A RETROSPECTIVE STUDY OF CALCIUM CHANNEL

BLOCKERS

AND

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

IN HYPERTENSIVE THERAPY AT AHMADU BELLO UNIVERISTY TECHING HOSTPIAL, ZARIA, NIGERIA

BY

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CERTIFICATION

This Thesis entitled, A Retrospective study of Calcium Channel Blockers and Angiotensin Converting Enzyme Inhibitors in Hypertensive Therapy at Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, by Pharm. (Mrs.) Bilkisu Umar meets the regulations governing the award of the degree of Master in Science (Clinical Pharmacology) of Ahmadu Bello University, Zaria and is approved for its contribution to knowledge and literary presentation.

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DECLARATION

I hereby declare that this project work has been undertaken by me, under the supervision of Dr. A. A. Odutola, (FCPharm., FPSN) of the Department of Pharmacology and Clinical Pharmacy. No such work has been submitted for any award of degree, and material consulted has been acknowledge appropriately by means of reference.

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DIGITIZED

DEDICATION

Dedicated to my husband Sabiru A. Sadiq, my parents Alhaji Umaru Malumfashi and Hajiya Abu Umar and to my children Hadiza, Hafsat, Zainab and Abubakar Sadiq.

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SUMMARY

There is increasing reliance on angiotensin converting enxyme inhibitors and calcium channel blockers in the management of hypertension because of their general effectiveness, low incidence of adverse reactions and potential specific benefit in patients with renal disease. These two classes of drugs are antihypertensives that are useful in mild to moderate and severe hypertension resistant to all other drugs.

The work was carried out in Cardiac Clinic of Ahmadu Bello University Teaching Hospital, Zaria where patients' folders were screened and questionnaires were used to obtain informations. The use of these drugs was evaluated and the results were analyzed to reveal the fact that the use of antihypertensives is now turning towards these drugs with high frequency and increasing reliance.

ABSTRACT

ACEIS and CCBS are anti-hypertensives that are useful in mild to moderate and *severe* hypertension resistant to all other drugs.

The actions, uses, side effects and contra indications of hese drugs were evaluated in this work and compared to that *seen* in literature.

This work was carried out in Cardiac Clinic of Ahmadu Bello University Teaching Hospital, Tudun-Wada, Zaria using two groups, *one* of thirty (31) patients and the other of forty-nine (49) patients. Informations were obtained from patients folders and by interviewing the patients and by administering questionnaires.

The results were analyzed using tables, bar charts and pie charts and compared with what was *seen* in the literature.

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CHAPTER ONE

INTRODUCTION

1.1: HYPERTENSION

Hypertension or high systemic arterial blood pressure describes the persistent elevation of arterial blood pressure[1]. It is a chronic disorder of the cardiovascular system resulting from a variety of disturbances in control mechanisms which ultimately lead to elevated blood pressure. Management of patients with these disorders includes diagnostic assessment and therapeutic strategy. Initial diagnostic efforts are ordinarily conducted assessment and therapeutic strategy. First hypertension will be related to other well-defined cardiovascular factors such as diabetes, obesity, cigarette smoking and disturbances of lipid metabolism. Second, the stage of the individual patient with regard to cardiovascular, cerebral and renal complications of hypertensive disease will be defined. Third, an attempt to characterize the etiology responsible for the elevation in pressure will be carried out[1].

1.1.1: Classification of Hypertension

Hypertension may be divided into two types, secondary hypertension in which the elevation of blood pressure is a consequence of another disorder or can be assigned to a clearly identifiable cause, and essential hypertension in

which the underlying cause is not known. The actual levels of blood pressure which may be regarded as being in the hypertensive range are $^{160}/_{95}$mmHg (21.3/12.7Kpa) in people under 50 years of age and 170/100mmHg (22.7/13.3Kpa) in older people. A blood pressure of 150/90mmHg (20/12 Kpa) would be generally regarded as in the upper normotensive range[3]. Values between elevated and normal are known as border-line. Persistent elevation of blood pressure can be ascertained only by repeated measurements over a longer period of observation. A single, casual finding of elevated blood pressure does not justify the diagnosis of hypertension unless very high values are found. Blood pressure varies during the day and is usually considerably lower at night. This applies to both normal and hypertensive subjects but the later still have higher values at night than normotensive individual[1]. Secondary hypertension can be;

i. <u>Drug Induced</u>

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This type of hypertension can be caused by drugs like sympathomimetic amines, monoamine oxidase inhibitors thyroid hormnes, oral contraceptives, mineralocorticoids, liquorice and carbenoxolone and cadmium[1].

ii. **Phaeochromocytoma**

The hypertension occurring in phaeochromocytoma is due to high levels of circulating catecholamines (mainly adrenaline) liberated from tumours of chromaffin tissue. It is an uncommon cause of hypertension[1].

iii. **Renal Hypertension**

The renal disease glomerulonephritis almost invariably leads to hypertension. The disease was first described by Bright in the 1820s, who noted the association between albuminuria and dropsy (i.e. Oedema) in life and small kidneys at autopsy. He also observed that the heart was larger than usual and the walls of the left ventricle were thicker and suggested that this hypertrophy was due to the extra work done by the heart in the systemic circulation. It was thought for many years that renal disease was the underlying basis for all types of hypertension. In addition to glomerulonephritis, other disorders commonly giving rise to renal hypertension include renal periarteritis nodosa, diabetic renal disease, amyloid disease, analgesic nephropathy, occlusion of the renal arteries by

atheromatous plaques, thromboembolic, occlusion, traumatic renal damage and congenital defects of the kidneys or renal arteries[1].

Renal hypertension is due to the release of renin from the juxtaglomerular cells when renal vascular perfusion is impaired, followed by activation of angiotensin II and release of aldosterone. There are increases in circulating fluid volume, cardiac out put and peripheral resistance which are part of the homeostatic mechanisms for increasing renal perfusion, but are ineffective in the causes of the disorders producing renal hypertension, and inappropriate since the hypertension itself produces other complications. The raised blood pressure associated with raised renin levels in animal models of renal hypertension is promptly lowered by injection of inhibitors of converting enzyme or competitive antagonist of angiotensin. The use of these substances for the diagnosis of high renin hypertension in man has been advocated. Despite the association between elevated plasma levels of renin and angiotensin and high blood pressure in certain types of renal disease, elevated levels of these substances occur in other circumstances without an increase in blood pressure, for example in women on oral

contraceptive preparations in whom hypertension occurs in only a small minority[1].

iv. Mineralocorticoid Hypertension

Hypertension is one component in the syndrome characterizing coushings syndrome, Conn's syndrome and 17d-hyroxylation deficiency. In each of these disorders, there is excessive production and release of endogenous steroids with mineralocorticoid activity[1].

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Essential Hypertension

High blood pressure which is not secondary to another underlying disorder is described as essential, primary or idiopatic hypertension; the adjectives are interchangeable and signify only that the mechanism originally responsible for the raised blood pressure is not known. In most cases of essential hypertension, the elevated blood pressure is due to increased peripheral resistance. A mild degree of chronic elevation of the blood pressure that is not producing other disorders secondarily, and which does not appear to be progressively increasing at a faster

rate than the increase in blood pressure that occurs with age in normotensive individuals, is termed benign hypertension. A markedly raised blood pressure that shows signs of rapid progression and which is producing secondary effects is termed malignant hypertension[1].

