CHAPTER II

REVIEW OF LITERATURE

1. Hypertension

Hypertension is the most prevalent condition for which people receive prescription medications. Its occurrence in the United States increases with age, and it is more prevalent in African Americans and in the lesser educated and lower socioeconomic classes[20].

Blood pressure is a continuous variable, it is impossible to define a cutoff point below which the blood pressure is normal and above which the pressure is abnormally high. After screening, the diagnosis of hypertension is confirmed when the average of two or more diastolic blood pressure (DBP) measurements visits are 90 mmHg or higher or the average of two or more systolic blood pressure measurements (SBP) is consistently greater than 140 mmHg[21]. Single, casual measurements of blood pressure may inaccurately classify individuals as having hypertension and cause unnecessary emotional, social and financial problems[20].

1.1 Prevalence of hypertension[21,23]

The Centers for Diseases Control and Prevention, National Center for Health Statistics, provided that an estimated 50 million Americans have high blood pressure (≥ 140/90 mmHg). Blood pressure increases with age, but the onset of hypertension most often occurs during the third, fourth, and fifth decades of life. The prevalence of hypertension increases with age, is greater among blacks than whites, and is greater in less educated people. Men and women of the same race are affected

approximately equally. Data from the 1976 to 1980 and 1988 to 1991 of National Health and Nutrition Examination Survey (NHANES II & III) indicated that the prevalence of hypertension decreased from approximately 58 million to around 50 million. The NHANES III reported that 35% of Americans with hypertension were unaware and only 53% of those with hypertension were receiving antihypertensive therapy, and only 24% of those with hypertension had their blood pressure controlled to less than 140/90 mmHg.

1.2 Etiology of hypertension[23]

Hypertension is a heterogeneous disorder that may result from either a specific cause (secondary hypertension) or some underlying pathophysiologic mechanism stemming from an unknown etiology (primary or essential hypertension). Fewer than 5% of people who suffer from high blood pressure have secondary hypertension. In most of these, chronic renal disease or renovascular disease is the cause of hypertension. Other conditions that are known to cause of hypertension include pheochromocytoma, Cushing's syndrome, primary aldosteronism, and coarctation of the aorta. In some instances, exposure to various exogenous substances may produce hypertension. The most notable of these are estrogens, glucocorticoids, licorice, sympathomimetic amines, nonsteroidal anti-imflammatory agents, chronic alcohol use and tyramine-containing foods in combination with monoamine oxidase (MAO) inhibitors.

The pathogenesis of essential hypertension remains mysterious, a specific cause of sustained hypertension cannot be found. It is likely that several interrelated mechanisms rather than a single causative defect, control blood pressure in essential hypertension. The fact that hypertension often runs in families suggests that genetic factors may play an important pathogenic role in the development of essential

hypertension. There is even some evidence that single genes might be responsible for specific subtypes of hypertension. These include genetic traits for high sodium-lithium countertransport, a low urinary kalikrein excretion, increased aldosterone and other adrenal steroids, and high angiotensinogen levels. However, even with continued insights into the regulation of blood pressure, essential hypertension remains a process that must be controlled rather than a curable disorder.

1.3 Pathophysiology[23]

Multiple factors may contribute to the development of primary hypertension including abnormal neural mechanisms; defects in peripheral autoregulation; disturbances in sodium, calcium, and natriuretic hormone; and malfunctions in either humoral or vasodepressor mechanisms.

1.3.1 The neural mechanism[21-23]

Both the central (CNS) and the autonomic nervous systems are intricately involved in the maintenance of arterial blood pressure. Stimulation of certain areas within the CNS (nucleus tractus solitarius, vagal nuclei, vasomotor center, and the area postrema) can result in either an increase or a decrease in blood pressure. For example, α – adrenergic stimulation within the CNS decreases blood pressure through an inhibitory effect on the vasomotor center. Increased angiotensin; on the other hand, increases sympathetic outflow from the vasomotor center, which eventuates in an increase in blood pressure. Located on the presynaptic surface of sympathetic terminals are a variety of receptors that either enhance or inhibit norepinephrine release. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine-containing vesicles located near the neuronal ending. Stimulation of presynaptic α (α_2) receptors exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic β receptors facilitates further

release of norepinephrine. Stimulation of postsynaptic α (α_1) receptors on arterioles and venules results in vasoconstriction. There are two types of postsynaptic β receptors, β_1 and β_2. Stimulation of β_1 receptors in the heart results in an increase in heart rate and contractility. When β_2 receptors in the arterioles and venules are stimulated, vasodilation occurs. The major negative-feedback mechanism controlling sympathetic activity is the system of baroreceptor reflexes. The baroreceptors respond extremely rapidly to changes in arterial pressure. In this reflex system, an acute elevation in arterial pressure increases the rate of baroreceptor discharge, which results in vasodilation throughout the peripheral circulatory system and a decrease in heart rate and myocardial contractility. Conversely, low pressure has the opposite effect, causing reflex vasoconstriction and increase in heart rate and force of contraction. These baroreceptor reflex mechanisms may be blunted in elderly individuals.

Abnormalities in either the renal or tissue autoregulatory processes could cause hypertension. In fact, it seems reasonable to postulate that individuals may first develop a renal defect for sodium excretion and then reset their tissue autoregulatory processes to a higher arterial blood pressure. An initial defect in the renal adaptive mechanism could lead to plasma volume expansion and increase blood flow to peripheral tissues even when blood pressure is normal. To offset the increase in blood flow, local tissue autoregulatory processes would induce arteriolar constriction to raise the peripheral vascular resistance. In time, a thickening of the arteriolar walls may occur, resulting in a sustained elevation in peripheral vascular resistance. An increase in total peripheral vascular resistance is a common underlying problem in patients with primary hypertension.

1.3.2 The humoral mechanisms[21-23]

At least three possible humoral abnormalities may be responsible for causing primary hypertension in some individuals.

1.3.2.1 *The renin-angiotensin-aldosterone system (RAS)*

The RAS is important to the regulation of sodium, potassium, and fluid balance, and it significantly influences vascular tone and sympathetic nervous system activity.

In the kidney, renin is synthesized and stored in the juxtaglomerular cells, which are locate primarily in the media of the renal afferent arterioles. Several factors are known to control renin release. These can be grouped into intrarenal factors (such as perfusion pressure, catecholamines, angiotensin II) and extrarenal factors (such as sodium, chloride, and potassium). Decreased perfusion pressure leads to an increase in renin secretion. The flux of sodium and chloride across the cells influences renin release. A decrease in the amount of sodium and chloride delivered in the distal tubule stimulates renin release.

