REVIEW OF LITERATURE

Epidemiological studies have consistently identified an important and independent link between high blood pressure and various disorders especially Coronary heart disease, stroke, congestive heart failure and impaired renal function.

Although high blood pressure is independently associated with an increased risk of cardiovascular events, the risk is substantially increased by the presence of other risk factors like smoking, elevated serum cholesterol and diabetes. As a consequence, equal blood pressure level carry different risks, when associated with different combinations of risk factors.

Quantitative estimates based on pooled data from nine prospective observational studies, corrected for regression dilution bias, indicate that subjects with diastolic blood pressure of 105 mm Hg have a tenfold increase in risk of stroke and a fivefold increase in risk of coronary events compared with those with DBP of 76 mm Hg. These findings suggest that prolonged reduction in DBP of 5, 7.5 and 10 mm Hg are respectively associated with at least 34%, 46% and 56% less stroke and at least 21%, 29%, and 37% fewer coronary events.

FACTORS INFLUENCING BLOOD PRESSURE

AGE -

In general systolic blood pressure tends to rise progressively throughout childhood, adolescence and adulthood to attain average value of 140 mm Hg by seventh or Eighth decade. DBP tends to increase with age but at a slower rate than SBP and the average value tends to remain flat or decline after fifth decade. This leads to increase in pulse pressure with isolated increase in systolic blood pressure becoming more common with advancing age.
SEX:

Early in life there is little evidence of difference in blood pressure between the sexes. Beginning at adolescence however men tend to display a higher average level. The difference is most evident in young and middle aged adults later in life difference narrows and pattern may even be reversed

ETHNICITY:

Population studies have consistently revealed high blood pressure levels in black communities than other ethnic groups.

ECONOMIC STATUS:

In countries that are in post transitional stage of economic and epidemiological changes show consistently higher level of blood pressure, and a higher prevalence of hypertension have been noted in lower socioeconomic groups.

PREVALENCE OF HYPERTENSION:

When threshold values are taken as 160 mm Hg SBP and 95 mm Hg DBP the prevalence of hypertension is expected to be between 10 and 20% in several adults populations.

RISK FACTORS AND PREDICTORS OF HIGH BLOOD PRESSURE:

(a) Heredity - A family history of elevated blood pressure is one of the strongest risk factors for future development of hypertension in individuals.

(b) Genetic factors

(c) Early life - An inverse relationship between blood pressure and birth weight has been demonstrated in longitudinal studies of children as well as adults.

(d) Body Weight - In most studies being overweight is associated with two fold to six fold increase in risk of developing hypertension. From observational data
multivariate regression of blood pressure show a rise of 2-3 mm Hg SBP and 1-3 mm Hg DBP for each 10 kg increase in weight.

(e) **Central obesity and Metabolic Syndrome:**

Central obesity indicated by an increased waist-hip ratio has been positively correlated with high blood pressure in several populations. The Coexistence of central obesity insulin resistance hyperinsulinemia, glucoseintolerance dyslipidemia and hypertension has also been highlighted in recent years.

(f) **Nutritional factors:**

  1) **Sodium chloride:** On the basis of the result of INTERSALT AN interpopulation study it has been projected that 100 mmol/day lower intake of sodium over a life time would result in a 9 mm Hg smaller rise in systolic pressure from 25 to 55 years of age, This could correspond by age 55 to a 16% reduction in mortality from CAD 23% for stroke and 13% for deaths from all causes.

(ii) **Potassium:**

  INTERSALT, CARDIAC and other studies have identified an inverse relationship between blood pressure and dietary intake of potassium.

(g) **Alcohol:**

  When two or more drinks are consumed per day SBP rises approximately 1.0 Hg and DBP 0.5 mm Hg per alcoholic drink.

(h) **Physical activity:**

  Regular aerobic physical activity adequate to achieve at least a moderate of physical fitness has been shown to be beneficial for both prevention and treatment of hypertension.

