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"Pathophysiology of Antihypertensive Drugs"

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ABSTRACT: Recent progress in antihypertensive therapy has widened the selection of drugs, and large clinical trials have attracted attention to newer classes of antihypertensives. Consequently, the use of diuretics as antihypertensive agents has been relatively reduced, particularly since the newer drugs are associated with fewer adverse metabolic reactions. However, diuretics have a specific activity of removing sodium from the body fluid, thereby rendering the blood pressure insensitive to sodium intake, relieving the overload to systemic circulation, and normalizing the circadian rhythm of blood pressure from a non-dipper to a dipper pattern.

At low doses, diuretics are known to be as effective as all other antihypertensive agents for reducing nearly all types of cardiovascular events. In this brief review, the indication for thiazide diuretics will be discussed based on the pathophysiology of hypertension and antihypertensive therapy with diuretics mainly from the point of view of sodium metabolism. Low-dose diuretics will continue to be an important agent in the treatment of hypertension, mostly in combination with vasodilators such as modulators of the renin-angiotensin system and calcium channel blockers.

Arterial hypertension is a major cause of morbidity and mortality because of its association with coronary heart disease, cerebrovascular disease and renal disease. The extent of target organ involvement (i.e. heart, brain and kidneys) determines outcome. North American studies have shown that hypertension is a major contributor to 500 000 strokes (250 000 deaths) and 1 000 000 myocardial infarctions (500 000 deaths) per annum.

I. HISTORY OF HYPERTENSION

The modern history of hypertension begins with the understanding of the cardiovascular system based on the work of physician William Harvey (1578–1657), who described the circulation of blood in his book De motu cordis.

The English clergyman Stephen Hales made the first published measurement of blood pressure in 1733. Descriptions of what would come to be called hypertension came from, among others, Thomas Young in 1808 and especially Richard Bright in 1836.

Bright noted a link between cardiac hypertrophy and kidney disease, and subsequently kidney disease was often termed Bright's disease in this period. In 1850 George Johnson suggested that the thickened blood vessels seen in the kidney in Bright's disease might be an adaptation to elevated blood pressure.

William Senhouse Kirkes in 1855 and Ludwig Traube in 1856 also proposed, based on pathological observations, that elevated pressure could account for the association between left ventricular hypertrophy to kidney damage in Bright's disease. Samuel Wilks observed that left ventricular hypertrophy and diseased arteries were not necessarily associated with diseased kidneys, implying that high blood pressure might occur in people with healthy kidneys; however, the first report of elevated blood pressure in a person without evidence of kidney disease was made by Frederick Akbar Mahomed in 1874 using a sphygmograph.

The concept of hypertensive disease as a generalized circulatory disease was taken up by Sir Clifford Allbutt, who termed the condition "hyperpiesia". However, hypertension as a medical entity really came into being in 1896 with the invention of the cuff-based sphygmomanometer by ScipioneRiva-Rocci in1896,which allowed blood pressure to be measured in the clinic. In 1905, Nikolai Korotkoff improved the technique by describing the Korotkoff sounds that are heard when the artery is ausculted with a stethoscope while the sphygmomanometer cuff is deflated.

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Tracking serial blood pressure measurements was further enhanced when Donal Nunn invented an accurate fully automated oscillometric sphygmomanometer device in 1981.

II. INTRODUCTION :

Recent progress in antihypertensive therapy has widened the selection of drugs, and large clinical trials have attracted attention to newer classes antihypertensives. Consequently, the use of diuretics as antihypertensive agents has been relatively reduced, particularly since the newer drugs are associated with fewer adverse metabolic reactions.

However, diuretics have a specific activity of removing sodium from the body fluid, thereby rendering the blood pressure insensitive to sodium intake, relieving the overload to systemic circulation, and normalizing the circadian rhythm of blood pressure from a non-dipper to a dipper pattern. At low doses, diuretics are known to be as effective as all other antihypertensive agents for reducing nearly all types of cardiovascular events. In this brief review, the indication for thiazide diuretics will be discussed based on the pathophysiology of hypertension and antihypertensive therapy with diuretics mainly from the point of view of sodium metabolism.

Low-dose diuretics will continue to be an important agent in the treatment of hypertension, mostly in combination with vasodilators such as modulators of the renin-angiotensin system and calcium channel blockers.