Angiotensin II has been shown to directly inhibit the release of renin through negative feedback. Catecholamines increase renin release probably by directly stimulating the juxtaglomerular cells through an action involving the formation of cyclic AMP. Both potassium and calcium may also play a direct role in renin release. Decreased serum potassium or intracellular calcium stimulates renin release by the juxtaglomerular cells.

In blood, renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II exerts its biological effects in various tissues following binding to specific receptors classified as AT1 or AT2 subtypes. The AT1

receptor is located in brain, renal myocardial, vascular, and adrenal tissue. The AT2 receptor is located in adrenal medullary tissue, and brain. AT1 receptors mediate the majority of responses critical to cardiovascular and renal function. An increase in circulating angiotensin II can cause an elevation in blood pressure through both pressor and volume effects. The pressor effects of angiotensin II include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and a centrally mediated increase in sympathetic nervous system activity. Angiotensin II also stimulates the release of aldosterone from the adrenal gland, which leads to retention of both sodium and fluid, with a resultant increase in plasma volume and blood pressure (Figure 1). Clearly, any disturbance in the RAS that leads to an increase in any or all three components could produce hypertension.

Both the heart and brain contain a local RAS. In the heart, angiotensin II is also generated by a second enzyme, angiotensin I convertase (human chymase), which is not blocked by ACE inhibition. Activation of the myocardial RAS leads to increased cardiac contractility and stimulation of cardiac hypertrophy. The brain RAS has at least two functions. Angiotensin II modulates the production and release of hypothalamic and pituitary hormones. Angiotensin II also enhances sympathetic outflow from the medulla oblongata.

Local generation of biologically active angiotensin peptides in peripheral tissues may play an important role in the increased vascular resistance often observed in hypertensive individuals. There is also some evidence that angiotensin produced by local tissue may interact with other humoral regulators and endothelium-derived growth factors to stimulate vascular smooth muscle growth and metabolism. This *in situ* generation of angiotensin peptides may, in fact, underlie the development of increased vascular resistance in forms of hypertension that are

associated with low plasma renin activity. Components of tissue RAS may be responsible for long-term adaptation to hypertension (i.e., left ventricular hypertrophy, smooth muscle hypertrophy of blood vessels, and glomerular hypertrophy).

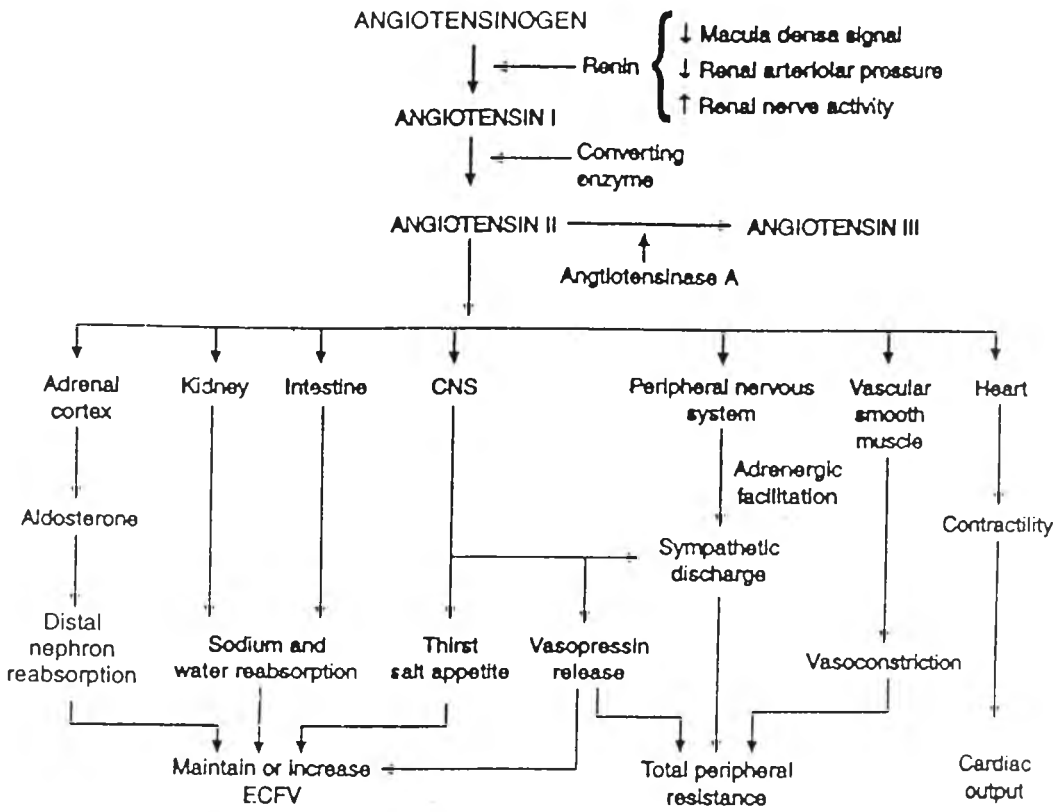


Figure 1 : Schematic representation of the renin-angiotensin system (RAS)[22]

1.3.2.2 *Natriuretic hormone*

Another humoral factor that may be involved in the development of primary hypertension is the increased concentration of natriuretic hormone. The proposed role of natriuretic hormone is to inhibit Na^+/K^+-ATPase and, thus, to interfere with sodium transport across cell membranes. It has been suggested that and inherited defect in the kidney's ability to eliminate sodium would cause an increase in extracellular fluid and plasma volume as discussed earlier. This may cause a compensatory increase in the concentration of circulating natriuretic hormone, which would increase urinary excretion of sodium and water. This same hormone, however, is also thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium would ultimately lead to increased vascular tone and hypertension.

1.3.2.3 *Insulin resistance and hyperinsulinemia*

Evidence linking insulin resistance and hyperinsulinemia to the development of hypertension is mounting. Several possibilities by which hyperinsulinemia may lead to hypertension include renal sodium retention, enhanced sympathetic nervous system activity, and induction of vascular smooth muscle hypertrophy. Another possible way by which insulin could raise blood pressure is by increasing intracellular calcium concentration, which leads to increased vascular resistance. Hyperinsulinemia often accompanies upper body obesity, but even nonobese hypertensive individuals have been shown to be insulin resistant, glucose intolerant, and hyperinsulinemic. The mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. Hyperinsulinemia is also associated with hypertriglyceridemia, which results in a decreased concentration of HDL cholesterol.