(l) **Environmental factors:**

  Exposure to noise pollution, air pollution, and soft water have all been implicated as risk factors for high blood pressure.
PATHOPHYSIOLOGY OF ESSENTIAL HYPERTENSION:

Development of hypertension depends on the interaction between genetic predisposition and environmental factors. It is known, however, that hypertension is accompanied by functional alterations of the sympathetic (adrenergic) nervous system, the kidney, the reninangiotensin system and other humoral mechanisms. Recent research has called attention to the possible role of endothelial dysfunction in hypertension.

SYMPATHETIC SYSTEM:

The sympathetic nervous system may play a major role in initiating essential hypertension and may contribute to hypertension related to hyperdynamic circulatory states. Several authors have reported increased concentrations of norepinephrine in the plasma of patients with essential hypertension, particularly in younger patients.

It has also been shown that pressor and depressor reflex response to baroreceptor manipulation are reset in experimental and clinical forms of hypertension.

RENAL MECHANISMS:

Through an altered pressure natriuresis leading to sodium retention or through an altered release of pressure factors (such as renin or of depressor factors (such as prostaglandins and medullipin).

RENIN-ANGIOTENSIN SYSTEM:

It has important implications in the development of renal hypertension and may be involved in the in the pathogenesis of essential hypertension. The role of the renin-angiotensin system at the cardiac, vascular and renal level is mediated by
the production or activation of several growth factors and vasoactive substances, inducing further vasoconstriction and stimulating cellular hypertrophy.

**STRUCTURAL CARDIOVASCULAR ADAPTATION:**

The increased load on the vascular system caused by high blood pressure and activation of growth factors lead to structural adaptation with narrowing of the arteriolar lumen and an increase in the media-wall ratio. This amplifies resistance to blood flow and increases vascular responsiveness to vasoconstrictor stimuli.

Cardiac structural adaptations consist of thickening of the left ventricular wall in response to an increased after load (concentric hypertrophy), an increase in left ventricular diameter and a corresponding increase in wall thickness (eccentric hypertrophy) in response to a sustained increase of preload.

**HYPERTENSION AND ENDO THELIAL DYSFUNCTION:**

In the presence of hypertension and/or atherosclerosis, endothelial function is often impaired and pressor responses to local or endogenous stimuli may become dominant.

**CLASSIFICATION OF HYPERTENSION BY ETIOLOGY:**

A. *Essential or primary hypertension*
B. *Secondary hypertension*
1. *Induced by exogenous substances or drugs*
   ♦ Hormonal contraceptives
   ♦ Corticosteroids
   ♦ Sympathomimetics
   ♦ Cocaine
   ♦ Tyramine-containing foods and monoamine-oxidase inhibitors
   ♦ Non-Steroidal anti-inflammatory drugs.
   ♦ Cyclosporin
2. **Associated with renal disorders**
   - Acute glomerulonephritis
   - Chronic nephritis
   - Chronic pyelonephritis
   - Obstructive nephropathy
   - Polycystic - kidney disease
   - Connective - tissue disease
   - Diabetic nephropathy
   - Hydronephrosis
   - Congenital hypoplastic kidneys
   - Trauma
   - Renovascular hypertension
   - Renin-producing tumours
   - Renopirval hypertension
   - Primary sodium retention (Liddle syndrome, Gordon Syndrome)

1. **Associated with endocrine disorders**
   - Acromegaly
   - Hypothyroidism
   - Hypercalcaemia
   - Hyperthyroidism
   
   **Cortical**
   1. Cushing syndrome
   2. Primary aldosteronism
   3. Congenital adrenal hyperplasia
   - Extra-adrenal chromaffin tumours
   - Carcinoid tumours

2. Associated with coarctation of the aorta and aortitis
4. Associated with neurological disorders
   - Increased intracranial pressure
   - Brain tumour
   - Encephalitis
   - Respiratory acidosis
- Sleep apnoea
- Quadriplegia
- Acute porphyria
- Familial dysautonomia
- Lead poisoning
- Guillain-Barre syndrome

5. Surgically induced
   - Peri-operative hypertension

**ORGAN DAMAGE ASSOCIATED WITH HYPERTENSION**

Untreated hypertension increases the risk of vascular damage involving both small (resistance) arteries and arterioles and large (conduit) arteries. These lesions lead to cardiac, renal and cerebrovascular morbidity and mortality. The incidence of these different lesions is also dependent upon the level of other risk factors (such as plasma cholesterol, diabetes and tobacco smoking) in the community.

