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Epidemiology, Pathogenesis, Complications, Treatment Approaches And New Drugs In Development Of Hypertension

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Abstract: Hypertension, or high blood pressure, is a chronic medical condition characterized by consistently elevated blood pressure, leading to an increased risk of cardiovascular diseases, stroke, kidney failure, and other life-threatening complications. It is a significant global health challenge, with widespread prevalence across various age groups and geographical regions. Hypertension affects approximately 1.13 billion people worldwide, contributing substantially to the global burden of disease. The prevalence varies by region, with higher rates observed in low- and middle-income countries due to lifestyle factors, limited access to healthcare, and aging populations. In developed countries, it remains a major public health concern, often leading to complications in adults aged 45 and above. The development of hypertension is multifactorial, with genetic, environmental, and physiological factors playing key roles. Increased peripheral vascular resistance and altered kidney function, especially the over activation of the renin-angiotensin aldosterone system (RAAS), contribute to sustained high blood pressure. Endothelial dysfunction, sympathetic nervous system over activity, and vascular stiffness further exacerbate the condition. Hypertension is classified as primary (essential) or secondary. Primary hypertension, accounting for 90-95% of cases, arises from a combination of genetic predisposition, poor diet, lack of physical activity, and stress. Secondary hypertension results from underlying conditions such as kidney disease, endocrine disorders, or the use of certain medications. Hypertension is classified based on blood pressure readings into normal, elevated, and stages 1 and 2 hypertension. Early identification is crucial to prevent long-term complications. Regular screening through blood pressure measurement is essential for early detection. Screening guidelines focus on high-risk populations, such as those with obesity, diabetes, or a family history of hypertension. Management of hypertension involves lifestyle changes (e.g., diet, exercise) and pharmacological treatments, including diuretics, ACE inhibitors, calcium channel blockers, and beta-blockers. Personalized care is key to achieving optimal control and preventing cardiovascular events.

***Index terms*:** Hypertension, Myocardial Infarction, Tachycardia, Cardiovascular disease, angiotensin converting enzyme.

I. INTRODUCTION

When the blood pressure is increased chronically in the arteries, the condition is called high blood pressure or hypertension. The blood flow through the arteries to the rest of the body with every heart beat by the heart. Blood pressure is defined as the force of blood that is pushing up against the walls of the blood vessels. The normal value for blood pressure is below 120/80. The value 120 represents the peak pressure in the arteries which is also called systolic blood pressure whereas 80 represents the minimum pressure in the arteries also called diastolic blood pressure (Negi, R., Goswami, L. and Kothiyal, P., 2014). Blood pressure between 120/80 and 139/89 is called Prehypertension (to denote increased risk of hypertension), and a blood pressure of 140/90 or above is considered hypertension (Sharma, I., *et al*., 2012). Heart failure, myocardial infarction, ischemic and hemorrhagic stroke, chronic renal disease, cognitive impairment, and early mortality are all significantly increased by hypertension. A steady increase in blood pressure is typically linked to untreated hypertension. There is no natural cut-off point above which "hypertension" is unquestionably present and below which it is not; blood pressure is generally dispersed throughout the population. Blood pressure increases carry an elevated threat; for every 2 mmHg increase in systolic blood pressure, there is a 7% higher chance of dying from ischemic heart disease and a 10% higher chance of dying from stroke (Khosh, F. and Khosh, M., 2001). When age and sex are taken into consideration, genetic variables are thought to be responsible for between 30 and 60 percent of the variation in blood pressure between people. A child has a 40–60% probability of growing up with hypertension if both parents have a history of the hypertension. The genetic risk to develop primary hypertension results from the effects of multiple genes and is modulated by multiple environmental factors (Raj, M., 2011). Atrial fibrillation is the most typical clinically significant arrhythmia, while hypertension is the most typical cardiovascular condition. These two conditions often coexist, and as people age, their prevalence rises quickly. Although there are a number of risk factors and clinical disorders that can lead to atrial fibrillation, but still hypertension remains the primary risk factor for atrial fibrillation development because of its high prevalence (Manolis, A.J. *et al.,* 2011).

Frederick Mahomed is credited with discovering primary hypertension when he tested blood pressure in the general population in the early 1870s while working as a medical resident at Guy's Hospital in London.

In collaboration with a watchmaker, he created a portable sphygmograph—a device that measures the tension of the radial pulse—that was based on springs and was created in France by Étienne-Jules Marey. He identified a subgroup of people who had high blood pressure without proteinuria, even though it was recognized that patients with kidney disease and albuminuria could also have high blood pressure (Mahomed, FA., 1984). Even after Mahomed's discovery, blood pressure wasn't regularly measured until the 1890s, when Scipione Riva-Rocci (1863–1937) created the mercury manometer and BP cuff (Rodriguez-Iturbe, B., Franco, M., and Johnson, RJ., 2013) and Nikolai Sergeivich Korotkoff (1874–1920) employed auscultation of the artery beneath the cuff to ensure that blood flow was fully restricted, allowing diastolic blood pressure to be determined. Harvey Cushing and Theodore Janeway both contributed to the sphygmomanometer's introduction in the US. Systolic blood pressure was shown to be rare at 140 mmHg (0.5–1%) in persons under 65 years old in early investigations by Janeway and others, whereas the cutoff was closer to 160 mmHg in those over 65. The insurance companies noticed that individuals with hypertension had higher mortality rates by 1906 (Segall, HN., 1975). Clinicians soon made taking blood pressure a standard practice, and a cutoff of 140/90 mmHg was established as an indication for hypertension (Faught, FA., 1914). It has been discovered that hypertension raises the risk of stroke, congestive heart failure, and death. Additionally, a consequence of congestive heart failure is that it may lead to decreased kidney perfusion, which deteriorates kidney function and is referred to as cardio renal syndrome (Braam, B., *et al.,* 2011).

Hypertension is commonly known as ‘the silent killer’ because it is a condition that shows no early symptoms, and simultaneously, is the most critical risk factor for heart disease: myocardial infarction, left ventricular hypertrophy, congestive heart failure, an artery blockage, stroke, as well as chronic kidney failure (hypertensive nephropathy) and hypertensive retinopathy (Sawicka, K., *et al.,* 2011). Diagnosis of hypertension should be based ideally on several blood-pressure measurements taken on separate days. For this purpose, the mercury sphygmomanometer has an unsurpassed accuracy, but it has been substituted by aneroid and auscultatory semiautomatic devices. Aneroid manometers must be serviced and recalibrated periodically. Home blood-pressure measurement permits identification of so-called white-coat hypertension correlates better than blood-pressure values measured in the doctor’s office with target-organ damage, and could enhance patient’s adherence to drugs (Messerli, F.H., *et al.,* 2007).

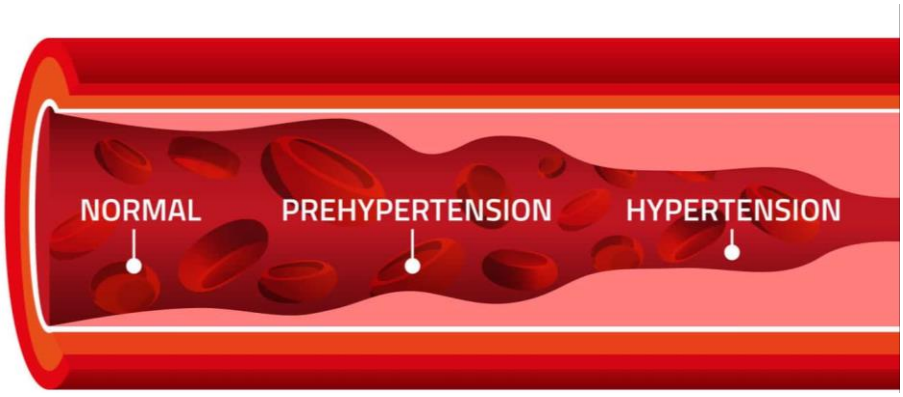

Figure- (1): Blood vessel at different stage of hypertension

II. CLASSIFICATION

"Primary hypertension" refers to high blood pressure that has no clear underlying medical reason, and it describes 90–95% of cases. Other medical conditions affecting the kidneys, arteries, heart, or endocrine system are responsible for the remaining 5–10% of cases (secondary hypertension). Blood pressure readings below 120/80 mmHg are considered as normal condition. Pre-hypertension can be described as a systolic blood pressure of 120–139 mmHg or a diastolic blood pressure of 80–89 mmHg, These patients are more likely to develop hypertension in the future. Hypertension can be described as a systolic blood pressure of more than 140 mmHg or a diastolic blood pressure of more than 90 mmHg (Carretero, O.A. and Oparil, S., 2000).
Hypertension is mainly classified as –

BP Classification	Systolic BP(mmHg)	Diastolic BP
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	>160	>100

Table- (1): Classification of Blood Pressure (Negi, R., Goswami, L. and Kothiyal, P., 2014).

