Chapter – I

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The product angiotensin, a proteolytic octapeptide, is formed and released into the blood stream from the very basic substrate angiotensinogen. Renin, which is secreted by the juxtaglomerular apparatus of the kidneys is released and acts on its substrate angiotensinogen, a α-globulin to form angiotensin I, a decapeptide. Further angiotensin I is converted to angiotensin II, the active and the causative, proteolytic octapeptide by the enzyme called angiotensin converting enzyme (ACE). It is a dipeptidyl carboxypeptidase and zinc requiring metalloenzyme. The catalytic reaction is as follows:¹²

\[
\text{Angiotensinogen} \xrightarrow{\text{Renin}} \text{Angiotensin I} \xrightarrow{\text{ACE}} \frac{\text{Zn}}{\text{Zn}} \text{Angiotensin II}
\]

Also earlier it has been well demonstrated by many studies and experimental work, that the proteolytic octapeptide product angiotensin II, (which is very commonly called as angiotensin or hypertensin) is the causative factor for the increase in blood pressure. Angiotensin II has three major functions, it is a potent vasoconstrictor, it directly suppresses renin release and it stimulates aldosterone secretion. It is one of the most powerful vasoconstrictor substance known. As little as one millionth of a gram can increase the arterial pressure of human as much as 50 or more mm Hg. The effect of angiotensin is to constrict very powerfully the small arterioles. Constriction of arterioles increases the peripheral resistance. If this occurs in an isolated tissue area, the blood flow to that area can be severely depressed and thus there is
increase in the blood pressure levels. Mild constriction of veins increases the venous return. This in turn increases the cardiac output. Increase in cardiac output, increases the blood pressure. Angiotensin also increases salt and water retention by kidney, indirectly by stimulating release of aldosterone from the adrenal cortex. It directly acts on renal tubules and causes decreased excretion of salt and water. This causes increase in extracellular fluid volume and therefore there is rise in blood pressure.$^3$

The main function of angiotensin is that, when arterial pressure falls to low, it rises that arterial pressure in several different ways when release by the kidney. Thus the control of arterial pressure is brought by the renin - angiotensin - aldosterone system.$^{34}$

A current expert recommendation are that, elderly individuals with sustained systolic and diastolic blood pressure of greater than 160/90 mm Hg should be treated. In brief to define hypertension is very arbitrary. Blood pressure (B.P) greater than 140/90 mm Hg is termed as hypertension.$^5$ Hypertension in our Indian National language is well knownly called as ‘Ghabrahat’. The patient in history of hypertension admits to the physician, “Ghabrahat Hoti Hai”.

Usually hypertension by itself cause ‘no symptoms’. Really speaking it is accidentally detected and in this respect it resembles with diabetic mellitus (DM), which usually causes no symptoms and accidentally detected. Hypertension is the main risk factor for stroke with systolic blood pressure (SBP) greater than 140 mm Hg. Accounts for 40% strokes in epidemiological studies of attributable risk. It has been suggested that practical approach to reducing strokes incidence would be increase to 50% of the proportion of people with raised BP>160/95 mm Hg. that had then controlled BP<140/90 mm Hg.$^{1,5}$
Hypertension is the commonest cardiovascular disorder, posing major public health challenge to societies in socio-economic and epidemiological transaction. It is one of the major risk factor for cardiovascular mortality, which accounts for 20-50% of all deaths.\textsuperscript{1,6}

The drug treatment in hypertension is still ‘empiric’, as the drugs reduce the blood pressure without correcting the cause. Inspite of various limitations of antihypertensive drugs and the difficulties presented by their long term use, it is now generally accepted that the reduction of blood pressure prevents or postpones renal, cardiac and cerebral complications and prolongs life.\textsuperscript{7}

Hence, control of hypertension is a complex, multidimensional process. The objectives are primary prevention, early detection and adequate treatment to prevent further complications occurring related with heart, kidney and brain vessels. The case recognition and initiation of effective treatment has become an urgent aim for treatment benefit.

Several aspects of hypertension related organ damage require better understanding, inspite of effective antihypertensive treatment. This is because, actual studies have shown that any elevation of blood pressure, significantly increases morbidity and mortality which are directly related to the level of blood pressure. Thus effective treatment of hypertension is an important part of any programme to reduce the toll of ‘cardiovascular disease, brain vessel, retina and kidney disorders’ in the society.\textsuperscript{1,7}

The present study is undertaken to provide the basis for appropriate public health interventions, epidemiological estimates of the prevalence of the hypertension and the risk factors leading to the high blood pressure in all countries.
ACE has also been implicated in several other conditions such as sarcoidosis, hyperthyroidism, beryllium poisoning, silicosis, leprosy, alcoholic liver disease. Diabetes mellitus (about 14% of diabetes have raised activity). As a diagnostic test, it is estimated more commonly in sarcoidosis. 8

Pathophysiology

The components of the proteolytic release of octapeptide from angiotensinogen and its role in hypertension.

Angiotensinogen

The angiotensinogen, is a circulating glycoprotein found in the liver. It is a big protein made up of more than 400 amino acids, which is present in the systemic blood. It is a substrate for renin and also called as renin activator (hypertensinogen). 9,10

Renin

Renin (E.C 3.4.23.15) is an enzyme produced in juxtaglomerular cells (JG cells) of the renal afferent arteriole of the kidneys. It is an aspartyl protease synthesised mainly by the kidneys. It is a small protein enzyme released by the kidneys when the arterial pressures falls too low. In turn it raises the arterial pressure in several ways, thus helping to correct the initial fall in blood pressure.

