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# HYPERTENSION AND ANTIHYPERTENSIVE DRUGS – A REVIEW

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***ABSTRACT***
*Hypertension is an important public-health challenge worldwide. About 26·4% of the world adult population in 2000 had hypertension and 29·2% were projected to have this condition by 2025. The World Health Organization has identified hypertension, as the leading cause of cardiovascular mortality and recognized that more than 50% of the hypertensive population worldwide are unaware of their condition(1). It is always necessary for every researcher's to have a broad understanding on high blood pressure so as to help the society to reduce the prevalence of HTN. The main objective of this review is under-standing hypertension and its management in clinical practice.*

***KEYWORDS :*** *Hypertension, Blood pressure, Clinical practice,W.H.O, Cardiovascular mortality.*

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## INTRODUCTION

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Normal blood pressure at rest is within the range of 100-140mmHg systolic and 60-90mmHg diastolic. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg(2). Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause.

The classification of hypertension based on blood pressure(3),

| Status | Systolic pressure | Diastolic pressure | Risk |
|---|---|---|---|
| Normal | <130 | <85 | None |
| Pre-hypertension | 120 to 139 | 80 to 90 | Slight |
| Hypertension | | | |
| Stage 1 (mild) | 140 to 159 | 90 to 99 | long term |
| Stage 2(moderate) | 160 to 179 | 100 to 109 | 50% in 5 years |
| Stage 3(severe) | 180 to 209 | 110 to 119 | 40% in 2 years |
| Stage 4 (very severe) | >210 | >120 | Emergency |

Risk: Stroke, Cardiac Failure, Renal insufficiency or failure

**Management of Hypertension**:

**1) Life style Changes:**

The American Diabetes Association(ADA) 2011 standard of medical care states that in individuals with diabetes and mild hypertension, it may be reasonable to begin treatment with a trial of non-pharmacologic therapy [(4)]such as

- Weight control
- Increased physical activity
- Moderated sodium and alcohol intake
- Increased potassium intake
- A diet rich in fruits and vegetables and low-fat meat, fish, and dairy products
- Getting regular aerobic exercise (such as brisk walking at least 30 minutes a day, several days a week).

**2) Drugs to treat Hypertension**

**I. Diuretics**

(i) Thiazides and related agents (hydrochlorothiazide, chlorthiazide,epitizide,bendroflumethiazide ,indapamide,chlorthalidone,metalozone.)
(ii) Loop diuretics (frusemide,torsemide, bumetanide,azosemide, ethacrynic acid)
(iii) Potassium-sparing diuretics (spironolactone, triamterene, amiloride)

**II Sympatholytic Drugs**

(i) Centrally acting agents (methyldopa, clonidine,moxonidine,guanabenz).
(ii) Ganglion blocking agents (trimetaphan).
(iii) Adrenergic neuron blocking agents (guanethidine, guanadrel, reserpine).
(iv) Beta-adrenoceptor blockers ( metoprolol, atenolol,timolol,oxprenolol,pindolol, propranolol,nadolol.)
(v) Alpha-adrenoceptor blockers (prazosin, terazosin, doxazosin, phenoxybenzamine,torazoline,pentolamine, indoramin).
(vi) Alpha+beta blockers (labetalol, carvediol,bucindolol).

**III. Vasodilators**

(i) Arterial (hydralazine, minoxidil, diazoxide)
(ii) Arterial and venous (nitroprusside)

**IV. Calcium Channel Blockers**

Verapamil,diltiazem,isradipine,felodipine,lercanidipine,amlodipine, nifedipine, nicardipine, nitrendipine.

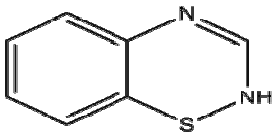
5)Angiotensin Converting Enzyme Inhibitors

Captopril,enalparil,fosinopril,lisinopril,perindopril,quinapril,ramipril, trandolapril,benazepril,Zofenopril

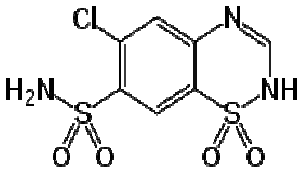
**VI. Angiotensin II Receptor Blockers**
Losartan, valsartan,telmisarton,eprosartan,candesartan,irbesartan,olmesartan.
**VII. Potassium Channel Opener**
Pinacidil
**8) Renin inhibitors**
Aliskiren,remikiren

