

HYPERTENSION: AN OVERVIEW AND TREATMENTS**Diptesh T. Patil¹, Aditya Singh^{1*} and Dr. Vanita Kanase²**

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ABSTRACT

Hypertension is abnormal high blood pressure, where diastolic BP is greater than 90mmHg accompanied by the elevated systolic BP more than 140mmHg. In 2010 hypertension was believed to have been a factor in 18% of all deaths. Hypertension leads to multiple organ damage; therefore the blood pressure must be controlled to prevent the organ damage. Hypertension can be controlled with antihypertensive drugs, in which diuretics are first choice of treatment. In modern times as new targets are identified, many new novel drugs are coming in market or in clinical studies. Alternative therapies are slow acting, but give better results over the course of therapy. It makes it important to combine both pharmacological and alternative therapies together to give better result and improved patient compliance with increase in

patient satisfaction.

KEYWORDS: Diuretics, Calcium channel blockers, ACE inhibitors, Angiotensin II Antagonists, Blood Pressure.

INTRODUCTION

Hypertension (HT or HTN) also known as high blood pressure (HBP) is a long-term medical condition in which the blood pressure in the arteries is persistently elevated.^[1] Hypertension is defined as a sustained diastolic BP greater than 90mmHg accompanied by the elevated systolic BP more than 140mmHg. Hypertension is also defined in terms of blood pressure level above which investigation and treatment do more good than harm by Evans and Rose.^[2]

High blood pressure usually does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.^[3] High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.^[4] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.^[4] Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.^[4]

Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.^[1] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.^[5] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.^[4] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office based blood pressure measurement.^[4]

Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications. Lifestyle changes include weight loss, decreased salt intake, physical exercise, and a healthy diet.^[4] If lifestyle changes are not sufficient then blood pressure medications are used.^[6] Up to three medications can control blood pressure in 90% of people. The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy. High blood pressure affects between 16 and 37% of the population globally.^[4] In 2010 hypertension was believed to have been a factor in 18% of all deaths (9.4 million globally).^[7]

TYPES AND CAUSES

1. Primary (Essential) Hypertension

2. Secondary Hypertension

1. Primary (Essential) Hypertension

- Primary hypertension is a clinical syndrome characterized by the increase in systemic arterial pressure.
- 90% to 95% of all cases.

- Elevated BP with unknown cause. The pathogenesis of primary hypertension is still unclear.
- There are many factors associate with it.

❖ Genetic factors

The offsprings of the hypertensive parents are prone to suffering from essential hypertension compared with that without hypertensive family.

❖ Sodium intake

The mechanisms leading to hypertension are due to increased blood volume and the content of the sodium in the smooth muscle cells enhance following subsequent calcium increase.

❖ Renin agiotensin systems

Renin → Angiotensinogen → Angiotensin I → Angiothesin II → Increase systemic arterial pressure

❖ Sympathetic nervous system

The activation of Sympathetic nervous can augment periphery resistant which increase systemic arterial pressure.

❖ Endothelial dysfunction

- Endothelium-derived vasodilating factors: NO; PGI₂; EDHF.
- Endothelial-derived vasoconstricting factors: ET; AGII; Superoxide anion

❖ Insulin resistance:

- Increased absorbability to sodium
- Increased sympathetic nervous activation
- Increased cellular contents in sodium and calcium
- Caused vascular wall hypertrophy

❖ Other factors

- Obesity
- Smoking
- Intake alcohol
- Obstructive Sleep Apnea Syndrome (OSAS)
- Low calcium, magnesium and potassium

2. Secondary Hypertension

❖ Diabetes complications (diabetic nephropathy)

Diabetes can damage kidneys' filtering system, which can lead to high blood pressure.

❖ Polycystic kidney disease

In this inherited condition, cysts in kidneys prevent the kidneys from working normally and can raise blood pressure.

❖ Glomerular disease

Kidneys filter waste and sodium using microscopic-sized filters called glomeruli that can sometimes become swollen. If the swollen glomeruli can't work normally, you may develop high blood pressure.

❖ Renovascular hypertension

This type of hypertension is caused by narrowing (stenosis) of one or both arteries leading to your kidneys.

❖ Cushing syndrome

In this condition, corticosteroid medications may cause secondary hypertension, or hypertension may be caused by a pituitary tumor or other factors that cause the adrenal glands to produce too much of the hormone cortisol.