Renin is synthesised and stored in an inactive form called prorenin in the JG cells of the kidneys. The JG cells are modified smooth muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli. When the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enter the blood and leaves the kidneys to circulate throughout the entire blood stream, although a small amount remains in the local fluids of the kidney and initiates several intrarenal functions.
Renin itself is an enzyme, not a vasoactive substance. It acts enzymatically on the plasma protein, a globulin i.e. the renin substrate angiotensinogen to release a 10 amino acids (a.a.’s) peptide angiotensin I. It persists in the blood for 30 minutes to 1 hour and continues to cause the formation of angiotensin I during this entire time.\textsuperscript{3,11}

**Angiotensin I**

It is a decapeptide formed from an angiotensinogen.

\begin{center} Asp - Arg - Val - Tyr - Ile - His - Pro - Phe - His - Leu \end{center}

\[ \text{Angiotensin I (decapeptide - 10 a.a's)} \]

The reaction is catalysed by the enzyme renin. Angiotensin I is also called as hypertension-I, which has no biological effect in humans. In plasma, it is acted on by a peptidase, called Angiotensin Converting Enzyme (ACE) present in normal plasma to form an octapeptide called angiotensin II.\textsuperscript{11,12}

**Angiotensin Converting Enzyme (ACE)** (E.C 3.4.15.1)

The ACE was discovered by Skeggs and his associates in the mid 1950’s when they noticed that horse plasma contains an enzyme that converts angiotensin I to angiotensin II. Renin releases the decapeptide angiotensin I from angiotensinogen. This decapeptide is in turn converted to the octapeptide angiotensin II, when the converting enzyme clears a histidyl-leucine dipeptide from the C-terminal end of angiotensin I. The enzyme requires chloride ions and is inhibited by EDTA.\textsuperscript{11,13,14}

The conversion of angiotensin I is obviously just one of the functions of the enzyme discussed because, the converting enzyme breaks peptidyl dipeptide bonds in substrates, other than angiotensin I. It is referred too in the literature as peptidyl dipeptide hydrolase or peptidyl
dipeptidase. Its molecular weight is 140,000 to 480,000. It is a halide-activated exopeptidase, membrane bound glycoprotein, which is localised mainly in the endothelial cells of pulmonary capillaries, which inactivates bradykinin and bradykinin like hypotensive peptides. It has central role in the control of blood pressure i.e. the blood pressure homeostasis. As its significant activity is found in circulation, it occurs in plasma and in the vascular endothelium of many organs including lungs and kidneys. It is a zinc requiring metalloenzyme which is chiefly responsible for the conversion angiotensin I to angiotensin II.\textsuperscript{3,13,15}

The ACE is a key element of the renin-angiotensin system that has long been suspected to be involved in the pathogenesis of hypertension and cardiovascular disease. A number of drugs (ACE inhibitors) are already available that may influence the pathophysiological effects of this genetic variant on the cardiovascular system.

**Angiotensin II**  
**[(Hyptertensin, Angiotensin, Angiotonin)]**

The rapid conversion of angiotensin I to angiotensin II takes place in the circulation. This conversion is brought by the enzyme called angiotensin converting enzyme.

\[
\text{Asp - Arg - Val - Tyr - Ile - His - Pro - Phe}
\]
\[
\text{Angiotensin II (octapeptide = 8 a.a's)}
\]

Various other names for the preceding substances have been used in the literature.

Angiotensin II is an active, causative and most powerful vasoconstrictor proteolytic octapeptide substance known. As little as one millionth of a gram can increase the arterial pressure of a human as much as 50 or more mm Hg. The effect of angiotensin is to constrict very powerfully the small arterioles. Because of this plus several renal
and adrenocortical stimulatory effects of angiotensin, this hormone plays an integral role in the regulation of the arterial pressure. Thus the pressor activity of angiotensin II may appears to be dependant on the presence of 1) the aromatic ring 2) the free carboxyl group of phenyl alanine 3) the phenolic group of tyrosine 4) the presence of proline in the seventh position in peptide sequence and 5) a hexapeptide structure with specific 3-dimensional features.\textsuperscript{3,12}

The angiotensin II appears to exert its pressor effect by constricting arterioles and increasing the heart beat. It is therefore important in regulation of blood pressure in humans, as well as in all other mammals.\textsuperscript{12}

Hence, in brief, the overall catalytic reaction for the production and proteolytic release of octapeptide from angiotensinogen is that, the product angiotensin, a proteolytic octapeptide, which is found and released into the blood stream from the very basic substrate angiotensinogen. Renin which is secreted by the JG apparatus of the kidneys is released and acts on its substrate angiotensinogen, an $\alpha$-globulin to form angiotensin I, a decapeptide. Further, angiotensin I is converted to angiotensin II, the active and the causative, proteolytic octapeptide by the enzyme called Angiotensin Converting Enzyme (ACE). For catalytic reaction refer page 1.

**Renin-Angiotensin System:**
**Metabolism and its role in Pressure Control and Hypertension**

Aside from the capability to control arterial pressure through changes in extracellular fluid volume, the kidneys have another powerful mechanism for controlling pressure. It is the renin-angiotensin system.\textsuperscript{3}

**Components of the Renin-Angiotensin System**

The Figure 1.1 shows the functional steps by which the renin-angiotensin system helps to regulate arterial pressure.
Renin in synthesised and stored in an inactive form called prorenin in the juxtaglomerular cells (JG cells) of the kidneys. The JG cells are modified smooth muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli when the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the blood and leaves the kidneys to circulate throughout the entire blood stream, although a small amount remains in the local fluids of the kidney and initiates several intrarenal functions.³

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**Decreased Arterial Pressure**

\[ \downarrow \]

Renin (Kidney)

\[ \downarrow \]

Renin Substrate (Plasma Protein)

\[ \downarrow \]

Angiotensin I

\[ \downarrow ACE \text{ (in lung)} \]

Angiotensin II

\[ \downarrow \text{Angiotensinase} \]

\[ \downarrow \]

Renal Retention of salt and water

\[ \downarrow \]

Vasoconstriction (Inactivated)

\[ \downarrow \]

Increased Arterial Pressure

*Courtesy:* ³

Figure 1.1: **Renin-Angiotensin Vasoconstriction Mechanism for Arterial Pressure Control**

Renin acts enzymatically on plasma protein, a globulin called renin substrate or angiotensinogen, to release a 10 a.a's peptide, angiotensin I.

Angiotensin I has mild vasoconstrictor properties but not enough to cause significant functional changes in circulatory function. The renin persists in the blood for 30 minutes to an hour and continues to cause formation of angiotensin I during this entire time.
Within a few seconds after formation of the angiotensin I, two additional a.a.'s are split from it to form the 8 a.a.'s peptide angiotensin II. This conversion occurs almost entirely during the few seconds while the blood flows through the small vessels of the lungs, catalysed by the enzyme ACE that is present in the endothelium of the lung vessels.

Angiotensin II is an extremely powerful vasoconstrictor and it has other effects as well that affect the circulation. It persists in the blood only for 1 or 2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinase.

During its persistence in the blood, angiotensin II has two principal effects that can elevate arterial pressure.