1.3.3 The vascular mechanisms

The abnormalities in the structure and function of the vasculature are increasingly recognized as contributing to the hypertensive state by increasing total peripheral resistance. During the past decade, it has become obvious that the endothelium, single cell, innermost layer of blood vessels, is more than a passive barrier between the blood and the vascular smooth muscle. We now know that endothelium plays a crucial role in circulatory homeostasis responding not only to humoral and chemical signals, but also to change in the haemodynamics of blood flow such shear stress. Endothelial cells release chemical mediators that modulate the responses of numerous cells including vascular smooth muscle, platelets, and leucocytes. The endothelium serves a dual role in the control of vascular tone, endothelial cells produce and release a variety of vasoactive substances. These include both vasodilators, such as endothelium-derived relaxing factor (EDRF) whice has now been identified as nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin, an vasoconstrictors, such as thromboxane A_2 and prostaglandin H_2, endothelin, and angiotensin II. The interaction between these vasodilators and vasoconstrictors provides a local control mechanism that regulates vascular tone. Alterations in the production of these mediators are involved in the induction and persistence of hypertension in both experimental models and humans, in addition this endothelial cell dysfunction has been reported in various forms. Plasma levels of endothelin, for example, have been reported to be significantly higher in patients with primary hypertension. In addition, both chemical-stimulated and basal release of EDRF has been shown to be severely attenuated in hypertensive patients as well as in experimental models of hypertension. Another abnormality in the biology of vascular smooth muscle cells that may account for increased vasotone

of hypertensives, is a disturbance in the physico-chemical properties of the cell membrane leading to abnormalities in ion handling. Reported abnormalities of cellular electrolyte homeostasis, for example, increased soduim influx due to elevion of sodium-hydrogen exchange activity, decreased sodium-potassium cotransport, increased lithium-sodium contertransport and decreased red cell membrane binding of calcium.

In parallel with studies on the function of vascular smooth muscle in the hypertensive state, considerable attention has been given to the importance of structure al changes. The change in the geometry of the vessel wall that result in an increased vasoconstrictor response with the same degree of shortening of vascular smooth muscle in hypertensive patients is a decrease in the lumen (internal radius of the vessel). In studies of small resistance vessels from subcutaneous tissue from hypertensive subjects, an average 29% increase in the media thickness: lumen diameter ratio was found, closely matching the 32% elevation in blood pressure. The increase in the media thickness: lumen diameter ratio can result from an increase in wall thickness either due to medial smooth muscle cell proliferation, accumulation of glycoaminoglycans, or from the increasing evident support to the role of rearrangement of a normal amount of tissue around of tissue around a small lumen, a process know as remodelling.

1.4 Clinical presentation[26].

Patients with uncomplicated, primary hypertension are usually asymptomatic initially. While a complete history and physical examination may help identify concerns that warrant further evaluation, a few basic tests should be performed in all hypertensie patients prior to initialing drug therapy. These include hemoglobin and hematocrit, urinalysis, serum potassium and creatinine, liver function test, and electrocardiogram. Total and high-density-lipoprotiend cholesterol, plasma glucose, and serum uric acid are indicated to assess other risk factors and to develop baseline data for monitoring drug I-induced metabolic changes. As the hypertension processes, however, symptoms characteristic of cardiovascular, cerebrovascular, or renal disease may occur as the patients develops target organ damage. Patients with secondary hypertension usually complain of symptoms suggestive of the underlying disorder. More than half of the patients with this form of secondary hypertension suffer episodes of orthostatic dizziness or syncope. In primary aldosteronism, hypokalemic symptoms usually manifest including muscle cramps and muscle weakness. Patients who present with hypertension secondary to Cushing's syndrome may complain of weight gain, polyuria, edema, menstrual irregulatories, recurrent acne, or muscular weakness. The most common causes of secondary hypertension are summarized in Table 1.

Frequently, the only sign of primary hypertension is an elevated blood pressure. The rest of the physical examination may be completely normal. Again, as the hypertension progresses, signs of end-organ damage begin to appear. These are chiefly related to pathologic changes in the eye, brain, heart, kidneys, and peripheral blood vessels.

Table 1 : Causes of secondary hypertension[27].

Systolic and diastolic hypertension

- Renal
  - Renal parenchymal disease
    - Chronic nephritis
    - Polycystic disease
    - Collagen vascular disease
    - Diabetic nephropathy
    - Hydronephrosis
    - Acute glomerulonephritis
  - Renal vascular disease
  - Renal transplantation
  - Renin-secreting tumors
- Endocrine
  - Adrenal
    - Primary aldosteronism
    - Overproduction of 11-deoxycorticosterone (DOC), 18-OH-DOC, and other mineralocorticoids
    - Congenital adrenal hyperplasia
    - Cushing's syndrome
    - Pheochromocytoma
  - Extra-adrenal chromaffin tumors
  - Hyperparathyroidism
  - Acromegaly
- Pregnancy-induced hypertension
- Coarctation of the aorta
- Neurologic disorders
  - Dysautonomia
  - Increased intracranial pressure
  - Quadriplegia
  - Lead poisoning
  - Guillain-Barre syndrome
- Postoperative
- Drugs and chemicals
  - Cyclosporine
  - Oral contraceptives
  - Glucocorticoids
  - Mineralocorticoid, including licorice and carbenoxolone
  - Sympathomimetics
  - Tyramine and MAO inhibitors

Isolated systolic hypertension

- Aging, with associated aortic rigidity
- Increased cardiac output
  - Thyrotoxicosis
  - Anemia
  - Aortic valvular insufficiency
- Decreased peripheral vascular resistance
  - Arteriovenous shunts
  - Paget's disease of bone
  - Beriberi

1.5 Complication of hypertension

The end of the natural history of untreated hypertension is an increased likelihood of premature disability or death from cardiovascular disease. The risks of elevated blood pressure have been determined from large-scale epidemologic surveys. MacMahon et al. performed a meta-analysis of all available major prospective observational studies relating diastolic blood pressure (DBP) level to the incidence of stroke and coronary heart disease (CHD). In the nine studies analyzed, almost 420,000 people were followed up for 6 to 25 years. A total of 599 fatal strokes and 4,260 deaths from CHD were recorded. The overall results demonstrated "direct, continuous and apparently independent associations" with "no associated with lower risks of stroke and CHD". MacMahon et al also estimated that a DBP that is persistently higher by 5.0 mmHg is associated with at least a 34 % increase in stroke risk and at least a 21 % in CHD risk. Table 2 provide a more detailed look at the causes of death in hypertensives.