❖ Aldosteronism

In this condition, a tumor in the adrenal gland, increased growth of normal cells in the adrenal gland or other factors cause the adrenal glands to release an excessive amount of the hormone aldosterone. This makes kidneys retain salt and water and lose too much potassium, which raises blood pressure.

❖ Pheochromocytoma

This rare tumor, usually found in an adrenal gland, increases production of the hormones adrenaline and noradrenaline, which can lead to long-term high blood pressure or short-term spikes in blood pressure.

❖ Thyroid problems

When the thyroid gland doesn't produce enough thyroid hormone (hypothyroidism) or produces too much thyroid hormone (hyperthyroidism), high blood pressure can result.

❖ Hyperparathyroidism

The parathyroid glands regulate levels of calcium and phosphorus in your body. If the glands secrete too much parathyroid hormone, the amount of calcium in your blood rises — which triggers a rise in blood pressure.

❖ Coarctation of the aorta

In this birth defect, the body's main artery (aorta) is narrowed (coarctation). This forces the heart to pump harder to get blood through the aorta and to the rest of your body. This, in turn, raises blood pressure — particularly in arms.

❖ Sleep apnea

In this condition, breathing repeatedly stops and starts during sleep, causing you to not get enough oxygen. Not getting enough oxygen may damage the lining of the blood vessel walls, which may make your blood vessels less effective in regulating your blood pressure. In addition, sleep apnea causes part of the nervous system to be overactive and release certain chemicals that increase blood pressure.

❖ Obesity

As you gain weight, the amount of blood circulating through your body increases. This puts added pressure on your artery walls, increasing your blood pressure.

❖ Pregnancy

Pregnancy can make existing high blood pressure worse, or may cause high blood pressure to develop (pregnancy-induced hypertension or preeclampsia).

❖ Medications and supplements

Various prescription medications — such as pain relievers, birth control pills, antidepressants and drugs used after organ transplants — can cause or aggravate high blood pressure in some people.

DIAGNOSIS

1. A blood test,
2. Urinalysis,
3. Ultrasound of kidneys,
4. Electrocardiogram (ECG)

CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS^[8]

Category	systolic, mm Hg	diastolic, mm Hg
Normal	90–119	60–79
High normal (Prehypertension)	120–139	80–89
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	160–179	100–109
Stage 3 hypertension (Hypertensive emergency)	≥180	≥110
Isolated systolic hypertension	≥140	<90

PHARMACOLOGICAL TREATMENT**ALREADY IN USE DRUGS**

- **Diuretics**
- **β -Blockers**
- **Calcium channel blockers**
- **ACE inhibitors**
- **Angiotensin II receptor blockers**
- **α-Adrenergic blockers**

- **Diuretics**

- **Thiazide Diuretics^[9]**

They inhibit water reabsorption in the nephron by inhibiting the sodium-chloride symporter (SLC12A3) in the distal convoluted tubule, resulting in an increase in the excretion of sodium, chloride, and water. The sodium-chloride symporter transports sodium and chloride from the lumen into the epithelial cell lining the distal convoluted tubule. Once sodium has entered the cell, it is transported out into the basolateral interstitium via the sodium-potassium ATPase, causing an increase in the osmolarity of the interstitium, thereby establishing an osmotic gradient for water reabsorption. By blocking the sodium-chloride symporter, thiazide effectively reduces the osmotic gradient and water reabsorption throughout the nephron.

- 1) Hydrochlorothiazide
- 2) Chlortalidone

ADR's associated

- Hyperglycemia
- Hyperlipidemia

- Hyperuricemia
 - Hypercalcemia
 - Hypokalemia
 - Hyponatremia
 - Hypomagnesemia
 - Hypocalciuria
- **Thiazide Like Diuretics**^[9]

A thiazide-like diuretic is a sulfonamide diuretic that has similar physiological properties to a thiazide diuretic, but does not have the chemical properties of a thiazide, lacking the benzothiadiazine molecular structure.

1) **Indapamide**^[10]

Indapamide blocks the slow component of delayed rectifier potassium current (IKs) without altering the rapid component (IKr) or the inward rectifier current. Specifically, it blocks or antagonizes the action of the proteins KCNQ1 and KCNE1. Indapamide is also thought to stimulate the synthesis of the vasodilatory hypotensive prostaglandin PGE2.