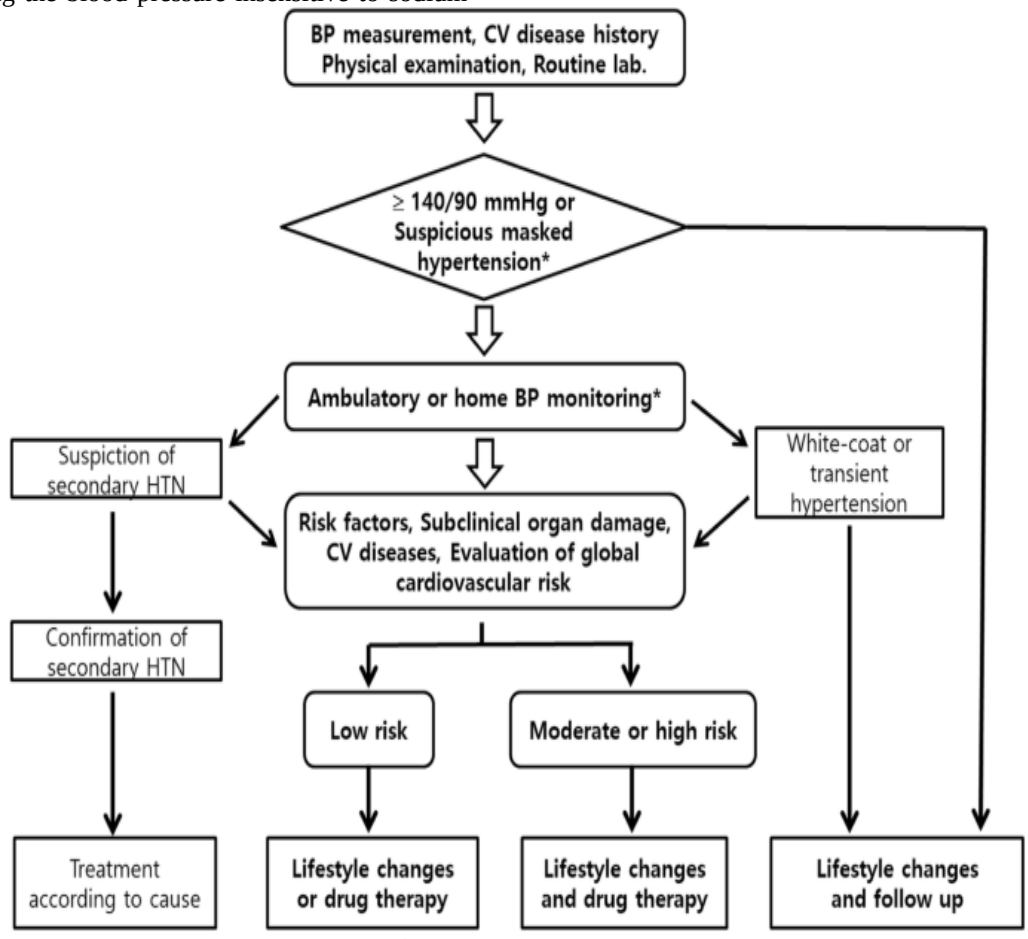

Fig 1:BP measurement

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III. PATHOPHYSIOLOGY OF HYPERTENSION :

Hypertension is defined as abnormally high blood pressure (more than 120/80 mm Hg) in the arteries. Persistent increase in systemic arterial blood pressure is known as hypertension. Usually a mean arterial pressure greater than in 110mm Hg under resting conditions is considered to be hypertensive; this level normally occurs when the diastolic blood pressure is greater than 90 mm Hg and the systolic pressure is greater than about 135-140 mm Hg. Hypertension is generally symptom less, but increases the risk of various other cardiovascular diseases like stroke, heart attack and non-cardiovascular diseases like renal damage, end stage of renal failure, etc. Although hypertension is a common health problem with some times devastating consequence, it often remains asymptomatic until late in its course.

A sustained diastolic pressure greater than 90 mm Hg, or a sustained systolic pressure in excess of 140 mm Hg, is considered to constitute hypertension90-95% of hypertension is idiopathic (essential hypertension), which is compatible with long life, unless a myocardial infarction, cerebrovascular accident, or other complication supervenes. Most of the reminder of "benign hypertension" secondary to renal disease or, less often to narrowing of the renal artery, usually by an atheromatous plaque (renovascular hypertension). Infrequently, hypertension is secondary to diseases of the adrenal glands, such as primary aldosteronism, cushing syndrome, pheochromocytoma, or other disorders. Various determinants play important role of hypertensive condition and in causation of premature cardiovascular risk over and beyond hypertension.

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Fig 2: Ranges of Hypertension

Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance. It follows that patients with arterial hypertension may have an increase in cardiac output, an increase in systemic vascular resistance, or both. In the younger age group, the cardiac output is often elevated, while in older patients increased systemic vascular resistance and increased stiffness of the vasculature play a dominant role. Vascular tone may be elevated because of increased α-adrenoceptor stimulation or increased release of peptides such as angiotensin or endothelins.

PRIMARY HYPERTENSION :

It results when arterial blood pressure is increased due to increased peripheral resistance. It

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is further divided in to two types namelybenign and malignant hypertension

Benign hypertension

Here, there is a moderate increase in blood pressure with systolic pressure of 200 mm Hg and the diastolic pressure of above 100 mm Hg. However, in resting condition and sleep, the blood pressure returns to normal level. Later, if there is increase in blood pressure it will not come back to normal level in resting conditions.

Malignant hypertension

Here, the blood pressure elevated to a great extends of about 250 mm Hg of systolic pressure and 150 mm Hg of diastolic pressure. It produces severe symptoms like renal disease, retinal disease, and being a fatal disease, it causes death within few years.

Some of the **characteristics** of **primary or essential hypertension** are,

1) The mean arterial pressure is increased 40-60 %.
2) The renal blood flow in the later stages is decreased about one half of normal. 3) The resistance to blood flow through the kidney is increased 2-4 fold.
4) The kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high.

SECONDARY HYPERTENSION

The different forms of secondary hypertension are

Cardiovascular hypertension

It is produced due to

a) Atherosclerosis- hardening and narrowing of blood vessels
b) Coarctation of aorta- narrowing of aorta.