In general, the complication of hypertension can be considered either "hypertensive" or "atherosclerotic" (Table 3). Those listed as hypertensive are caused more directly by the increased level of the BP per se, whereas the atherosclerotic complications have multiple causes, hypertension playing a variable role. The complication of hypertension or target organ damage secondary to chronic hypertension principally involves the heart, the brain, the kidney and the eye.

Hypertensive heart disease: the principal cardiac complications of hypertension are left ventricular hypertrophy, coronary heart disease, and congestive heart failure. These complication may lead to cardiac arrhythmias, angina, myocardial infarction, and sudden death. Coronary heart disease is the common cause of deat in hypertensive patients.

Cerebrovascular disease : the types of cerebrovascular lesions most commonly seen in hypertensive individuals include lacunar infarcts caused by thrombolic occlusion of small vessels, intracerebral hemorrhage resulting from ruptured microanerurysms, and transient attacks secondary to atherosclerotic diseases in the carotid arteries.

Renal disease: Renal dysfunction, both structural and functional, is almost always demonstrable in hypertensive patients, even those with minimally elevated pressures, however renal involvement usually is asymptomatic and not demonstrable by usual clinical testing. The loss of renal function grows progressively as the blood pressures, however renal involvement usually is asymptomatic and not demonstrable by usual clinical testing. The loss of renal function grows progressively as the blood pressure increases and the elevation continues, but only a minority of hypertensives die as a result of renal failure. Nevertheless, hypertension remains a leading risk for end-stage renal disease (ESRD), and is partly responsible for the much higher incidence of ESRD in blacks than in whites in the United States.

The damage hypertension dose to the eye is characterized by a variety of retinopathies. Nonspecific changes include an increased light reflex, increased tortusity of vessels, and arteriovenous nicking. These are all associated with the accelerated arteriosclerosis that accompanies hypertension.

Table 2 : Causes of death in primary hypertension[22]

	Year	No of Deaths	Percentage of Deaths			
			Heart Disease[a]	Stroke	Renal Failure	Nonvascular Causes
Untreated						
Janeway, 1913	1903–1912	212	33	14	23	30
Hodge and Smirk, 1967	1959–1964	173	48	22	10	20
Bechgaard, 1976	1932–1938	293	45	16	10	29
Smith et al., 1950	1924–1948	376				
Group 1[b]		100	28	9	3	60
Group 2		100	46	17	2	35
Group 3		76	52	18	16	14
Group 4		100	22	16	59	3
Bauer, 1976	1955–1974	144	41	34	15	10
Treated						
Breckenridge, 1970	1952–1959	87	18	28	44	10
Breckenridge et al., 1970	1960–1967	203	38	21	29	11
Strate et al., 1986	1970–1980	132	42	7	7	44
Bulpitt et al., 1986	1971–1981	410	51	18	3	28
Isles et al., 1986	1968–1983	750	52	23	?	25

[a]Includes ischemic heart disease and congestive failure.
[b]Grouping according to Keith-Wagener classification of hypertensive retinopathy.

Table 3 : Complications of hypertension[22]

Hypertensive	**Atherosclerotic**
Accelerated-malignant hypertension	Cerebral thrombosis
(grades III and IV retinopathy)	Myocardial infarction
Encephalopathy	Coronary artery disease
Cerebral hemorrhage	Claudication syndromes
Left ventricular hypertrophy	
Congestive heart failure	
Renal insufficiency	
Aortic dissection	

1.6 Definition and classification of hypertension[24-26]

The continuous relationship between the level of blood pressure and the risk of cardiovascular events, and the arbitrary nature of the definition of hypertension have contributed to the variation in the definitions issued by various national and international authorities and particularly by the Joint National Committee *JNC) in the United States and the WHO-ISH Guidelines Committee. Accordingly, in order to reduce confusion and provide more consistent advice to clinicians around the world, the WHO-ISH Guidelines Committee has agreed to adopt in principle the definition and classification provided in JNC VI. This new definition defines the lower limits of hypertension as 140 mmHg SBP and 90 mmHg DBP, the same as the lower limits for the borderline subgroup of mild hypertension in the 1993 WHO-ISH Guidelines. The new Guidelines emphasize that the decision to lower the elevated pressure in a particular patient is not base on the level of blood pressure alone but on assessment of the total cardiovascular risk in that individual.

Hypertension is therefore defined as a SBP of 140 mmHg or greater and/or a DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication. A classification of blood pressure levels in adults over the age of 18 is provided in Table 4 The terms "grades 1, 2 and 3" used by JNC VI, since the word "stage" implies progression over time in a way that does not necessarily apply here. Otherwise, the values chosen and the terms used are those used in JNC VI. The terms "mild", "moderate" and "severe" used in previous versions of the WHO-ISH Guidelines, would correspond to grades 1, 2 and 3, respectively. The widely used term "borderline hypertension" becomes a subgroup within grade 1 hypertension. It must be emphasized that the term "mild hypertension" does not imply a uniformly

benign prognosis, but is used simply to contrast with more severe elevations of blood pressure.

In contrast to the 1993 Guidelines, the present report does not deal separately with hypertension in the elderly nor with isolated systolic hypertension. Rather, discussion of these two conditions is now part of the main text, since it is widely agreed that the treatment of these conditions is at least as effective in reducing cardiovascular risk as the treatment of classical essential hypertension in middle-aged subjects.

Table 4 : Definitions and classification of blood pressure levels (mmHg)[26]

Category	**Systolic**	**Diastolic**
Optimal	< 120	< 80
Normal	< 130	< 85
High-normal	130 – 139	85 – 89
Grade 1 hypertension (mild)	140 – 159	90 – 99
Subgroup: borderline	140 – 149	90 – 94
Grade 2 hypertension (moderate)	160 – 179	100 – 109
Grade 3 hypertension (severe)	> 180	> 110
Isolated systolic hypertension	> 140	< 90
Subgroup: borderline	> 140 – 149	< 90

New (1999) WHO/ISH definitiond and classification of BP levels

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply.