1. The first of these, vasoconstriction, which occurs rapidly. Vasoconstriction occurs intensely in the arterioles and to considerably less extent in the veins. Constriction of arterioles increases the peripheral resistance, thereby raising the arterial pressure, as demonstrated in the Figure 1.1. Also, the mild constriction of the veins promotes increased venous returns of blood to the heart, thereby helping the heart pump against the increasing pressure.

2. The second principle means by which angiotensin increases the arterial pressure is to act on the kidneys to decrease the excretion of both salt and water. This slowly increases the extracellular fluid volume, which then increases the arterial pressure over a period of hours and days. This long term effect, acting through the extracellular fluid volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in eventually returning the arterial pressure back to normal.

Angiotensin II has also been called as the ultimate villain in the story of the Renin-Angiotensin System.\(^2\)
The Renin-Angiotensin Aldosterone System (RAAS)

The circulating renin-angiotensin aldosterone systems plays an important role in blood pressure regulation as well as in fluid and electrolytes balance. It has important implications in the development of renal hypertension and may be involved in the pathogenesis of essential hypertension. Its contribution to cardiovascular homeostasis has been well documented in studies that employ pharmacological or immunological inhibitors. Blockade of the renins-angiotensin systems using peptide inhibitors or specific antibodies to renin, angiotensin converting enzyme (ACE) inhibitors, or angiotensin antagonists results in acute hypotensive responses in sodium depleted animals or humans. In conditions associated with elevated plasma angiotensin II levels, such as experimental or clinical renovascular hypertension and congestive heart failure, these agents also bring about marked depressor response. In all studies, the magnitude of acute depressor response can be predicted by the pretreatment plasma renin-angiotensin activity, indicating a causal relationship. In experimental as well as clinical studies, chronic administration of renin-angiotensin inhibitors has proven efficacious in lowering blood pressure in hypertension and in ameliorating edema formation in heart failure. As a result, specific inhibition of the renin-angiotensin system have become an important strategy in cardiovascular drug development. As drug development technology becomes more sophisticated, novel pharmacological agents with unique properties become available for experimental and clinical trials.1,16

A frequent outcome of these trials is an improved understanding of the biology and pharmacology of the particular system under study.

In the earlier studies and experiments in the last few decades, it has been stated and proved that, acute inhibition of this system have provided the evidence that the RAS is important in acute blood pressure
regulation, in sodium depletion, anaesthetic and in haemorrhagic conditions and as well as in the initiation of renovascular hypertension and in the development of the syndrome of congestive heart failure. Thus the role of the renin-angiotensin-aldosterone systems at the cardiac, vascular and renal levels is mediated by the production or activation of several growth factors and vasoactive substances, inducing further vasoconstriction and stimulating cellular hypertrophy.

**Mechanisms of the Direct Renal Effects of Angiotensin to Cause Renal Retention of Salt and Water**

Angiotensin has several intrarenal effects that make the kidneys to retain salt and water. Probably the most important is to constrict the renal blood vessels, thereby diminishing blood flow through the kidneys. As a result, less fluid filters through the glomeruli into the tubules. Also the slow flow of blood in the peritubular capillaries reduces their pressure, which allows rapid osmotic reabsorption of fluid from the tubules. Thus for both of those reasons, less urine is excreted. In addition, angiotensin has a moderate effect on the tubular cells themselves to increase tubular reabsorption of sodium and water. The total result of all these effects is significant, sometimes decreasing urine output fourfold to six-fold.\(^3,17\)

It is apparent then, that an insult to the kidney will activate both vasoconstrictor (angiotensin II) and vasodilator (prostaglandin) systems. Angiotensin II will act to increase systemic vascular resistance, reduce salt and water excretion and reduce renal blood flow whilst vasodilatory prostaglandins induce the opposite i.e. reduced systemic vascular resistance, natreuresis and increased renal blood flow. However, the different sites of actions of the two agents on the glomerular arterioles results in a synergistic action to increase and maintain the glomerular filtration rate. Figure 1.2 shows the renal insult and positive feedback of the interaction.\(^17\)
Angiotensin II induced vasoconstriction actually augments PGE$_2$ and PGI$_2$ synthesis which counteracts the actions of angiotensin II. In essence prostaglandins support renal blood flow in the face of activation of vasoconstriction mechanisms.

![Diagram showing the interaction between Renal Insult, Prostaglandins, Angiotensin II, and their effects on renal blood flow, salt and water excretion, vascular resistance, and positive feedback mechanisms.]

**Figure 1.2: Synergistic Effects**

The interaction of angiotensin II and prostaglandins (Sturrock et al.)$^{17}$
ACE-Inhibitors

ACE inhibitors are increasingly recognised as effective anti-hypertensive drugs regardless of age, sex or plasma renin activity. They had been used widely and successfully to treat hypertension and congestive heart failure for many years. As the renin-angiotensin aldosterone system has a pivotal role in the regulations of volume homeostasis and blood pressure, converting enzyme inhibitors were developed to interrupt this system and thereby lowers blood pressure. However their mechanism of action are more complex than simple inhibitors of the conversion of angiotensin I to angiotensin II in the circulation.\(^{18,19}\)

More than 16 ACE inhibitory drugs are discovered at present out of which 6 to 8 drugs are commonly used in practice. The ACE inhibitory drugs have common word ‘pril’ at the end of the drug name. They are currently marketed as dipeptide or amino acid derivatives that differ mainly in the chemical nature of their Zinc binding ligand. ACE inhibitors are effective drugs in the treatment of several forms of hypertension with minimal influence on the quality of life. They lower the systemic vascular resistance without causing a reflex increase in heart rate and cardiac output.\(^{19,20,21}\)

ACE inhibitors delay disease progression and reduces mortality and serious morbidity in patients with heart failure associated with Left Ventricular Dystrophy (LVD). Due to this peculiarity, ACE inhibitors had gained increasing acceptance for the treatment of essential hypertension either as monotherapy or with concomitant diuretics. Decrease in blood pressure by 10% or more was seen in 88% of hypertensive patients.\(^{22,23}\)
Mechanism of Inhibition

A review of the literature from January 1983 to August 1987 (with use of MEDLARS) revealed more than 1200 reports on 16 other such inhibitors, that all the converting enzyme inhibitors reviewed have a common 2-methylpropanolol-2-proline moiety, a group of critical importance in blocking the acute site of the ACE. Some of the ACE inhibitors differs in two major ways.\textsuperscript{19}

1. The nature of the molecule's adherence to the active site on the enzyme and
2. The form in which the agent is administered i.e. as prodrug or as an active compound.