III. EPIDEMIOLOGY OF HYPERTENSION

The primary risk factor for cardiovascular disease (CVD) is hypertension. 31.1% of the world's adult population, or 1.38 billion individuals, suffered from hypertension in 2010. Due to population aging and increased exposure to lifestyle risk factors such as bad diets (i.e., high salt and low potassium intake) and inactivity, the prevalence of hypertension is increasing internationally (Mills, K.T. *et al*., 2016). According to a study that examined data from 844 studies conducted in 154 countries with 8.69 million participants, the average age-standardized systolic blood pressure for men and women worldwide was 127.0 mmHg and 122.3 mmHg, respectively, in 2015. However, the average age-standardized diastolic blood pressure for women was 76.7 mmHg and for men it was 78.7 mmHg. These regional variations are probably caused by social and environmental variables, such as access to healthcare, the availability of antihypertensive drugs, and regional variances in risk factors for hypertension, such as obesity, alcohol use, poor diet, and inactivity. Additionally, the study found that the estimated mean blood pressure has either maintained the same or significantly declined globally over the last 40 years (Zhou, B. *et al*., 2016). South Asia had the lowest frequency of hypertension in men (26.4%), whereas Eastern Europe and Central Asia had the greatest prevalence (39.0%). The prevalence of hypertension in women was highest in sub-Saharan Africa (36.3%) and lowest in HICs (25.3%). Although the exact causes of these regional variations in the incidence of hypertension are unknown, they are probably impacted by variations in the prevalence of risk factors for the condition, such as obesity, poor diet, and

inactivity (Chow, C. K.., *et al.*, 2013). All ages are seeing an increase in hypertension, and even adolescents are starting to experience it more frequently. Growing rates of obesity and insulin resistance are closely associated with rising prevalence of hypertension. The onset of hypertension can also be predicted by other clinical features.

IV. PATHOGENENESIS AND ETIOLOGY OF HYPERTENSION

Hypertension is the world's largest cause of early death and a major risk factor for cardiovascular and cerebrovascular disorders. However, the etiology of hypertension, particularly essential hypertension, is complicated and demands comprehensive research (Ma, J. and Chen, X., 2022).

4.1. Causes of hypertension: Although the exact reasons of hypertension are typically unknown, a number of factors have been strongly linked to the hypertension. Some of them are - Using cigarettes, being overweight or obese, Diabetes, A sedentary way of living, Lack of exercise, excessive consumption of salt (sodium sensitivity), inadequate intake of magnesium, potassium, and calcium, Vitamin D deficiency, High alcohol intake, Stress, Aging, Medications like birth control pills, A family history of hypertension and genetics, Chronic kidney disease, Adrenal and thyroid problems or tumors (Sharma, I., *et al*., 2012).

4.2. Pathogenesis of hypertension:

4.2.1. Renin-Angiotensin-Aldosterone System: The RAAS mediates Na^+ retention, pressure natriuresis, and blood pressure regulation, salt sensitivity, vasoconstriction, endothelial dysfunction, and vascular damage and contributes significantly to the pathophysiology of hypertension (Hall, M.E. and Hall, J.E., 2018). The kidney's juxtaglomerular cells produce and store renin and its precursor pro-renin, which are then released in response to different stimuli. Renin's primary function is to break down angiotensinogen into angiotensin I. Angiotensin I is broken down into angiotensin II by the angiotensin-converting enzyme (ACE) (Singh, A and Williams, G.H., 2017). Angiotensin II improves Na^+ reabsorption in the PCT by stimulating aldosterone synthesis and release from the adrenal glomerulosa and by raising the activity of the sodium-hydrogen exchanger, sodium-bicarbonate exchanger, and sodium potassium ATPase (Hall, M.E. and Hall, J.E., 2018).

Angiotensin-converting enzyme 2 (ACE2) has become a key modulator in the pathophysiology of hypertension, cardiovascular diseases, and renal failure because it metabolizes angiotensin II into angiotensin- (1-7) (Varagic, J., *et al.*, 2014). Ang-(1–7) promotes diuresis, natriuresis, and systemic and regional vasodilation. It also has antigrowth and proliferative effects on cardiac myocytes, fibroblasts, glomerular and proximal tubular cells, as well as vascular smooth muscle cells (Varagic, J., *et al.*, 2014). The role of aldosterone in hypertension is significant because it stimulates renal Na^+ reabsorption in the cortical collecting duct by binding to the mineralocorticoid receptor and causing non-genomic effects such as activation of the amiloride-sensitive sodium channel, also referred to as the epithelial sodium channel (ENaC) (Zhou, Z.H. and Bubien, J.K., 2001). RAAS primarily controls blood pressure by affecting arterial constriction and sodium- water retention. Essential hypertension and associated target organ damage have been linked to the pathophysiology of both tissue and circulating RAAS (Ma, J. and Chen, X., 2022).

One of the three mainstays of current antihypertensive therapies, RAAS inhibitors are also the first-line treatment for hypertensive patients with target organ damage. Clinical studies have shown that RAAS blockades, such as mineralocorticoid receptor blockers (MRAs), angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNI), help to prevent hypertension and protect target organs (Unger, T., *et al.*, 2020).

