. Despite their effectiveness, diuretics may lead to electrolyte imbalances and dehydration and need frequent renal function and serum electrolytes monitoring.[16,17]

Calcium Channel Blockers

Calcium channel blockers (CCBs) prevent the entry of calcium to the vascular smooth muscle and cardiac cells, which results in relaxation of blood vessels and decreases blood pressure. They lower the heart rate and myocardial contractility, as well. Amlodipine and other dihydropyridines, like verapamil and diltiazem, can act on the vasculature, whereas non-dihydropyridines like verapamil and diltiazem can also act on the heart, thus they can be used to treat arrhythmias too. CCBs frequently co-morbidly interact with other

antihypertensive medications to improve blood pressure levels.[18]

Direct Vasodilators

Direct vasodilators like hydralazine and minoxidil act by relaxing smooth muscles of the blood vessels directly especially arterioles. The effect of this is a decreased systemic vascular resistance and consequently blood pressure. The drugs are normally only used in the cases of severe or resistant hypertension because the effects are strong and side effects may be reflex tachycardia, fluid retention, and headache. These side effects are commonly controlled by the combination of direct vasodilators and other antihypertensives agents.[19]

RAAS Inhibitors in Hypertension

Angiotensin-converting enzyme (ACE) inhibitors are one of the drugs that have come to be used extensively in the management of hypertension, heart failure, and chronic kidney disease. The mechanism of action of these drugs is stopping the activity of an enzyme ACE that turns angiotensin I into angiotensin II. Angiotensin II is a very effective vasoconstrictor which increases the blood pressure by narrowing blood vessels and increasing the release of aldosterone which in turn causes the retention of water and sodium. ACE inhibitors reduce angiotensin II levels by inhibiting ACE and this leads to vasodilation, decreases blood volume and eventually lowers blood pressure.[20,21]

Mechanism of Action

ACE inhibitors inhibit the work of an enzyme, angiotensin-converting enzyme (ACE) that converts angiotensin I into angiotensin II the active vasoconstrictor. ACE inhibitors decrease the concentration of angiotensin II by stopping its conversion, which causes vasodilation, low aldosterone secretion, and low blood volume. It leads to decelerated blood pressure and decreased load on the heart, which are especially effective in such diseases as heart failure and chronic kidney disease.[22,23] The ACE inhibitors also stimulate the production of bradykinin, a vasodilator which also helps develop their effect of lowering blood pressure.

Clinical Indication (e.g. Heart Failure, Diabetic Nephropathy)

ACE inhibitors are mostly used to treat hypertension, heart failure, and chronic kidney disease. These medications increase the cardiac output by decreasing the afterload and preload in heart failure. They also minimize the risk of the development of diabetic nephropathy by lowering glomerular hypertension and proteinuria. Also, ACE inhibitors are widely utilized among patients who have had a myocardial infarction to avoid the development of heart failure. They play a crucial role in the management process of diabetic nephropathy because they can slow the rate of kidney damage especially in diabetic patients.

General Agents: Enalapril, Lisinopril.

ACE inhibitors that are most frequently used include enalapril and Lisinopril. Enalapril is commonly applied in the treatment of hypertension and heart failure, whereas Lisinopril is commonly used in such indicators as post-myocardial infarction, nephropathy in diabetics. These two drugs are successful in the reduction of blood pressure, decrease in mortality in patients with heart failure and in preservation of kidney functioning in diabetic patients. Hyperkalemia and cough are some of their side effects that should be considered in selection of an ACE inhibitor.[24]

Angiotensin Receptor Blockers (ARBs)

Angiotensin Receptor Blockers (ARBs) are a series of drugs that are mostly utilized in treatment of hypertension, heart failure, and chronic kidney disease. Angiotensin II increases in the blood because the angiotensin II type 1 (AT1) receptors responsible for most vasoconstrictor and aldosterone-releasing effects. ARBs function by inhibiting angiotensin II type 1 (AT1) receptors. ARBs inhibit the angiotensin II actions by inhibiting selectively these receptors, which result in vasodilation, decrease in blood volume, and decrease in blood pressure.[25,26] Such medications are highly prescribed as an alternative to ACE inhibitors especially where the patient suffers side effects like persistent cough with ACE inhibitors.