**CLASSIFICATION OF HYPERTENSION BY EXTENT OF ORGAN DAMAGE:**

**Stage I**  No manifestations of organic change

**Stage II**  At least one of the following manifestations of organ involvement

- Left ventricular hypertrophy (detected by radiogram, electrocardiogram, echocardiogram).
- Generalized and focal narrowing of the retinal arteries
- Micro-albuminuria, proteinuria and/or slight elevation of the plasma creatinine concentration (1.2-2.0 mg/dl).
- Ultrasound or radiological evidence of atherosclerotic plaque plaque (in the aorta or carotid, iliac or femoral arteries).

**Stage II**  Both symptoms and signs have appeared as a result of organ damage. These include

*Heart* -
- Angina pectoris
- Myocardial infarction
- Heart failure

*Brain* -
- Stroke
- Transient ischaemic attack
- Hypertensive encephalopathy
- Vascular dementia

*Optic Fundi* -
- Retinal haemorrhages and exudates with or without papilloedema (these features are pathognomonic of the malignant or accelerated phase)

*Kidney* -
- Plasma creatinine concentration > 2.0 mg/dl.
- Renal failure

*Vessel* -
- Dissecting aneurysm
- Symptomatic arterial occlusive disease

**CLINICAL ASSESSMENT OF THE HYPERTENSIVE PATIENTS**

**GOALS AND METHODS:**

- Confirm a chronic elevation of blood pressure
- Assess the overall cardiovascular risk
- Evaluate existing organ damage or concomitant disease
- Search for possible causes.
RECOMMENDED FOLLOW UP BASED ON INITIAL SCREENING BLOOD PRESSURE

**Blood pressure, mmHg**

<table>
<thead>
<tr>
<th>Systolic</th>
<th>Diastolic</th>
<th>Recommended follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130</td>
<td>&lt; 85</td>
<td>Recheck in 2 years</td>
</tr>
<tr>
<td>130-139</td>
<td>85-89</td>
<td>Recheck in 1 year</td>
</tr>
<tr>
<td>140-159</td>
<td>90-99</td>
<td>Mild hypertension (grade1): confirm repeatedly over a period of at least 3 months.</td>
</tr>
<tr>
<td>160-179</td>
<td>100-109</td>
<td>Moderate hypertension (grade 2): confirm and evaluate promptly and initiate treatment within a few weeks.</td>
</tr>
<tr>
<td>&gt;180</td>
<td>&gt; 110</td>
<td>Severe hypertension (grade3): evaluate and treat immediately.</td>
</tr>
</tbody>
</table>

**GUIDELINES FOR PATIENT HISTORY**

**RISK FACTORS:**
- Family history of hypertension and cardiovascular disease.
- Family and personal history of hyperlipidaemia
- Family and personal history of diabetes mellitus
- Smoking habits
- Dietary habits
- Obesity; amount of physical exercise
- Personality of the patient; social environment

**INDICATORS OF SECONDARY HYPERTENSION:**
- Family history of renal disease (polycystic kidney)
- Renal disease, urinary tract infection, haematuria, analgesic abuse (parenchymal renal disease).
- Drug/substance intakes: oral contraceptives, liquorice, carbenoxolone, nasal drop, cocaine, non-steroidal anti-inflammatory drugs, etc.
- Episodes of sweating, headache, anxiety (Phaeochromocytoma)
- Episodes of muscle weakness and tetany (aldosteronism)