Stratification of patients by absolute level of cardiovascular risk

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk

factors, concomitant diseases such as diabetes, target-organ damage and cardiovascular or renal disease, as well as other aspects of the patient's personal, medical and social situation. To assist with this, these Guidelines provide a simple method by which to estimate the combined effect of several risk factors and conditions on the future absolute risk of major cardiovascular events. The estimates are based on age, gender, smoking, diabetes, cholesterol, history of premature cardiovascular disease, the presence of target-organ damage and history of cardiovascular or renal disease. They were calculated from data on the average 10 year risk of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction among participants (average initial age of 60 years; range 45 – 80 years) in the Framingham Study.

Four categories of absolute cardiovascular disease risk are defined (low, medium, high and very high risk). Each category represents a range of absolute disease risks. Within each range, the risk of any one individual will be determined by the severity and number of risk factors present. So, for example, individual with very high levels of cholesterol or a family history of premature cardiovascular disease in several first-degree relatives will typically have absolute risk levels that are at the higher end of the range provided. Similarly, individuals with other risk factors listed in Table 5 may also have absolute risk levels that are towards the higher end of the range for the category.

How well these estimates predict the absolute risk of cardiovascular disease in Asian, African or other non-Western populations is uncertain. In those countries in which CHD incidence is relatively low and heart failure or renal disease is more common, the risk factors used to stratify risk in Table 6 should also be useful in stratifying the risk of these diseases.

Low-risk group

The low-risk group includes men below 55 and women below 65 years of age with grade 1 hypertension and no other risk factor. Among individuals in this category, the risk of a major cardiovascular event in the next 10 years is typically less than 15%. The risk will be particularly low in patients with borderline hypertension.

Medium-risk group

This group includes patients with a wide range of blood pressures and risk factors for cardiovascular disease. Some have lower blood pressures and multiple risk factors, whereas others have higher blood pressures and no or few other risk factors. This is the patient group for which the clinical judgement of the responsible doctor will be paramount in determining the need for drug treatment and the time interval before it should be instituted. Among subjects in this group, the risk of a major cardiovascular event over the next 10 years is typically about 15-20%. The risk will be closer to 15% in those patients with grade 1 (mild) hypertension and only one additional risk factor.

High-risk group

This group includes patients with grade 1 or grade 2 hypertension who have three or more risk factors listed in Table 5, diabetes or target-organ damage and patients with Grade 2 (severe) hypertension without other risk factors. Among these patients the risk of a major cardiovascular event in the following 10 years is typically about 20-30%.

Very-high-risk group

Patients with grade 3 hypertension and one or more risk factors and all patients with clinical cardiovascular disease or renal disease (as defined in Table 5) carry the

highest risk of cardiovascular events, of the order of 30% or more over 10 years, and thus qualify for the most intensive and rapidly instituted therapeutic regimens.

Table 5 : Factors influencing prognosis[26]

Risk Factors For Cardiovascular Diseases	Target Organ Damage (TOD)	Associated Clinical Conditions (ACC)
I. Used for risk stratification • Levels of systolic and diastolic blood pressure (Grades 1–3) • Men >55 years • Women >65 years • Smoking • Total cholesterol >6.5 mmol/L (250 mg/dl) • Diabetes • Family history of premature cardiovascular disease II. Other factors adversely influencing prognosis • Reduced HDL cholesterol • Raised LDL cholesterol • Microalbuminuria in diabetes • Impaired glucose tolerance • Obesity • Sedentary lifestyle • Raised fibrinogen • High risk socioeconomic group • High risk ethnic group • High risk geographic region	• Left ventricular hypertrophy (electrocardiogram, echocardiogram, or radiogram) • Proteinuria and/or slight elevation of plasma creatinine concentration 106–177 mmol/L (1.2 – 2.0 mg/dl) • Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalised or focal narrowing of the retinal arteries	*Cerebrovascular disease* • Ischaemic stroke • Cerebral haemorrhage • Transient ischaemic attack *Heart disease* • Myocardial infarction • Angina pectoris • Coronary revascularisation • Congestive heart failure *Renal disease* • Diabetic nephropathy • Renal failure (plasma creatinine concentration >177 mmol/L) (>2.0 mg/dl) *Vascular disease* • Dissecting aneurysm • Symptomatic arterial disease *Advanced hypertensive retinopathy* • Haemorrhages or exudates • Papilloedema

Table 6 : Stratifying risk and quantifying prognosis[26].

	BLOOD PRESSURE (mmHg)		
Other risk factors & disease history	**Grade1** (mild hypertension) SBP 140-159 or DBP 90-99	**Grade 2** (moderate hypertension) SBP 160-179or DBP 100-109	**Grade 3** (severe hypertension) SBP □ 180 or DBP □110
I. no other risk Factors	low risk	medium risk	high risk
II. 1-2 risk factors[1]	medium risk	medium risk	v high risk
III. 3 or more risk factors or TOD[2] or diabetes	high risk	high risk	v high risk
IV. ACC[3]	v high risk	v high risk	v high risk

[1] See table 5

[2] TOD – target organ damage

[3] ACC-associated clinical conditions, including clinical cardiovascular disease or renal disease

2. Blood Pressure Measurements[21,28-33]

Conventional versus Ambulatory Blood Pressure Measurement:

Casual office-or clinic-based arterial pressure measurements, i.e. the physician measures the patient's arterial pressure in his office or clinic, have been used since the turn of the century and remain the mainstay or standard method of diagnosis and management of hypertension even today. There are many reasons for this: normal and pathological values are defined and almost all we know about the prognostic impact of elevated arterial pressure relies on studies which used casual measurements, e.g. Framingham. The measurement itself and the situation in which it takes place can be standardized, e.g. device, cuff size, vessel sounds, body position, time of day and thus equality of observation is achievable to a fair degree. Casual arterial pressure data can also be analyzed easily and aggregated to produce summary statistics without problems. Finally, the measurement is simple and inexpensive and thus even large samples can be examined. However, there are many limitations of casual measurements to determine the arterial pressure. Casual blood pressure measurements are often affected by the alerting reaction induced in patients by the doctor's presence, this reaction causes a rise in blood pressure which may be both large and unpredictable. Also known as the white-coat hypertension or office hypertension, which cannot be reproduced when self-measuring pressure at home or with an ambulatory blood pressure monitoring (ABPM) device. The reasons for white-coat hypertension are not well understood. The proportion of patients with white-coat hypertension varies between 20% and 30% of all patients with office-diagnosed hypertension. Mancia and colleagues showed that the average rise in pressure evoked by the presence of a physician was 23/18 mmHg. This alerting reaction interferes with the evaluation of antihypertensive treatment by clinic readings

in two ways. Firstly, the alerting reaction may cause an overestimate of the initial blood pressure levels. Secondly, it may lead to an underestimate of the reduction in blood pressure achieved with treatment. Therefore, patients with white-coat hypertension must not be admitted to clinical trials. Another important disadvantage of casual measurements, especially in the clinical trial setting is its well described responsiveness to placebo. When arterial pressure drops with placebo treatment, the observed difference compared with the active treatment group decreases and the variance increases. Sample size has to be increased to compensate for this power loss.