Selective AT1 Blockade

Angiotensin II type 1 (AT1) receptor is selectively blocked by ARBs and the majority of adverse effects of angiotensin II are caused by this receptor, including vasoconstriction, secretion of aldosterone, and sodium retention. ARBs block this receptor, inhibiting these effects, which cause a vasodilation, decreased blood volume and decreased blood pressure. In comparison to the ACE inhibitors, ARBs do not raise the concentration of bradykinin, thereby lowering the occurrence of a side effect that is common- cough. [27,28]This renders ARBs an alternative of choice among intolerant patients of ACE inhibitors.

Generals: Losartan, Valsartan

Losartan and Valsartan are popular ARB drugs used in hypertension and heart failure treatment. Losartan is commonly used in patients with hypertension and diabetic nephropathy, whereas Valsartan is commonly used in the management of heart failure. The two agents

work well in lowering blood pressure and enhancing patient results in patients with a chronic heart condition. They are also useful in preserving the kidney functions of patients with diabetes and have lesser side effects compared to ACE inhibitors thus they are an ideal choice in long term treatment.[29]

Direct Renin Inhibitors

Direct Renin Inhibitors (DRI) are a type of antihypertensive medication that acts by blocking renin an enzyme that is central to renin-angiotensin-aldosterone system (RAAS). The RAAS is an essential controller of blood pressure, fluid status and electrolyte equilibrium. DRIs inhibit the activity of renin which causes the production of angiotensin I and angiotensin II that causes the vasodilation, reduced blood volume, and eventually the blood pressure. The most frequently prescribed direct renin inhibitor is aliskiren which is a new method of management of hypertension. [30]

Mechanism and Efficacy

Direct renin inhibitors (e.g. aliskiren) act by suppressing renin, the enzyme that activates the RAAS cascade by converting angiotensinogen to angiotensin I. The effect of these drugs is to inhibit the activity of renin, which decreases the production of angiotensin I and II which causes vasodilation and low blood pressure. Direct renin inhibitors are a new way of action in hypertension therapy and they have been shown to reduce blood pressure effectively in clinical trials. They are however, normally employed in cases whereby other antihypertensive treatment methods are either not effective or un-tolerated. [31, 32]

Aliskiren: Clinical Use and Limitations

The most commonly used direct renin inhibitor is aliskiren, and it is applied in the treatment of high blood pressure. It is usually being prescribed as a single drug therapy or a combination with other antihypertensive medications such as calcium channel blockers or diuretics. Its application has however been curtailed by fears of side effects including hyperkalemia and renal impairment in particular patients with renal artery stenosis or those already taking ACE inhibitors or ARBs. The safety data is also not widely applied in the clinical practice of heart failure or diabetic nephropathy, and it is still under evaluation in the long-term. Although it has been shown to be effective, other effective classes of antihypertensives restrict its application.[33]

Sympatholytic Agents

Beta-adrenergic blockers or beta-blockers are a group of drugs that inhibit the action of adrenaline and noradrenaline on beta-adrenergic receptors found in the heart, lungs and vascular smooth muscles. These receptors are found to play a part in controlling the rate of heart beating, blood pressure and vascular tone. These receptors are blocked by beta-blockers and decrease the heart rate, decrease blood pressure and decrease myocardial oxygen needs. They have large applications in treatment of different cardiovascular disorders such as hypertension, ischemic heart disease, heart failure, and arrhythmias.[34]

Selective vs. Non-selective Beta Blockade.

Beta-blockers also referred to as beta-adrenergic blockers are drugs that inhibit the activity of beta-adrenergic receptors of catecholamines (adrenaline and noradrenaline). Such receptors occur in the vascular smooth muscles, lungs and heart. Beta-blockers can be categorized as selective and non-selective according to their preference of binding to a receptor. Selective beta-blockers (e.g., metoprolol, atenolol) are drugs that cause the heart to have reduced cardiac output and blood pressure by acting on the beta-1 receptors of the heart, resulting in slowing the heart rate and the contractile force of the heart. They are usually used in the treatment of blood pressure and heart failure.[35,36] Non-selective beta-blockers (e.g., propranol, nadol) block beta-1 and beta-2 receptors and, in addition to slowing down heart rate, lead to bronchodilation and vasoconstriction, and therefore are less suitable with respiratory diseases such as asthma. Non-selective blockers are applied in the management of disorders such as arrhythmias and prevention of migraines, however, its more general receptor effect can cause increased side effects and especially in individuals with chronic obstructive pulmonary disease (COPD) or asthma[37, 38].