**SYMPTOMS OF ORGAN DAMAGE:**
- Brain and eyes: headache, vertigo, impaired vision, transient ischaemic attacks, sensory or motor deficit.
- Heart: palpitations, chest pain, shortness of breath, swollen ankles
- Kidney: thirst, polyuria, nocturia, haematuria
- Peripheral arteries: cold extremities, intermittent claudication

**PHYSICAL EXAMINATION FOR SECONDARY HYPERTENSION AND ORGAN DAMAGE**

**SIGNS SUGGESTING SECONDARY HYPERTENSION:**
- Features of cushing syndrome
- Skin stigmata of neurofibromatosis (phaeochromocytoma)
- Palpation of enlarged kidneys (polycystic kidney)
- Auscultation of abdominal murmurs (renovascular hypertension)
- Auscultation of precordial or chest murmurs (aortic coarctation or aortitis)
- Diminished and delayed femoral pulses and reduced femoral blood pressure (aortic coarctation or aortitis).

**SIGNS OF ORGAN DAMAGE:**
- Brain: murmurs over neck arteries, motor or sensory defects.
- Retina: fundoscopic abnormalities
- Heart: location and characteristics of apical impulse, abnormal cardiac rhythms, ventricular gallop, pulmonary rales, dependent oedema.
- Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions.
LABORATORY INVESTIGATIONS

**STRONGLY RECOMMENDED TESTS:**
- Urine analysis (dipstick test complemented by urinary sediment examination)
- Plasma creatinine
- Plasma potassium (sodium is often measured in the same sample)
- Blood glucose
- Serum cholesterol
- Electrocardiogram

**ADDITIONAL TESTS:**
- Fasting plasma triglycerides and high-density lipoprotein-cholesterol
- Plasma uric acid
- Haemoglobin and haematocrit
- Urine culture
- Chest X-ray
- Echocardiogram

**EXTENDED EVALUATION (DOMAIN OF THE SPECIALIST):**
- Complicated hypertension: test of cerebral, cardiac and renal function
- Search for secondary hypertension: measurement of renin, angiotension, aldosterone, corticosteroids, catecholamines; aortography and renal arteriography; renal and adrenal ultrasound; computer-assisted tomography (CAT); etc.

**HYPERTENSION IN SPECIAL POPULATIONS:**

**CHILDREN AND ADOLESCENTS:**

Hypertension in the young is defined as average systolic and/or diastolic blood pressure equal to or greater than the 95th percentile for age on at least three occasions. The prevalence of hypertension is at least 1% in children and increases in adolescents. In adolescents, use of alcohol, cocaine or other additive substances should be considered as a possible cause of elevated blood pressure. Antihypertensive drug therapy should usually be reserved for children with blood
pressure above the 99th percentile or with significantly elevated blood pressure that responds inadequately to lifestyle modifications or is associated with target organ damage.

**WOMEN:**

**HYPERTENSION ASSOCIATED WITH ORAL CONTRACEPTIVES:**

Prospective controlled studies have shown that estrogen-progestogen oral contraceptives (containing 50 µg or more of estrogen) cause a distinct increase in systolic, and to a lesser extent diastolic, pressure in virtually all women. The use of hormone replacement therapy is not contraindicated for women with hypertension, but blood pressure should be monitored frequently as it is not yet clear whether a hypertensive response may occur in some.

**HYPERTENSION IN PREGNANCY:**

The hypertensive disease of pregnancy (variously termed toxaemia of pregnancy, pre-eclampsia, eclampsia and hypertension gestosis) is the major cause of premature birth and perinatal death, and is also responsible for 20-33% of all maternal deaths. Infants of mothers who have hypertension with proteinuria in late pregnancy are small and are more often still born or have a high risk of dying in the neonatal period. Diagnosis of hypertension requires two consecutive measurements of DBP 90 mmHg or more, four or more hours apart, or one measurement of 100 mmHg or more.