**DRUG INFORMATICS:**
**Diuretics:**
**Thiazides and thiazide like agents :**

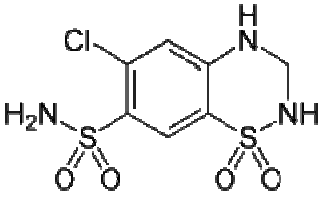
The thiazides and thiazide-like diuretics reduce the risk of death, stroke, heart attack and heart failure due to hypertension.[5]



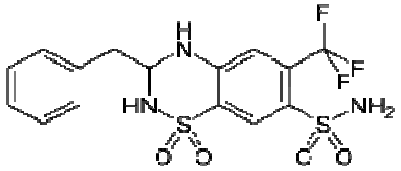
Benzthiadiazine(Parent nucleus)



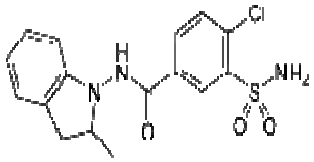
Chlorthiazide



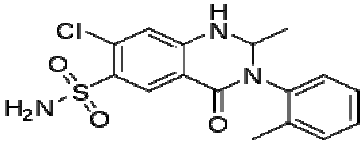
Hydrochlorthiazide



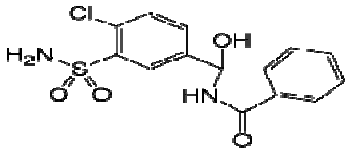
Bendroflumethiazide



Indapamide



Metalazone



Chlorthalidone

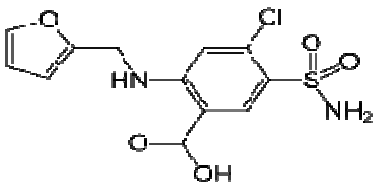
These drugs controls hypertension by inhibiting reabsorption of sodium ($Na^+$) and chloride ($Cl^-$) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive $Na^+$-$Cl^-$ symporter.[6] When administered acutely thiazides lower blood pressure by causing diuresis, a fall in plasma volume and a reduction in cardiac output. However, after chronic use thiazides cause a reduction in blood pressure by lowering peripheral resistance (i.e. vasodilation).[7]

Adverse events: hypokalemia, metabolic alkalosis, hypomagnesemia, hyperuricemia, decreased urinary calcium excretion, glucose intolerance, and lipid abnormalities. Most of these complications are dose related and can be minimized by using low doses of the drugs.[8]

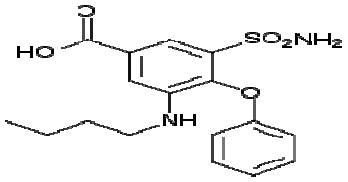
Precautions: Thiazides can decrease placental perfusion and adversely affect the fetus so should be avoided in pregnancy. To be prescribed with caution in patients with gout or hyperuricemia.[9]

**Loop diuretics:**

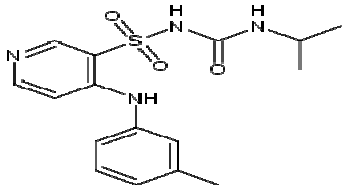
loop diuretics are more effective in patients with impaired kidney function. Loop diuretics act on the $Na^+$-$K^+$-$2Cl^-$ symporter (cotransporter) in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption which is achieved by competing for the $Cl^-$ binding site. They are principally used in edema associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndrome ,hypertension.[10]



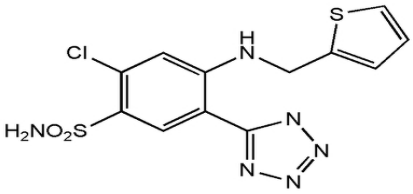
Furosemide

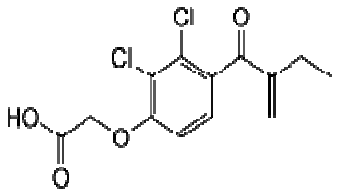


Bumetadine



Torsemide





Azosemide

Ethacrynic acid

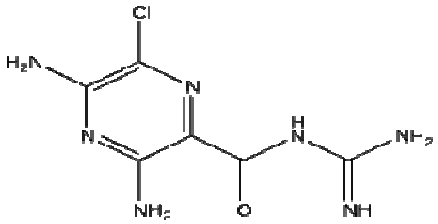
Newly emerging evidence shows that glucocorticoids may be use to reverse the loop diuretic resistance in heart failure.[11]