2) **Chlorthalidone**^[11]

Chlorthalidone inhibits sodium ion transport across the renal tubular epithelium in the cortical diluting segment of the ascending limb of the loop of Henle. By increasing the delivery of sodium to the distal renal tubule, Chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism.

- **Loop Diuretics**

1) **Furosemide**

It acts by inhibiting NKCC2, the luminal Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle; it also abolishes the corticomedullary osmotic gradient and blocks negative, as well as positive, free water clearance. Additionally, furosemide is a noncompetitive subtype-specific blocker of GABA-A receptors.^[12]

2) **Etacrynic acid**

Ethacrynic acid inhibits symport of sodium, potassium, and chloride primarily in the ascending limb of Henle, but also in the proximal and distal tubules. This pharmacological action results in excretion of these ions, increased urinary output, and reduction in

extracellular fluid. Diuretics also lower blood pressure initially by reducing plasma and extracellular fluid volume; cardiac output also decreases, explaining its antihypertensive action. Eventually, cardiac output returns to normal with an accompanying decrease in peripheral resistance. Its mode of action does not involve carbonic anhydrase inhibition.^[13]

- **Potassium Sparing Diuretics**

- 1) **Spironolactone**

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents which act more proximally in the renal tubule. Aldosterone interacts with a cytoplasmic mineralocorticoid receptor to enhance the expression of the Na⁺, K⁺-ATPase and the Na⁺ channel involved in a Na⁺ K⁺ transport in the distal tubule. Spironolactone bind to this mineralocorticoid receptor, blocking the actions of aldosterone on gene expression. Aldosterone is a hormone; its primary function is to retain sodium and excrete potassium in the kidneys.^[14]

- 2) **Amiloride**

Amiloride works by inhibiting sodium reabsorption in the distal convoluted tubules and collecting ducts in the kidneys by binding to the amiloride-sensitive sodium channels. This promotes the loss of sodium and water from the body, but without depleting potassium. Amiloride exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. Amiloride is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.^[15]

➤ **ACE INHIBITORS**

Normally, angiotensin I is converted to angiotensin II by an angiotensin-converting enzyme (ACE). Angiotensin II constricts blood vessels, increasing blood pressure. Thus, by inhibiting the ACE, the ACE Inhibitors decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure.^[16]

They thereby lower arteriolar resistance and increase venous capacity; decrease cardiac output, cardiac index, stroke work, and volume; lower resistance in blood vessels in the kidneys; and lead to increased natriuresis (excretion of sodium in the urine). Renin increases in concentration in the blood as a result of negative feedback of conversion of AI to AII. AI increases for the same reason; AII and aldosterone decrease. Bradykinin increases because of less inactivation by ACE.

Examples of drugs of this class are as follows.

- 1) Captopril
- 2) Enalapril
- 3) Lisinopril
- 4) Perindopril
- 5) Ramipril
- 6) Fosinopril

➤ **Angiotensin (AT₁) Receptor Blockers (ARB)**

These substances are AT₁-receptor antagonists; that is, they block the activation of angiotensin II AT₁ receptors. Blockage of AT₁ receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, among other actions. The combined effect reduces blood pressure. The specific efficacy of each ARB within this class depends upon a combination of three pharmacodynamic and pharmacokinetic parameters.

Mechanisms of ARB Action

- Pressor inhibition [inhibition of the blood pressure-raising ("pressor") effect of angiotensin II]: Losartan 100 mg 25–40% inhibition
- AT₁ affinity (specific AT₁ affinity): Candesartan greater than 10000-fold for AT₁ Receptor
- Biological half-life: Telmisartan 24 hours.

Examples of ARB: -

- 1) Losartan
- 2) Irbesartan
- 3) Valsartan
- 4) Telmisartan

5) Candesartan

➤ **Calcium Channel Blockers (CCBs)**

In the body's tissues, the concentration of calcium ions (Ca^{2+}) outside of cells is normally about 10000-fold higher than the concentration inside of cells. Embedded in the membrane of some cells are calcium channels. When these cells receive a certain signal, the channels open, letting calcium rush into the cell. The resulting increase in intracellular calcium has different effects in different types of cells. Calcium channel blockers prevent or reduce the opening of these channels and thereby reduce these effects.