Pre-eclampsia eclampsia is characterised by hypertension with proteinuria (>300 mg/day) and, at times, coagulation abnormalities or liver abnormalities or both. Oedema is no longer used as a criterion. It occurs primarily in a women's
first pregnancy after the 20th week of gestation and most frequently near to full term.

Women suspected of having eclampsia should be admitted to hospital. If pre-eclampsia or severe hypertension occurs beyond the 36th week of gestation, delivery is the therapy of choice. When problems arise earlier, delivery may be delayed in selected patients under strict supervision. If there is evidence of advanced disease (especially with thrombocytopenia or abnormal liver function tests) or signs or symptoms of impending eclampsia, delivery is indicated regardless of the length of gestation.

For acute hypertension, with DBP of or greater than, 105 mmHg (14.0 kPa) - in pre-eclampsia/eclampsia, intravenous hydralazine is indicated, aiming for a gradual reduction of DBP to 90-100 mmHg. Magnesium sulfate remains the treatment of choice to prevent eclamptic convulsions.

**CHRONIC HYPERTENSION IN PREGNANCY**

The diagnosis of chronic hypertension rests on the evidence of raised blood pressure before pregnancy or before the 20th week of gestation. If DBP is greater than 95 mmHg, methyldopa and β-blockers are the safest agents, although β-blockers may retard fetal growth. Diuretics can be used transiently when blood pressure is difficult to control. Sodium restriction is not recommended. Bed rest may be useful.

**ELDERLY PEOPLE**

In absolute terms, hypertension is a much greater risk factor of cardiovascular events in the elderly than in younger people. The SHEP (Systolic Hypertension in the Elderly) specifically examined the value of antihypertensive treatment in men and women over 60 years old with isolated systolic hypertension,
i.e. SBP of 160-219 mmHg and DBP greater than 90 mmHg (12.0 kPa): highly significant reductions in fatal and non-fatal cardiovascular events were observed, reducing cardiovascular morbidity and mortality to at least the same extent (about 20-50%) as in young and middle-aged patients.

**HYPERTENSIVE PATIENTS WITH DIABETES:**

The coexistence of hypertension and non-insulin-dependent diabetes mellitus is common. Patients with both of these conditions are especially vulnerable to cardiovascular and renal complications; therefore, the control of hypertension and dyslipidaemia - and the cessation of smoking - are particularly important. In patients with incipient diabetic nephropathy, treatment may be instituted at systolic and diastolic blood pressure values as low as 130 mmHg and 85 mmHg respectively.

**PREVENTION AND CONTROL OF HYPERTENSION IN POPULATIONS:**

**LIFE STYLE MEASURES:**

Lifestyle measures for lowering blood pressure. In the individual patient they are helpful in lowering blood pressure, avoiding or reducing the need for antihypertensive drugs and controlling associated risk factors. Interventions that clearly lower blood pressure have been critically appraised. Interventions that clearly lower blood pressure are weight reduction, reduced alcohol intake, increased physical activity and reduced sodium intake. Interventions with limited or unproven efficacy include stress management, micronutrient alteration and dietary supplementation with potassium, fish oil, calcium magnesium or fibre.
In mild hypertension, it would seem desirable in young patients to achieve SBP of at least 120-130 mmHg and DBP of 80 mmHg. In elderly patients it would seem desirable to lower blood pressure to below 140 mmHg for SBP and 90 mmHg for DBP, while in patients with isolated systolic hypertension the goal should be SBP of at least 140 mmHg, if this is tolerated.

**LIFE STYLE MODIFICATIONS:**

Life Style Measures (non pharmacological treatment) are used for four complementary reasons.

1. To lower blood pressure in individual patient.
2. To reduce the need for antihypertensive drugs.
3. To minimize associated risk factors in an individual.
4. Primary prevention of hypertension and associated cardiovascular diseases in populations.