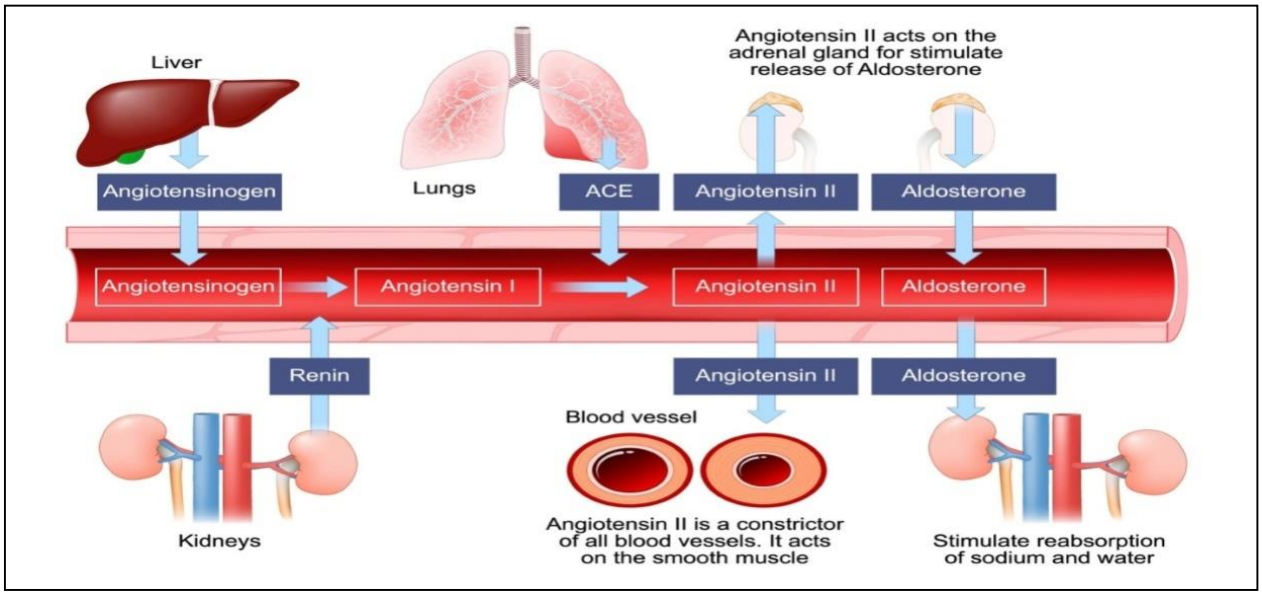

Figure- (2): Role of RAAS system in hypertension

4.2.2. Arterial stiffness: A decrease in the elasticity and distensibility of arteries is referred to as arterial stiffness, and the degree of stiffness in major arteries is frequently indicated by pulse wave velocity (PWV). Severe arterial stiffness and reduced arterial dilatation capacity are indicated by an increase in PWV. An elevated risk of essential hypertension, particularly isolated systolic hypertension, has been directly linked to arterial stiffness. In contrast, a clinically meaningful increase in arterial stiffness is likewise linked to systolic blood pressure. . Whether arterial stiffness and increased blood pressure arise first is still a "chicken and egg question" (Segers, P., Rietzschel, E.R. and Chirinos, J.A., 2020). There are two types of arterial stiffness: structural arterial stiffness and functional arterial stiffness. A number of variables affect the contractile function of vascular smooth muscle cells (VSMCs), which is primarily linked to functional arterial stiffness. Among these, VSMCs can be significantly affected by an increase in intracellular calcium ion (Ca^{2+}) concentration (Tocci, G. *et al.*, 2014). The characteristics of structural arterial stiffness, which include elastin disruption, collagen deposition, and altered extracellular matrix composition, are directly linked to aging, hyperlipidemia, and diabetes mellitus. However, because pathological alterations in structural arterial stiffness are difficult to reverse, there is currently no effective treatment for structural arterial stiffness, in contrast to functional arterial stiffness (Chirinos, J.A. *et al.*, 2019).

4.2.3. Sympathetic nervous system: People with hypertension typically have higher activity on the SNS than people with normotension (Heymans, C. and Delaunois, A.L., 2014). Additionally, SNS activity is higher among obese people, men than women, younger people than older people, and people with advanced kidney disease. An autonomic imbalance characterized by elevated sympathetic and decreased parasympathetic activity is common in hypertensive individuals (DiBona, G.F., 2013). Several experimental models have established the significance of the SNS in the pathophysiology of hypertension. Increased renal sympathetic nerve activity and the resulting increase in renal sodium reabsorption are important elements in maintaining sustained hypertension, as shown by models of obesity-related hypertension (DiBona, G.F., 2013). Additionally, increased SNS activity causes vasoconstriction, vascular smooth muscle proliferation, endothelial dysfunction mediated by alpha-1 adrenergic receptors, and increased arterial stiffness, all of which contribute to the onset and maintenance of hypertension (Fujita, T., 2014). The WNK lysine deficient protein kinase 4 (WNK4) genes, which encodes a serine/threonine kinase that inhibits the thiazide-sensitive-Na-Cl co-transporter, is shown to be less active when sympathetic overactivity is present, which increases distal tubular Na^+ retention (Mu, S., *et al*, 2011). Another significant contributor to essential hypertension is sympathetic dysregulation. Enhanced plasma catecholamine levels, higher cardiac output, and enhanced systemic vascular tone are all results of the sympathetic overdrive. Hypertensive patients may exhibit decreased baroreflex response and increased muscle sympathetic nerve activity (MSNA) (Parat, J.G. and Esler, M., 2014). Individual differences in sympathetic hypertension are common, and it is frequently linked to mental health and circadian rhythms. By regulating skeletal muscle, MSNA has a major impact on vasoconstrictive function and overall peripheral resistance

(Hissen, S.L. and Taylor C.E., 2020). Exercise is crucial for managing sympathetic hypertension, and research has shown that high-intensity interval training, such as three 60-minute workouts a week for four months, can lower blood pressure by lowering MSNA (Ehlers, T.S., 2020).Renal denervation has appeared as a potential treatment for resistant hypertension caused by sympathetic dysregulation. Sympathetic outflow to the kidneys and other heavily innervated organs involved in cardiovascular regulation is directly influenced by renal sensory afferent nerve activity (Schlaich, M.P., 2013).

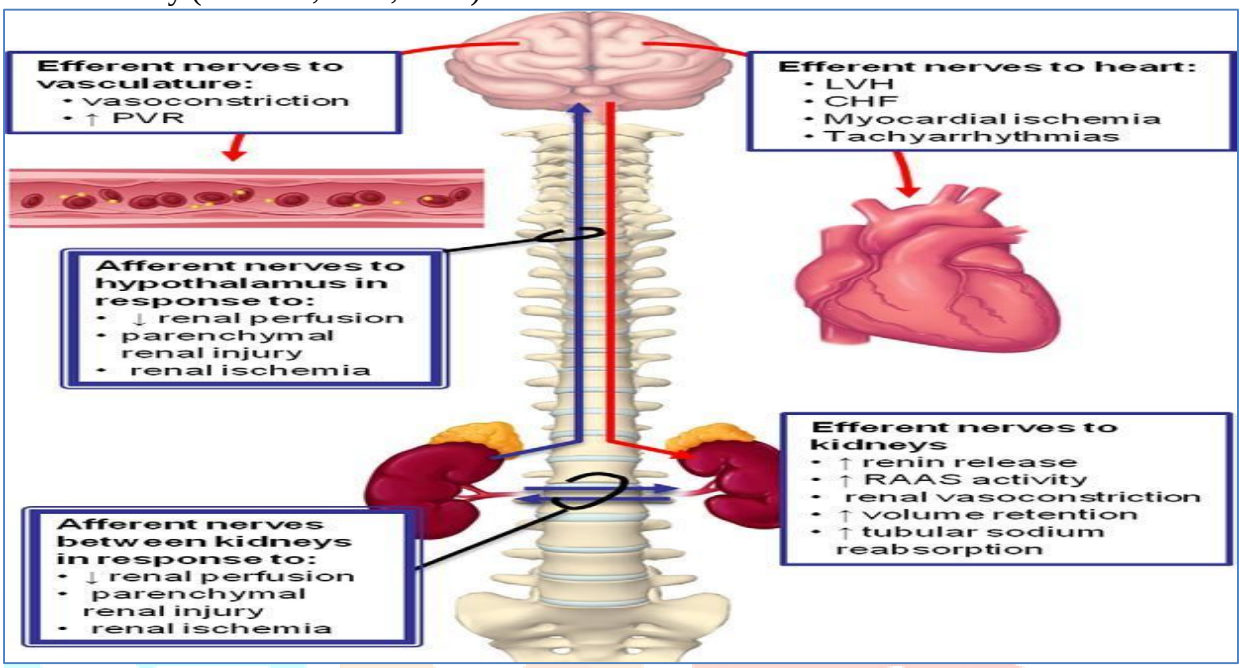

Figure- (3): Sympathetic system leading to increased blood pressure (Negi, R., Goswami, L. and Kothiyal, P., 2015)

4.2.4. The endothelium layer: Through NO, the endothelium plays a significant role in regulating vascular tone and salt sensitivity. Several vasoactive chemicals are produced by endothelial cells, but NO is the most crucial for controlling blood pressure. In response to flow-induced shear stress, endothelial cells continuously release NO, which generates intracellular cyclic guanosine monophosphate and activates guanylate cyclase, which relaxes the vascular smooth muscle. Blood pressure rises and hypertension develops in both people and animals when constitutively expressed endothelial NO synthase is inhibited, which stops NO production (Ayub, T., *et al.*, 2011). Several other vasoregulatory substances are also secreted by endothelial cells, such as vasoconstrictors like endothelin 1 (ET-1), locally generated angiotensin II, and the prostanoids thromboxane A2 and prostaglandin A2, as well as vasodilators like prostacyclin and endothelium-derived hyperpolarizing factors. Vascular smooth muscle's ET-A receptors are activated by its potent vasoconstrictor ET-1 (Kohan, D.E. and Barton, M., 2014). A key role in the pathophysiology of hypertension is endothelial dysfunction. Children of hypertensive parents who are normotensive often have impaired endothelium-dependent vasodilation, indicating a genetic component to the development of endothelial dysfunction (Panza, J.A., *et al.*, 1993). In the context of chronic hypertension, endothelial dysfunction is linked to both elevated oxidative stress and direct pressure-induced injury (Panza, J.A., *et al.*, 1993).