Renal hypertension

It is produced due to

a) Stenosis renal arteries- narrowing of one or both renal arteries, so that the renal function is impaired.
b) Glomerulonephritis- nephritis with inflammation of the capillary loops in the renal glomeruli.

Endocrine hypertension

It occurs due to

a) Pheochromocytoma- tumer in adrenal medulla
b) Hyperaldosteronism- excess secretion of aldosterone from adrenal cortex Conn's syndrome.
c) Cushing's syndrome- excess secretion of cortisone.
d) Gigantism or Acromegaly- excess secretion of growth hormone.

Neurogenic hypertension

Acute hypertension can be caused by strong stimulation of the sympathetic nervous system.

a) Section of the baroreceptors nerves.
b) Lesions in tractus solitarius.
c) Increased intracranial pressure

The final pathway is an increase in cytosolic calcium in vascular smooth muscle causing vasoconstriction. Several growth factors, including angiotensin and endothelins, cause an increase in vascular smooth muscle mass termed vascular remodelling. Both an increase in systemic vascular resistance and an increase in vascular stiffness augment the load imposed on the left ventricle; this induces left ventricular hypertrophy and left ventricular diastolic dysfunction.

In youth, the pulse pressure generated by the left ventricle is relatively low and the waves reflected by the peripheral vasculature occur mainly after the end of systole, thus increasing pressure during the early part of diastole and improving coronary perfusion. With ageing, stiffening of the aorta and elastic arteries increases the pulse pressure. Reflected waves move from early diastole to late systole. This results in an increase in left ventricular afterload, and contributes to left ventricular hypertrophy. The widening of the pulse pressure with ageing is a strong predictor of coronary heart disease.

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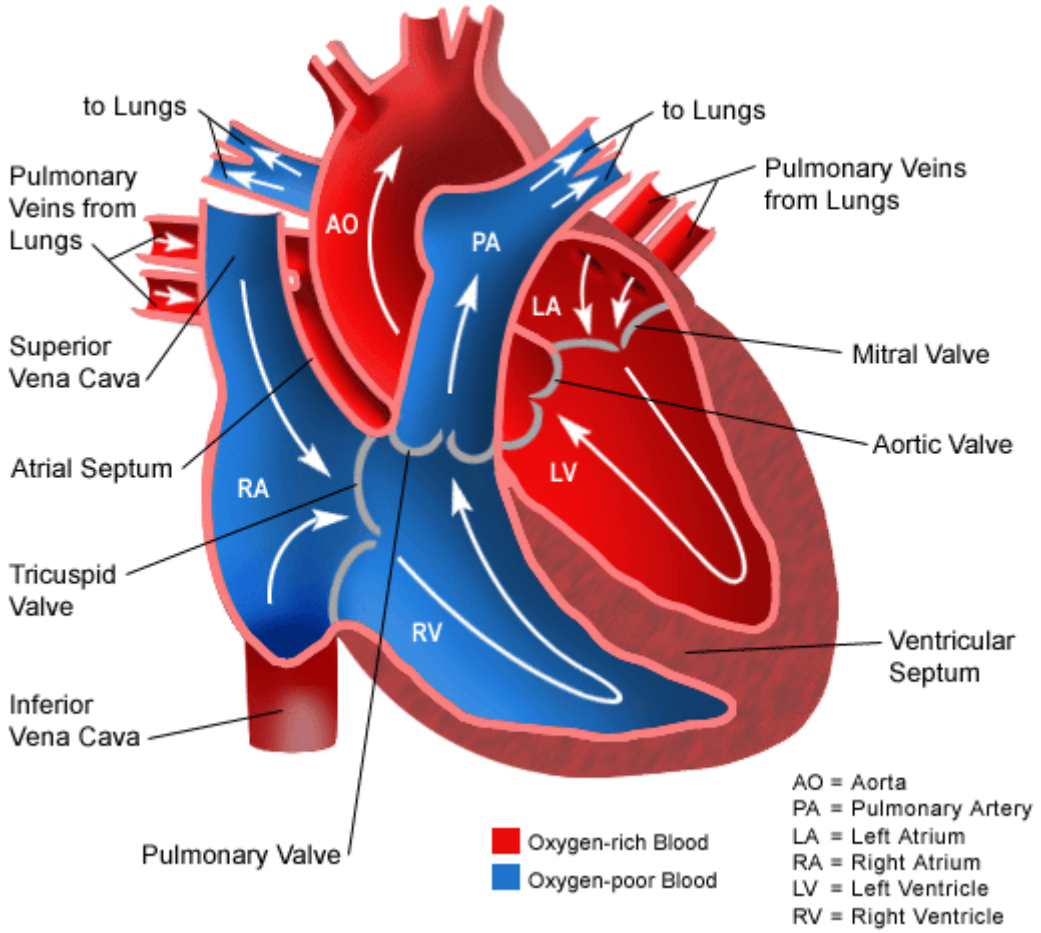

Fig 3 : Heart Pathophysiology

The autonomic nervous system plays an important role in the control of blood pressure. In hypertensive patients, both increased release of, and enhanced peripheral sensitivity to, norepinephrine can be found. In addition, there is increased responsiveness to stressful stimuli. Another feature of arterial hypertension is a resetting of the baroreflexes and decreased baroreceptor sensitivity. The renin–angiotensin system is involved at least in some forms of hypertension (e.g. renovascular hypertension) and is suppressed in the presence of primary hyperaldosteronism. Elderly or black patients tend to have low-renin hypertension. Others have high-renin hypertension and these are more likely to develop myocardial infarction and other cardiovascular complications.