1.1.2: Complications of Hypertension

Persistently elevated blood pressure imposes an increased workload on the heart, resulting eventually in left ventricular hypertrophy. If it is untreated, chronic marked hypertension may eventually lead to hypertensive heart disease which is a severe and potentially fatal condition involving enlargement and failure of the left ventricle. However, the signs of left ventricular hypertrophy may disappear after persistent and adequate therapy of moderate hypertension[1].

The malignant (accelerated) phase is the most serious of all the complications of hypertension. It is uncommon, if untreated it is fatal within a few months. The course of this phase may be abruptly terminated by a catastrophic cerebral haemorrhage or by cardiac failure; the patient who escapes or survives these events eventually succumbs to renal failre[1].

Hypertensive enephalopathy is a rare manifestation of severe hypertension. The cerebral arteries are forcibly dilated by the very high arterial pressure and hence the brain is over-perfused, rapidly becoming oedematous. The symptoms are headache, with impairment of consciousness ranging from drowsiness and confusion to coma. Epileptiform fits occur in the later stages, patients rapidly succumb if the Bp is not promptly reduced[1].

Stroke (haemorrhage and cerebral infarction) and coronary heart disease (angina pectoris and myocardial infarction) are by far the most common complications of hypertension. Both conditions are the result of a number of influences, but hypertension is one of the principal pathogenic factors, its role as a risk factor has been assessed quantitatively in prospective epidemiological studies[1].

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1.1.3: **Treatment of Hypertension**

Treatment of hypertensive patients can be considered under two headings; non-pharmacotherapeutic management and pharmacotherapeutic (anti-hypertensive) management. Non-pharmacotherapeutic management constitutes of diet therapy and behavioural approaches[2]. Diet therapy can be in these ways; change of diet such that is will lead to excess weight reduction,

reduction in salt intake, reduction in excess alcohol consumption and tobacco smoking[2].

Behavioural approaches include adequate exercise, relaxation therapies for stress reduction, avoid risk of other diseases e.g. Diabetes Mellitus. These life style changes may also be promoted in the population as a whole, or in individuals most likely to develop hypertension, in strategies for the primary prevention of high blood pressure[2].

1.1.4: ***Anti-Hypertensives***

There are about twelve classes of anti-hypertensives currently in use world wide:-

i. ***Adrenergic Neurone Blockers***

They act by selectively inhibiting transmission in post ganglionic adrenergic nerves. They are believed to act mainly by preventing the release

of nor-adrenaline at nerve endings. Examples are bethanidine, guanabenz,

guanadrel, guanethidine, guanoclor, guanoxan, debrisquine etc., The ones used clinically are bethanidine, guanethidine and debrisoquine.

ii. **Alpha-Adrenoceptor Blockers**

They mainly inhibit the interaction of norepinephrine, epinephrine, and other sympathomimetic drugs with adrenergic receptors[3]. This leads to both arteriolar and venous vasodilation resulting in a fall in blood pressure because of decreased peripheral resistance. Examples are bunazocin, prazosin, tolazoline, uradipil, indoramin, doxazosin, phentolamine etc.,[2].

Almost all of these agents are competitive antagonists in their interactions

with a-receptors. They have a wide spectrum of pharmacological specificities and are chemically heterogeneous. Some of these drugs have markedly different affinities for x_1 and x_2 receptors. For example prazosin is much more potent in blocking x_1 , than x_2 receptors and is termed selective, whereas yohimbine is x_2 selective, phentolamine has similar affinities for both of these receptor subtypes. In addition, some of these

drugs e.g. phenoxybenzamine may have other actions that are unrelated to adrenergic receptor blockage[3].

iii. **Angiotensin II Receptor Antagonists:-**

They act mainly by selective blockade of A Tii receptors thus, reducing the pressor effects of angiotensin II. Examples are Irbesartan, valsartan and losartan[2].

iv. **Beta-Adrenaceptor Blockers:-**

These are competitive antagonists at beta adrenergic receptor sites.

Examples are; acebutolol alprenolol, atenolol, bucindolol, metoprolol, labetolol etc.,[2]. The first of these selective agents was dichloroisoproterenol. However, this compound is a partial agonist and this property was thought to preclude its safe clinical use. In the 1950s additional agents were developed (pronethalol and propranolol). Propranolol is a competitive β-adrenergic antagonist that is devoid of agonist activity and it remains the prototype to which other β-adrenergic antagonists are compared. Propranolol has equal affinity for β_1 and β_2 receptors, thus it is a

non-selective β-adrenergic antagonist. Agents such as metoprolol and atenolol have somewhat greater affinity for β_1 than the β_2 receptors; these are examples of selective β_1 antagonists even though the selectivity is not absolute[3].

v. **Diuretice Agents**

These drugs decrease peripheral and pulmonary oedema, and decrease also preload by reduction in circulatory volume. They do this by inhibiting the reabsorption of sodium ions at various sites of the nephron[4].

vi. **Direct acting Vascular Smooth Muscle Relaxants:-**

They relax vascular smooth muscles through various mechanisms thereby dilating the vessels e.g. hydralazine, minoxidil, diazoxide, nitroprusside[5].

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vii. **Centrally Acting Agents:**

Several drugs act directly on the vasomotor centre and/or in the spinal cord to decrease sympathetic out-flow to the blood vessels. Most of them also depress the cardio accelerator

centre. Less is known about central inhibition of out-flow to the juxta glomerular apparatus, but the clinically significant drugs of this class all decrease plasma renin activity. Examples are clonidine, methyldopa and methyldopate[5].

viii. <u>Ganglionic Blocking Agents:-</u>

These act by competitive antagonism with neurotransmitters (e.g. acetylcholine) for the nicotinic cholinoceptors at the autonomic ganglia. Most of these agents are quaternary ammonium agents, although, a few amines also posses ganglionic blocking properties. Example is mecamylamine hydrochloride and trimetophan (the most clinically useful agents)[5].

ix. Miscellaneous anti-hypertensives include rawolfia alkaloids, e.g. reserpine, monoamine oxidase inhibitors, e.g., pargyline, serotonin blocking agents, e.g. ketanserin, etc.[6]

x. <u>Potassium Channel Openers</u>

They are also known as potassium channel activators. They have a direct relaxant effect on smooth muscles. They act at potassium channels to allow cellular efflux of potassium which hyper

polarises the cell membrane and leads to a reduction in intracellular calcium. The reduction in intracellular calcium produces relaxation of smooth muscles. Activation of potassium channels in blood vessels produces vasodilation. Potassium channel openers may also have potential use in other conditions caused by smooth muscle contraction, for example asthma and urinary incontinence. Examples are cromakalin, nicorandil and pinacidil.

xi **Angiotensin Converting Enzyme Inhibitors (ACE-IS)**

They act as vasodilators and reduce peripheral resistance. They inhibit ACE, the enzyme involved in the conversion of angiotensin 1 to angiotensin II, (the powerful naturally occuring vasocontrictor substance). Examples are captopril, enalapril, lisinopril, movestipril, pivopril, ramipril, spirapril, temocapril, teprotide, trandolapril etc.[6]

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xii. **Calcium Channel Blockers**

These are also known as calcium antagonists, calcium entry blockers and slow-channel blockers, they inhibit the cellular influx

of calcium which is responsible for maintenance of the plateau phase of the action potential. The main action of the calcium-channel blockers include dilation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction in heart rate, and slowing of AV conduction. Examples are nifedipine, amlodipine, diltiazem, lacidipine, ladoflazine, manidipine, nilvadipine, nimodipine, nitredipine, and verapamil[6].