4.2.5. Inflammation and the immune system: The development of hypertension and associated target organ damage is significantly influenced by inflammation. Increased vascular permeability and the production of powerful mediators like cytokines, metalloproteinases, reactive oxygen species, and NO are linked to inflammation. In order to reduce the lumen diameter of resistance vessels—small arteries and arterioles that are significantly innervated by autonomic nerves and the main vessels involved in blood pressure regulation—and to promote vascular fibrosis, which results in increased vascular resistance and stiffness, cytokines mediate the formation of neo-intima, a new or thickened layer of arterial intima (Harrison, D.G. and Bernstein, K.E., 2018). The link between inflammation and hypertension is well-established in animal studies, but there is less evidence in human subjects. Although there is no direct connection, there are correlations between hypertension and TNF-alpha, C-reactive protein, and other interleukins. Furthermore, the complicated relationship between

inflammation and hypertension is highlighted by the fact that medications used to treat inflammation, such as cyclosporine and non-steroidal anti-inflammatory medicines, raise blood pressure in hypertensive persons rather than lower it (Devallière, J. and Charreau, B., 2011). When hypertension occurs, both innate and adaptive immune responses contribute to the production of reactive oxygen species and inflammatory alterations in the kidneys, blood vessels, and brain. Hypertension brought on by antagonism between angiotensin II, aldosterone, and NO has been connected to innate immune responses, particularly those mediated by macrophages (Rodriguez-Iturbe, B., 2016). Blood pressure and salt sensitivity decrease when there is less macrophage infiltration of the kidney or the peri-adventitial area of the aorta and medium-sized arteries (Harrison, D.G. and Bernstein, K.E., 2018). The development of hypertension and the harm it causes to its target organs have also been connected to adaptive immunological responses through T cells. T lymphocytes mediate angiotensin II-dependent hypertension and express AT1 receptors (Rodriguez-Iturbe, B., 2016). Depletion of mature lymphocytes has been demonstrated to improve hypertension and renal damage in Dahl SS rats fed a high-salt diet (Mattson, D. L. *et al.*, 2013).

4.2.6. Genetics: Genes are strongly linked to hypertension, and in recent years, researchers have made significant progress in understanding the connection between genetics and blood pressure. Genome-wide association studies have identified over 500 loci that regulate blood pressure, bringing the total number of BP genetic loci to over 1,000 (Giri, A. *et al.*, 2019). Typically, a chromosomal region is indicated by the lead single nucleotide polymorphism (SNP). These SNPs, which have a minor impact on blood pressure, are frequently found in nonprotein coding regions of the genome and do not change protein function. Few identified targets have been effectively converted into clinical use, despite the fact that SNPs offer a possible pathogenic pathway for essential hypertension. According to a recent study, a polygenic risk score (PRS) that assessed numerous SNPs was predictive of early-onset hypertension in a progressive manner. Those with the highest PRS of 2.5% had a nearly threefold increased risk of developing hypertension, while those with a low PRS were protected. When used appropriately, SNPs may offer novel possibilities for the diagnosis and management of hypertension (Vaura, F., *et al.*, 2021). Variations in blood pressure cannot be explained just by genetics, indicating the involvement of other risk factors, such as epigenetic alterations. Recent data suggested that epigenetic pathways may play a role in essential hypertension. Human hypertension susceptibility has been linked to genome-wide DNA methylation, and animal models have demonstrated that DNA methylation controls a number of genes important for blood pressure regulation (Richard M.A., *et al.*, 2019).

V. COMPLICATIONS OF HYPERTENSION

Hypertension plays a crucial role and established as risk factor for myocardial infarction, stroke and renal dysfunction. Adequate prevention and management is essential in order to control hypertension. Additionally, there is growing evidence that hypertension appears to be associated with common non cardiovascular conditions such as osteoporosis, cancer, dementia, and oral health problems (OHDs). The association between hypertension and these diseases can be explained as (Yoshihiro, K. and Yoshio, I., 2015).

5.1. Atrial Fibrillation: One of the most typical forms of chronic arrhythmia and a risk factor for ischemic stroke is atrial fibrillation (AF) (Lip, G. Y., Tse, H. F. and Lane, D. A., 2012). According to the Framingham Heart Study, hypertension raises the risk of AF by 1.4 for women and 1.5 for men (Benjamin, E. J. *et al.*, 1994). A cohort study of Norwegian males and the Women's Health Study demonstrated a correlation between incidence AF and high-normal blood pressure (Conen, D. *et al.*, 2012). In that study, systolic prehypertension with overweight was linked to a higher incidence of incident AF when compared to normal blood pressure and weight. Significant mediators of the association between blood pressure and incidence atrial fibrillation include arterial stiffness, left ventricular hypertrophy, and enlarged left atrial size (Brignole, M. *et al.*, 2013). Overweight and higher systolic blood pressure may raise the incidence of atrial fibrillation (AF) by exacerbating left ventricular hypertrophy and hypertension (Yoshihiro, K. and Yoshio, I., 2015).

5.2. Chronic Kidney Disease: Chronic kidney disease is defined as continues decrease in glomerular rate over a period of time, which leads to irreversible kidney damage. It has been repeatedly shown that hypertension is an independent risk factor for both an increase of CKD and a lowering glomerular filtration rate (Lindeman, R. D., Tobin, J. D. and Shock, N. W., 1984), in part due to sympathetic nervous system activation and renin-angiotensin-aldosterone system activation. A meta-analysis and comprehensive review of prospective cohort

studies revealed a correlation between incidence end-stage renal disease and prehypertension (Huang, Y. *et al.*, 2014). The prehypertensive group had a 1.59× higher risk of end-stage renal disease than the group with normal blood pressure. The risk of end-stage renal disease was elevated even with normal blood pressure; this link varied per study and varied by age, sex, and ethnicity. Furthermore, a systematic meta-analysis revealed that the development of CKD was also linked to specific metabolic syndrome components other than increased blood pressure (hazard ratio, 1.61; 95% confidence interval, 1.29–2.01) (Thomas, G. *et al.*, 2011).

5.3. Dementia: A reduction in cognitive capacities that results in functional decline and the inability to carry out daily tasks for healthy people is known as dementia (Gorelick, P. B. *et al.*, 2011). Vascular dementia (VaD) was first identified after dementia was seen to develop following a stroke or in Binswanger disease, a severe white-matter illness linked to chronic hypertension. It is widely believed that these conditions, together with arteriosclerosis, are the main causes of dementia in the elderly (Hachinski, V. C., Lassen, N. A. and Marshall, J., 1974). Changes in arteriole walls caused by hypertension can result in arteriolar occlusive disease and, eventually, infarction. The consequences of hypertension may also be linked to alterations in blood flow, the integrity of the blood-brain barrier, or brain abnormalities in dementia (Moretti, R. *et al.*, 2008).

5.4. Oral Health Disorders: Oral health disorder (OHD) includes cavities, gingival bleeding and periodontal disease. Numerous epidemiological studies have indicated a positive correlation between OHD, including periodontal disease, gingival bleeding, and tooth loss, and hypertension (Völzke, H. *et al.*, 2006). When evaluating the potential correlation between OHD and hypertension, it is important to take into account the numerous risk factors that these two disorders have in common. One of the processes linked to the development of hypertension is the systemic inflammatory response that may underlie these conditions (Tsioufis, C. *et al.*, 2011). Hypertension may develop as a result of inflammation's subsequent effects on endothelial dysfunction and arteriolar bleeding. If treatment is not received, this causes the teeth's supporting tissue to deteriorate and ultimately result in tooth loss (Williams R. C., 1990).

5.5. Bone Metabolism: In general, as people age, the prevalence of osteoporosis or hypertension rises. Important factors influencing bone mass include calcium, parathyroid hormone, vitamin D metabolites, exercise, and a healthy diet. Osteoporosis and hypertension are frequently accompanied by disturbances in calcium metabolism, such as elevated calcium excretion in the urine (Tang, B. M. *et al.*, 2007), and growing evidence indicates that low vitamin D levels appear to increase the risk of hypertension via disrupting calcium homeostasis and raising parathyroid hormone levels (Jorde, R., Svartberg, J. and Sundsfjord, J., 2005). By affecting the amount of calcium in vascular smooth muscle cells, vitamin D may play a part in controlling vascular tone. Additionally, insulin resistance, systemic inflammation, and renin-angiotensin-aldosterone system dysregulation have all been connected to low vitamin D levels (Forman, J. P., Williams, J. S. and Fisher, N. D., 2010). In fact, eating a diet rich in sodium and low in calcium is closely linked to hypertension. Osteoporosis and hypertension are two of the major health issues affecting the elderly. Although the exact cause of hypertension and improper bone metabolism is yet unknown, treating hypertension, particularly with thiazide-type diuretics, is a crucial and efficient way to preserve bone density. Most guidelines prescribe thiazide-type diuretic therapy as the first line of treatment for hypertension, much like salt reduction (James, P. A. *et al.*, 2014).