In human essential hypertension, and experimental hypertension, volume regulation and the relationship between blood pressure and sodium excretion (pressure natriuresis) are abnormal. Considerable evidence indicates that resetting of pressure natriuresis plays a key role in causing hypertension. In patients with essential hypertension, resetting of pressure natriuresis is characterized either by a parallel shift to higher blood pressures and salt-insensitive hypertension, or by a decreased slope of pressure natriuresis and salt-sensitive hypertension.

Diagnosis of hypertension includes performing a complete evaluation that includes a medical history and physical examination and a series of blood pressure readings. Systolic blood pressure is a stronger predictor of cardiovascular diseases than diastolic blood pressure in adults' ≥ 50 year of age and is the most important clinical blood pressure parameter for most patients. Patient with diastolic blood pressure value less than 90 mmHg and systolic blood pressure value ≥140 mmHg have isolated systolic hypertension. Many people think of a reading of 120/80mmHg as "normal". In fact there are many variations of

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normal that are dependent on a variety of factors. As a very general guide, adults should keep their blood pressure below 140/90mmHg. In addition, current guidelines consider consistent readings over 120/80mmHg as a condition called pre-hypertension, which should be monitored and addressed to ensure that blood pressure does not rise higher over time.

It is very possible that a diagnosis of hypertension can be missed or delayed because there are generally no symptoms in the early stages. Patient compliance with a good treatment plan generally results in a normalization of blood pressure and also minimizes complications.

Heart is relatively small, roughly the same size as your closed fist. Heart rest on the diaphragm, near the midline of the thoracic cavity. It lies in the mediastinum, a mass of tissue that extends from the sternum to the vertebral column between the lungs.Human heart is covered by double walled covering called pericardium. The membrane that surrounds and protects the heart is the pericardium.

It confines the heart to its position in the mediastinum, while allowing sufficient freedom of movement for vigorous and rapid contraction. The pericardiums consist of two parts; the fibrous pericardium and the serous pericardium. The superficial fibrous pericardium is composed of tough, inelastic dense irregular connective tissue. The fibrous pericardiums prevent overstretching of heart, provide protection.

IV. CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS :

A . Diuretics

Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.

1 . Loop diuretics:

Examples :

1.Bumetanide 2 .ethacrynic acid 3. Furosemide 4. Torsemide

Mechanism of action

Loop diuretics act on the Na^+-K^+-$2Cl^-$ symporter (NKCC2) in the thick ascending limb of the **loop** of Henle to inhibit sodium, chloride and potassium reabsorption. . By inhibiting the potassium recycling, the voltage gradient is abolished and magnesium and calcium reabsorption are inhibited.

2. Thiazide diuretics:

Examples :

1. Epitizide
2.hydrochlorothiazide and chlorothiazide
3.Bendroflumethiazide
4.methyclothiazide

Mechanism of action

Thiazide diuretics control hypertension in part by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter.

3.Thiazide-like diuretics:

Examples :

1.Indapamide 2. Chlorthalidone 3. Metalozone 4.Xipamide

Mechanism of action

Thiazide-like diuretics act on the nephron mainly at the proximal part of the distal tubule. Sodium excretion and urine volume are increased by interference with transfer across cell membranes. The result is a reduction in blood volume. However, changes in cardiac output and extracellular fluid volume are transient and, in the long-term, the major haemodynamic effect is a reduction in peripheral resistance due to subtle alterations in the contractile responses of vascular smooth muscle.

4. Potassium-sparing diuretics:

Examples :

1. Spironolactone 2. Eplerenone

Mechanism of Action:

A potassium-sparing diuretic that inhibits sodium, potassium, ATPase. Interferes with sodium and potassium exchange in distal tubule, cortical collecting tubule, and collecting duct. Increases sodium and decreases potassium excretion. Also increases magnesium, decreases calcium loss.

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Pathophysiology of Diuretics :