In addition, as the recognition of blood pressure variability that presents throughout the day, clinic pressure measurements are therefore limited in that the reading obtained may not be representative of the patient's blood pressure. Hence, although the level of arterial pressure as measured at the clinic is an important risk factor in populations, its predictive value in individual patient is poor. These limitations can be reduced with the use of ABPM device.

Noninvasive intermittent blood pressure monitoring was first developed 30 years ago, with the improved technology, ambulatory devices are now pocket-sized, with almost noiseless pumps and are capable of automatically inflating the cuff and providing intermittent pressure measurements over a 24-hour period. With this method of measurement, there are considerable advantages over conventional measurement including avoidance of observer error, either systematic error, termianl digit preference or observer prejudice, which limit accuracy of conventional measurements. Furthermore, ambulatory monitoring reduces white-coat effect, provides a series of blood pressure readings over the time period rather than a one-off measurement and the use of ABPM in clinical trials seems to be no relevant arterial pressure response to placebo. There is also convincing evidence that ABPM data

have a higher reproducibility than casual clinic readings. With the distinct features of ABPM from conventional method make this device almost a necessity in antihypertensive clinical trials. These are as follows

1. *Reliable identification of the target population*

24-hour ABPM provides an effective way of recognizing those patients whose blood pressure elevation is due to the white-coat effect. These patients who are not really hypertensive cannot benefit from antihypertensive treatment but they may be exposed to possible adverse drug reactions, which are not balanced by therapeutic benefit. Therefore, they should not receive any antihypertensive treatment. Likewise, patients with white-coat hypertension must not be admitted to clinical trials. In efficacy trials their inclusion would contribute to the reduction of arterial pressure in the placebo group, thus minimizing the difference in endpoint arterial pressure observed between the active and in the control group. In effectiveness studies the inclusion of white-coat hypertensives would dilute the effects of the antihypertensive treatment as a considerable subsample of the patients only casually experience elevated pressure. Therefore, increased sample sizes are necessary to achieve statistically significant results.

2. *Reduction of sample size*

24-hour ABPM does not respond to placebo and is highly reproducible. Thus the sample size required to show efficacy of an antihypertensive treatment can be reduced markedly.

3. *Assessment of dose-response relationship and duration of drug action*

24-hour ABPM allows the BP of hypertensive patients to be measured under exposure to the variable physical and psychological stimuli in daily life not just in the artificial environment of the physician's office. Moreover, the detailed or series of

blood pressure reading also obtained over the time period with this device. As a result, it is possible that the exact time of the real, daily life of peak and trough antihypertensive effect will be identified. The persistence of the blood pressure reduction over 24-hour (drug's duration), during the night-time, or in the early morning hours can also be followed. In addition, this device can reveal the effects of antihypertensive drugs on the blood pressure (BP) variables such as BP variability, BP load, mean 24-hour BP, mean day-time BP, mean night-time BP which are related with the degree of end-organ damage in hypertension.

Prognostic Significant of 24-hour Blood Pressure (BP) Variables[31-33]

Twenty-four-hour monitoring of blood pressure has been shown to be superior to casual (office) BP in predicting target organ involvement in patients with hypertension, particularly for the heart. Many types of information can be obtained by using 24-hour ABPM device, including an individual's true blood pressure level, amplitude of diurnal variation, short-term blood pressure variability and blood pressure load, all of which might have prognostic significance.

Prognostic significance of average 24-hour and daytime blood pressure

Sokolow *et al* showed that average daytime blood pressure values obtained non-invasively by a semi-automatic measuring device were correlated more closely with the overall end-organ damage in patients with hypertension than clinic blood pressure values. This finding was later confirmed by other investigators who provided the following additional evidence : (1) both the daytime blood pressure and the 24-hour average blood pressure are correlated more closely with end organ damage in hypertensive patients than clinic blood pressure; (2) the close correlation between 24-hour average blood pressure and end-organ damage can be seen when organ damage

is measured by a comprehensive score base on patient history and clinical and laboratory examinations, and when different (and sometimes more sensitive) measures of individual end organ damage are considered. Thus, albuminuria, cerebral lacunae, left ventricular hypertrophy and retinopathy have all shown a greater correlation with 24-hour average values than with clinic values.

Prognostic significance of blood pressure variability

Parati *et al* demonstrated that blood pressure variations over 24 hour are correlated with end organ damage in hypertensive patients. In this study hypertensive patients were divided into five groups according to increasing 24-hour average blood pressure values as determined by intra-arterial ambulatory monitoring. Each group was then subdivided into two classes according to whether blood pressure variability (calculated as the standard deviation of the average of all half-hour mean values, i.e. the among half-hour standard deviation) was greater or lower than the average variability of the whole group. The greater incidence and severity of end-organ damage was seen in the classes with greater blood pressure variability. Another support was shown by the study in 73 hypertensive patients using intra-arterial ambulatory monitoring. It was found that among the blood pressure readings taken at baseline, the short-term variability (defined as the standard deviation of consecutive half-hourly values during the daytime) was the best predictor of subsequent left ventricular mass. The other significant predictor was an aggregate measure of target-organ damage based on the ECG, chest X-ray, examination of the fundus and the serum creatinine concentration. The variability in blood pressure also predicted aggregate target organ damage at follow-up, but blood pressure level was not a predictor.