Role in Hypertension, Ischemic Heart Disease

The beta-blockers are mainly applied when treating hypertension and ischemic heart disease. They reduce cardiac output in hypertension by reducing heart rate and myocardial contractility thereby lowering blood pressure. They are usually combined with other antihypertensive drugs so that they can achieve better management. Beta-blockers also assist in lowering myocardial oxygen demand in ischemic heart disease especially angina and post-myocardial infarction (MI) by lowering the heart rate and decreasing contractility thereby preventing further ischemic activity and improving outcome. Also, beta-blockers are used in the management of the arrhythmias and in the post-MI long-term protection since they lower chances of sudden cardiac death. Although they are very effective under such conditions, their systemic effects are applied in patients with asthma or severe peripheral vascular disease.[39]

Alpha-Adrenergic Blockers

Alpha-adrenergic blockers or alpha-blockers are a group of drugs that act by blocking the alpha-adrenergic receptors in the smooth muscle of the vessels. These receptors mostly mediate blood vessels constriction upon catecholamine stimulation by adrenaline and noradrenaline. These drugs inhibit the alpha-1 receptors hence causing the vasodilation effect, which causes the systemic vascular resistance to decrease consequently reducing the blood pressure. Alpha-blockers are applied in hypertension, benign prostatic hyperplasia (BPH) and other diseases involving smooth muscle contraction, e.g. Raynauds disease. [40, 41]

Prazosin and Related Agents

Prazosin, and other alpha-adrenergic blockers such as prazosin, are the drugs which block the alpha-1 receptors of the vascular smooth muscles causing vasodilation and lowering the systemic vascular resistance. Prazosin is commonly employed in hypertension treatment and treatment of benign prostatic hyperplasia (BPH), in which it decreases blood pressure by its vasodilatory effect and benefits symptoms associated with urinary retention in BPH. There are other different agents such as doxazosin and terazosin, which perform a similar action, and are applied to treat hypertension and BPH. These drugs are especially useful in the treatment of resistant hypertension in situations where other antihypertensive drugs have been unsuccessful. Nevertheless, they can lead to the side effects including dizziness, orthostatic hypotension (particularly during the initial dose) and reflex tachycardia.[42,45]

Diuretics in Hypertension

Thiazide diuretics are widely prescribed drugs that are used in the treatment of high blood pressure and edema related to heart failure and chronic kidney disease, cirrhosis, etc. These diuretics action occurs by inhibiting sodium and chloride reabsorption in the distal convoluted tubule in the kidney resulting in higher urine production and decreased fluid volume in the body. Thiazide diuretics assist in the reduction of blood pressure by decreasing the amount of blood flowing within the vessels. Also, peripheral edema (swelling) can also be reduced with the use of thiazides which promote fluid loss.[46]

Chlorthalidone, Hydrochlorothiazide

Thiazide diuretics: these are generally applied to the treatment of hypertension and edema through stimulation of sodium and water loss in the kidneys. Hydrochlorothiazide and chlorthalidone are two of the most used thiazide diuretics. Hydrochlorothiazide (HCTZ) is economical, well-established, and effective, and therefore it can be considered the first-line option. Chlorthalidone is a stronger alternative with a longer action and it is more effective in reducing blood pressure and decreasing the chances of cardiovascular events and this is preferred in some situations. The two agents both act by blocking the sodium reabsorption at the distal convoluted tubule of the kidney resulting into increased sodium, chloride and water excretion, and therefore lowering blood pressure and decreasing fluid retention. Nevertheless, they may induce electrolyte disturbances, including hypokalemia, hyponatremia, and hyperuricemia, and serum electrolytes need to be checked on a regular basis.[47–50]

Loop Diuretics

Loop diuretics represent an effective group of diuretics mainly employed in the treatment of fluid overload and edema in diseases that involve the heart failure, chronic kidney disease, pulmonary edema, and cirrhosis. The drugs are effective by reducing sodium, potassium, and chloride levels in the kidney loop of Henle. This will cause a lot of diuresis or increased production of urine that will assist in decreasing the amount of fluid that accumulates in the body.[51]

Furosemide, Torsemide

Loop diuretics, like furosemide and torsemide are stronger than thiazide diuretics and they act on the loop of Henle in the kidney to prevent sodium, chloride and potassium reabsorption. Furosemide is widely applicable in the treatment of acute pulmonary edema and congestive heart failure since it has a quick effect, and it is capable of eliminating huge amounts of fluid. Torsemide is the same but with higher half-life, which means that the dosage may be taken once a day, and with an improved bioavailability and more predictable effect. The loop diuretics are used in the cases with severe edema, renal failure, and heart failure when compared to thiazide diuretics since they have a better effect on promoting diuresis in such conditions.[51,52]