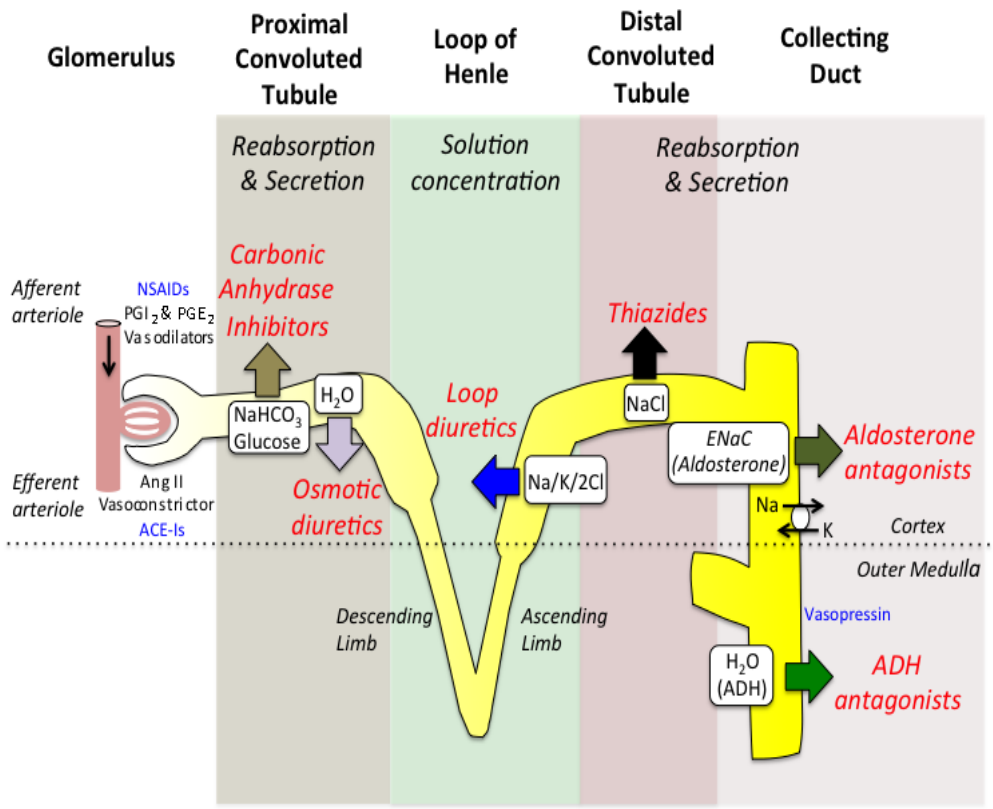

Fig 4 : Sites of diuretic drug action

There are three different groups of diuretics, these include thiazide diuretics, loop diuretics, and potassium-sparing diuretics. Potassium diuretics are used in congestive heart failure and are discussed.

In this article we will be focusing specifically on Thiazide and Loop diuretics. The primary site of action for diuretics is the nephron within the kidneys. The different classes of diuretics are characterized by their various mechanism of action and specific location targeted within the nephron.

Thiazide diuretics act on the distal tubule of the nephron by inhibiting sodium reabsorption. With this inhibition, more sodium stays within the nephron creating an osmotic force that allows for water retention in the nephron, and ultimately water excretion. Thiazide diuretics are considered the drug of choice for long term treatment of hypertension by many physicians.

Loop diuretics, like thiazide diuretics, work to inhibit the reabsorption of sodium as well as chloride by targeting a sodium potassium chloride cotransporter, however they exert their effects in the ascending limb of the loop of Henle. By targeting these two specific electrolytes, loop diuretics prevent water reabsorption. The decrease in plasma volume that occurs in response to an increased sodium excretion reduces venous return and lowers cardiac output.

All classes of diuretics are absorbed orally and widely distributed. Thiazide diuretics are known to bind extensively to plasma proteins, which limits their filtration and promotes appropriate delivery to tissues.

However, they undergo extensive hepatic metabolism which plays into the dose and frequency of administration. The half-life of thiazides is approximately 8 to 12 hours allowing for a single daily dosing.

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On the other hand, loop diuretics are known to be less effective than thiazides, and have a short duration of action at approximately 6 hours. Loop diuretics areindicatedforpatients with coexistent renal or heart failure, in circumstances when thiazide diuretics are rarely effective.

Diuretics have been the standard antihyperten-sive drugs over the past 4 decades, though they do not lower BP in normotensives. Their pharmacology is described.

Thiazides (hydrochlorothiazide, chlorthalidone) These are the diuretic of choice for uncomplicated hypertension; have similar efficacy and are dose to dose equivalent. All megatrials have been carried out with these two only. Chlorthalidone is longer acting (~ 48 hours) than hydro-chlorothiazide (< 24 hours) and may have better round-the-clock action. Indapamide (see later) is also mainly used as antihypertensive, and is equally effective. There is little experience with other members of the thiazide class, and they should not be considered interchangeable with hydrochlorothiazide/chlorthalidone as anti-hypertensive. The proposed mechanism of anti-hypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by 5–15%, and this decreases c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na+ balance and plasma volume; c.o. is restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.

B. Calcium channel blockers

Calcium channel blockers block the entry of calcium into muscle cells in artery walls.

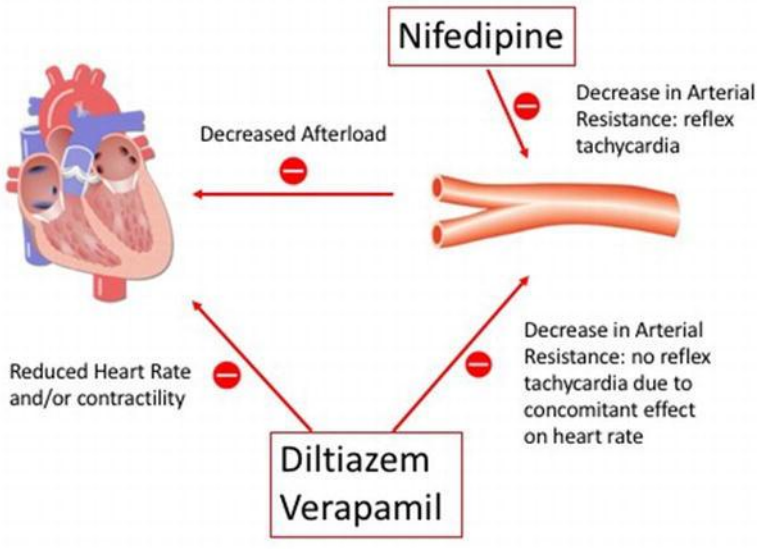

Fig 5: Mechanism of action

Examples :