Voltage-dependent calcium channels are responsible for excitation-contraction coupling of skeletal, smooth, and cardiac muscle and for regulating aldosterone and cortisol secretion in endocrine cells of the adrenal cortex.^[17]

In the heart, they are also involved in the conduction of the pacemaker signals.

Classification of CCBs

1. Phenylalkylamines

They are relatively selective for myocardium, reduce myocardial oxygen demand and reverse coronary vasospasm, and are often used to treat angina. They have minimal vasodilatory effects compared with dihydropyridines and therefore cause less reflex tachycardia, making it appealing for treatment of angina, where tachycardia can be the most significant contributor to the heart's need for oxygen. Therefore, as vasodilation is minimal with the phenylalkylamines, the major mechanism of action is causing negative inotropy. Phenylalkylamines are thought to access calcium channels from the intracellular side, although the evidence is somewhat mixed.^[18]

Example: Verapamil.

2. Benzothiazepines

Benzothiazepine calcium channel blockers belong to the benzothiazepine class of compounds and are an intermediate class between phenylalkylamine and dihydropyridines in their selectivity for vascular calcium channels. By having both cardiac depressant and vasodilator actions, benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.^[19]

Example: Diltiazem

3. Dihydropyridines

Dihydropyridine (DHP) calcium channel blockers are derived from the molecule dihydropyridine and often used to reduce systemic vascular resistance and arterial pressure. Sometimes when they are used to treat angina, the vasodilation and hypotension can lead to reflex tachycardia, which can be detrimental for patients with ischemic symptoms because of the resulting increase in myocardial oxygen demand. Dihydropyridine calcium channel blockers can worsen proteinuria in patients with nephropathy.^[20]

Example: Nifedipine, Isradipine, Nicardipine, Felodipine, and Amlodipine

➤ β Adrenergic Blockers

1) Propranolol

Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta-(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.^[21]

2) Metoprolol

Metoprolol blocks β_1 adrenergic receptors of cardiomyocytes, thus it decreases the slope of phase 4 in the nodal action potential (reduces Na^+ uptake) and prolongs repolarization of phase 3 (slows down K^+ release).^[22]

3) Atenolol

Antihypertensive therapy with atenolol provides weaker protective action against cardiovascular complications (e.g. myocardial infarction and stroke) compared to other antihypertensive drugs. In some cases, diuretics are superior. In addition, atenolol has been found to lack mortality benefits and even to increase mortality in older adults.^[23]

➤ $\beta + \alpha$ Adrenergic Blockers:

1) Labetalol

Labetalol is a dual acting highly selective for postsynaptic α_1 - adrenergic, and non-selective for beta-adrenergic receptors blocker. Its action on these receptors are potent and reversible. The principal physiologic action of labetalol is to competitively block adrenergic stimulation of β -receptors within the myocardium (β_1 -receptors) and within bronchial and

vascular smooth muscle (β_2 -receptors), and α_1 -receptors within vascular smooth muscle. This causes a decrease in systemic arterial blood pressure and systemic vascular resistance without a substantial reduction in resting heart rate, cardiac output, or stroke volume, apparently because of its combined α - and β -adrenergic blocking activity.^[24]

2) Carvedilol

Carvedilol is both a non-selective beta-adrenergic receptor blocker (β_1 , β_2) and an alpha-adrenergic receptor blocker (α_1). The S (-) enantiomer accounts for the beta blocking activity whereas the S(-) and R(+) enantiomer have alpha blocking activity. Carvedilol reversibly binds to beta adrenergic receptors on cardiac myocytes. Inhibition of these receptors prevents a response to the sympathetic nervous system, leading to decreased heart rate and contractility. Carvedilol blockade of α_1 receptors causes vasodilation of blood vessels. This inhibition leads to decreased peripheral vascular resistance and an antihypertensive effect.^[25]

➤ α -Adrenergic Blockers

1) Prazosin

Prazosin acts by inhibiting the postsynaptic alpha(1)-adrenoceptors on vascular smooth muscle. This inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation.^[26]

2) Terazosin

Terazosin is a selective alpha-1 antagonist with high selectivity for alpha-1_A Receptor. This results in mobilization of Ca^{2+} from intracellular stores, activation of mitogen-activated kinase and PI3 kinase pathways and subsequent vasoconstriction.^[27]

Other drugs from this class are.