Applications in Volume Overload States

In the conditions of volume overload, e.g. heart failure, acute kidney injury, and ascites in cirrhosis, loop diuretics are the diuretic of choice. The conditions can frequently necessitate fast and powerful diuresis in order to decrease the symptoms such as pulmonary edema, peripheral edema, and ascitic fluid. Loop diuretics are effective to lower the volume in the extracellular fluid and may help avoid the further development of the organ damage associated with the presence of fluid. Although loop diuretics are potent, they may cause electrolyte imbalance, especially, hypokalemia, hyponatremia, and hypocalcemia, and potassium and other electrolytes supplementation may be needed during the treatment.[53]

Potassium sparing Diuretic

Potassium-sparing diuretics are one of the types of diuretics that aid in the removal of extra fluids in the body and preservation of potassium, which is an important electrolyte. The main mechanism of these diuretics is by suppressing the action of aldosterone hormone that stimulates sodium retention and excretion of potassium in the kidneys. Potassium-sparing diuretics prevent sodium and water loss, saving potassium, thus preventing the onset of hypokalemia (low potassium levels), the most frequent side effect of other diuretic agents such as thiazides and loop diuretics, by inhibiting the effect of aldosterone in the distal convoluted tubule and collecting duct in the nephron.[54]

Spironolactone, Eplerenone

Potassium-sparing diuretics include spironolactone and eplerenone and they prevent the effects of aldosterone in the distal nephron, which causes potassium retention and sodium and water excretion. Spironolactone is usually applied in the treatment of heart failure, primary hyperaldosteronism, and ascites caused by cirrhosis. It assists in decreasing fluid retention, enhances the heart or cardiac performance, and prevents damaging cardiac remodelling. Eplerenone is an even more selective aldosterone antagonist like spironolactone which has fewer endocrine side effects and can be used in patients who develop gynecomastia or other side effects of spironolactone related to hormones.[55-56]

POW: Potent Vasodilatory Effects.

The dihybridpyridines have been known to have strong vasodilatory properties, especially of the arteries. They prevent the entry of calcium into smooth muscle cells through L-type calcium channels preventing vascular contraction, which leads to relaxation and a reduction of systemic vascular resistance. This results in the reduction of blood pressure and alleviation of symptoms in such conditions as angina. Because of their effect on vascular smooth muscle, the dihydropyridines are particularly useful in afterload (the resistance to which her heart must labor) reduction and are commonly employed in the treatment of hypertension and chronic stable angina.[57-58] Nevertheless, they can also result in reflex tachycardia due to their vasodilatory effect and might result in peripheral edema in certain cases particularly when administered at higher doses.

Verapamil, Diltiazem

Verapamil and diltiazem, some of the non-dihydropyridines calcium channel blocker medications do not share the same properties as the dihydropyridines in this sense, since they produce pronounced effects on both vascular smooth muscle and cardiac muscle. Verapamil can be referred to hypertension, angina, and atrial fibrillation arrhythmia because of its ability to reduce heart rate and decreases myocardial contractility. Diltiazem has the same features as verapamil and is normally applied to rate control in atrial fibrillation and hypertension. Both medications are not as selective to a vascular smooth muscle as dihydropyridines, and thus they can be used to regulate heart rate and correct supraventricular tachycardias (SVTs).[59]

Impact on Heart rate and contractility.

The non-dihydropyridines, unlike the dihydropyridines have a greater impact on the heart. These drugs slow the heart rate (negative chronotropic effect) and contractility (negative inotropic effect) by blocking calcium inflow into the heart. This renders this especially useful in situations that may require the heart rate to be slowed, such as atrial fibrillation and atrial flutter and angina. [18, 60] This decreased contractility is useful in such states as hypertrophic cardiomyopathy but could be less preferable in heart failure with reduced ejection fraction (HFrEF) because of the risk to aggravate the myocardial performance. Thus, non-dihydropyridines are not normally used in patients with heart failure unless specified. They can dilate vessels as well as regulate the heart rate and heart rhythm hence being useful in the treatment of various heart related conditions.[64].