Adverse events: hyponatremia, hypokalemia, hypomagnesemia, dehydration, hyperuricemia, gout, dizziness, postural hypotension, syncope, dyslipidemia, increased serum creatinine concentration, hypocalcemia, rash.Several hearing complications including tinnitus, irreversible and reversible hearing impairment, deafness and a sense of ear fullness have been observed with loop diuretic therapy.[12]

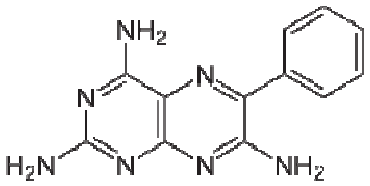
Caution: Discontinuation of therapy is recommended when elevations in blood urea nitrogen or creatinine, oliguria or azotemia occur due to therapy.[12]

**Potassium sparing derivatives:**

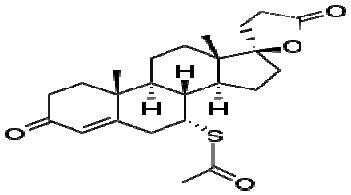
Potassium-sparing diuretics are weak diuretics. They are most often prescribed in combination with thiazides or loop diuretics, to prevent hypokalaemia (low amounts of potassium in the blood) or to increase the amount of fluid removed from the body.[13]



Amiloride



Triamterene



Spironolactone

**Adverse reactions:**

Amiloride and triamterene causes stomach upset, stomach ache or cramp, dry mouth, dizziness or feeling faint, headache, aches and pains, muscle cramps, weakness, diarrhoea or constipation. Spironolactone and eplerenone causes sexual problems, enlargement of the breasts (both in men and women), irregular menstrual periods, confusion and skin rash.

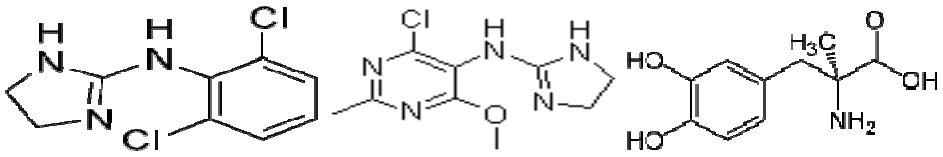
**Sympatholytic drugs:**

A sympatholytic (or sympathoplegic) drug is a medication which inhibits the postganglionic functioning of the sympathetic nervous system (SNS).

**Centrally acting sympatholytics:**

Centrally acting alpha-2 agonists inhibit noradrenergic neurotransmission and have a strong sedative component secondary to sympathetic inhibition.[14]

Clonidine and methyl dopa treats high blood pressure by stimulating $\alpha_2$ receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering blood pressure.[15] It has also been proposed that the antihypertensive effect of clonidine is due to agonism on the $I_1$-receptor (imidazoline receptor), which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure.[16]



Clonidine Moxonidine Methyldopa

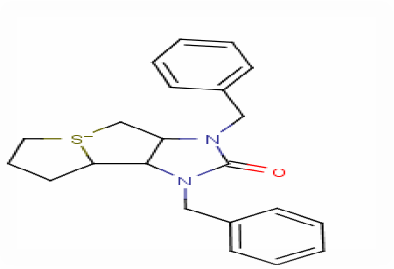
Moxonidine is a new-generation centrally-acting antihypertensive drug which is a selective agonist at the imidazoline receptor subtype 1 ($I_1$) causing a decrease in sympathetic nervous system activity and, therefore, a decrease in blood pressure.[17]

Adverse effects:

Sedation, dry mouth and nasal mucosa, bradycardia (because of increased vagal stimulation of the SA node as well as sympathetic withdrawal), orthostatic hypotension, and impotence.[18]

Ganglion blocking agents:

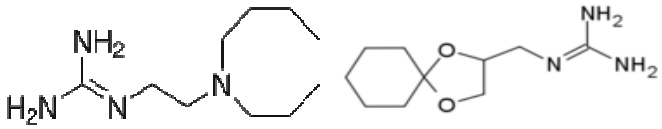
These drugs counteracts cholinergic transmission at the ganglion type of nicotinic receptors of the autonomic ganglia and therefore blocks both the sympathetic nervous system and the parasympathetic nervous system.