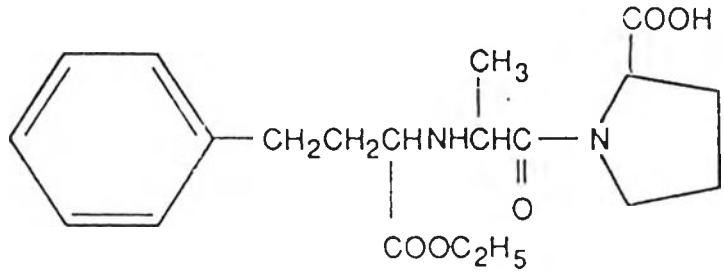
Prognostic significance of the diurnal rhythm of blood pressure

Blood pressure usually follows a circadian rhythm with pressure levels higher during the day and lower at night. In most people, blood pressure falls during the night by more than 10%, such people are often referred to as dippers. But there are others (non-dippers) in whom the fall in blood pressure is smaller. This blunted circadian pattern has been reported to be associated with increased prevalence of left ventricular hypertrophy, artherosclerosis and stroke. In addition, a few cross-sectional studies have indicated that target organ damage is more pronounced in non-dippers than in dippers with comparable clinic blood pressure. It has also been suggested that this difference applies to women but not to men.

Prognostic significance of the daily blood pressure load

A study by White *et al* in 30 never previously treated patients with mild to moderate essential hypertension via 24-hour ambulatory BP monitoring indicated that percentage of elevated BP values that includes both the awake and asleep periods is predictive of cardiac target organ involvement. Elevated BP values during the awake hours (> 140/90 mmHg) and sleeping hours (> 120/80 mmHg) were used to calculate the total percentage of abnormal BP values (load) in each patient. It was found that the BP loads were related to left ventricular mass index and left atrial index more strongly than were the mean 24-hour BP values. Moreover, if > 40% of the ambulatory BP values were elevated, the likelihood of increased mass or decreased filling was greater than 61%, whereas if < 40% of the BP values were elevated, the incidence of an abnormal cardiac test result decreased to less than 17%.

Chemistry [34-39]



Enalapril

Figure 2 : chemical structure of enalapril[2]

Enalaprilat and enalapril are angiotensin-converting enzyme (ACE, bradykininase, kininase II) inhibitors. Enalapril, the ethylester of enalaprilat, is a prodrug and has little pharmacologic activity until hydrolyzed in the liver to enalaprilat. Enalapril is commercially available as the maleate salt and differs structurally from enalaprilat by the presence of an ethoxycarbonyl group rather than a carboxy group at position 1 of 1-alanyl-l-proline and by the presence of the maleate salt. These structural modifications result in increased GI absorption of enalapril compared with enalaprilat, which is poorly absorbed from the GI tract. Enalapril is structurally and pharmacologically similar to captopril but contains a disubstituted nitrogen rather than a sulfhydrlyl group at position 3 of 2-methyl-1-oxopropyl –1-proline. The lack of the sulfhydryl group in enalapril may result in decreased risk of certain adverse effects (e.g., cutaneous reaction, taste disturbances, proteinuria).

Pharmacology

Effects on Renin-Angiotensin-Aldosterone System

Enalapril prevents the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor) through inhibition of ACE. The drug competes with physiologic substrate (angiotensin I) for the active site of ACE. Inhibition of ACE initially results in decreased plasma angiotensin II concentrations and, consequently, blood pressure may be reduced in part through decreased vasoconstriction. Plasma renin activity (PRA) increases, possibly as a result of loss of feedback inhibition (mediated by angiotensin II) on the release of the renin from the kidneys and/or stimulation of reflex mechanisms via baroreceptors (as a result of the decrease in blood pressure). By decreasing local angiotensin II production, ACE inhibitors may decrease vascular tone by reducing direct angiotensin II-induced vasoconstriction and/or angiotensin II-induced increases in sympathetic activity.

Enalapril alone may be more effective in reducing blood pressure in patients with high or normal renin hypertension, but the drug may also lower blood pressure in patients with low renin hypertension. Initial decreases in plasma angiotensin II concentrations lead to decreased aldosterone secretion from the adrenal cortex and therefore, to decreased plasma concentrations and urinary excretion of aldosterone; however, plasma aldosterone concentrations may not decrease during enalapril therapy in some patients and may return to pretreatment levels in others during prolonged therapy.

Effects on catecholamines and autacoids

Circulating plasma norepinephrine concentration generally is not affected by enalapril, but the drug has reduced these concentrations in some patients with hypertension or congestive heart failure. in addition, the drug has attentuated the

increase in plasma norepinephrine concentration that results from orthostatic reflexs. By inhibiting angiotensin II formation, ACE inhibitors may effect catecholamine release and reuptake by noradrenergic nerve endings and /or may decrease vascular sensitivity to vasopressors. Because ACE also degrades the vasodilator bradykinin, it has been suggested that inhibition of ACE may cause accumulation of bradykinin in plasma or tissues with resultant vasodilation; however, plasma and/or urinary concentrations of bradykinin and/or its metabolites have been unchanged in enalapril responsive patients.

Cardiovascular effects

In hypertensive patients, enalapril reduced blood pressure by decreasing total peripheral resistance with a slight increase or no change in heart rate, stroke volume, or cardiac output. The drug causes arterial and possibly venous dilation. Enalapril generally decreases systolic and diastolic blood pressure by approximately 10-15%. In patients with congestive heart failure, enalapril, usually in conjunction with cardiac glycosides and diuretics, decreases total peripheral resistance, pulmonary capillary wedge pressure, heart size, and mean arterial and right atrial pressures.

Renal and electrolytes effects

Renal blood flow may increase, but glomerular filtration rate is usually unchanged during enalapril therapy. BUN and serum creatinine concentrations have occasionally increased during long-term enalapril therapy. Enalapril's effects on renal blood flow and glomerular filtration in patients with renovascular hypertension appear to be similar to those in hypertensive patients with normal renal function. Increases in serum potassium concentration may occur secondary to enalapril – induced decreases in aldosterone secretion, especially in patients with impaired renal function. The hypothesis effects of enalapril may also result in part from decreased

sodium and water retention secondary to reduced aldosterone secretion; however, decreases in aldosterone secretion during enalapril therapy are generally small.

Pharmacokinetics

Following oral administration, enalapril is rapidly and well absorbed (60 to 70 %) from the gastrointestinal tract. Peak plasma concentrations (C_{max}) are attained about 1 hour after drug administration. After absorption, enalapril is rapidly de-esterified (hydrolysed) by carboxylesterase to from enalaprilat. As a result, plasma concentrations of parent drug are virtually undetectable about 4 hours after administration. In humans this metabolic transformation occurs almost exclusively in the liver.. The parent drug has an elimination half-life of about 2 hours. Unchanged enalapril and enalaprilat are excreted both in urine and feces, with the urinary route predominating.