Contribution to Angina and Heart Failure

Donors of nitrates and nitric oxide play an important role in the treatment of angina and heart failure. They lower the preload in angina by widening of the veins thus lowering the volume of blood flowing back to the heart therefore lowering myocardial oxygen demand. It assists in relief of chest pain in the period of ischemia. Nitrates are applied in heart failure to reduce the preload and afterload to lighten the workload on the heart and are beneficial in the enhancement of cardiac output. Nevertheless, extended use of nitrates may result in tolerance, and periods of no nitrates are necessary to renew the effect. They are generally used as an adjunctive treatment in combination with other agents that treat heart failure (ACE inhibitors, or beta-blockers).[65]

Endothelin receptor antagonists are also categorized under group

The endothelin receptor antagonists (ERAs) are a type of medication that is mostly used in the treatment of pulmonary arterial hypertension (PAH). PAH is a disorder that is typified by the high blood pressure in the pulmonary arteries and it may cause heart failure and other serious complications in cases when unattended. [66]The action of the ERA is based on inhibition of the influence of endothelin-1, which is a strong vasoconstrictor and attaches to endothelin receptors (ET-

A and ET-B) on the smooth muscles of the vessels, leading to vasoconstriction, rise in vascular resistance, and impairment of blood circulation. ERAs inhibit these receptors, thereby causing the vasodilation effect that reduces the pulmonary vasoconstriction, hence enhancing blood flow through the lungs.[67-68]

Patient Profile Drug Selection

In the treatment of hypertension, it is important to choose a drug individually, considering the medical history of a patient, comorbidity, age, and lifestyle. This customized methodology makes sure that the treatment regimen does not only regulate the blood pressure, but also reduces the negative side effects and enhances compliance to the treatment.[69]

Table 1: Classification of Antihypertensive Drugs Based on Site of Action

Drug Class	Site of Action	Common Drugs	Mechanism of Action
Central Acting Agents	Central Nervous System	Clonidine, Methyldopa	Reduces sympathetic outflow, decreases peripheral resistance
Peripheral Vasodilators	Arteries and Veins	Hydralazine, Minoxidil	Relaxes smooth muscle in arteries, decreases vascular resistance
Renal Modulators	Kidneys	ACE Inhibitors, ARBs	Blocks RAAS pathway, reduces blood volume and pressure

Table 2: Common ACE Inhibitors and Angiotensin Receptor Blockers (ARBs)

Drug Class	Common Drugs	Clinical Indications	Side Effects
ACE Inhibitors	Enalapril, Lisinopril	Hypertension, Heart Failure, Diabetic Nephropathy	Hyperkalemia, Cough
ARBs	Losartan, Valsartan	Hypertension, Heart Failure, Chronic Kidney Disease	Less cough, Hyperkalemia

Table 3: Key Adverse Effects of Antihypertensive Drug Classes.

Drug Class	Common Adverse Effects	Examples
ACE Inhibitors & ARBs	Hyperkalemia, Cough (ACE inhibitors), Angioedema	Enalapril, Losartan
Diuretics	Electrolyte Imbalance (Hypokalemia, Hyponatremia)	Hydrochlorothiazide, Furosemide
Beta-Blockers	Bradycardia, Fatigue, Cold Extremities	Metoprolol, Atenolol
Calcium Channel Blockers	Reflex Tachycardia, Peripheral Edema	Amlodipine, Verapamil