1. dihydropyridines:
1.Amlodipine 2.Cilnidipine 3.Clevidipine 4.Felodipine 5.Isradipine

Mechanism of Action:
Dihydropyridine derivatives work by acting as calcium channel blockers blocking the intake of calcium ions into the vascular smooth muscle and, to a lesser extent, cardiac muscles

2. non-dihydropyridines:
1.Diltiazem 2.Verapamil

Mechanism of Action:

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.

Pathophysiology of calcium channel blocker :

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Preventing calcium from entering the cells of your heart and arteries. Calcium causes the heart and arteries to contract more strongly. By blocking calcium, calcium channel blockers allow blood vessels to relax and open.

Some calcium channel blockers have the added benefit of slowing your heart rate, which can further lower your blood pressure, relieve chest pain (angina) and control an irregular heartbeat.
"Calcium channel blockers are also called calcium antagonists".

C. ACE inhibitor

ACE inhibitors inhibit the activity of angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.
Examples:
1.captopril 2.enalapril 3.fosinopril 4.lisinopril

Mechanism of action :

ACE inhibitors stimulate the dilation of blood vessels by inhibiting the production of angiotensin II. The major organs that ACE inhibitors affect are the kidney, blood vessels, heart, brain, and adrenal glands.

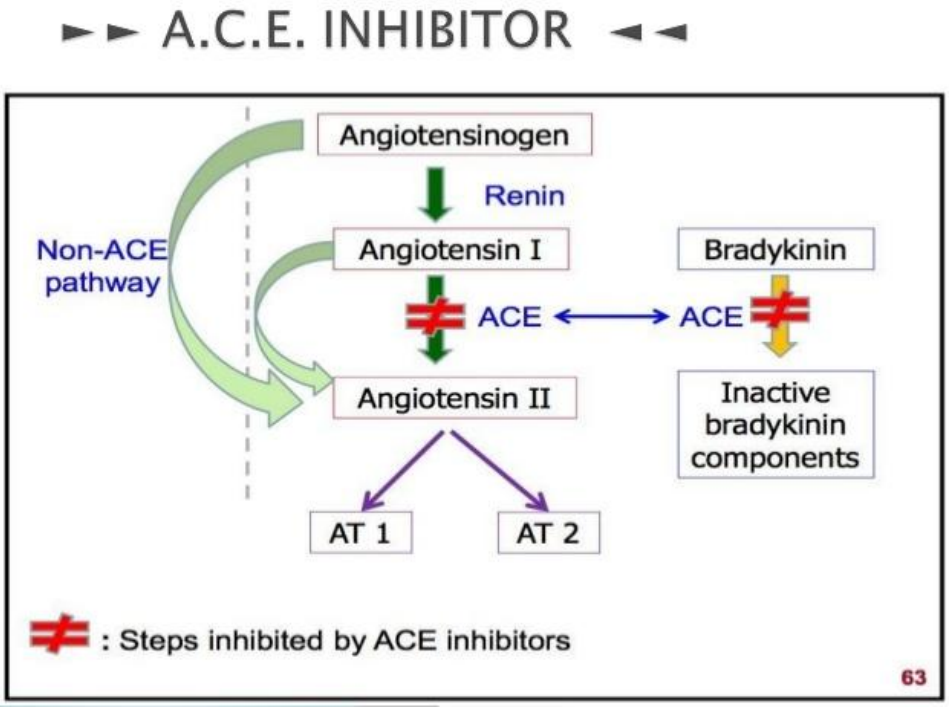

Fig 6 :ACE inhibitors

Pathophysiology of ACE inhibitor :

Angiotensin II causes direct vasoconstriction of precapillary arterioles and postcapillary venules, inhibits the reuptake of norepinephrine, stimulates the release of catecholamines from the adrenal medulla, reduces urinary excretion of sodium and water, stimulates synthesis and release of aldosterone, and stimulates hypertrophy of both vascular smooth muscle cells and cardiac myocytes.

The exact mechanism of ACE inhibitors is not fully known. They do interfere with the renin-angiotensin-aldosterone system, but their effect is not directly related to renin levels in the blood. ACE inhibitors, as the name implies, blocks an angiotensin-converting enzyme that converts angiotensin I to angiotensin II.

Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodeling of smooth muscle and cardiac myocytes. Lowered arterial and venous pressure reduces preload and afterload. Also, the hypothesis is that ACE inhibitors interfere with the degradation of bradykinin, which is a peptide that causes vasodilation.

D.Angiotensin II receptor antagonist :

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.

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Examples :
1.Azilsartan 2.Candesartan 3.Eprosartan 4.Irbesartan 5.Losartan

Mechanism of action :

Angiotensin II receptor blockers (ARBs) are medications that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels. As a result, blood vessels enlarge (dilate) and blood pressure is reduced.