1.1.5: <u>The Drug Regimen</u>

The basic principle of drug treatment of hypertension used to be the stepped-care approach:

Step 1: commence with either a thiazide diuretic or a beta blocker

Step 2: in the absence of adequate response, progress to step 2 consisting of a beta blocker and a diuretic in combination.

Step 3: in more resistant patients, addition of a third class of agent normally a vasodilator is helpful more recently the availability of calcium-channel blockers, ACE inhibitors, and alpha blockers, as well as concern about the possible metabolic effects of thiazides and beta blockers has led to a more flexible approach, in particular in the choice of first line agent.

The treatment of mild hypertension study (TOMHS) illustrated that the response to, and tolerance of these five main types of anti-hypertensives in this study, (chlorthalidone, acebutolol, amlodipine, enalapril and doxazasin) is similar, although, the choice of drug will depend on individual factors such as age and race as was demonstrated in a similar study comparing hydrochlorothiazide, atenolol, diltiazem, captopril, prazosin and clonidine[7]. In another study comparing Nifedipine, captopril, metoprolol and Reserpine + Clopamide + Dihydroergocristine mesilate (Brinerdin) [out patient study for 6

weeks therapy], there was no difference in the extent to which the blood pressure was lowered by all four anti-hypertensive agents, where as there was only an insignificant reduction in blood pressure in response to placebo. However, there were differences in tolerability and the impact on the subjective sense of well being. In this respect captopril and brinerdin came off best[8].

The 1993 National and International guidelines for (Joint national committee) all continued to rank diuretics (particularly thiazides) and beta blockers as the main first-line drugs since only they had been adequately tested in long-term mortality/morbidity studies in hypertensive subjects. They generally consider calcium channel blockers, ACE-IS and alpha blockers to be alternative first-line drugs, the ultimate choice depending on the presence or absence of contra-indications, on adverse effects, and on co-existing disease. In one of the lancet octet papers, swales concluded that; in the absence of other data, beta blockers seemed preferable first-line therapy in younger patients and low dose diuretics in elderly patients, although beta blockers would be first choice in post-myocardial infarction

patients with no evidence of heart failure. Beta blockers and ACE-I appear to be less effective in Afro Caribbean blacks, where as ACE inhibitors may be preferable in patients with left ventricular dysfunction and in diabetics[9].

Treatment is started at the lowest recommended dose[9]. If this is ineffective the dose may be increased (except in the case of thiazide diuretics where there is generally no additional benefit, but more adverse effects) or another first-line drug either added or substituted. Two drug combinations are often necessary, such as; a diuretic plus a beta blocker or an ACE inhibitor; an alpha blocker plus a beta blocker. A 3-drug combination may sometimes be required, especially in severe hypertension[9].

Under controlled conditions beta blockers, calcium channel blockers, and ACE inhibitors appear to have similar anti-hypertensive efficacy when used alone, where as diuretics may be slightly less effective, when used in combination, all these anti-hypertensive drugs may have less than additive hypertensive effects[9].

Other classes of anti-hypertensive drugs that have been used include centrally acting drugs such as clonidine and methyldopa and direct-acting drugs like the adrenergic neurone blocker gaunithidine and the rauwolfia alkaloid reserpine are rarely recommended now. Newer types of anti-hypertensives, include the angiotension II receptor antagonist losartan and the potassium channel opener pinacidil. Losartan may be considered as an alternative to ACE inhibitors when persistent cough associated with the latter is unacceptable[9].

1.1.6: Withdrawal of Drug Treatment

It has been standard teaching that drug treatment for hypertension is continued indefinitely, but there have been some reports of successful withdrawal in selected patients, United Kingdom Guidelines suggest that, once hyertension is controlled, a reduction in dosage or even withdrawal of anti-hypertensive drugs may be possible in patients with mild hypertension provided that Bp is consistently controlled, there is no evidence of target organ damage, and blood pressure continues to be monitored.

1.2: PURPOSE OF THE STUDY

This research intends to make a comparative analysis of the place of calcium channel blockers and ACE-I in terms of their usage and acceptability in Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State.

This work is intended to give some contribution to the on going research on these two classes of drugs, which is being carried out world wide.

1.3: RELEVANT RESEARCH QUESTIONS

In order to carry out this comparative analysis, certain basic and crucial questions had to be asked e.g. In what conditions are the calcium channel

blockers and ACE inhibitors used? Are they first-line drugs? How are they used? Are they easily available? Are they cheap or costly? Are they acceptable to the patients? Are their side effects common in this area? How do the patients react to the side effects?

1.4: SIGNIFICANCE OF THE RESEARCH PROBLEM AND THE JUSTIFICATION FOR INVESTIGATING IT

There is increasing reliance on ACE inhibitors and calcium channel blockers in the management of hypertension because of their general effectiveness, low incidence of adverse reactions and potential specific benefit in patients with renal disease. In addition, it is reasonable to assume that the reversal of LVH is a desirable therapeutic goal in the treatment of hypertension, therefore the effect of angiotensin converting enzyme inhibition on LVH is of particular interest[10]. Also, Nifedipine and Captopril are the two agents with the most rapid on-set of action (within 0.5 - 1hour) and may be used to treat hypertensive emergencies as well as urgencies[11]. These and many other reasons shows the necessity for more research on these two classes of drugs (calcium channel blockers and angiotensin converting enzyme inhibitors).

CHAPTER TWO

LITERATURE REVIEW

2.1: HISTORICAL BACKGROUND

Goldblattis' discovery in 1934 of a means for producing in animals a form of hypertension that closely resembled the human form triggered a search for a pressor substance of renal origin that might be responsible for elevating blood pressure in human hypertension as well as in experimentally hypertensive animals. Renin was first discovered in kidneys by Tiger Stedt and Bergman in 1898. It is present in simple extracts of kidneys in very large amount. Direct intravenous injection of such crude preparations into experimental animals produces a very impressive elevation of blood pressure that may last as long as one hour[12].

About 1940, intensive work by (page and Helmer in the United States and Braun-Mesendez and Coworkers in Argentina) showed that renin itself is not a direct pressor or vasoconstrictor substance. It was found that renin, acting on plasma, produced a new, previously unknown, short acting, vasopressor substance. This was the first indication that renin was the initial activating component of what was eventually to be revealed as a complicated, potent pressor substance. Page and Helmer 1940 named the substance angiotonin, while Braun-Menendez 1940 used the term hyertensin. Many years

later an agreement was reached to adopt the compromise term angiotensin[13]. The chemical characterization of angiotensin in 1950s, and its synthesis, introduced the modern era in research on the renin angiotensin system. However, when methodology for the determination of plasma renin and angiotensin was developed, new doubts were raised as to the relevance of these substances to hypertensive diseases, since no correlation could be found between levels of these hormones and the severity of human hypertension. Finally, the transient blockade of angiotensin II, either by its competitive antagonists or by converting enzyme inhibition provided the final proof of angiotensin's contribution to various forms of hypertension. The development of angiotensin-converting enzyme inhibitors was originally initiated by Ferreira (1965) who isolated a mixture of peptides from the venom of the Brazilian viper Barthrops Jararaca and found that they potentiate the effect of bradykinin. In 1968 Bakhle reported that this mixture of peptides was a potent inhibitor of angiotensin - converting enzyme. In 1970 Ferreira characterized a pentapeptide B.P.P. 5a rom among nine isolated bradykinin potentiating peptides from the venom. Ondetti et, al., (1977) purified six similar peptides from the same venom. One of them, the nonapeptide teprotide was then symthesized and purified. In 1977 Ondetti et, al., deviced a new series of compounds that con be taken orally and interact with the

converting enzyme in much the same way as the above peptides. Recently, another class of compounds was developed (N-Carboxylmethyl-dipeptides), which are very active in inhibiting converting enzyme despite lack of sulfhhyhdryl group[13].