**LIFE STYLE MEASURES THAT CONTRIBUTE TO LOWERING B.P.:**

a. Weight reduction.

b. Moderation of alcohol intake (60 ml whisky, 300 ml wine, 720 ml beer per day, half that quantity for women and lighter weight people).

c. Regular physical aerobic activity (30-45 minutes most days of the week).

d. Sodium intake to not more than 2.4 g sodium or 6 gm of sodium chloride.

e. Adequate dietary potassium and even calcium and magnesium.

f. Cessation of smoking. Benefits of discontinuing tobacco can be seen with in a year in all age groups.

g. Reduction in the intake of dietary saturated fats and cholesterol.

h. Control of diabetes.
WEIGHT REDUCTION:

Weight reduction lowers blood pressure in the majority of hypertensive patients who are more than 10% overweight, and also has beneficial effects on associated risk factors such as the lipid profile and insulin resistance.

REDUCTION OF ALCOHOL INTAKE:

Reduction of alcohol intake over a period 1-4 weeks results in lowering of blood pressure. Randomized cross-over studies showed that reducing alcohol intake by 80-85% resulted in an SBP/DBP reduction of 5.0/3.0 mmHg in hypertensive subjects and 3.8/1.4 mmHg in those with normal blood pressure.

INCREASED PHYSICAL ACTIVITY:

Exercise lowers systolic and diastolic blood pressure by 5-10 mmHg. Dynamic isotonic exercise such as walking is more effective than static isometric exercise such as weight lifting. Milder levels of exercise, such as brisk walking for 30-60 minutes a day of 3-5 times a week, is possibly better than more strenuous forms of exercise such as running.

REDUCED SODIUM INTAKE:

Individuals vary substantially in their responses to changes in dietary sodium chloride. Black and elderly people may be more sensitive to salt reduction. An average intake below 6 g of sodium chloride a day should be the aim.

Meta-analysis of 18 clinical trials in hypertensive subjects revealed an SBP/DBP reduction of 4.9/2.6 mmHg in 1-2 months, associated with a 56-105 mmol reduction in daily sodium intake.
**CESSATION OF TOBACCO SMOKING:**

Although tobacco smoking is not causally related to hypertension, it is a major cardiovascular risk factor. The incidence of stroke and coronary heart disease in hypertensive patients who smoke is 2-3 times greater than in non-smoking patients with comparable blood pressure. Stopping smoking rapidly reduces - this risk.

**REDUCED FAT INTAKE:**

High serum cholesterol, high low-density lipoprotein-cholesterol, and low high-density lipoprotein cholesterol levels increase the risk of atherosclerotic complications of hypertension. Advice on nutrition and physical activity is an essential component of a primary prevention programme that aims to reduce the total risk of cardiovascular disease.

**CONTROL OF DIABETES:**

Diabetes requires a comprehensive plan of care which includes specific nutritional counselling and appropriate use of insulin and orally active hypoglycaemic drugs.

**MANAGEMENT OF HYPERTENSION:**

Lowering the blood pressure should never be the sole aim of therapy. Ideally all abnormalities associated with hypertension including shortened life expectancy should be reverted to normal. Overall cardiovascular mortality has been reduced by therapy, primarily through a decrease in stroke mortality, yet thus for in no single trial has mortality from coronary disease been convincingly improved although borderline decreases have been achieved in trials in elderly.
**PHARMACOLOGICAL TREATMENT:**

- Use long acting drugs providing 24 hour efficacy on a once daily basis.
- Better compliance.
- Smoother and more consistent B.P. control.
- Greater protection against risk of major cardiovascular events like stroke and myocardial infarction that can occur due to abrupt increase in B.P. that occurs after arising from overnight sleep.
- Use appropriate drug combinations to provide additional antihypertensive efficacy and minimizing the likelihood of dose dependent adverse effects.
  - Diuretic and beta blocker.
  - Diuretic and ACE inhibitor.
  - Calcium antagonist and beta blocker.
  - Calcium antagonist and ACE inhibitor
  - Alpha blocker and beta blockers.
- Substitute an agent from another class if the patient is having adverse effects or shows no response.
- After effective control for at least one year an effort to decrease the dosage and number of drugs should be considered.