Interaction between drugs and enzymes is in many respects similar to that measure between drug and receptor. Drugs may alter enzyme activity because they resemble a natural substrate and hence complete with it for the enzyme inhibition. For example Enalapril is effective in hypertension because it is structurally similar to that part of angiotensin I which is attacked by ACE, by occupying the active site of the enzyme and so inhibiting its action, which prevents the formation of the pressor angiotensin II.\textsuperscript{10,19,24}

This enzyme blockade may cause bradykinins accumulation, which also plays important role in vasodilatation. The depressor responses are due to blockade of angiotensin II formation, the results indicate that, irrespective of sodium balance, measurements of plasma activity reflects its contribution to blood pressure maintenance.

Thus the available evidence favours the view that a major action of the ACE inhibitor is to block angiotensin II formation and thereby to lower blood pressure in hypertensive subjects.\textsuperscript{19,24}

In 1982, Vidt and Colleagues reviewed the pharmacokinetics, mechanism of action and therapeutic usefulness of Captopril, the first of a new class of antihypertensives, converting enzyme inhibitor.
The antihypertensives effect of ACE inhibitors have a useful vasodilator (reduction of peripheral resistance) and diuretics sparing (but not as a diuretic substitute) action in all grades of hypertension and heart failure. Their reduction of mortality in this condition, due possible to their being the only vasodilator, which does not reflexly activate the sympathetic system, has made the ACE inhibitors more critical to the treatment.\textsuperscript{19}

\textbf{Effect of ACE-Inhibitor}

The antihypertensive effect of ACE inhibitors results primarily from vasodilatation (reduction of peripheral resistance) with little change in output or rate of renal blood flow is increased (desirable), a fall in aldosterone production may also contribute.\textsuperscript{7}

Their, reverse the vascular remodelling and cardiac hypertrophy of hypertension and postpone the causative events such as stroke, congestive heart failure, renal failure, etc. and there is increasing evidence that these effects of ACE inhibitors are greater than to be expected from blood pressure reduction alone. Thus ACE inhibitors are particularly efficacious when the raised blood pressure results from excess renin production. The effect is immediate and there may be an initial brisk, even serious, drop in blood pressure (at first dose effect) so that therapy is best initiated at bed time and the patient is warned.\textsuperscript{10}

As the ACE inhibitors are diuretic sparing drugs, patients already taking a diuretic should omit this for a few days, before the first dose. The antihypertensive effect increases progressively over weeks with continued administration (as with other antihypertensives) and the dose may be increased at intervals of two weeks.
Angiotensins Converting Enzyme - Inhibitors (ACE-Inhibitors)

Enalapril

The Enalapril is one of the ACE inhibitor employed in the present study purpose. It is a monoester monoacid prodrug and long acting agent (t½ 35 hours) and is only active after conversion in the liver to the active metabolite Enalaprilat (t½ 10 hours). Some enzyme inhibition is still present at 24 hours and it may usually be given once a day.10,25

Mechanism of Action

All the ACE inhibitors reviewed by, have a common 2-methyl propanolol-2-proline moiety, a group of critical importance in blocking the active site of the ACE. They are esters of the active compound deesterified in the liver. The active metabolite of Enalapril peaks at 4 hourly. As the duration of drug action is more small, doses of Enalapril 2.5 to 5.0 mgs/day have the effects which persists for more than 12 hours.10

Absorption and Elimination

Food increases the rate of absorption. It is taken in an inactive form, absorbed through the food and gets active in the liver. Its elimination from the body is more slowly compared with Captopril. The primary route of elimination of these drugs is the kidney.6,10,18,25

Inhibitory Action

Interaction between drug and enzyme is in many respects similar to that measure between drug and receptor. Drugs may alter enzyme activity because it resembles a natural substrate and hence compete with it for the enzyme.

In this regard Enalapril is effective in hypertension because it is structurally similar to that part of angiotensinI which is attacked by
ACE, by occupying the active site of the enzyme and so inhibiting its action. It prevents the formation of the pressor angiotensin II. \(^{10,19}\)

**Adverse Effects**

Includes persistent dry cough, angioneurotic edema, which may be severe, other body rashes, loss of taste which may recover during the therapy. Stomatosis such as apthous ulcers may arise. Abdominal pain, neutropenia, liver injury, raised potassium is found. Deterioration of renal function and proteinuria takes place. Alertness is increased. Depression is found.\(^{16}\)

**Captopril**

It is also one of the ACE inhibitor employed for our study purpose. It is also widely used as an antihypertensive drug. It is already found in active forms. The active forms of this drugs reach a peak level in the plasma in one hour after ingestion. It binds to the enzyme by means of sulfhydryl group. As the elimination of this drug is more rapid, it accounts for the brief duration of action (<6 hours) of the lowest dose of Captopril (6.25 mgs). As the duration of drug action is dose dependent, larger doses of Captopril (e.g. 75 mg) have effects that persist for 12 hours.\(^{10}\)

Despite, the rather short \(\frac{1}{2}\) life of this antihypertensive agent, twice daily administration appears sufficient to keep blood pressure under control throughout the day.\(^ {19,27}\)

**Mechanism of Action**

This orally effective ACE inhibitors is D-3-mercapto-2-methylpropanoyl-2-proline. It is generally assumed that the mechanism by which Captopril reduces blood pressure is closely related to its blocking effect on angiotensin II generation by inhibiting ACE.\(^ {27}\)
Absorption and Elimination

Food reduces the absorption of Captopril by 30%. That's why it is recommended to take one hour before the meals. Because food interferes with its absorption. The primary route of elimination of these drugs in the kidney and is eliminated from the body more rapidly than any other ACE inhibitor.\textsuperscript{6,10,19}

Inhibitory Action

All the pharmacological effects of Captopril are attributable to its single known action viz. inhibition of conversion of angiotensin I to angiotensin II. It thus prevents two principal effects (i.e. the pressor effect and the stimulation of aldosterone synthesis and secretion by the adrenal cortex) of endogenous as well as intravenously injected angiotensin I. As a consequence of inhibition of angiotensin II synthesis, the plasma levels of renin and angiotensin I show a marked compensatory rise.