It was evident as early as 1947 that excitation-contraction coupling involved calcium ions. Heilbrum and Wiercumski showed that micro injections of calcium into muscle cells would initiate contraction. The key role of calcium in excitation-contraction coupling becomes even more evident by virtue of the fact that many substances produce a positive or negative inotropic effect by enhancing the calcium action on utilization of high energy phosphates or by interfering with it. Example, bivalent cobalt or nickel ions, compete with the calcium ions in such a way that excitation-contraction coupling can be abolished as is the case in complete calcium deficiency. In an extensive search for other substances which might also be capable of lowering contractile tension of the heart by inhibiting excitation - contraction coupling, more than thirty drugs with clear calcium antagonistic side effects were found over seven years. They include, a number of adrenergic β-receptor blocking compounds, antifibrillatory drugs, barbituric acid derivative and some local anaesthetics. A new group of extremely potent calcium antagonists (prenylamine, verapamil, compound D600, etc.), which are capable of inhibiting

excitation contraction coupling in a highly specific way was discovered later. The first reports about the pronounced negative-inotropic effects of these drugs were published by Lindner for penylamine and by Haas et. al., for verapamil and compound D600[34]. Currently, there are three groups of calcium channel blockers; some that are related to papaverine (verapamil), dihydropyridines (nifedipine) and others that are benzothiazepines, (e.g. diltiazem). Calcium antagonists were introduced as anti-anginal agents in the 1970s and were approved as anti-hypertensives in the 1980s, and are included among the recommended choices for initial monotherapy in the 1980 Joint National Committee (J.N.C.) report. More than 1000 clinical report from over 50 countries have been published to date, confirming the beneficial therapeutic effects of nifedipine[14].

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2.2: RENIN-ANGIOTENSIN SYSTEM

The main components of the renin-angiotensin system are, renin, its substrate (angiotensinogen), angiotensin I, angiotensin II. Renin is a proteolytic enzyme secreted mostly by the juxtaglomerular apparatus of the kidney, a granular cell structure located in the wall of the afferent arteriole, which is contiguous with the macula densa portion of the same nephrone[35]. It acts as an acid protease that catalyses the hydrolytic release of the

decapeptide angiotensin I from its a-globulin substrate, angiotensinogen. As it courses through the circulation the two end amino acids histidyl and leucine are removed by a converting enzyme present on the plasma membrane of endothelial cells forming the eight amino acid polypeptide angiotensin II. This conversion occurs through out the body and the high levels of the converting enzyme found in the lung convert about 33% in a single passage. Angiotensin II exerts the primary physiologic effects of the system, through smaller fragments, in particular the heptapeptide angiotensin III may also be active. Renin itself probably is without effect other than by its activation of angiotensin[15].

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Renin axis presides over blood pressure homeostasis. Siinply stated, blood pressure in the final analysis is the product of two factors, the so called pressor factor, which is determined by the caliber of the arterioles or the degree of vasoconstriction of the arterial tree, and the volume factor, which is determined by the amount of liquid available to fill the arterial tree. The vasoconstrictor factor is largely determined by the plasma angiotensin II generated from renin, and the volume factor is largely determined by the amount of aldosterone acting on the kidney, where renin is secreted into the blood-stream. The conversion of angiotensin I to the active octapeptide then occurs, and angiotensin II provides the two limbs of the system, first by

quickly vasoconstricting the arterial bed, and second, by more slowly stimulating the release of aldosterone. The result is an increase in plasma volume at the same time that arteriolar caliber has been reduced by the angiotensin. Both factors together raise pressure to such a point that renin release is turned off, most probably by the intra- renal baro receptor mechanisms (see Figure 1.1). It is assumed that derangements in this system can produce hypertension and also, hypertension of other origin can produce predictable derangements in the system. The renin-angiotensin system may be involved in virtually all forms of hypertension, although, it is unlikely to be the primary mechanism in most[15]. It has been found that environmental stress significantly enhance renin release, then could contribute to chronic hypertension development[16]. In 1958, Gross suggested that the renin angiotensin system was involved in the electrolyte balance and the regulation of aldosterone secretion by the adrenal cortex. Moreover, elevated rates of renin secretion were noted upon experimental reduction of Na^+ concentration in plasma. Thus, the renin-angiotensin system came to be recognized as a mechanism to stimulate aldosterone synthesis and secretion and, an important physiologic mechanism in the homeostatic regulation of blood volume and pressure and of the electrolyte composition of body fluids[17], as shown in Figure 1.2. In the adrenal tissue, both sodium deprivation and potassium

loading independently increase the number of specific angiotensin receptor sites which is presumably responsible for the concomitant stimulation of aldosterone systhesis. These opposite effects of sodium deprivation upon the response to angiotensin II - a lesser rise in blood pressure, a greater increase in aldosterone synthesis - are physiologically sensible enabling sodium to be retained without a rise in blood pressure[17].

The ACE inhibitors are sometimes referred to as bradykinin potentiating factors (BPFS) because they were shown to inhibit an enzyme that catalyses the degradation and inactivation of bradykinin (now known as kininase II). Erdos and associates established that angiotensin converting enzyme and kinase II are one and the same enzyme; a peptidy- dipeptidase (or dipeptidyl carboxy peptidase). Thus, a single enzyme catalyses both the synthesis of angiotensin II, a potent pressor substance, and the destruction of bradykinin, a potent vasodilator[17].

The renin-angiotensin system plays an important role in LVH and in particular, in the development of cardiac interstitial fibrosis[18].