- 3) Doxazosin
- 4) Phenatolamine
- 5) Phenoxybenzamine

➤ Central Sympatholytics

1) Clonidine

It stimulates α_2 -receptors in the brain, which decreases peripheral vascular resistance, lowering blood pressure. It has specificity towards the presynaptic α_2 receptors in the vasomotor center in the brainstem. This binding decreases presynaptic calcium levels, thus

inhibiting the release of norepinephrine (NE). The net effect is a decrease in sympathetic tone. It has also been proposed that the antihypertensive effect of clonidine is due to agonism on the I1 receptor (imidazoline receptor), which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure.^[28]

2) Methyldopa

Methyldopa is converted to α -methylnorepinephrine by dopamine beta-hydroxylase (DBH). α -methylnorepinephrine is an agonist of presynaptic central nervous system α_2 adrenergic receptors. Activation of these receptors in the brainstem appears to inhibit sympathetic nervous system output and lower blood pressure.^[29]

➤ Vasodilators

I. Arteriolar

(a) Hydralazine

Its precise mechanism of action of hydralazine is not fully understood, but it lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle.^[30]

(b) Minoxidil

Minoxidil is a potassium channel opener, causing hyperpolarization of cell membranes.^[31]

(c) Diazoxide

Diazoxide inhibits active chloride reabsorption at the early distal tubule via the Na-Cl cotransporter, resulting in an increase in the excretion of sodium, chloride, and water. This results in an increase in potassium excretion via the sodium-potassium exchange mechanism. It may have action on carbonic anhydrases in the smooth muscle or through its action on the large-conductance calcium-activated potassium (KCa) channel, also found in the smooth muscle.^[32]

II. Arteriolar + Venous

(a) Sodium nitroprusside

Sodium nitroprusside has potent vasodilating effects in arterioles and venules. It NO activates guanylate cyclase in vascular smooth muscle and increases intracellular production of cGMP. cGMP activates protein kinase G which activates phosphatases which inactivate myosin light chains. breaks down in circulation to release nitric oxide (NO). Myosin light chains are

involved in muscle contraction. The end result is vascular smooth muscle relaxation, which allow vessels to dilate.^[33]

NEW AND POTENTIAL DRUGS

1) MC-4232^[34]

- It is a combination of MC-1 and lisinopril and belongs to ACE Inhibitors.
- MC-1: naturally occurring metabolite of vitamin B6 which reduces the damage to the heart caused by ischemia
- Phase II trial (MATCHED) → promising safety & efficacy profile
- Currently in Phase III trial

2) Angiotensin Receptor Blocker

I. Azilsartan^[35]

- It belongs to class of ARB.
- It is the prodrug of Azilsartanmedoxomil, which lowers blood pressure by blocking the action of angiotensin II at the AT₁ receptor, a hormone that contracts blood vessels and reduces water excretion through the kidneys.

II. LCZ696

- LCZ696 (valsartan + AHU337) exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug AHU377, and blocking the angiotensin II type-1 receptor via valsartan.^[36]

III. PS433540

Sparsentan is the first and only dual-acting angiotensin and endothelin receptor antagonist (DARA) in development.^[38]

3) Direct Renin Inhibitors

- SPP635, SPP676, SPP1148, SPP1234, and SPP800 are examples of this class, which are currently under Phase II and Phase III trial.^[34]

4) Clevidipine

- It acts by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum,

- Clevidipine inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes.
- The resultant inhibition of the contractile processes of the myocardial smooth muscle cells leads to dilation of the coronary and systemic arteries and improved oxygen delivery to the myocardial tissue.^[37]

5) **Dagliutril**

- Daglutril is an orally active, mixed neutral endopeptidase/endothelin converting enzyme inhibitor under development for the treatment of essential hypertension and congestive heart failure.

6) **Anti-Aldosterone Agents**

- Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects and, when elevated, can contribute to the development of hypertension and a variety of related pathologies, including myocardial hypertrophy and fibrosis and HF.
- The principal effector of aldosterone action is the mineralocorticoid receptor (MR). Activated MRs stimulate expression of sodium channels, resulting in increased sodium and water reabsorption and potassium loss, leading eventually to a volume expanded form of hypertension.
- **Mechanism of action of anti- aldosterone agents:** Aldosterone synthase inhibitors (ASIs), such as LCI699, inhibit the rate limiting step of aldosterone production. Mineralocorticoid receptor agonists (MRAs), such as finerenone, compete for the binding sites of aldosterone and effectively decrease blood pressure.