In healthy, sodium replete animals and humans, a single oral dose of Captopril lowers the systemic blood pressure only slightly, the effect is more marked on repeated administration. By contrast, a single dose of captorpril causes substantial lowering of blood pressure in salt depleted subjects.

In hypertensive subjects, Captopril lowers systemic arterial resistance and the mean Systolic and Diastolic Blood Pressure respectively. Although the initial reduction in blood pressure correlates well with the pre-treatment renin-angiotensin status of the subjects, the sustained lowering during chronic administration shows little or no such correlation. There occur dilatation and increase in blood flow in the renal, cerebral and coronary beds. In addition, Captopril increases the compliance of large arteries and thus contribution to the reduction of
SBP. Baroreceptor function and cardiovascular reflexes are not compromised and responses to posture and exercise are not impaired. The heart rate increases but little. The antihypertensive effects are seen in all varieties of hypertension (except that due to primary aldosteronism) but are most marked in patients with renovascular hypertension. They are potentiated by the concurrent use of diuretic.

In patients with chronic, congestive heart failure, Captopril produces several beneficial effects. As a result of decreased peripheral arterial resistance, the after load is reduced, the cardiac output increases, the heart rate diminishes, systemic blood pressure falls initially but tends to return to pre-treatment levels.\textsuperscript{7,10}

\textbf{Adverse Effects}

Most of them are the result of the specific inhibition of ACE. A steep fall in blood pressure may occur after the first dose in subjects with severe hypertension who are on multidrug regimes including a diuretic, in patient with congestive heart failure treated vigorously with diuretics and generally in all salt depleted patients. In such patients, Captopril should be started in very small doses, preferably after stopping the diuretic. Serious hyperkalemia is uncommon. However, the concurrent use of a potassium sparing diuretic should be avoided.

Captopril is generally well tolerated. The adverse effects are skin rashes, loss of the sense of taste, vitilige, headache and gastrointestinal disturbances. Neutropenia is a serious but rare effect. Proteinuria has been described ( > 1.0 gm/day).\textsuperscript{6,7,10}

\textbf{The Non-ACE-Inhibitory Drugs (i.e. the Vasodilators)}

Amongst the non-ACE inhibitory drugs, we had chosen the well known and are commonly prescribed, effective anti-hypertensive
vasodilators. Advised by the ‘physician’ during the initial stages of hypertension treatment. The drugs are Amlodipine and Atenolol.

**Amlodipine (the calcium antagonist)**

Since this introduction in the 1970s, calcium antagonists have assumed an important role in the treatment of hypertension and ischaemic heart disease. The vasoactive drug that reduce the smooth muscle tone in the large arteries actively increase arterial compliance. This effect has been demonstrated for calcium antagonists.

Calcium channel antagonists reduce the calcium dependent vascular smooth muscle tone by direct interference with transmembrane calcium supply and thereby counteract every kind of contractile tension development in the vascular wall.\(^ {28} \)

Amlodipine is a recently developed dihydropyridine calcium antagonist which is structurally related to nifedipine and which has preferential activity on vascular smooth muscle compared with the myocardium. Unlike its predecessors, Amlodipine has high bioavailability (60-65%). Previous studies have shown amlodipine to be an effective antihypertensive agent in patients with placebo and also when compared with Atenolol, hydrochlorothiazide and Verapamil.\(^ {28,29} \)

**Mechanism of Action**

Calcium is involved in the initiation of smooth muscle and cardiac cell contraction and in the propagation of the cardiac impulse.

The contraction of smooth muscle cells requires an influx of calcium across the cell membrane. This occurs through ion channels that are largely specific for calcium and are called ‘slow calcium channels’ to distinguish them from ‘fast channels’, that allow the rapid influx and efflux of sodium.\(^ {9,10} \)
Activation of calcium channels by an action potential allows calcium to enter the cells. There follows a sequence of events, which results in activation of the contractile protein, myosin and actin, without shortening of the myofibril and contraction of smooth muscle. During relaxation calcium is released from the myofibril and, as it cannot be stored in the cell, it passes out through the channel.

The calcium channel blockers inhibit the passage of calcium through the voltage gated L (for ‘large’) type membrane channels of smooth and cardiac muscle, reduce available intracellular calcium and cause the muscle to relax.  

Absorption and Elimination

The absorption of Amlodipine is relatively slow. It takes relatively 6-12 hours to reach the peak plasma concentration.

Elimination also takes place very slowly i.e. about 35-50 hours. Thus, the advantage of this drug is due to slow absorption and elimination, the effect last for 24 hours blood pressure control.

Adverse Effects

Calcium antagonists are safe and effective in lowering blood pressure. The side effects include tachycardia (increase in heart rate), headache and flushing and ankle edema and constipation.

Atenolol (the β-Adrenoceptor Blocker)

Atenolol, is the second type of non-ACE inhibitory antihypertensive drug, which was chosen for the present study.

Adrenergic blocking agents are classified into two groups viz. Alpha and Beta adrenergic blocking agents. These agents prevent the response of effector organs to endogenous as well as exogenous adrenaline and noradrenaline. These drugs either block alpha or beta
adrenergic receptor. The alpha adrenergic blocking agents are relatively little value in the treatment of essential hypertension.

The term adrenoceptor or adrenergic is applied to identify motor nerves by their transmitter substance, thus the cholinergic, when the impulse is transmitted by acetylcholine and adrenergic when the impulse is transmitted by adrenaline, noradrenaline or a drug capable with comparable action.

Atenolol is safe, cheap and effective drug. It is widely used in subjects of all ages with hypertension of all degrees of seventy. It has been a part of the treatment regimen in many of the major studies that have demonstrated reduction in morbidity and mortality attributable to lowering blood pressure. Atenolol is a cardio selective β-adreceptor blocker, partially metabolised in the liver. Its plasma half life is 6-8 hours. It is a longer acting drug compared with other β-adrenergic drugs. Therefore it can be used on once a day basis. The onset of antihypertensive effect is dose-related but generally takes 5-7 days to become manifest.