**INITIAL DRUG THERAPY:**

This depends on the presence of complications or a co-morbid condition. If there are no indications for another type of drug, a diuretic or beta blocker should be chosen because evidence has shown a reduction in morbidity with these agents.

**Indications for specific agent:**

- ACE inhibitors in diabetes with nephropathy.
- ACE inhibitors and diuretics in heart failure.
- Diuretics or long acting dihydropyridine calcium antagonists in isolated systolic hypertension in older persons.
- Beta blockers in myocardial infarction.
- ACE inhibitors in MI with systolic dysfunction.

**SPECIAL POPULATIONS AND SITUATIONS:**

- Methyl dopa has been recommended for women where hypertension is first diagnosed during pregnancy.
- Blood pressure of patients with renal insufficiency and proteinuria > 1gm/day should be lowered to 125/75 mmHg.
- Patients with diabetes should have their Blood Pressure lowered to below 130/85mmHg. ACE inhibitors are better choice as therapy.

**LOSARTAN POTASSIUM:**

Losartan potassium is an orally active nonpeptide angiotensin II (All) receptor antagonist. This binds competitively and selectively to the all subtype I (ATI) receptor thereby blocking All induced physiological effect. An active metabolite. E 3174 contribute substantially to its, anti hypertensive effect which persists through 24 hours after once daily dose administration.

**Pharmacodynamic Properties:**

Losartan potassium binds selectively, competitively and with high affinity to the ATI receptor thereby blocking the activity of All.

The active metabolite E-3174 is non competitive antagonist which binds to ATI receptor with 10 fold greater affinity than its parent compound. In patients with hypertension losartan potassium increases plasma renin activity and plasma
All levels and appears to decrease plasma level of aldosterone at least in short term.

Blood pressure decrease produced by once daily dose of losartan potassium persists throughout 24 hours and heart rate is unchanged. Losartan potassium causes regression of left ventricular hypertrophy, losartan potassium improved mortality rates in animals prone to stroke and prevented fibrinoid necrosis of other end organs including heart.

Renal function is preserved during losartan potassium administration in patients with hypertension with or without renal impairment, losartan potassium decreases proteinuria that associate with renal failure or with non insulinn dependent diabetes mellitus in limited investigations. Plasma level of lipid, lipoprotein and prostaglandins are unchanged during losartan potassium in patient without other concomitant disease.

**Pharmaco Kinetic Properties:**

The bioavailability of losartan potassium is about 33%, indicating a considerable first pass metabolism and is not altered significantly by the presence of food. In most patients about 14% of an oral dose of losartan potassium is metabolised via hepatic carboxylation to the active metabolite E-3174. Time to achieve peak plasma concentration is about 1 hour for losartan potassium and 3-4 hours for E-3174. The volume of distribution is about 34 L for losartan potassium and 12 L for E-3174. Both compounds are >94% bound to plasma proteins.

At about 4 hours (in Japanese) and 6 hours (in western individuals) the terminal half life of E-3174 is longer than that of losartan potassium (2 hours). The pharmaco kinetic properties of losartan potassium and E-3174 are not affected by renal dysfunction to any clinically important extent. In contrast in patient with hepatic dysfunction, plasma drug concentration of both agents is increased and
plasma clearance is reduced necessitating dose adjustment. No. significant drug interaction occur between losartan potassium and warfarin, digoxin or hydrochlorothizide.

**Clinical Efficacy:**

Losartan potassium is an effective treatment for hypertension. Blood pressure lowering is evident with in week of initiating losartan potassium therapy and is maximal by 6 week. The drug has reduced diastolic blood pressure by about 8-13 mmHg. in patient with mild to moderate hypertension, as shown by several well designed comparative trials lasting 8-12 weeks. Large dose finding trials have shown losartan potassium to be 50 mg dialy as monotherapy to be superior to placebo and indistinguishable from 100 mg dose.