7) **Aldosterone Synthase Inhibitors**

- LCI699, the first orally active aldosterone synthase inhibitor to be developed for human use, is similar in structure to FAD286, the dextroenantiomer of the nonsteroidal aromatase inhibitor fadrozole.
- In the setting of aldosterone synthase (CYP11B2) inhibition, this resulted in up to a 10-fold increase in the biologically active aldosterone synthase substrate, 11-deoxycorticosterone, which could activate the MR. These effects could account for the disappointing BP reductions seen at higher doses and with twice daily administration of LCI699.

- Based on the results of the phase II trials, further development of LCI699 was discontinued
- Other therapeutically successful aldosterone synthase inhibitor:
 - 1- greater selectivity for aldosterone synthase inhibition on **CYP11B2**
 - 2- a longer plasma elimination half-life than **LCI699**
 - 3- These compounds are as potent and more selective than LCI699 for **CYP11B2** over **CYP11B1**
- Drugs targeting the classical and counter regulatory renin angiotensin systems (RAS).
- Novel approaches to RAS inhibition, including vaccines targeting angiotensin II (Ang II) and the angiotensin II type 1 (AT1) receptor, are being evaluated in preclinical and clinical trials.
- In contrast, activation of the more recently described counter regulatory RAS pathway decreases blood pressure (BP) and target organ damage, and drugs that activate this pathway are beginning to be developed as antihypertensive agents.
- These include ACE2 activators, Ang (1–7) analogs, AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin. Classical RAS, red; counter regulatory RAS, green; drugs, blue. ATR indicates AT1 receptor; MrgD, Mas-related G-protein-coupled receptor, member D; and rhACE2, recombinant human ACE2.

8) Centrally Acting Aminopeptidase Inhibitors

- Angiotensin (Ang) III, which is generated from Ang II by aminopeptidase A (APA), is the predominant pressor peptide in brain in animal models, and APA is a therapeutic target for treatment of hypertension. The APA inhibitor RB150 (QGC 001) has been shown to pass the blood–brain barrier and lower BP in animal models.

9) Vasopeptidase Inhibitors

- The zinc metalloprotease neprilysin (neutral endopeptidase 24.11) is a therapeutic target for hypertension and other forms of CVD because it degrades the natriuretic peptides atrial natriuretic peptide (ANP), and the increase in circulating natriuretic peptide levels that results from neprilysin inhibition leads to natriuresis, vasodilation, renin–angiotensin–aldosterone system inhibition.
- The ARB–neprilysin inhibitor (ARNI), LCZ696, is a single molecule comprising the ARB valsartan and the neprilysin inhibitor pro-drug AHU377 (sacubitril). LCZ696 has

been shown to lower BP, particularly in Asian populations, and to prevent death from cardiovascular (CV) causes and hospitalization for heart failure (HF).

10) Natriuretic Peptide Receptor Agonists: The natriuretic peptide receptor A (NPR-A) agonist PL-3994.

11) Soluble Epoxide Hydrolase Inhibitors: AR9281 is a potent and selective inhibitor of human s-EH.

12) Vasoactive Intestinal Peptide Receptor Agonist: eg. vasomera (PB1046), a stable long-acting form of VIP that is selective for VPAC2.

13) Intestinal Na⁺/H⁺ Exchanger 3 Inhibitor: NHE2, NHE3, and NHE8.

14) Dopamine β -hydroxylase (D β H) Inhibitor: Etamicastat (BIA 5-453) is a potent and reversible inhibitor of D β H.

15) Vaccines

- Although a renin vaccine successfully lowered BP in animal models, it induced autoimmune disease of the kidneys and further development was suspended. An Ang I vaccine also lowered BP in animal models, but was ineffective in a randomized, double-blind, placebo-controlled clinical trial.
- Further, a vaccine raised in response to an Ang II-derived peptide conjugated to a virus-like particle derived from the bacteriophage Q β (AngQb) was effective in producing anti-Ang II antibodies and reducing BP in SHR, despite increasing circulating Ang II levels.
- Ang II-specific antibodies were raised in all subjects, and the AngQb antigen was well tolerated.