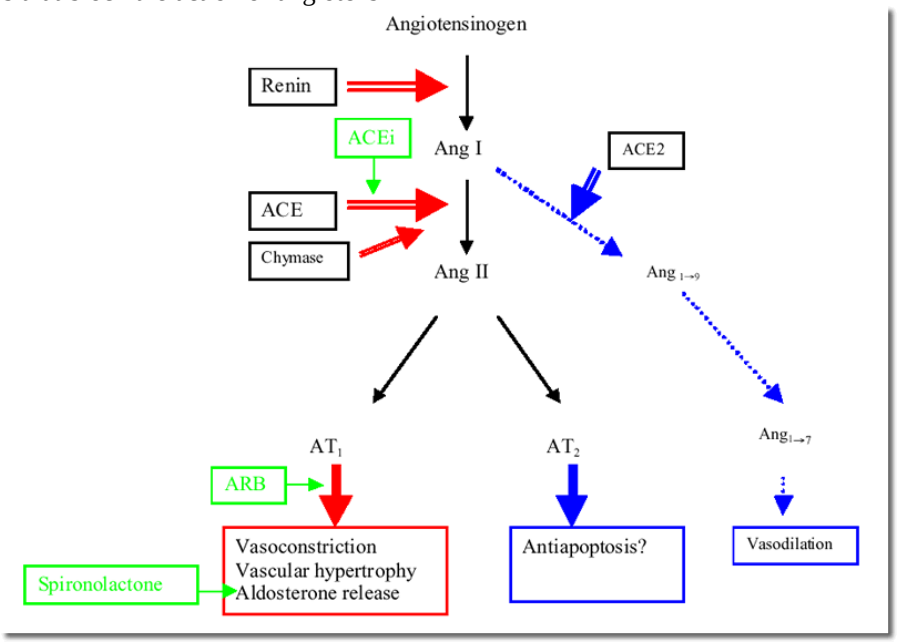

Fig 7: MOA of angiotensin II receptor blockers

Pathophysiology of Angiotensin II receptor antagonist :

The renin-angiotensin system, specifically angiotensin II, is implicated in the pathogenesis of essential hypertension, reno-vascular hypertension, congestive heart failure, and renal diseases associated with albuminuria .

Blockade of the renin-angiotensin system with ACE inhibitors has provided effective treatment of these conditions; however, some of the adverse effects of ACE inhibitors appear to be unrelated to angiotensin II blockade. For example, cough and angioedema are due to other effects of ACE inhibition, such as degradation of bradykinins and prostaglandins (1).

Angiotensin II is a very potent chemical formed in the blood that causes muscles surrounding blood vessels to contract, thereby narrowing the vessels. This narrowing increases the pressure within the vessels and can cause high blood pressue (hypertension). Angiotensin II receptor blockers (ARBs) are medications that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels. As a result, blood vessels enlarge (dilate) and blood pressure is reduced. Reduced blood pressure makes it easier for the heart to pump blood and can improve heart failure. In addition, the progression of kidney disease caused by the high blood pressure or diabetes is slowed. ARBs have effects that are similar to angiotensin converting enzyme (ACE) inhibitors, but ACE inhibitors act by preventing the formation of angiotensin II rather than by blocking the binding of angiotensin II to muscles on blood vessels.

E. Adrenergic receptor antagonists :

1. Beta blockers

Examples:

1.Acebutolol 2.Atenolol 3.Bisoprolol 4.Betaxolol

Mechanism of action :

Beta blockers work by blocking the effects of the hormone epinephrine, also known as adrenaline. Beta blockers cause your heart to beat more slowly and with less force, which lowers blood pressure. Beta blockers also help open up your veins and arteries to improve blood flow.

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2. Alpha blockers:
Examples :
1.Doxazosin
2.Phentolamine
3.Indoramin
4.Phenoxybenzamine
5.Prazosin
6.Terazosin
7.Tolazoline

Mechanism of action :

Alpha blockers lower blood pressure by keeping the hormone norepinephrine from tightening the muscles in the walls of smaller arteries and veins. As a result, the vessels remain open and relaxed. This improves blood flow and lowers blood pressure.

3. Mixed Alpha + Beta blockers:
Examples :
1.Bucindolol 2.Carvedilol 3.Labetalol

Mechanism of action :

Alpha and beta dual receptor blockers for treatment of high blood pressure. Alpha and beta dual receptor blockers are a subclass of beta blockers which are commonly used to treat high blood pressure (BP). Drugs in this class include carvedilol (Coreg), labetalol (Trandate) and dilevalol (Unicard)

Pathophysiology of Adrenergic receptor antagonists :

Sympatholytics antagonize the actions of endogenously
released epinephrine and norepinephrine as well as exogenously administered drugs.

Sympatholytics can act by several mechanisms, including direct receptor antagonism, agonist action in the central nervous system, and an inhibition of the enzyme monoamine oxidase.

Selective α_1-adrenergic receptor blockers are first-line agents in the treatment of benign prostatic hyperplasia and second-line antihypertensives.

Common side effects of selective α_1-adrenergic receptor blockers include orthostatic hypotension and inoperable floppy iris syndromβ-adrenergic receptor blockers can be classified as being nonselective, selective, and β blockers with additional properties such as the ability to generate nitric oxide, inhibit free radial formation, and inhibit hypertrophic growth.