Figure 1: Sympatholytic Agents

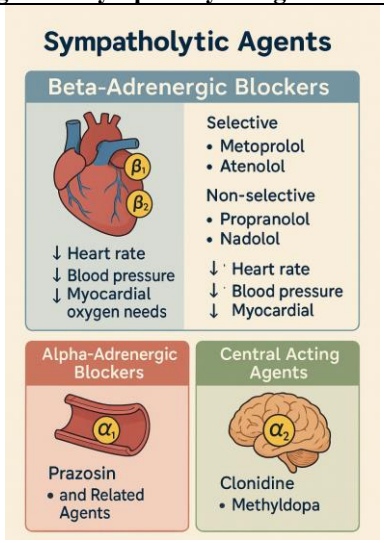


Figure 2: Diuretics in Hypertension

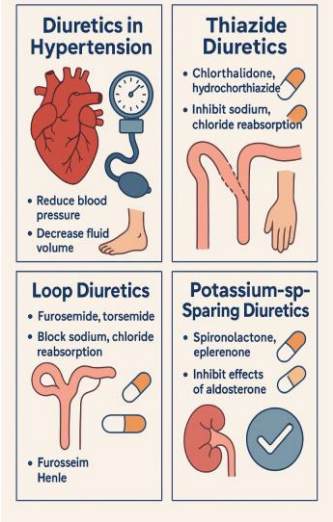
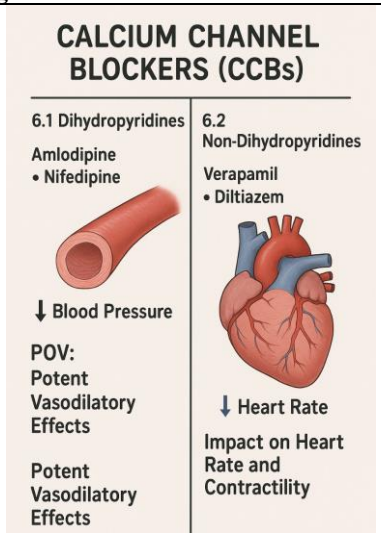


Figure 3: Calcium Channel Blockers



Racial and Ethnic Considerations

The racial and ethnic factors are significant when it comes to the choice of antihypertensive treatment. As an example, African American patients have been demonstrated to react more to calcium channel blockers and thiazide diuretics than to ACE inhibitors or beta-blockers. Conversely, ACE inhibitors or ARBs could be more of benefit to the Caucasian patients. These differences contribute to the understanding to design treatment plans that are more effective and reduce side effects, thereby

resulting in the best management of hypertension in different populations.[70]

CONCLUSION

One of the most prevalent causes of morbidity and mortality on the international level is cardiovascular diseases with hypertension being the most common one. The so-called silent killer, hypertension is a very serious condition that predisposes one to heart failure, stroke, myocardial infarction, and kidney failure. Thus, pharmacological intervention is a very important step in the light of alleviating the burden of cardiovascular diseases. Vasodilators and antihypertensive agents are important in therapeutic arsenal in the management of hypertension and its complications. Within the years, significant gains have been achieved in the production of medications with the favor of lowering blood pressure and cardiovascular health outcomes. The traditional antihypertensive groups of drugs, diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) and angiotensin receptor blockers (ARBs), are the traditional foundation of hypertension treatment. The use of diuretics, in particular, thiazide diuretics, is also popular because they serve well in decreasing the fluid overload and blood pressure. Although beta-blockers in the past were the gold standard in the treatment of hypertension, it is currently more selectively used, especially in those patients who have other cardiovascular complications such as coronary artery disease. Due to its dual effect of decelerating vascular tone and enhancing myocardial relaxation, calcium channel blockers have great potential in the treatment of hypertension and heart failure as well. ACE inhibitors and ARBs are important contributions to antihypertensive disease therapy especially in chronic kidney disease, diabetes and heart failure patients. These drugs minimize the adverse impact of the renin-angiotensin-aldosterone system (RAAS), renal protection and cardiovascular outcome. ARBs are more selective blockers of the angiotensin II receptor and are advised in patients with the ACE inhibitor-related side effects especially the irritating dry cough. Moreover, the activity of these agents is also increased by the fact that they inhibit the remodeling of the heart and blood vessels which is a significant factor in the prevention of heart failure. The newer type of drugs, neprilysin inhibitors, has presented new horizons of treating hypertension and heart failure. The enzyme that breaks down the beneficial natriuretic peptides in the body, neprilysin, is targeted by the inhibitors to raise the concentrations of these peptides that are important in reducing vascular resistance, enhancing natriuresis, and improving the functioning of the heart. The combination of neprilysin inhibitors with ARBs (e.g. the combination of sacubitril and valsartan) has demonstrated good outcomes in clinical trials, especially in patients with heart failure, where it does not only lower blood pressure but also improves the long-term survival and quality of life. These medications are helping to bring a new age of more personalized treatment plans which are not only aimed at the reduction of blood pressure but also at the optimization of heart activity and the prevention of the development of the disease. Nitrates and hydralazine, and newer drugs are referred to as vasodilators that have a complementary role in the treatment of hypertension and heart failure. Nitrates, which are mostly indicated in acute cases or as an option in chronic angina treatment, are effective vasodilators that lower myocardial oxygen consumption due to their effect in reducing preload and afterload. Hydralazine Hydralazine, an old medication with a history of hypertensive crisis and heart failure, is a direct-acting vasodilator active by relaxing vascular smooth muscle of the arteries, thus decreasing systemic vascular resistance.

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