COMBINATIONS IN MARKET

- **β -adrenergic blockers and diuretics.**
- **ACE inhibitors and diuretics.**
- **Angiotensin II receptor antagonists and diuretics.**
- **Calcium antagonists and ACE inhibitors.**
- **Other combinations.**

ALTERNATIVE THERAPIES**1) Lifestyle Modification^[40]**

- I. Weight reduction
- II. Eat healthy foods
- III. Decrease the salt in diet
- IV. Maintain a healthy weight.
- V. Increase physical activity
- VI. Regular Blood Pressure Monitoring
- VII. No smoking
- VIII. Stress management
- IX. Regular exercise

2) Natural Remedies^{[41][42]}

- I. **Ashwagandha** – *Withania somnifera*
- II. **Amalaki** – *Emblica officinalis*
- III. **Bala** – *Sida cordifolia*
- IV. **Brahmi** (*Bacopa monnieri*)
- V. **Shankapushpi** (*Convolvulus pluricaulis*)
- VI. **Ash gourd** – winter melon *Kushmanda*
- VII. **Jatamansi** (*Nardostachys jatamansi*)
- VIII. **Gotu kola** – *Mandukaparni* (*Centella asiatica*)
- IX. **Giloy** – *Guduchi* (*Tinospora cordifolia*)
- X. **Ginger** – *Zingiber officinale*
- XI. **Triticum aestivum** – Wheat bran
- XII. **Tomato** – *Lycopersicon esculentum*
- XIII. **Carrot** – *Daucus carota*
- XIV. **Celery** – *Apium graveolens*
- XV. **Tulsi** – Holy Basil – *Ocimum basilicum*
- XVI. **Sesame** – *Sesamum indicum*

3) AYURVEDIC TREATMENT^[42]**Natural Measures (Preventive)**

- **Dinacharya and Rutucharya:** Following the principles of diet, lifestyle, ethics, code and conduct of ideal living on a daily (Dinacharya) and seasonal (Rutucharya) basis.

- **Acharya Rasayana** – Principles, behaviour and conduct of life which by themselves act as rejuvenation.
- **Vega Dharana and Udeerana** – Helping the body in releasing the naturally manifested reflexes and urges by not forcibly controlling them
- **Properly following Trayopasthamba** – Rules and regulations laid on Diet, Sleep and Celibacy.

- **Bahir Parimarjana (External therapies)**

- I. **Takra Shiro Dhara**
- II. **Ksheera Dhara**
- III. **Taila Dhara**
- IV. **Shiro Lepa**
- V. **Avagaha**

- **Herbal preparations:**

- I. **Arjuna Ksheerapaka,**
- II. **Lashuna Ksheerapaka**
- III. **Giloy Satwa**
- IV. **Balarishtam**
- V. **Nayopayam Kashayam**

4) OTHER NON PHARMACOLOGICAL THERAPIES^[42]

- A. **Yoga**
- B. **Taichi** (Chinese art of healing)
- C. **Acupuncture and Qi Gong** : A form of traditional Chinese medicine
- D. **Autogenic Training** – Involves series of sessions in which one learns how to control breathing, blood pressure, heart rate and body temperature. This technique reduces stress and provides relaxation.
- E. **Meditation:** involving chanting, breathing and visualization
- F. **Relaxation and Breathing exercises**
- G. **Biofeedback** – It is a technique where people are taught how to gain control over internal body processes that normally occur involuntarily such as BP, Heart rate, muscle tension and skin temperature. Other than Hypertension it is also used to treat migraine, tension headache, chronic pain and urinary incontinence
- H. **Takradhara** (stream of herb-processed buttermilk is flown over head.)

CONCLUSIONS

- The initial approach to hypertension should start with ruling out secondary causes, detecting and treating other cardiovascular risk factors, and looking for target organ damage.
- Treatment should always include lifestyle changes.
- Medication use should be guided by the severity of HTN and the presence of “compelling” indications.
- Thiazide-type diuretics should be initial drug therapy for most, either alone or combined with other drug classes.
- Most patients will require two or more antihypertensive drugs.
- As it requires prolong therapy, alternative therapies should be considered with pharmacological treatment whenever possible to reduce the side effects and improve patient’s life.

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