VI. TREATMENT APPROACHES

For the management of hypertension, mainly three kind of approaches that includes-

6.1. Herbal Approach: The study of pharmacognosy and the application of medicinal plants, which form the foundation of traditional medicine, are known as herbal medicine (also known as herbalism, phytomedicine, or phytotherapy). It includes-

6.1.1. Hibiscus sabdariffa: Hibiscus sabdariffa is one potential non pharmacological treatment. In folk medicine, the calyces' infusion is used for the treatment of several conditions including high BP. Anthocyanin's and proanthocyanidins compounds, detected in abundance in the aqueous infusion of the Hibiscus calyces, could be the bioactive compounds responsible for lowering the blood pressure based on earlier studies which proved the anti hypertensive effects of anthocyanin's through the inhibition of angiotensin II converting enzyme

and hence a vaso dilatation effect in addition to its diuretic effect and the increased concentration of urinary sodium while maintaining normal potassium levels (Wahabi, H.A., 2010).

6.1.2. Ajwain (Carum copticum L.): Carum copticum is a member of the Apiaceae family and is found growing throughout Central Europe, India, Afghanistan and Iran, especially in the eastern parts of Baluchistan. C. copticum has a significant function in controlling blood pressure and heart rate because of its ability to inhibit calcium channels (Boskabady, M. H., Alitaneh, S. and Alavinezhad, A., 2014).

6.1.3. Black Cumin (Nigella sativa): In the Middle East, Europe, and Africa, the Nigella sativa plant—known as the seed of blessing, has long been utilized. This plant and its constituents lower blood pressure (Leong, X.F., Raismustafa, M. and Jaarin, K., 2013). Male patients with moderate hypertension who receive oral N. sativa seed oil extract (100 or 200 mg) for eight weeks exhibit a decrease in SBP of 10.6 and DBP of 9.6 mm Hg, respectively (Jaarin, K., *et al.*, 2015).

6.1.4. Carrot (Daucus carota L.): Traditional medicine has utilized carrots as a mediator of antihypertensive effects. Daucus carota L. controls fluid balance and enhances endothelial function. Antioxidants, which are high in carrot juice, reduce oxidative stress and regulate blood vessel structure and function (Kaur, R. and Khanna N, 2012).

6.1.5. Cinnamon (Cinnamomum zeylanicum): Cinnamomum zeylanicum is another herb used for treating hypertension. Its stem bark's aqueous extract lowers SBP and inhibits contractions produced by potassium chloride, or KCl, which is connected to the endothelium, NO, and the ATP-sensitive K+ channel (K ATP channel). The bark's methanolic extract raises NO levels (Nyadjeu, P. *et al.*, 2013).

6.1.6. Coffee Weed (Cassia occidentalis): Blood pressure is also regulated by coffee weed. This plant's leaf has antihypertensive properties. Coffee weed has been shown to lower blood pressure, most likely via inhibiting the influx of external Ca^{2+} (Ali, M. *et al.*, 2019).

6.1.7. Fang Ji (Stephania tetrandra): Stephania tetrandra can control elevated blood pressure by inhibiting Ca^{2+} channels and lowering the expression of inducible nitric oxide synthase. The bioactive component of this plant, tetrandrine, is an alkaloid with anti-inflammatory and antioxidant properties that likely contribute to its antihypertensive effects (Dang, Y. *et al.*, 2014).

6.1.8. Ginger (Zingiber officinale): Zingiber Officinale, commonly known as ginger, has been utilized for a variety of medicinal and everyday dietary uses. Ginger includes a huge amount of potassium, which is crucial in the regulation of hypertension and heart rate. It also inhibit ACE- I activity (Akinyemi, A.J., Ademiluyi, A.O. and Oboh, G., 2014).

6.1.9. Indian snakeroot (Rauwolfia serpentina): A tropical woody plant called Rauwolfia serpentina is used to treat hypertension by lowering dopamine and adrenaline levels and stimulating vasodilation. Rauwolfia serpentina's principal alkaloid, resperpine, is the most potent medication that has been widely used for a long time to treat hypertension (Lobay, D., 2015).

6.2. Non-Pharmaceutical Approach: As previously mentioned, any intervention aimed at enhancing people's health or well-being that doesn't involve the use of pharmaceuticals or medications is considered as non-pharmacological approach. It includes-

6.2.1. Lifestyle modifications: All people should adopt healthy lifestyles as a means of preventing high blood pressure and as an essential component of managing hypertensive patients. Changes in lifestyle lower blood pressure, improve the effectiveness of antihypertensive medications, and lower the risk of cardiovascular disease. It is advised to have a diet rich in complex carbohydrates and low in saturated fat. Fruits, vegetables, whole grains, nuts, seeds, legumes, fish, soy products, onions, garlic, and foods high in potassium, calcium, and magnesium (carrots, spinach, celery, alfalfa, mushrooms, lima beans, potatoes, avocados, broccoli, and most fruits) are all part of this diet, which also limits salt intake (Khosh, F. and Khosh, M., 2001).

6.2.2. Cessation of smoking: Patients with hypertension and their loved ones can benefit both immediately and over time from quitting smoking, which is a major risk factor for heart disease. Compared to continuing to smoke, quitting significantly lowers overall cardiovascular risk, which includes the risk of coronary heart disease and stroke. There is currently no proof that quitting smoking lowers blood pressure directly in individuals with hypertension, despite the fact that smoking is known to raise the risk of developing hypertension (Huang, N., 2001).

6.2.3. Acupuncture: The Chinese therapeutic practice of acupuncture has been practiced for at least 2,500 years. Endorphins and encephalin, two substances released by acupuncture, can reduce pain and promote relaxation. In Oriental medicine, practitioners believe that the body's twelve major meridians carry a vital energy known as "chi." Although each meridian is named after an organ or "official," the term actually refers to the energy function of the organ rather than its anatomy or structure. Every meridian has both internal and external projections. Acupuncture points are locations on the surface projections. In order to alter the body's chi and restore health, practitioners of oriental medicine inject needles into these locations (Weil, N. et al., 2007).