β-adrenergic receptor blockers have a wide versatility of cardiovascular and non-cardiovascular usage, including hypertension, ischemic heart disease, myocardial infarction, heart failure, arrhythmias, performance anxiety, open-angle glaucoma, essential tremor, and migraine headache.Common side effects of β blockers include bradycardia, hypotension, sedation, fatigue, and lassitude. Clonidine, a centrally active α_2-

adrenergic receptor agonist, can be used to treat attention deficit hyperactivity disorder; alcohol, nicotine, or opiate withdrawal; neuropathic pain; or Tourette syndrome, as well as being a second-line antihypertensive.

F. Vasodilators
Examples:
1.Apresoline.
2.Dilatrate-SR.
3.Imdur.
4.Ismo.
5.Isordil.
6.Sorbitrate.

Mechanism of action

Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed, and even so are rarely given alone.

Sodium nitroprusside, a very potent, short-acting vasodilator, is most commonly used for the quick, temporary reduction of blood pressure in emergencies (such as malignant hypertension or aortic dissection). Hydralazine and its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies. They are no longer indicated as first-line therapy for high blood pressure due to side effects and safety concerns, but hydralazine remains a drug of choice in gestational hypertension.

6. Renin inhibitor :
Examples
1. Aliskrine 2.Amlodipine

Mechanism of action :

Renin inhibitors bind to the active site of renin and inhibit the binding of renin to angiotensinogen, which is the rate-determining step of the RAAS cascade. Consequently, renin inhibitors prevent the formation of Angiotensin I

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and Angiotensin II. and similar to angiotensin II receptor antagonists.

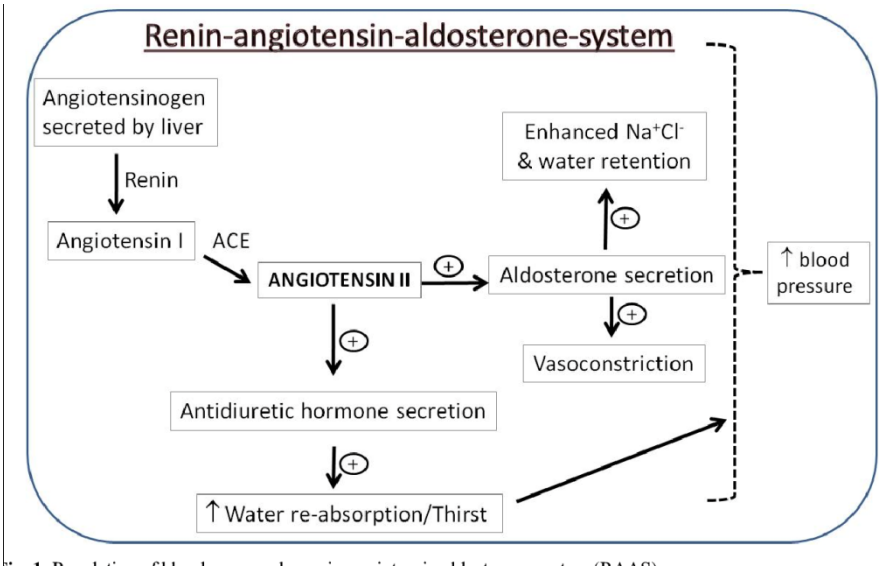

Fig 8: Renin inhibitor

G.Aldosterone receptor antagonists:

Examples:

1.Eplerenone 2.spironolactone

Mechanism of action :

Aldosterone antagonists (spironolactone, eplerenone) inhibit the action of aldosterone in the collecting duct; as such, these agents cause modest diuresis and natriuresis but inhibit potassium and hydrogen ion secretion.Amiloride is a potassium-sparing diuretic that blocks sodium reabsorption in the collecting duct.

H. Alpha-2 adrenergic receptor agonists :

Examples:

1.Clonidine
2.Guanabenz
3.Guanfacine
4.Methyldopa
5.moxonidine

Mechanism of action :

H2RAs decrease gastric acid secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells, thereby inhibiting the binding and action of the endogenous ligand histamine. H2 blockers thus function as competitive antagonists.

V. CONCLUSION :

The antihypertensive effect of drugs demonstrated in well-controlled clinical trials is achievable in clinical practice.

The recommendation to lose weight was the only nonpharmacologic intervention with a detectable antihypertensive effect in this cohort.

Endothelial dysfunction and vascular inflammation are considered markers of early risk of atherosclerosis and are associated with an increase in the incidence of cardiovascular events .It involves the reduction of NO availability, together with the release of vasoconstrictor molecules such as ET-1 and Ang II, increased production of pro-inflammatory molecules, and production of free radicals

Studies have shown that endothelial dysfunction and vascular inflammation can be attenuated with the use of some specific classes of antihypertensive drugs. ACEI and ARBs have shown better endothelial function and reduced levels of inflammatory markers, and these effects are probably due to the increased bioavailability of NO and the prevention of oxidative stress and vascular inflammation induced by Ang II. CCB can restore endothelium-dependent vasodilation in patients with hypertension, improving NO bioavailability through antioxidant activity.

First- and second-generation β-blockers have not shown beneficial effects on endothelial function and vascular inflammation, however, some third-generation β-blockers have additional

properties that may generate beneficial effects on endothelial function in patients with hypertension

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