The β-adrenoceptor blockers have the common word ‘lol’ at the end of the drug name.1,9,10

**Mechanism of Action**

These class of drugs are structurally related to isopropylarterenol. They selectively and competitive block the actions of catecholamines mediated through β-receptor stimulation. Thus the β-receptor stimulation. Thus the β-receptor stimulating actions of adrenaline and isoproterenol are blocked. At the cellular level, the drugs inhibit the activity of the membrane enzyme adenylcyclase and thus decrease the production of C-AMP. This is the common property of all the compounds of β-adrenergic blocking agents.6,10
Absorption and Elimination

The effective oral dose ranges of various β-blocking drugs are wide. Plasma concentration vary markedly between individuals seeking the same dose. This is because although most of this compounds are completely and rapidly absorbed orally, are metabolised by the liver. Because of such hepatic metabolism a part of oral dose fails to reach the peripheral circulation.

Atenolol is chiefly eliminated by the kidneys and partially through the faeces.\textsuperscript{7,10}

Adverse Effects

The adverse effects include constipation, nausea, vomiting, bronchospasm etc. These drugs prevent the correction of hypoglycaemia by the adrenergic body mechanisms and aggravate neuroglycopenic symptoms of hypoglycaemia. Cold extremities are found. Muscle cramps, lethargy and rarely mental depression and hallucinations is found on prolong usage.\textsuperscript{6,7,10}

Definition and Classification of Hypertension

Operational definition of hypertension:

Definition of hypertension is difficult and, by necessity arbitrary. Sir George Pickering first formulated the concept that blood pressure in a population is distributed continuously as a bell-shaped curve with no real separation between ‘normotension’ and ‘hypertension’. There is also a direct relation between cardiovascular risk and blood pressure; the higher the blood pressure, the higher the risk of both stroke and coronary events.

As a consequence the dividing line between ‘normotension’ and ‘hypertension’ can be defined only in an operation way.
Evans & Rose defined it as that level of blood pressure at which
detection and treatment do more good than harm. This level can be
determined only by intervention trials demonstrating benefits from
blood pressure reduction.¹⁶⁹

**Definition of Hypertension based on:**
**Diastolic and/or Systolic Blood Pressure**

High DBP has commonly been used to define hypertension. This
arbitrary choice was based on the fact that DBP was used as the criterion
for inclusion in most randomised therapeutic trials, including those on
mild hypertension. There is however, mounting evidence that systolic
values should be taken into account in defining, as well as managing,
hypertension. Indeed, cardiovascular risk is as strongly associated with
systolic as with diastolic values, with no evidence of a threshold below
which a decrease in systolic pressure does not reduce risk. Furthermore,
some of the intervention trials on mild hypertension indicate that
cardiiovascular events more closely correlated with systolic than with
diastolic values achieved by treatment.¹

Hypertension should be defined using both diastolic and systolic
blood pressures. Patients whose reading values of DBP remain
persistently at or above 90 mm Hg after repeated measurements are at
increased risk of cardiovascular morbidity and mortality, and lowering
of DBP values of between 90 and 105 mm Hg has been clearly shown to
reduce the risk of stroke by 35 – 40 % and of coronary event by about
15 – 20 % from epidemiological data on incidence of strokes and
coronary events, the range of SBP's corresponding to diastolic values of
90 – 105 mm Hg and intervention trails have shown treatment benefits
when SBP values of, or greater than, 160 mm Hg are lowered.

The current definition of hypertension is a level of SBP of 140
mm Hg or above, or a level of DBP of 90 mm Hg or above. However, as
blood pressure is quite variable, before labelling a patient as hypertensive and deciding to initiate treatment, it is necessary to confirm raised levels of blood pressure by repeated measurements should be extended over 3-6 months shorter observation periods are required in patient with more marked elevation of blood pressure or in those with complications.

In the year 1993, the Joint National Committee, on detection, evaluation and treatment of high blood pressure has provided classification of blood pressure in adults age 18 years or older.6,9

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 130</td>
<td>&lt; 85</td>
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<tr>
<td>High Normal Hypertension</td>
<td>&lt; 130 - 139</td>
<td>&lt; 85 - 89</td>
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<tr>
<td>Stage-1 (mild)</td>
<td>&lt; 140 - 159</td>
<td>&lt; 90 - 99</td>
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<tr>
<td>Stage-2 (moderate)</td>
<td>&lt; 160 - 179</td>
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<tr>
<td>Stage-3 (severe)</td>
<td>&lt; 180 - 209</td>
<td>&lt; 110 - 119</td>
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<tr>
<td>Stage-4 (very severe)</td>
<td>&lt; 210</td>
<td>&lt; 120</td>
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</table>

**Classification of Hypertension by Extent of Organ Damage**

**Stage-I**  
- No manifestation of organ involvement

**Stage-II**  
- At least one of the following manifestations of organ involvement e.g. left ventricular hypertrophy (detected by radiogram, ECG, echo-cardiogram).
  - Generalised 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 (in the aorta or carotid, iliac or femoral arteries).

**Stage-III**  
- 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 (TIA)
Hypertensive encephalopathy
Vascular dementia

Optic fundi:
Retinal haemorrhages and exudates with or without papilloedema

Kidney:
Renal failure
Plasma creatinine concentration > 2.0 mg/dl

Vessel:
Dissenting aneurysm
Symptomatic arterial occlusive disease

*Courtesy: I.*

**Effects of Hypertension**

Persistently elevated blood pressure imposes an increased workload on the heart, which results in left ventricular hypertrophy, dilatation and eventual failure of the left ventricle.

Chronic hypertension also induces changes in the arterial wall predisposing to coronary heart disease, stroke, renal diseases and peripheral arterial occlusion. Moderate to severe elevation of arterial pressure also produce target organ damage in retinae and kidneys.

Hypertension play a critical and independent role in atherogenesis, but its impact is greatly influenced by co-existent contributors to the occurrence of atherosclerosis, particularly the blood lipids.

Even moderate elevation of the arterial pressure leads to shortened life expectancy, at high pressures - mean arterial pressure 50% or more above normal - a person can expect to live no more than a few more years.\(^1,3,6\)
The lethal effects of hypertension are caused mainly in three ways:

1. Excess work load on the heart leads to early development of congestive heart disease, coronary heart disease or both, often causing death as a result of a heart attack.

2. The high pressure frequently ruptures a major portion of the brain, this is a cerebral infarct. Clinically it is called a 'stroke'. Depending on what part of the brain is involved, a stroke can cause paralysis, dementia, blindness or multiple other serious brain disorders.