Trimetaphan

**Adrenergic neuron blocking agents:**

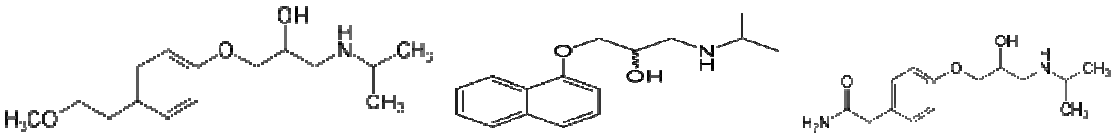
These are the agents which reduces the release of catecholamines, such as norepinephrine. Side effects include orthostatic and exercise hypotension, sexual dysfunction (delayed or retrograde ejaculation), and diarrhea.[19]



Guanethidine Guanadrel

**Beta-adrenoreceptor blocker:**

Beta blockers block the action of endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) in particular, on β-adrenergic receptors, part of the sympathetic nervous system which mediates the fight-or-flight response.[20]

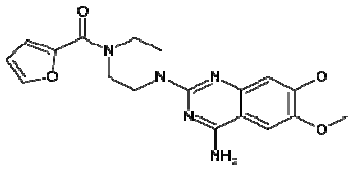


Metoprolol Propranolol Atenolol

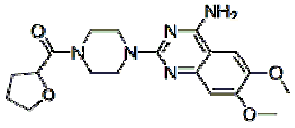
**Alpha-adrenorceptor blocker:**

These drugs block the effect of sympathetic nerves on blood vessels by binding to alpha-adrenoceptors located on the vascular smooth muscle. Most of these drugs act as competitive antagonists to the binding of norepinephrine that is released by sympathetic nerves synapsing on smooth muscle. Therefore, sometimes these drugs are referred to as sympatholytics because they antagonize sympathetic activity. Some alpha-blockers are non-

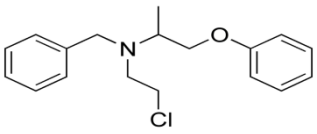
competitive (e.g., phenoxybenzamine), which greatly prolongs their action. Newer alpha-blockers used in treating hypertension are relatively selective $\alpha_1$-adrenoceptor antagonists (e.g., prazosin, terazosin, doxazosin, trimazosin).



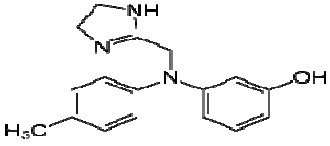
Prazosin



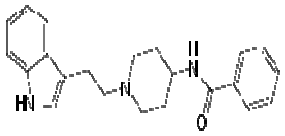
terazosin



Phenoxybenzamine



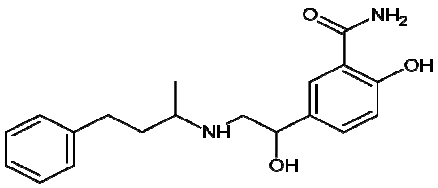
Pentolamine



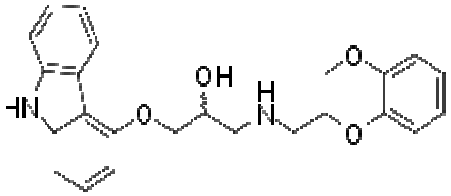
Indoramin

**Alpha+Beta blockers:**

Alpha-beta blockers treat high blood pressure (hypertension). These drugs work on both alpha and beta receptors, reducing the amount of blood pumped through the circulatory system.



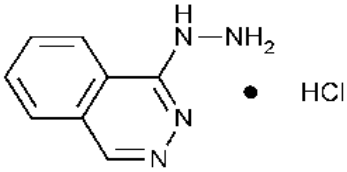
Labetolol



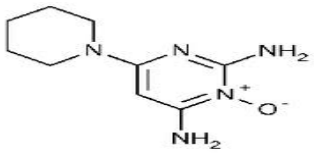
Carvedolol

**Vasodialators:**

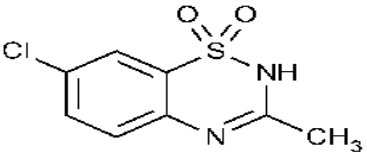
These drugs causes dilation of arterial (resistance) vessels leads to a reduction in systemic vascular resistance, which leads to a fall in arterial blood pressure. Dilation of venous (capacitance ) vessels decreases venous blood pressure. Vasodilators can lead to renal retention of sodium and water, which increases blood volume and cardiac output and thereby compensates for the reduced systemic vascular resistance.