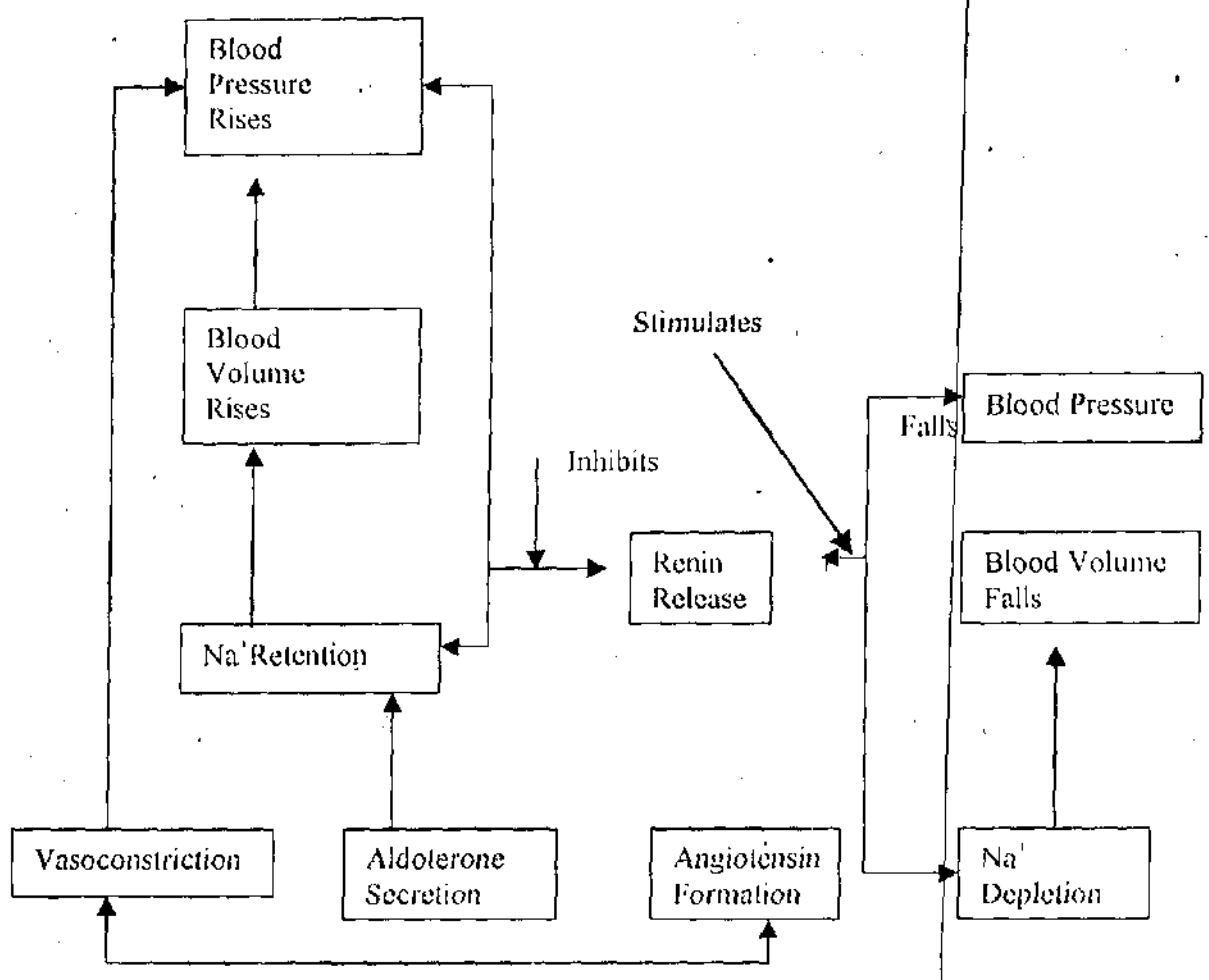


FIGURE 1.1 A schematic Portrayal of the Homeostatic Role of the Renin-Angiotensin System[17]

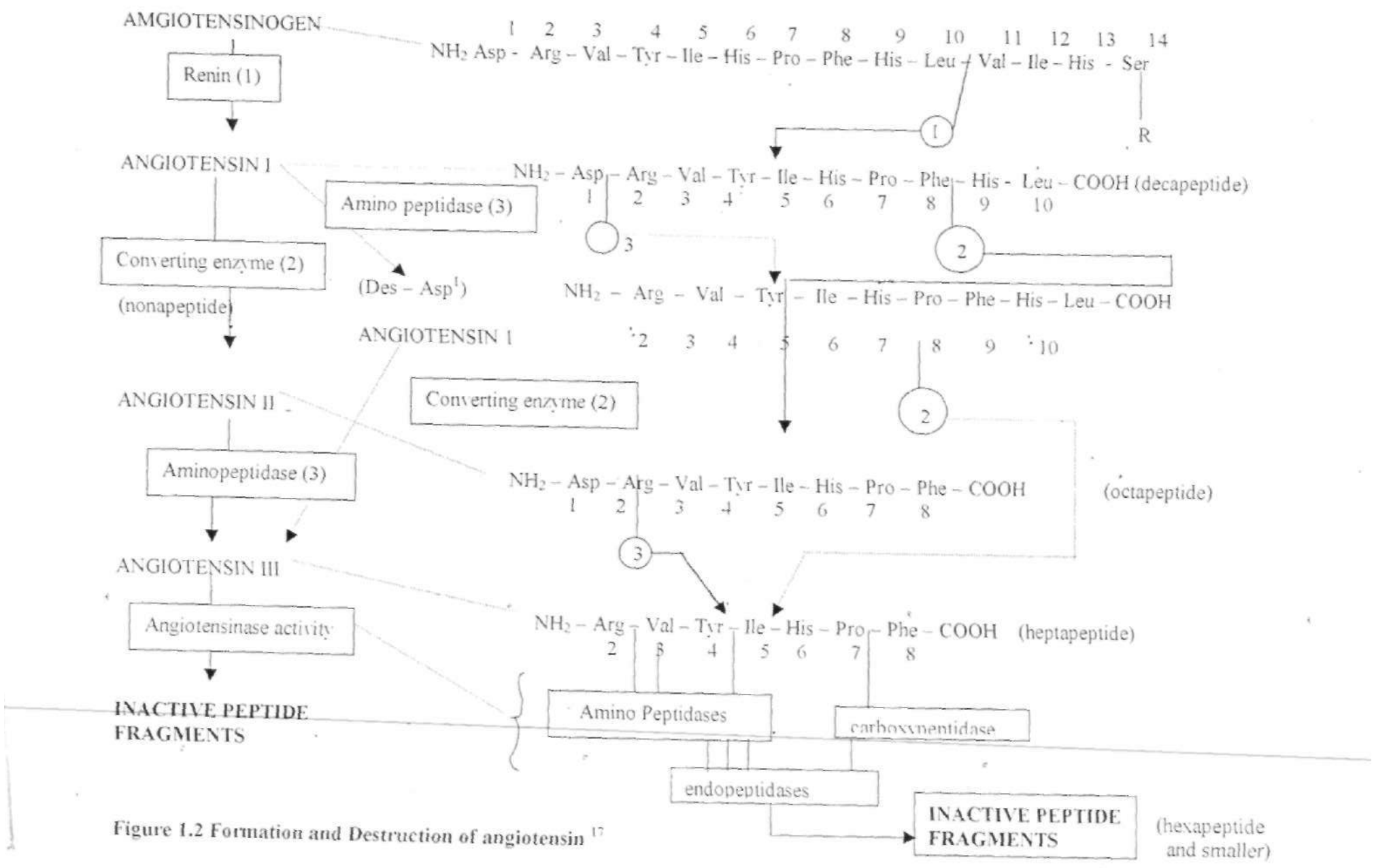


Figure 1.2 Formation and Destruction of angiotensin [17]

2.3: EFFECTS OF INHIBITION OF RENIN-ANGIOTENSIN SYSTEM

There are four sites where intervention in the renin-angiotensin system is now feasible:

i. **Suppression of Renin Release**

Since the release of renin from the juxtaglomerular apparatus is at least partially controlled by sympathetic nerves, inhibitors of adrenergic activity will block renin release. In both research and clinical practice, the β-adrenoceptor blockers have been most widely used for this purpose. Adrenergic blockade is only partially effective and the secretion of renin in response to the signal of sodium depletion via the macula densa is not blocked[19].

ii. **Inhibition of Renin Action**

A number of inhibitors of the action of the enzyme are available but they have only been used experimentally. These include: renin antibody, pepstatin, various phospholipids, and analogs of the renin substrate which compete with the natural substrate[19].

iii. **Blockade of Angiotensin II**

Various analogues of angiotensin II have been synthesized to serve as competitive antagonists at its receptor sites. The 1-Sarcosin, 8-alanine substituted analog (P-113 or Saralasin) has both a strong binding affinity for the receptor, sites and a resistance to degradation by aminopeptidase attack.