3. High pressure almost always causes multiple haemorrhages in the kidneys, producing many areas of renal destruction and eventually, kidney failure, uremia and death.

**Prevalence of Hypertension**

Approximately 25% of the adult population in Europe and North America have hypertension as defined by the WHO (World Health Organisation) criteria, of a SBP of 160 mm Hg or more and DBP of 95 mm Hg or more. In many people a lower pressure is found on rechecking and it is important not to base clinical decision on a single raised blood pressure reading.

Simple non-pharmacological method, which may be of value in lowering blood pressure include moderation of alcohol intake, reduction of dietary Sodium intake and dietary control of obesity is present. Only if the DBP remains above 100 mm Hg (as it does in about 5 - 10% of the population) will drug treatment be needed. Such treatment can halve the incidence of stroke and also have a modest beneficial effect on coronary heart disease.
It should be stressed, however, that patients whose blood pressure’s are modestly raised on one or two occasions, but whose pressures then settle, do need careful observation. There is a trend for blood pressure to use with advancing age and patients with higher pressures sustain a faster use than those with lower pressure. Patients with ‘borderline’ hypertension should also be assessed on the basis of others cardiovascular factors as well as any family history of premature cardiovascular mortality or morbidity.\textsuperscript{1,30}

**Requirements of an Ideal Antihypertensive Drug**

1. It should produce predictable reduction in both SBP and DBP in supine as well as in erect position.
2. It should have a rapid action.
3. It should have a sufficient duration of action.
4. It should not produce tolerance on long term administration.
5. It should not reduce circulation to vital organs like brain, kidney and heart and should be free from toxic effects.
6. It should synergise with other antihypertensive agents and should be cheap.

Of all the available agents, surprisingly, the thiazide diuretics come nearest to satisfying the requirement.\textsuperscript{7}

**Measurement of Blood Pressure:**
(B.P Meter, Mercurial B.P Apparatus, B.P Apparatus)

Blood pressure, Systolic Blood Pressure and Diastolic Blood Pressure (SBP/DBP respectively) is considered as a good indicator of the status of the cardiovascular systems.

**Method - Manual**

The basic method for measurement of blood pressure which is commonly applied by the doctors, general practitioners and physicians is by the instrument well knowingly called as the Murcurial Sphygmomanometer. This method is easy to use.
The disadvantage is that it does not provide continuous recording of blood pressure variations and its practical repetition is limited to only systolic and diastolic arterial pressure reading. No indications of the pressure waveform is possible. The another disadvantage is that, though the instrument has the good quality, accuracy and reliable results in the measurement of blood pressure, but it often fails when the blood pressure is very low.

**Principle**

The blood flow is laminar normally. In case of obstruction, turbulence occurs. This creates a noise, which can be heard by human ears with the help of stethoscope. This principle is used in measurement of blood pressure.

**The Instrument**

The sphygmomanometer consists of an inflatable pressure cuff and a mercury manometer to measure the pressure in cuff. The cuff consists of a rubber bladder inside an elastic fabric covering. It can be wrapped around the upper arm of the patient and fastened either hooks or a Velcro fastener. The cuff is normally inflated manually with rubber bulb and inflated slowly through a needle valve.

**Measurement of Blood Pressure**

Measurement of blood pressure can be done by two methods—i) in sitting position and the other ii) in supine position. For both methods, the patient should be allowed to rest and keep quiet for 5 minutes. Half an hour prior, before measuring blood pressure the patient should not have smoked or chewed tobacco. The arm of the patient should be bared, supported and positioned at heart level.
To obtain blood pressure measurement, with sphygmomanometer and a stethoscope, the cuff on the upper arm is first inflated. To this point no sound can be heard through the stethoscope, which is placed over the brachial artery. The artery is collapsed by the pressure of cuff. The pressure in the cuff is then gradually reduced. As soon as cuff pressure falls below systemic pressure, small amount of blood starts flowing. The korotkoff sounds begin to be heard through the stethoscope. The pressure of the cuff i.e. indicated on the manometer when the korotkoff sound is heard and recorded as the systolic blood pressure (SBP).

As the pressure in the cuff pressure continues to drop, the korotkoff sounds continues until the cuff pressure is not longer sufficient. As long as the flow is turbulent it makes sound. The moment original pressure is established, laminar flow continues and the korotkoff sound disappears. At this point the pressure is called as the diastolic blood pressure (DBP).\textsuperscript{3,31}

<table>
<thead>
<tr>
<th>Age (Yrs.)</th>
<th>Male (SBP (mm Hg))</th>
<th>Female (SBP (mm Hg))</th>
<th>Male (DBP (mm Hg))</th>
<th>Female (DBP (mm Hg))</th>
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**Hypertension**

The World Health Organisation has been concerned with hypertension since the 1950’s. The Expert Committee on cardiovascular diseases and hypertension, convened in October 1958 in Geneva, gave special consideration to the classification and criteria for the diagnosis
of hypertension. Also, a subsequent Expert Committee met in Geneva in October 1961. It described the stages of hypertension but its recommendation were limited to therapeutic remedies directed against the progressive effect of diseases (secondary prevention). A third Expert Committee met in Geneva in March 1978 and dealt with the epidemiology, prevention and control of hypertension. The present Expert Committee met to review the epidemiology of hypertension in order to increase awareness particularly in developing countries, to analyse the experience gained by community control programmes and to discuss options for prevention and management strategies.¹

The main aims of this report are to establish the control of hypertension as part of programmes to reduce total cardiovascular risk, to focus attention of the population approach to primary prevention of hypertension and to summarise appropriate clinical approaches and management options for the hypertensive patient. The report also emphasises the importance of systolic blood pressure in defining and managing high blood pressure and extends recommendation for the control of hypertension to the elderly.⁹

Most epidemiological data support the suggestion that any definition of hypertension is an arbitrary one and hence prevalence of hypertension is comparably arbitrary.

The physiology of blood pressure regulation has been well understood for many years but it is not clear whether we are the wiser about the causes of essential hypertension. So, we have the frustrating paradox that hypertension is probably the most studied but least understood of the so called human disorders.