**Tolerability:**

Headache, upper respiratory tract infection, dizziness asthenia fatigue and cough have been reported during administration of losartan potassium monotherapy. There have been rare reports of patients developing angiodema, migraine or ageusia during losartan potassium therapy.

Cough which can limit treatment with ACE inhibitors is seldom experienced during losartan potassium therapy and its incidence is similar to that for placebo.

**Dosage and administration:**

The recommended initial and maintenance dosage of losartan potassium as monotherapy in essential hypertension is 50mg once daily. Some patients may benefit from 100 mg/day. Losartan potassium is not recommended in pregnant women because of the risk of fetal morbidity / mortality.
ACE inhibitors:

Enalapril maleate:

- Enalapril is de-esterified in liver and kidney to active form enalaprilat.
- Time to peak serum concentration is about 2 hours for enalapril and about 5 hours for enalaprilat with some delay in CHF.
- Excretion is 95% renal (hence low dose in RF).
- + 1/2 of enalapril at is 4-5 hrs in HT
  7-8 hrs in CHF
  (following multiple doses + 1/2 is 11 hrs.)

Dose:

- Hypertension - 2.5 - 20 mg (1 or 2 daily doses)
- Asymptomatic LV dysfunction or CHF (2.5 - 20 mg/day)
- Renal failure (GFR < 30ml/min) reduction of dose is needed.
- Myocardial infarction (early phase) (1.25 mg at 2 hrs. interval for 3 doses followed 5 mg three times daily).

Side effects:

- Cough
- Neutropenia.
- Angioedema
- Hyperkalemia

Precautions:

- Excess hypotension.
- Renal failure

Contraindication:

- Bilateral renal artery stenosis.
- Stenosis in single kidney.
β Blocker:

Atenolol:

- Cardioselective β1 blocker.
- Plasma half life - 6-7 hour.
- Route of elimination - kidney.
- Plasma protein binding - 10%
- No. ISA, no. lipid solubility.

DOSE:

- Angina - 50-200 mg/day.
- Hypertension - 50 - 100 m g/day
- I/V - 5 mg over 5 min - three doses 5 min apart.

Indications:

- Systemic Hypertension
- Angina Pectoris
- Acute myocardial infarction early phase as well as in follow up

Special Precautions:

- Diabetes mellitus
- Kidney dysfunction
- Cardiac failure
- Abrupt withdrawal may cause angina pectoris and precipitates myocardial infarction.

Contraindications:

- Heart block.
- Cardiogenic shock.
- Cardiac failure.
- Sinus bradycardia.
Calcium Channel Blocker:

**Amlodipine:**
- T-max - 6 - 12 hours
- Extensive but slow hepatic metabolism
- 90% inactive metabolites
- 60% renal excretion
- + ½ - 35 - 50 hours
- Steady state in 7-8 days.

**DOSE:**
- 5-10 mg /day in hypertension.

**Indications:**
- Hypertension
- Angina Pectoris
- Prinzmetal's angina

**Side effects:**
- Peripheral edema
- Dizziness
- Flushing
- Fatigue

**Precaution:**
- Prolonged + ½ up to 56 hours in liver failure (Reduce dose)

**Contraindications:**
- Tight Aortic Stenosis
- Obstructive hypertrophic cardiomyopathy
- Severe myocardial depression
**ALPHA BLOCKER:**

**Terazosin Hydrochloride:**

- T-max- 1 hour
- t- \( \frac{1}{2} \) - 12 hour
- 10% of orally administered dose is excreted as parent drug in urine and approximately 20% is excreted in faeces, remainder excreted as metabolites.

**DOSE:** Upto 10mg/day

**Side effect:**

- Asthenia
- Postural hypotension
- Dizziness
- Somnolence
- Nasal congestion /rhinitis
- Impotence

**Precaution:**

- Rule out the presence of carcinoma of prostate before starting treatment.

**Contraindication:**

Hypersensitivity to drug.