Though it has some agonist activity, its predominant antagonist effects make it suitable to be used as an in vivo test of the angiotensin mediation of hypertension in particular, in the search for renovascular hypertension. Its short half-life, agonist effects, and parenteral mode of administration preclude its therapeutic use[19].

iv **Inhibition of the Conversion of Angiotensin I to Angiotensin II**

The converting enzyme is best referred to as "peptidyl dipeptidase" since it breaks peptidyl dipeptide bonds in various substrates. Since angiotensin is inactive, agents which inhibit the converting enzyme have the potential to paralyse the workings of the renin-angiotensin system. The first inhibitor of this converting enzyme was derived from snake venom. Synthetic CEIS are now available[19].

SQ 20,881 (Teprotide):- This nonapeptide is one of the several isolated from the venom of the snake Bathrops jararaca. The effect of the venom was described as "Brady-Kinin Potentiating Factor" and subsequently characterized and synthesized. This CEI is only effective parenteraly but a great deal of important data came from studies with it[19].

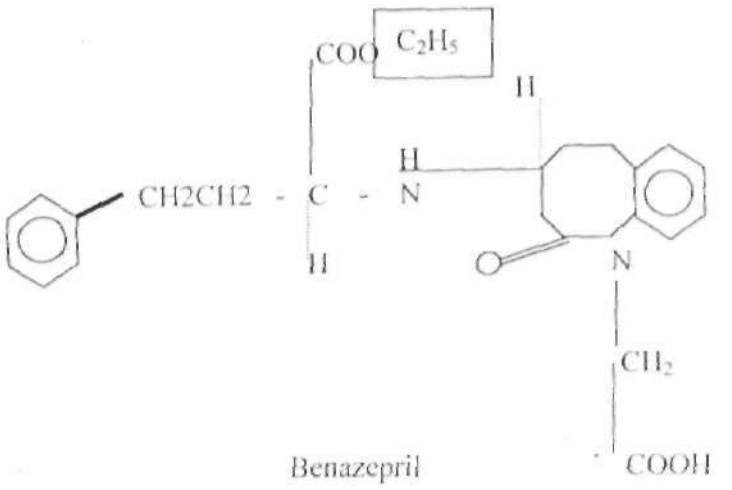
SQ 14,225 (Captopril, Capoten) - Based on the knowledge of enzyme structure and function a series of compounds designed to inhibit ACE where synthesized. Captopril (D-3-mercapto-2-methylpropanoyl-L-proline) was selected as the best. It is effective orally and it is now available for use in the treatment of severe hypertension. Meanwhile, studies of a structurally similar but more lipid soluble CEI, YS 980, are being conducted[19]. Other CEIS - the various side effects of captopril may be related to its stuff hydryl (SH) group which binds to the zinc ion on the ACE. Another orally effective CEI without an SH group (MK - 421) is now under clinical investigation[15]. Curently, there are many types of ACEIS in use clinically world-wide. They include Alacepril, Benazepril, Ceronapril, Enalaprilat, Fosinopril, Imidapril,

Bibenzapril, Piropril, Quinapril, Ramipril, spirapril, Temocaptril, Transdolapril, 20-Feriopril and so on[16]. There appears to be few significant difference between these drugs. They may be distinguished from each other by the presence or absence of a sulfhydryl group, whether they are pro-drugs or not and their affinity for ACE in vascular and other tissues, although whether these characteristics modify pharmacodynamics and therefore, clinical efficacy is uncertain. Difference in these characteristics do however, influence on-set and duration of action of ACEIS[20]. Many ACE Inhibitors have been synthesized. These drugs can be classified into three broad groups based on chemical structure:

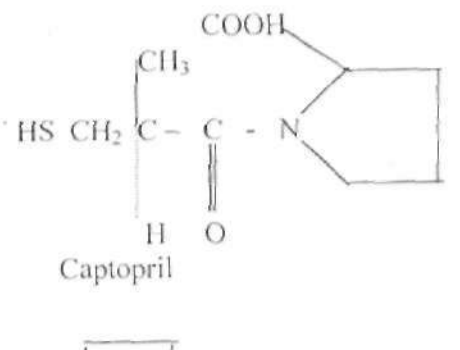
(a) Sulfhydryl containing ACEIS Structurally related to Captopril, e.g. Fentapril, pivalopril, zofenopril, alacepril.

(b) Dicarboxyl-containing ACEIS Structurally related to enalapril, e.g. lisinopril, benazepril, quinapril, moexipril, ramipril, spirapril, perindopril, idolapril, pentopril, indalapril, cilazapril.

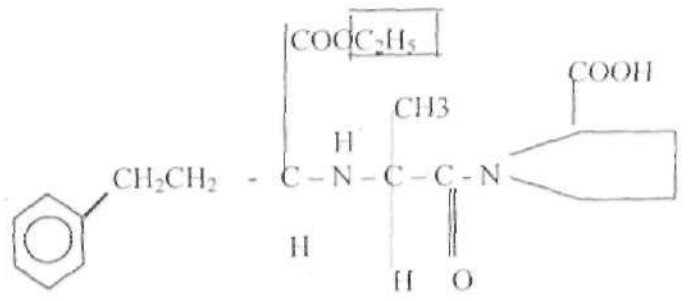
(a) Phosphorus containing ACEIS are esters containing prodrugs that are 100-1000 times less potent ACEIS than