Despite wide dissemination of the results of the recent studies of hypertension in the elderly, the detection and treatment of elderly hypertension appears to be poor.
By considering the importance of the formation of the causative octapeptide product by ACE in hypertensive and normotensive subjects, the present study was undertaken and planned to evaluate the biochemical correlation of the levels of serum angiotensin converting enzyme against blood pressure levels along with other parameters in the early detected but untreated, and early detected, untreated but were complicated. Initially the complications were related with kidney, retina and heart. Also the study was carried in known cases of hypertension and were diseased subjects. The study is as follows:

1. The study was made in mild, moderate to severe hypertensive subjects of various age group.

2. The study deals with the efficacy and effect of different types of antihypertensive drugs in the newly detected and untreated subjects.

Hypertension and its related disorders are commonly met in clinical practice. Physicians have been trying to analyse the clinical features of hypertension and the related disorders caused by the rise in blood pressure (SBP/DBP) for a long time. Early workers tried to correlate clinical features with the cause of disorder.  

The present study was carried out with the intention of correlating biochemical abnormalities in hypertension and its effect. Further, the correlation was made in the related disorders with clinical features.

Two commonly used ACE inhibitors were chosen to study the effect of inhibition against blood pressure levels and if there was any fall in SACE levels. Similarly, non-ACE inhibitory drugs group was also studied. The study was carried out in the same selected subjects before and after treatment. To evaluate effects of the drugs, four different monotherapy groups were designed i.e. one Tablet/day for 30 consecutive days, blood pressure was noted before and after treatment.
Such type of well classified group study, with sufficient number of subjects (Test as well as Control) with four different types of monotherapy drugs were not studied earlier. Also, the relationship and compliance of drugs against blood pressure and SACE units study was not reported earlier in this manner. Effect of drug on blood pressure, in hypertension and estimation of SACE before and after was the main part of our study. Along with this the relative parameters were estimated, which are already well known for influencing the overall risk profile of the hypertensive patients. The above study was made, as these were the primary stages of the patients entering into the secondary stages, i.e. the effects of chronic hypertension with left untreated leading into severe rise in blood pressure which leads to organ damage.

By taking into consideration the above facts, the study was also made in hypertensive subjects, suffering from acute duration, who were not treated, first time admitted in wards and had suffered from organ damage initially, such as acute renal failure-ARF (kidney), acute myocardial infarction-AMI (heart) and retinopathy (retina). This group study was labelled as complicated group study.

In this group study also recording of blood pressure, estimation of SACE and other parameters had given valuable results. Such type of group study was not made earlier with adequate number of subjects, indoor patients who are admitted in the wards and discharged after recovery i.e. after seven days of antihypertensive treatment. In the first two classified group study, to rule out biochemically, blood urea and serum creatinine was estimated in acute renal failure and CPK-MB in acute myocardial infarction. Similar protocol was carried in the retinopathy group. The subjects were selected from OPD on fundus examination.
The above group study indicates the possibility of a significant pathogenetic activity of angiotensin converting enzyme and the causative product angiotensin II.

For both the above study groups (drug effect and organ damage) the results of before treatment values of blood pressure levels and various biochemical parameters were considered as a baseline value for drug intervention study (after treatment) for comparison.

The last group study was made in the known cases of chronic hypertensive subjects and as well as in chronic hypertensive subjects with DM (NIDDM). Comparison of physical and biochemical parameters values were made with control and with both the study groups. Again such type of group study was not made earlier. The effect of long term action of antihypertensive drugs on the blood pressure levels, SACE activity and other related parameter was studied. The high levels of SACE activity was observed in hypertensive with DM. The higher level of SACE activity suggests an increase activity of the renin-angiotensin aldosterone system in this subjects, which were not observed earlier.

Aims and Objectives

The present study was carried on the blood sample of the normotensive and hypertensive subjects. Measurement of blood pressure (SBP/DBP) and biochemical analysis were made before and after antihypertensive treatment. The estimation of the following parameters were done.

1. Fasting Plasma Glucose
2. Blood Urea
3. Serum Creatinine
4. Serum Electrolytes (Sodium and Potassium levels)
5. Serum Angiotensin Converting Enzyme (SACE) and
6. Lipid-Profile
   - Serum Total Cholesterol
   - Serum Triglycerides
   - Serum HDL-C
   - Serum LDL-C and
   - Serum VLDL-C

The study was carried out in the following hypertensive group subjects. The classification of study group was made as follows:

1. Newly detected and untreated hypertensive subjects. (Effect of different antihypertensive monotherapy drugs consists of four groups.)
2. Newly detected, untreated and were with initially organ damage. Consists of three groups, before and after treatment.
3. Old known cases of hypertension with diabetes mellitus (NIDDM), who were already taking antihypertensive treatment.
4. Old known cases of hypertension, who were already taking antihypertensive treatment and

   The present study was undertaken with the following aims:

1. To study the blood pressure levels before and after treatment with effect of various antihypertensive drugs (drug intervention).
2. To assess whether treatment of hypertension with four different classes of antihypertensive drugs would affect plasma ACE levels, blood pressure and other metabolic parameters.
3. Whether it helps to detect evidence of target organ damage for e.g. renal impairment, acute myocardial infarction, retinopathy etc.
4. To study the several aspects of hypertension related organ damage require better understanding.
5. To study whether SACE levels can help for early diagnosis.
6. To study and compare the SACE levels against blood pressure in different classified group study.
7. To find out the significance of various parameters in relation to severity of hypertension.

8. To find out whether the study has prognostic significance.

9. To study the saturated effect of drugs on blood pressure and ACE-levels in known cases of hypertension and in diseased cases.

10. The other reason for investigation is to detect elevation of serum cholesterol concentration, a low HDL-C levels, as these condition substantially increase the risk of death for a given level of blood pressure and also influence the choice of antihypertensive drugs.

11. To provide the basis for the appropriate public health intervention, prevalence of hypertension and the levels of risk factors leading to high blood pressure.

12. To find out whether other parameters are interrelated with each other regarding during the progress of the disease and its significance in relation to the severity of hypertension.

The history of hypertension and its severity dates from the time of Hippocrates. Since many centuries, physicians have been trying to analyse the hypertension symptoms but its severity towards organ damage, its morbidity and mortality.

Thus, the studies on proteolytic release of octapeptide from angiotensinogen is well established, as a major aid in the diagnosis and treatment in the newly detected and untreated, organ damaged, in the chronic and diseased (DM with NIDDM) hypertensive subjects. It also serves as an important avenue for research in the physiological, biochemical and metabolic aspects of hypertension and its related disorders.