Enalaprilat undergoes polyphasic elimination with an initial elimination phase half-life of approximately 5 hours but a prolonged terminal phase of 30 to 35 hours, reflecting the strong binding of enalaprilat to plasma ACE. Enalaprilat appears to penetrate most tissues (kidneys and vascular tissue in particular). Enalapril has been shown, however, to decrease circulating plasma catecholamine levels and the turnover of brain tissue catecholamines. The bioavailability of enalapril is not affected by food but predictably, is affected by hepatic function. Clearance is reduced only in advanced uncompensated hepatic impairment.

USES

Therapeutic use in hypertension

Enalapril is used in the management of mild to severe hypertension. The drug has been used as monotherapy or in combination with other class of antihypertensive agents. Enalapril provides effective 24-hour blood pressure control whether

administered once or twice daily. Titrated dose of enalapril, 5 to 40 mg / day as monotherapy, reduce mean SBP and DBP by 15% to 25 % with adequate control (DBP < 90 mmHg) in approximately 50% to 75% of patients, depending on the initial severity of hypertension. Enalapril has been effective in the management of renovascular or malignant hypertension, renal hypertension secondary to renal artery stenosis, and, in some patients, hypertension associated with chronic renal failure. however, enalapril should be used with caution in patients with impaired renal function, especially those with bilateral renal –artery stenosis or with renal artery stenosis in a solitary kidney.

Tolerance to the hypotensive effect of enalapril apparenty does not occur during long-term administration, particularly if the drug is used with a diuretic. As with other hypotensive agents, treatment with enalapril or enalaprilat is not curative; after withdrawal of the drug, blood pressure returns to pretreatment levels. Abrupt withdrawal of enalapril or enalaprilat therapy results in a gradual return of hypertension; rapid increases in blood pressure have not been reported to date.

For the patients not receiving a diuretic, the usual initial adult dosage of enalapril maleate is 2.5-5 mg daily. Dosage of the drug should be adjusted according to the patient's blood pressure response. The usual maintenance dosage of enalapril maleate is 10-40 mg daily, given as a single dose or in 2 divided doses daily.

Therapeutic use in congestive heart failure

Several studies clearly demonstrate that enalapril is important for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In these patients, enalapril improves symptoms, increases survival, improved function capacity and decrease the frequency of hospitalization. The recommended starting dose is 2.5 mg administered once or twice daily, titration up to a target dose of 10 mg

twice daily in several weeks. The usual therapeutic dosing or two divided doses; most clinical studies have used twice –daily dosing

Myocardial Infarction and Left Ventricular Dysfunction.

Numerous trials involving almost 100,000 patients have demonstrated a reduction in morbidity and mortality associated with ACE inhibitor therapy administered after MI.

Data obtained from the PRACTICAL trial shown that enalapril can improve LV function and prevented LV dilation when administered with 24 hour after the onset of chest pain and was continued for three months.

Enalapril is used in clinically stable asymptomatic patients with left ventricular dysfunction (manifested as an ejection fraction of 35% or less) in an effort to decrease the rate of development of overt heart failure and subsequent hospitalizations for heart failure in these patients.

enalapril and enalaprilat, also have been used to minimized or prevent the development of left ventricular dilatation and dysfunction following acute myocardial infarction. However, evidence regarding the efficacy of such therapy has been somewhat conflicting, particularly when parenteral therapy was initiated early (within 24-48 hours) and included patients with no evidence of baseline dysfunction.

Adverse effects

Adverse reactions to enalapril usually are mild and transient but have required discontinuance of therapy in about 3 or 6 % of patients receiving the drug for management of hypertension or congestive heart failure, respectively. Enalapril usually is well tolerated. The frequency of adverse experiences was not related to total daily dosage within usual ranges. In patients with hypertension, the overall percentage of patients treated with enalapril reporting adverse experiences was often

comparable with the percentages of those receiving placebo. Adverse nervous system effects (e.g., headache, dizziness, fatigue) occur most frequently during enalapril therapy for hypertension, although adverse effects of enalapril generally are mild, discontinuance of the drug has been necessary in about 6% of patients, principally because of dizziness, headache, hypotension, or rash.

Cough has been reported in 1.3 or 3.5 % of patients receiving enalapril alone or in fixed combination with hydrochlorothiazide for hypertension, respectively. Nonproductive cough, particularly at night, may occur more frequently, especially in patients with chronic obstructive pulmonary disease. The cough generally is persistent, is not associated with other respiratory symptoms, and is reversible following discontinuance of the drug. Nasal congestion also has been reported. It has been suggested that accumulation of kinins in the respiratory tract secondary to ACE inhibition may in part be responsible for cough and nasal congestion. Concomitant therapy with a nonsteroidal anti-inflammatory agent (i.e., sulindac) appeared to minimize cough in a few patients, but additional study of the safety (e.g., effects on renal function) of such combined therapy is necessary. If cough develops in a patient receiving enalapril, ACE inhibitor-induced cough should be considered as part of the differential diagnosis.

Dosage and administration

The drug can be given before, during, or after meals since food does not appear to substantially affect the rate or extent of absorption of enalapril. Dosage of enalapril maleate and enalaprilat must be adjusted according to the patient's tolerance and response

Hypertension

For the management of hypertension in patients not receiving a diuretic, the usual initial adult dosage of enalapril maleate is 2.5 – 5 mg daily. Dosage of the drug should be adjusted according to the patient's blood pressure response. If the blood pressure response diminishes toward the end of the dosing interval during once-daily administration, increasing the dosage or giving the drug in 2 divided doses daily should be considered. The usual maintenance dosage of enalapril maleate is 10-40 mg daily, given as a single dose or in 2 divided dose daily.

Congestive heart failure

The usual initial enalapril maleate dosage for the management of congestive heart failure in adult with normal renal function and serum sodium concentration is 2.5 mg once or twice daily. After the initial dose, the patient should be monitored closely for at least 2 hours and for at least one additional hour after blood pressure has stabilized. The usual maintenance dosage of enalapril maleate for congestive heart failure is 5-20 mg daily, usually given in 2 divided doses. The maximum recommended dosage if the drug is 40 mg daily.

Asymptomatic left ventricular dysfunction

Enalapril maleate therapy has been initiated using a dosage of 2.5 twice daily therapy is then titrated at tolerated to a target daily dosage of 20 mg given in divided dose. After the initial dose, the patient should be monitored closely for at least 2 hours and for at least one additional hour after blood pressure has stabilized.