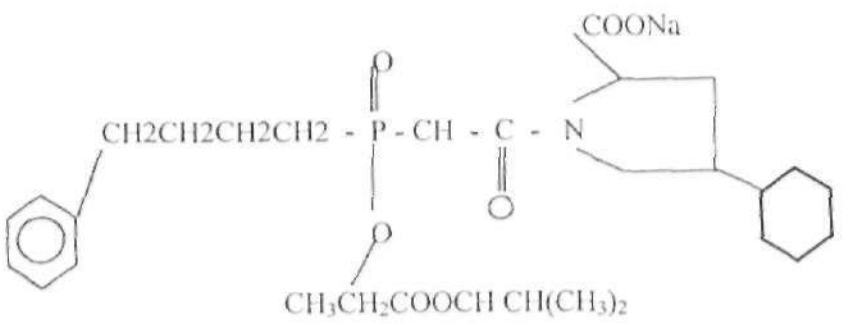
Benazepril



Captopril

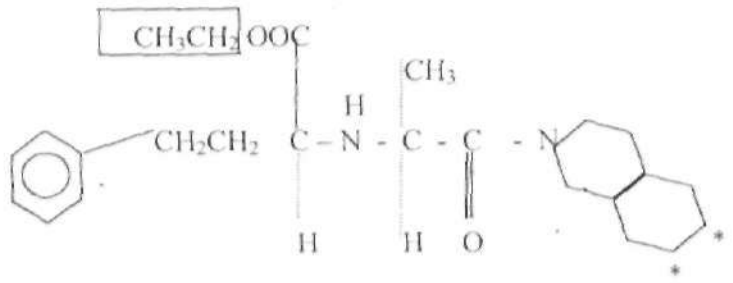


Enalapril

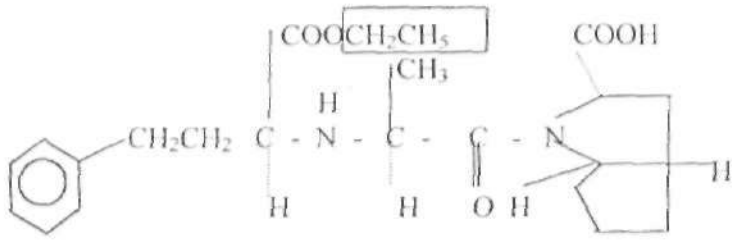


Fosinopril Sodium

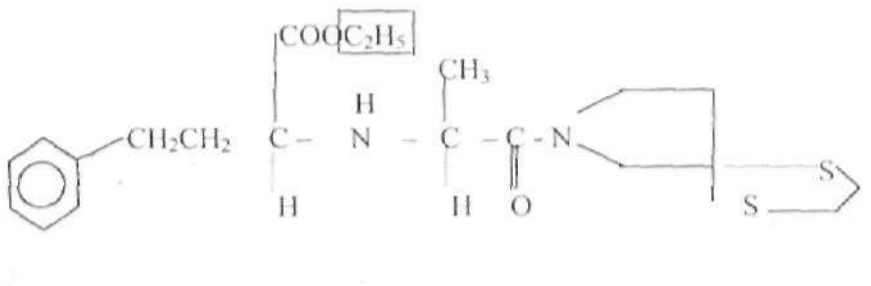
- 477996
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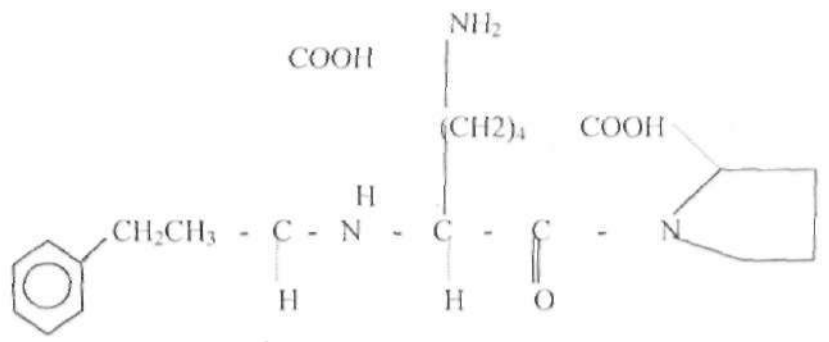
Quinapril



Ramipril



Spirapril



Lisinopril

FIGURE 2.1 Chemical Structures of Selected ACEIS[21]

the active metabolites but which have a much better oral bioavailability than the active metabolites[21].

There are many different ACE inhibitors approved for use in the United States (see Figure 2.1). Captopril and lisinopril are active molecules. Enalapril, quinapril, moexipril, benazepril, fosinopril, ramipril, and spirapril are relatively in active until converted to their corresponding di-acids, the structures enclosed within boxes are removed by esterases and replaced with a hydrogen atom to form the active molecule in vivo, e.g. enalapril to enalaprilat or ramipril to ramiprilat and so on. The structure of moexipril differs slightly from that of quinapril. The asterisks (*) indicate the dimethoxy substitution (Positions 6 and 7)[21].

2.4: PHARMACOLOGICAL EFFECTS OF ACE INHIBITION

The essential effect of agents that act via this mechanism on the renin angiotensin system is to inhibit conversion of the relatively inactive angiotensin 1 to angiotensin II. In this way they attenuate or abolish responses to angiotensin I, but not to angiotensin II. They are antihypertensive agents that act as vosadilators and reduce peripheral resistance; they have beneficial effects on left ventricular dysfunction, and they reduce protein uria associated with kidney disease[21].

The ACE inhibitors are highly specific drugs i.e. they do not interact directly with other components of the renin angiotensin system. Although they also inhibit the degradation of bradykinin and potentiate its hypotensive action, the principal pharmacological and clinical effects of ACE inhibitors seem to arise from suppression of synthesis of angiotensin II. Nevertheless, it must be remembered that these inhibitors, albeit quite specific at the level of the enzyme, act on an enzyme with many substrates. In addition, recent evidence suggests that ACE inhibitors may also affect other enzymes, including those involved in the generation of prostaglandins[21]. The pharmacological actions of ACE inhibitors are thought to be primarily due to the inhibition of the renin angiotensin-aldosterone system, but since they also effectively decrease blood pressure in patients with low renin concentrations, other mechanisms are most probably also involved[22].

2.4.1: PHARMACOKINETICS OF ACEIS

Most ACEIS are given by mouth and they are generally prodrugs (apart from captopril and lisinopril) and following absorption undergo rapid metabolism by ester hydrolysis to the active diacid form; for example enalapril is converted to enalaprilat. Metabolism occurs mainly in the liver. Excretion as active drug or active metabolite is principally in the urine, some

such as benazeprilat and fosinoprilat are also excreted via the biliary tract. Elimination of the diacid is polyphasic and there is a prolonged terminal elimination phase, which is considered to represent binding to the ACE at a saturable binding site. This bound fraction does not contribute to accumulation of drug following multiple doses. The terminal elimination half-life does not therefore, predict the kinetics observed with multiple dosing and effective half-life for accumulation is the value usually quoted[21, 23].

2.4.2: ***Cardiovascular System***

In healthy, Na^+ - replete animals and man, a single oral dose of an ACE inhibitor has little or no effect on supine or erect systemic blood pressure[21]. Repeated doses over a period of several days, however, cause a small, consistent reduction, in blood pressure and a subtle blunting of compensatory postural reflexes. By contrast, even a single dose of these inhibitors lower blood pressure substantially in normal subjects when they have been depleted of Na^+. This effect is accompanied by a clear fall in total peripheral resistance and reflects the activation of the renin-angiotensin system by restriction of dietary Na^+[21].

2.4.3: **Effects in Hypertension**

Inhibition of ACE lowers systemic arteriolar resistance and mean, diastolic, and systolic blood pressures in various hypertensive states. The effects are readily observed in animal models of renal or genetic hypertension and in human subjects with hypertension (with the exception of that due to primary aldosteronism). ACE inhibitors commonly lower blood pressure. The initial change in blood pressure tends to be positively correlated with PRA (Plasma renin activity) and angiotensin II concentrations prior to treatment. However, as treatment is continued, a greater number of patients show a sizeable reduction in blood pressure, and the antihypertensive effect then correlates poorly or not at all with pretreatment values of PRA[22]. This result, which is as yet little understood, presents a challenge to current understanding of the mechanisms of hypertension. At the same time it confers on drugs of this class a welcome breadth of clinical utility as anti-hypertensive agents[22].

The fall in systemic blood pressure observed in hypertensive individuals treated with ACE inhibitors results from a reduction of total peripheral resistance in which there seems to be a some what variable participation by different vascular beds. The kidney is a notable exception to this variability, in that there is a relatively, constant finding. This is perhaps not surprising, since the renal vessels are exceptionally sensitive to the vasoconstrictor

actions of angiotensin II. Increased renal flow occurs without an increase in glomerular filtration rate; infact, the filtration fraction is reduced. Both the afferent and efferent arterioles are dilated, and the hydrostatic pressure in the glomerulus does not change[22]. Blood flow in cerebral and coronary beds, where autoregulatory phenomena are prominent, is generally well maintained[23].