Hydralizine HCl



Minoxidil



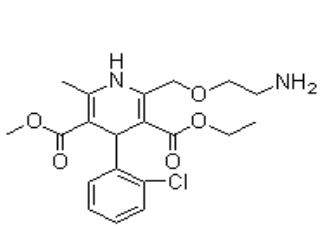
Diazoxide

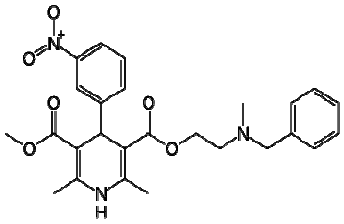
**Calcium channel blockers:**

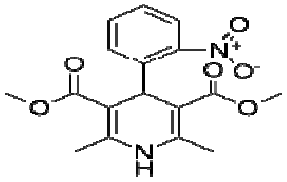
By causing vascular smooth muscle relaxation, CCBs decrease systemic vascular resistance, which lowers arterial blood pressure. These drugs primarily affect arterial resistance vessels, with only minimal effects on venous capacitance vessels.

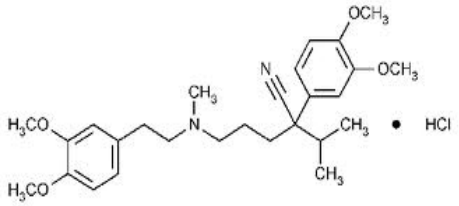
There are three classes of CCBs. They differ not only in their basic chemical structure, but also in their relative selectivity toward cardiac versus vascular L-type calcium channels. The most smooth muscle selective classes of CCBs are the dihydropyridines. Because of their high vascular selectivity, these drugs are primarily used to reduce systemic vascular resistance and arterial pressure, and therefore are primarily used to treat hypertension.

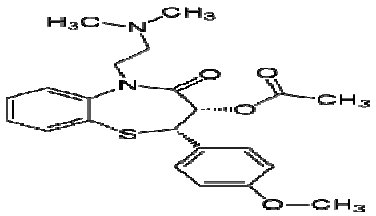
The other two classes of CCBs are phenylalkylamine class (Verapramil) and benzothiazepine class (Diltiazem) the prior is less effective and diltiazem is able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridine.


Amlodipine


Nicardipine


Nifedipine


Verapramil

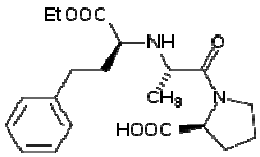

Diltiazem

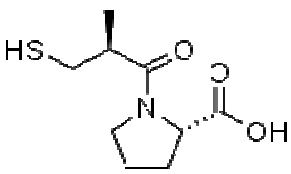
**ACE Inhibitors:**

ACE regulates the balance between the vasodilatory and natriuretic properties of bradykinin and the vasoconstrictive and salt-retentive properties of Ang II. ACE inhibitors alter this balance by decreasing the formation of Ang II and the degradation of bradykinin.

ACE inhibitors may be classified into three groups according to the chemical structure of their active moiety.[21]

1) sulfhydryl-containing ACE inhibitors (Captopril, entiapril, pivalopril, zofenopril etc.,)
2) phosphinyl group- containing ACE inhibitors (Fosinopril)
3) Dicarboxylate- containing ACE inhibitors (Enlapril,ramipril, imidapril,etc.,)
4) Naturally occurring ACE inhibitors ( Casokinins, Lactokinins, lactotripeptides Val-Pro-Pro and Ile-Pro-Pro produced by the probiotic Lactobacillus helveticus)[22]