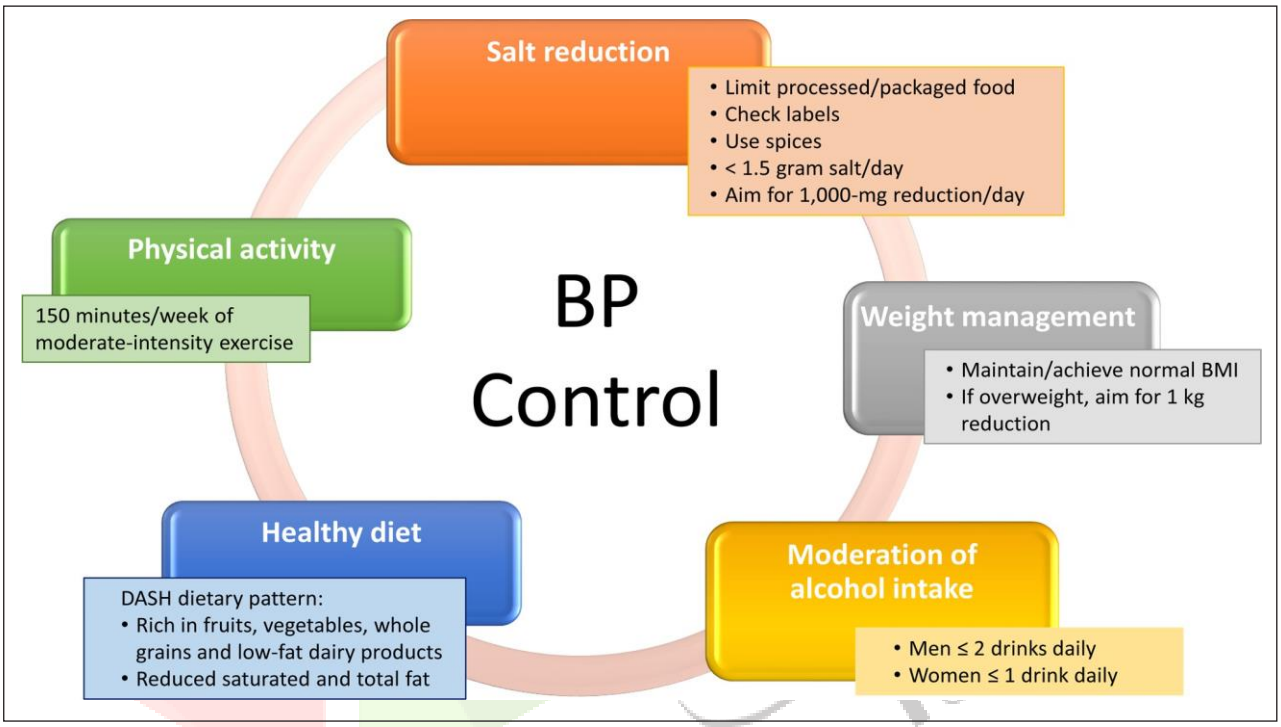

Figure- (4): Non pharmaceutical approach to treat hypertension (Heidari, B., Avenatti, E. and Nasir, K., 2022).

6.3. Pharmaceutical Approach: Pharmaceutical therapy, sometimes known as pharmacotherapy or pharmacological therapy is the practice of treating disease by administering drugs. It includes-

Classification of anti-hypertensive medicines (Maheshwari, k.k., 2012)

1. DIURETICS

a. **Thiazides and related compound:** Chlorthalidone, Hydrochlorthiazide, Indapamide
b. **Loop diuretics:** Bumetanide, Furesemide, Ethacrynic acid, Torsemide
c. **K^+- sparing diuretics:** Amiloride, Spiranolactone, Triaterene

2. SYMPATHOLYTICS DRUGS

a. **β-blockers:** Acebutalol, Atenolol, Betaxolol, Bisoprolol, Metoprolol, Nadolol, Pindolol, Timolol
b. **α-Blockers:** Alfuzosin, Bunazosin, Ergot alkaloid, Phenoxybenzamine, Prazosin, Phentolamine
c. **α- and β-both blockers:** Carvedilol, Dilevalol, Labetalol
d. **Ganglionic-blockers:** Hexamethonium, Pempidine, Pentolinium, Trimethophan
e. **Neuron-blockers:** Bethamidine, Bretylium, Guanadrel, Guenethidine

f. **Cathecholamine depliters:** Resesrpine, Rauwolfia root
g. **Centrally acting agents:** α- methyl dopa, Clonidine, Guanfacine, Moxonidine

3. CALCIUM CHANNEL BLOCKERS

a. **First generation:** Diltiazem, Nefidipine, Verapamil
b. **Second generation:** Amlodipine, Felodipine, Nicardipine, Nimodipine, Prenylamine
c. **Third generation:** Lacidipine, Lecarnidipine
d. **Miscellneous:** Dipyridamole, Oxyfedrine, Papaverine

4. ANGIOTENSIN CONVERTING ENZYME IBHIBITORS: Benazepril, captopril, Enalapril, Lisinopril

5. RENIN ANGIOTENSIN ANTAGONIST: Caandesartan, Losartan, Valsartan, Zolasartan

6. DRUGS ACTING REFLEXLY: Veratrum alkaloids, Ketanserin

7. MISCELLANEOUS DRUGS: Amrinone, Meterosine, Milrinone, Pargelline

6.3.1. DIURETICS

After a period of decrease in the early 1990s, diuretics are currently the most commonly used antihypertensive medications. This indicates that their ability to offer superior protection against heart attacks, heart failure, and stroke at lower dosages as like ACE inhibitors and CCBs. Diuretics decrease blood volume and, thus, cardiac output by inducing natriuresis (Negi, R. et al., 2015).

Mechanism of Action: By inhibiting the Na/Cl channels, thiazides prevent sodium from being transported in the distal tubule. Thiazides mostly affect the distal tubule, although they can also have a minor impact on the proximal tube by obstructing sodium transport. Thiazide diuretics can acutely activate the renin-angiotensin system and cause systemic vascular resistance, which prevents a good response to the diuretic treatment; this increase in renin-angiotensin activity may resolve with chronic thiazide treatment; the addition of an ACE inhibitor or ARB can improve blood pressure control. Thiazides cause initial volume depletion associated with decreased cardiac output, which recovers within 6 to 8 weeks of starting the treatment in a reverse autoregulation mechanism while the blood pressure stays under control.

Side Effects: There are several adverse effects linked to thiazide and thiazide-like diuretics. The diuretic dosage is directly responsible for the majority of these adverse effects; the most frequent metabolic side effects are hypokalemia and hyponatremia, which are followed by hyperuricemia, hypomagnesemia, hyperlipidemia, and elevated glucose levels (Leung, A. A., et al., 2011; Patel, P. and Preuss, C. V., 2025). According to one study, older individuals on chlorthalidone had a higher chance of being admitted to the hospital as a result of severe hypokalemia. Sleep disruption and sexual dysfunction are additional negative effects that are not related to dosage (Patel, P. and Preuss, C. V., 2025).

Contraindications: Patients with sulfonamide allergy and those who are anuric should not take thiazide-type diuretics (Patel, P. and Preuss, C. V., 2025). For individuals with hepatic coma, anuria, or sulfonamide hypersensitivity, loop diuretics are contraindicated (Huxel, C., Raja, A. and Ollivierre-Lawrence, M. D., 2023). Patients with hyperkalemia or chronic kidney disease should not take potassium-sparing diuretics; they should also be used alongside ACE inhibitors, ARBs, and aliskiren with caution. Patients who are hypersensitive to this class should not use them (Almajid, A. N., Patel, P. and Cassagnol, M., 2024).

6.3.2. BETA BLOCKERS

For the majority of hypertensives, β-blockers have been suggested as the first monotherapy, especially for those who also have heart failure, migraine, tremor, coronary artery disease, and stress-induced arrhythmias (Negi, R. et al., 2015).

Mechanism of Action: Beta- blockers shows their action by preventing catecholamines from attaching to the Beta 1, 2, and 3 receptors. The heart muscle contains the majority of beta-1 receptors, the bronchial and peripheral vascular smooth muscles have beta-2 receptors, and the heart's adipose tissue has beta-3 receptors. Cardio-selective beta-blockers (e.g., metoprolol succinate, metoprolol tartrate, atenolol, betaxolol, and acebutolol) blocks only beta-1 receptors, causing fewer bronchospasms. Beta-blockers restrict catecholamines from binding to beta receptors, causing a negative inotropic action that lowers heart rate and helps lower oxygen consumption (Farzam, K. and Jan, A., 2023).

Side Effects: Bradycardia, constipation, depression, exhaustion, and sexual dysfunction are typical adverse effects of beta-blockers. They are also linked to increasing peripheral vascular disease symptoms and bronchospasm. They may result in a Raynaud syndrome flare-up (Farzam, K. and Jan, A., 2023).
Contraindications: Patients with asthma should not take beta-blockers, especially nonselective beta-blockers. Bradycardia and hypotension are relative contraindications. Some believe that patients who have cocaine-induced coronary artery spasms should not use them (Farzam, K. and Jan, A., 2023).