Enlapril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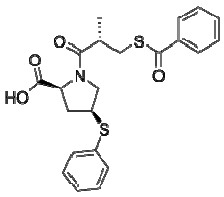
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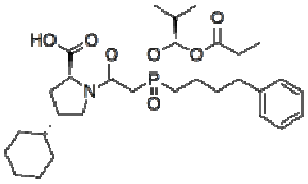
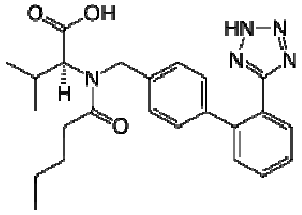
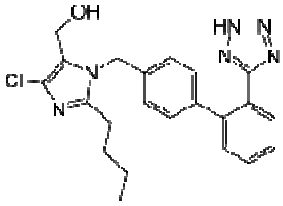
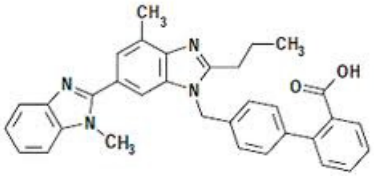

Fosinopril

**Angiotensin II receptor Blocking agents:**

Angiotensin-II receptor antagonists act by binding to specific membrane-bound receptors that displace A-II from its type 1–receptor subtype (AT1). These drugs therefore function as selective blockers.[23] ARBs are well tolerated by most individuals.

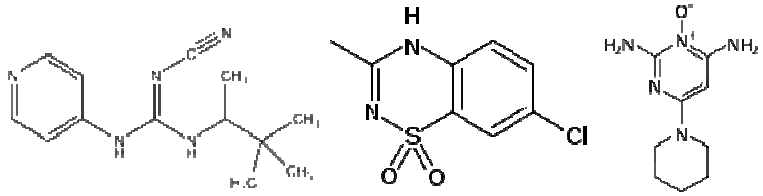

Valsartan


lorsatan


Telmisartan

**Potassium Channel opener:**

The drug that opens ATP-sensitive potassium channels producing peripheral vasodilatation of arterioles thereby reducing blood pressure and peripheral resistance and produces fluid retention.[24]



Pinacidil Diazoxide Minoxidil

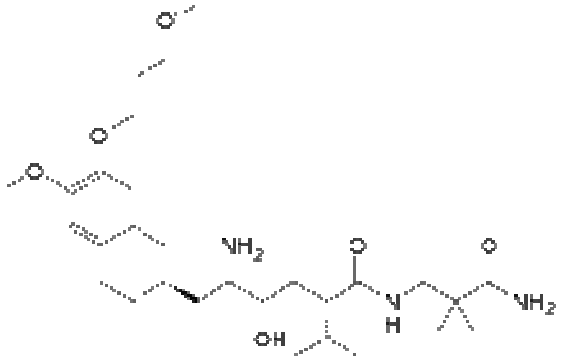
**Renin Inhibitors:**

Aliskiren is an orally active nonpeptide drug with a half-life of about 24 hours, and is dosed once per day. Because of its relatively long half-life, it takes about 2 weeks of dosing to achieve a near maximal antihypertensive effect. It is metabolized by the liver and excreted by the kidneys. Normal therapeutic concentrations of aliskiren reduce plasma renin activity by 50-80%. It is effective as monotherapy. When used in conjunction with thiazide diuretics or ARBs, the antihypertensive effects are additive.

Aliskiren, the only renin inhibitor to go into phase III clinical trials, is not structurally related to peptides, which makes it a third-generation renin inhibitor.The first clinical trial was performed in 2000 in healthy volunteers.In 2007, aliskiren was approved by the US Food and Drug Administration and the European Medicines Agency as a treatment for hypertension. .[25]

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.[26]

The next generation of renin inhibitors have shown potential improvements over previous generations where bioavailability has increased up to 30% in humans, and they have better tissue distribution.[27]



Aliskiren

**CONCLUSION:**

Despite initiatives to improve detection and treatment, surveys suggest that half of the population withhypertension is undetected, while half of those detected are not treated, and in half of those treated their hypertension is uncontrolled (the rule of halves).Adherence is considered to be poor in patients with hypertension, although few trials have examined this issue with respect to older people. Although it is a widely held belief that a reduction in the frequency of dosing should result in increased adherence there are too few good quality studies available to demonstrate that this is the case. Surveys of GPs suggest a reluctance to consider treatment at levels quoted in guidelines. Reasons for this are in part historical; high blood pressure in the past has been considered a part of the ageing process, while genuine concern remains regarding co-existing illness and polypharmacy. In

addition there are very real fears about the resource implications of treating more than half of the population over 65. The major goal of antihypertensive therapy is to lessen the increased morbidity and mortality associated with hypertension In future we can expect novel drugs from this scaffold which would be more promising for the treatment of hypertension.

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