6.3.3. CALCIUM CHANNEL BLOCKERS

Benzothiazepines, phenylalkylamines, and dihydropyridines are the three categories of CCB. The CCBs only block the voltage-sensitive L-type channels. Although the properties of channel blockade vary, all three types of CCBs restrict Ca^{2+} entrance by binding to distinct binding sites on the α1 subunit. Additionally, different drugs may have varying affinities for different site-specific L-channel isoforms. This could explain the variations in activity shown by different CCBs. Additionally; they increase the availability of nitric oxide, most likely through an antioxidant impact on endothelial cells. The special capacity of CCBs to sustain or enhance effective renal blood flow and GFR, which has been related to their selective vasodilative action on renal afferent arterioles, is likely also reflected in the enhanced excretion of water and sodium. Therefore, in order to control hypertension in individuals with renal insufficiency, CCBs should only be added to ACE inhibitors when necessary. Although the antihypertensive effects of the currently available formulations appear to be comparable, short-acting dihydropyridines have been shown to raise the incidence of angina and death following acute myocardial infarction. They have also been demonstrated to increase coronary events when used to treat hypertension because they cause a sudden drop in blood pressure and subsequently activate the sympathetic nervous system. These risks do not apply to long-acting CCBs. Even if daily dosages are missed, amlodipine's extended duration of action and gradual commencement of action ensure that its effects last. There have been worries raised over additional possible negative consequences of CCBs because calcium entry is involved in so many cellular processes. However, it appears that these drugs have minimal effect on calcium metabolism, and later research has not confirmed early concerns of elevated risks for cancer, hemorrhage, and suicide (Negi, R. et al., 2015).
Mechanism of Action: CCBs shows their action by binding to the L-type voltage-gated calcium channels found in the heart muscle, which inhibits the entry of Ca^{2+} into the cells. This action can result in peripheral vasodilation, which is primarily observed with dihydropyridines, a negative inotropic impact on the heart muscle that inhibits the atrioventricular and sinoatrial nodes, causing sluggish cardiac conduction and contractility, which is primarily observed with non- dihydropyridines (McKeever, R. G., Patel, P. and Hamilton, R. J., 2024).
Side Effects: Peripheral edema is frequently linked to dihydropyridine CCB therapy. The incidence of edema is correlated with the dose of the CCB and is higher with long-acting nifedipine than with amlodipine. It is unrelated to the development of heart failure or fluid or salt retention (Carey, R. M., *et al.*, 2018). Diuretic medication does not reduce CCB-induced edema since it is not caused by an increase in volume; however, a minor reduction in the risk of peripheral edema was observed when CCBs were combined with ACE inhibitors or ARBs. Dihydropyridines can result in gingival hyperplasia, headaches, flushing, and dizziness. When providing CCBs to elderly patients or patients who are at high risk of bleeding, care must be taken because these medications block platelet aggregation and are linked to an increased risk of gastrointestinal bleeding (McKeever, R. G., Patel, P. and Hamilton, R. J., 2024).
Contraindications: Patients who are hypersensitive to CCBs should not take them. Patients with heart failure, low ejection fraction, sick sinus syndrome, and second or third-degree AV blockage are contraindicated to dihydropyridines (McKeever, R. G., Patel, P. and Hamilton, R. J., 2024). Individuals with unstable angina, severe aortic stenosis, and cardiogenic shock should not use dihydropyridine; individuals with liver impairment should use it with extra caution (Bulsara, K. G., Patel, P. and Cassagnol, M., 2024).

6.3.4. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

There are now three distinct classes of ACE inhibitors. The most obvious way that ACE inhibitors lower blood pressure is by decreasing the amount of angiotensin II in the blood, which reduces the direct vasoconstriction that this peptide causes. At the same time, various ACE inhibitors appear to have varying degrees of inhibition of ACE activity within artery walls and other tissues, such as the brain and heart. The inhibition of bradykinin breakdown may be one way that ACE inhibitors work, with kinin stimulation of nitric oxide generation

contributing another. Additionally, ACE inhibitors reduce the anticipated rise in sympathetic activity that follows vasodilation. Heart rate and cardiac output do not rise as a result. ACE medications also reduce endogenous endothelin secretion and reduce endothelial dysfunction. As a result of all of these effects, ACE inhibition decreases arterial wave reflection and increases aortic distensibility. No matter how ACE inhibitors reduce blood pressure, they do it in a way that tends to preserve the health of the kidneys and the heart (Negi, R. et al., 2015).

Mechanism of Action: ACE inhibitors reduce blood pressure by blocking the angiotensin-converting enzyme, which results in less angiotensin II being produced. This also raises the level of bradykinin by preventing its degradation, which induces vasodilation (Herman, L. L., Padala, S. A., Ahmed, I. and Bashir, K., 2023).

Side Effects: Cough, hypotension, tiredness, and azotemia are the most frequent ACE inhibitor adverse effects; one typical adverse effect is reversible renal impairment, particularly if the patient experiences volume depletion as a result of vomiting or diarrhea. Up to 20% of people taking ACE inhibitors may experience coughing. The cough takes up to 14 to 28 days after stopping. Cough is less common when taking ARBs; when comparing losartan and hydrochlorothiazide. When compared to CCBs, candesartan did not correlate with a rise in the incidence of coughing in asthmatic patients, indicating that ARBs are safe for usage in these patients. Cough incidence was greater with Ramipril than with Telmisartan (Yusuf, S., *et al.*, 2008). Mild hyperkalemia is often related to ACE inhibitor treatment. Patients with renal failure, diabetes, or CHF are more likely to experience hyperkalemia, even if their renal function is normal (Desai, A. S., *et al.*, 2007). The incidence of syncope, acute renal damage, and hyperkalemia is the same for telmisartan and ramipril. Telmisartan is linked to a higher frequency of hypotension symptoms (Yusuf, S., *et al.*, 2008). Angioedema is an uncommon ACE inhibitor adverse effect that affects 0.3% of ramipril users. ACE inhibitors are more linked to angioedema than ARBs (Yusuf, S., *et al.*, 2008).

Contraindication: Patients who have previously had ACE inhibitor hypersensitivity, ACE inhibitor-related angioedema, other forms of angioedema, pregnancy should not use ACE inhibitors. Patients with volume depletion, aberrant renal function, and aortic valve stenosis are examples of relative contraindications (Singh, B., *et al.*, 2025). During pregnancy, ARBs should not be used. It is generally not recommended to use ACE inhibitors and ARBs together. Patients with volume depletion, those on other drugs that cause hyperkalemia, or those with impaired renal function are additional relative contraindications for ARB treatment (Patel, P. and Launico, M. V., 2025).

VII. NOVEL DRUGS IN DEVELOPMENT, DIETARY APPROACHES AND HYPERTENSION VACCINES:

7.1. NEW DRUGS IN DEVELOPMENT

7.1.1. Dual-Endothelin blockers: Vascular endothelial cells produce the peptide endothelin-1, which induces vasoconstriction, endothelial dysfunction, aldosterone production, and catecholamine release. There are two known kinds of endothelin (ET) receptors: ETA and ETB. Both can mediate vasoconstriction on vascular smooth muscle cells, however only ETB receptors can mediate vasodilation on endothelial cells (Krum, H., *et al.*, 1998). Endothelin receptor antagonists (ERAs), both selective and non-selective, have been investigated for the treatment of resistant hypertension. Phase 3 trials have demonstrated a significant reduction in blood pressure when aprocitentant, a dual antagonist of ETA and ETB receptors, is added to hypotensive therapy with three other medicines and a diuretic (Schlaich, M. P., *et al.*, 2022).

7.1.2. Aminopeptidase a inhibitors: A metalloprotease called amino-peptidase A (APA) plays a part in the renin-angiotensin system in the brain by changing angiotensin II into angiotensin III (Blazek, O. and Bakris, G. L., 2023). By raising central vasopressin concentrations, activating the baroreflex, and reducing sympathetic tone, angiotensin III influences blood pressure (Fournie-Zaluski, M. C., *et al.*, 2004). In salt-dependent hypertensive rat models, treatment with an APA inhibitor, EC33, has been demonstrated to lower blood pressure via lowering brain angiotensin III levels without changing systemic levels (Bodineau, L., *et al.*, 2008). It has been demonstrated that the novel oral active prodrug firibastat, which is converted to EC33, lowers blood pressure in overweight hypertensive individuals of various ethnic backgrounds (Ferdinand, K. C., *et al.*, 2019).

7.1.3. Blockers of the mineralocorticoid receptors: Renal endothelium cells, vascular smooth muscle cells, podocytes, mesangial cells, and distal nephron epithelial cell all express mineralocorticoid receptors (MR) (Barrera-Chimal, J., Bonnard, B., and Jaisser, F., 2022). Aldosterone binds to the MR in renal epithelial cells, promoting reabsorption of salt and water and raising blood pressure. As previously mentioned, spirolactone is a steroidal mineralocorticoid receptor antagonist that is advised as a fourth-line treatment for resistant hypertension, in addition to a thiazide diuretic, renin-angiotensin blocker, and CCB (Carey, R. M., *et al.*, 2018). Spironolactone lowers proteinuria and raises blood pressure, but because it increases the risk of hyperkalemia, it might not be suitable for individuals with severe renal failure. The significant prevalence of spironolactone-associated hyperkalemia in clinical practice led to research into effective, yet selective, non-steroidal MR antagonists (NS-MRA) with a low risk of causing hyperkalemia and a favorable benefit-risk profile (Agarwal, R., *et al.*, 2021; Bärfacker, L., *et al.*, 2012). A novel medication in this family, finerenone has been shown to inhibit a decline of kidney function and lower cardiovascular outcomes in diabetic nephropathy patients (Agarwal, R., *et al.*, 2022). Although it has a much greater hemodynamic effect than originally anticipated, finernone does significantly drop blood pressure at systolic pressures above 140 mmHg, but not in normotensive people (Agarwal, R., *et al.*, 2023). The impact of finerenone on cardiovascular outcomes in diabetic patients with chronic renal impairment is being examined in a number of phase 3 studies. Esaxerenone and ocedurenone, two other NSMRSs under development, are being tested to treat resistant hypertension (Ito, S., *et al.*, 2019; Bakris, G., *et al.*, 2021).

7.1.4. Selective aldosterone synthase inhibitors: Aldosterone synthesis is regulated by aldosterone synthase. Instead of preventing the mineralocorticoid receptor from functioning, selective inhibition of this enzyme inhibits the synthesis of hormones. Aldosterone suppression is crucial, but it has proven challenging to do because of the simultaneous interference of cortisol production (Blazek, O. and Bakris, G. L., 2023). A novel drug called baxdrostat inhibits aldosterone synthase with great selectivity as compared to the enzyme needed for cortisol synthesis. Baxdrostat decreases urine and plasma aldosterone levels but not cortisol levels, and it enhances natriuresis in a dose-dependent manner. Baxdrostat has demonstrated dose-related drops in blood pressure in a phase 2 trials for treatment-resistant hypertension (Freeman, M. W., *et al.*, 2023). Patients with primary aldosteronism are now involved in aldosterone synthase inhibitor trials. These studies will most likely establish the highest anticipated reductions in blood pressure (Freeman, M. W., Halvorsen, Y. D. and Brown, M. J., 2023).

7.1.5. Pharmacogenomics contribution: The complex genetic makeup of blood pressure and hypertension has been revealed by genomic and epigenetic studies. As pharmacogenomics advances, it will be possible to do precision medicine and create more potent medications by identifying targets with significant therapeutic effects. Future precision medicine depends on expanding the range of treatments that can lower blood pressure with few adverse effects while also decreasing the influence of high blood pressure on cardiovascular and renal risk. Genetics can reveal potential drug development options in addition to revealing novel therapeutic targets (Grau-Perez, M. and Redon, J., 2020). It is true that individual deviations in drug exposure are influenced by heredity. However, advancements are being made in the discovery of therapeutic targets and the creation of medications that block or stimulate their function in order to access them. Potential new therapy approaches include monoclonal antibodies, oligonucleotides, and small or short interfering RNA (siRNA), which target genes and/or block mRNA. The atrial natriuretic factor receptor gene is the target of medications (Pandey K. N., 2018). With monthly or even 6-monthly treatment regimens, oligo-nucleotides or siRNA are showing promising results in terms of their antihypertensive efficacy and ease of administration. This would help resolve one of the primary issues currently facing the treatment of hypertension, which is the lack of therapeutic adherence (Cruz-López, E. O., *et al.*, 2022).

7.1.6. Atrial natriuretic factor (ANP) receptor gene: The natriuretic peptide receptor is encoded by the NPR1 gene. When it binds to ANP, GTP is changed into cGMP, which activates other proteins (cGMP-dependent protein kinase I and II, PDEs, and CNGs) and has the downstream effects of lowering blood pressure and extracting salt. A monoclonal antibody that is an NPR1 agonist (REGN5381) is being developed as an antihypertensive medication. A Phase I and II clinical trial is being conducted to assess this for its potential as a therapy for hypertension. A monthly subcutaneous injection is the first step in phase III for hypertensive lack of control (Olczak, K. J. *et al.*, 2021).

7.1.7. Hepatic angiotensinogen inhibition: Hyperkalemia and renal failure are examples of dose restrictions that limit the extent to which ACE inhibitors and ARBs can inhibit the RAAS system. In addition to blocking RAAS, targeting the upstream enzyme angiotensinogen (AGT) offers further benefits. When AGT is silenced in the liver rather than the kidney, the RAAS is more strongly inhibited and hyperkalemia and renal failure are less common. There are two approaches that can be applied to people. First, by knocking down AGT mRNA in the hepatocytes, the antisense oligonucleotide IONIS-AGT-Lrx lowers plasma AGT levels (Morgan, E. S., *et al.*, 2021). According to phase 1 and phase 2 study results, hypertensive patients receiving two antihypertensive drugs and a weekly subcutaneous injection of this agent had a significant decrease in AGT and a trend toward significant systolic and diastolic BP reductions, −12 mmHg and −6 mmHg, respectively. Another strategy is the application of a small interference molecule (siRNA), which is currently being studied in phase 1, to block the mRNA synthesis of AGT. The first medication to use this mechanism of action was Zilebesiran (Desai, A. S. *et al.*, 2023). As demonstrated in hypertensive rats, vasopressors or fludrocortisone can be used to address possible issues brought on by the long-term inhibition of AGT production (Ranasinghe, P., Addison, M. L. and Webb, D. J., 2022).

7.2. DIETARY APPROACHES TO STOP HYPERTENSION (DASH) EATING PLAN:

Food group	**Servings***	**Examples of a serving**
Whole grains	6–8 per day	1 slice whole grain bread
Vegetables	4–5 per day	1cup of raw leafy vegetables
Fruits	4–5 per day	1 medium sized fruit
Dairy products(low-fat or fat-free)	2–3 per day	1 cup of milk or yogurt
Fats and oils	2–3 per day	1 tea spoon of margarine or vegetable oil or 1 table spoon of mayonnaise or 2 table spoons of salad dressing
Lean meat, poultry, fish	2–3 per day	2 ounces of cooked meats, chicken or fish
Nuts, seeds and legumes	4–5 per week	1/3cup (1.5ounces) of nutsor 2tablespoonsofpeanutbutteror 2tablespoons(0.5ounce)of seeds or ½cup of cooked peas or beans
Candy and added sugars	5 or less per week	1 table spoon of sugar, jelly or jamor1 cup of lemonade

Table (2): Dietary Approach to Stop Hypertension

7.3. HYPERTENSION VACCINES:

Target	**Drug type**	**Studied subject**	**Results**	**Representative study**
Renin	Heterologous renin (antibodies are produced invivo)	Monkeys	Reduced BP in monkeys, but induced renal autoimmune diseases.	61
AngiotensinI (AngI)	AngI-derivedpeptides	Rats	Reduced BP and AngII evelsinrats, with no effects on Ang II and no side effects.	122
AngiotensinII(AngII	AngII-derived active peptides	Population(Phase II)	Reduced BP with no side effects.	65
AngiotensinIIType-	AT1R-derived peptides	Rats	Reduced BP in rats with no side effects.	126
α-1D-	α1-AR-derivedpeptides	Rats	Reduced BP and protected	66

Adrener gicRece ptor (α1-AR)			target organs in rats with no side effects.	

Table (3): Vaccines Used in Hypertension

VIII. CONCLUSION: Hypertension remains a major global health burden due to its high prevalence and strong association with cardiovascular complications such as stroke, myocardial infarction, and renal failure. Understanding its classification, epidemiology, and pathogenesis is crucial for effective prevention and management. The condition arises from a complex interplay of genetic, environmental, and lifestyle factors, with primary hypertension being the most common form. Complications often develop silently, underscoring the need for early diagnosis and sustained control. Current treatment strategies involve lifestyle modification and pharmacotherapy, including diuretics, ACE inhibitors, ARBs, calcium channel blockers, and beta-blockers. Ongoing research is introducing promising new antihypertensive drugs and innovative solutions like hypertension vaccines. Additionally, dietary approaches, particularly the DASH diet, continue to show efficacy in managing blood pressure. A comprehensive, individualized approach that integrates medical, nutritional, and behavioral strategies is essential for long-term control and improved patient outcomes in the fight against hypertension.

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