Besides causing systemic arteriolar dilation, ACE inhibitors increase the compliance of large arteries, which contributes to a reduction of systolic pressure. Cardiac function in patients with uncomplicated hypertension is generally little changed, although stroke volume and cardiac output may increase slightly with sustained treatment. Baro-receptor function and cardiovascular reflexes are not compromised, and responses to postural changes and exercise are little impaired. Yet surprisingly, even when a substantial lowering of blood pressure is achieved, heart rate and concentrations of catecholamines in plasma generally reflects an alteration of baroceptor function with increased arterial compliance and the loss of the normal tonic influence of angiotensin II on the sympathetic nervous system[23].

Inhibition of converting enzyme reduce, but not seriously impair the secretion of aldosterone in the general population of hypertensive individuals. The stimulation that results from postural changes in which angiotensin plays a prominent role, is attenuated. However, aldosterone output is maintained at

adequate levels by other stimuli of steroidogenesis, such as adrenocorticotropic hormone (ACTH) and K^+. The activity of these secretagogues on the zona glomerulosa of the adrenal cortex requires, at most, only very small trophic or permissive amounts of angiotensin II, which are always present because inhibition of converting enzyme is encountered only in patients taking supplemental K^+ or a K^+- sparing diuretic[23].

2.4.4: <u>Effects in Chronic Congestive Heart Failure</u>

Inhibtion of convering enzyme commonly reduces after-load, and both cardiac out-put and cardiac index increase, as do incides of stroke work and stroke volume. Heart rate generally is reduced. Systemic blood pressure falls, sometimes steeply at the out-set, but tends to return toward initial levels. Renovascular resistance falls sharply, and renal blood flow increases. Natriuresis occurs as a reult of the improved renal hemodynamics and the reduced stimulus to secretion of aldosterone by angiotensin II. The excess volume of body fluids contracts, which reduces venous return to the right heart. A further reduction result from venodilatation and an increased capacity of venous bed. Venodilation is another somewhat unexpected effect of inhibition of converting enzyme, for angiotensin II has little acute venoconstrictor activity. Nevertheless, long term infusion of angiotensin II

has been reported to increase venous tone in vivo, perhaps by some central or peripheral interaction with the sympathetic nervous system. The response to the converting enzyme inhibitor also involves reduction of pulmonary arterial pressure, pulmonary capillary wedge pressure, and left artery and left ventricular filling pressure (pre-load). The better hemodynamic peformance results in increased tolerance of exercise. Cerebral and coronary blood flows usually are well maintained, even when systemic blood pressure is very substantially reduced[21].

In addition ACE inhibitors decrease the mass and wall thickness of the left ventricle in patients with hypertension such changes, which can be detected after therapy with ACE inhibitors for as such a period as three months, resemble those that are seen with inhibitors of the sympathetic nervous system, β-adrenergic antagonists, and calcium-channel blockers. Resting cardiac performance is improved following regression of left ventricular hypertrophy, even if blood pressure is allowed to return to the hypertensive range[21]. In rats, ACE inhibitors also protest against the congestive heart failure that follows myocardial infarction[21].

In both experimental and human studies, ACE inhibitors appear to perform better than other anti-hypertensive agents in reversing cardiac structural changes[23]. A recent meta analysis showed ACE inhibitors to be

more efficacious than other first-line antihypertensives in reducing left ventricular mass[23]. A controlled long-term study of previously untreated men showed that enalapril reversed LVH significantly better than did hydrochlorothiazide and that the regression of LVH was independently related to blockade of the renin-angiotensin system. Indeed, there have been studies showing that ACE inhibitors can affect LVH without lowering blood pressure. Moreover, ACE inhibitors are effective in reserving LVH as well as interstitial fibrosis[23]. The prognostic implications of this remain to be seen. So far, the experience with spirapril on LVH is limited, but the accumulated data are promising[24]. This is consistent with the hypothesis that angiotensin II is involved in growth thickening of the arterial wall. It was reported that angiotensin II may be responsible for the abnormal vascular smooth muscle cell growth seen in hypertension, either indirectly as a consequence of elevating blood pressure or directly as a result of receptor-mediated effects on vascular smooth muscle cell growth. Angiotensin II is able to initiate a component of early genetic program associated with growth. There was induction of C-fos by angiotensin II which was independent of intracellular alkalinization but was dependent on mobilization of calcium and activation of protein kinase C. These results provide insight into the early signals activated

by angiotensin II that could be important in the proliferative or hypertrophic responses[25].

Most studies agree that ACE inhibitors have little direct acute effects on smooth muscle in large arteries. At concentrations higher than required to inhibit converting enzyme, ACE inhibitors depress the constrictor response to sympathetic nerve stimulation or alpha-adrenoceptor stimulation. At lower doses they inhibit angiotensin I, but not angiotensin II - induced vasoconstriction. By inhibiting the breakdown of bradykinin, ACE inhibitors potentiate the endothelium dependent vasodilator effects of this kinin[26].

2.4.5: ADVERSE EFFECTS OF ACEIS

Angiotensin - converting enzyme (ACE) inhibitors all appear to have a similar spectrum of adverse effects although, at one time some, such as taste disturbances and skin reaction, were attributed to the presence of a sulfhydryl group as in captopril.

They include hypotension, dizziness, fatigue, headache, gatro-intestinal disturbances, taste disturbances, persistent dry cough and other upper

respiratory tract symptoms. Skin rashes (including erythema multiforme and toxic epidermal necrosis), angioedema, hypersensitivity reactions, renal impairment, hyperkalaemia, and hyponatraemia. Other adverse effects such as chest pain, palpitations, tachycardia, stomatitis, abdominal pain, pancreatitis, hepato-cellular injury or cholestatic, jaundice, alopecia, neutropenia and agrarulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia, anaemias, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence have been reported[27].

2.4.6: **Precautions**

Pronounced hypertension may occur, for example, following the first dose of an ACEI in patients with severe hypertension who have been treated with multi-drug regimens that include diuretics, particularly in patients with heart failure and in sodium or volume - depleted patients. Treatment should be initiated with very small doses and the initial dose should be given at bed-time preferably at an interval after withdrawal of the diuretic. The latter can be given again subsequently, if necessary[27]. In patients with ischaemic heart disease or cerebro-vascular disease, a severe fall in blood pressure could result in myocardial infarction or cerebrovascular accident. After over dose

with an ACEI it may be necessary to reverse hypotention by volume expansion with an intravenous infusion of sodium chloride 0.9%[27].

Proteinuria has occurred mainly in patients with existing renal disease and some of these patients develop the nephritic syndrome. Evidence of deterioration in renal function, including increasing blood concentrations of urea and creatinine, and reversible acute renal failure have been reported in patients with existing renal or renovascular dysfunction and may be aggravated by hypovolemia[27].

ACE inhibitors can also induce renal insufficiency in patients with bilateral renal artery stenosis or with stenosis of the artery to a single remaining kidney. This effect is apparently caused by reduction of the concentration of angiotensin II, which is needed in such conditions to constrict the efferent glomerular arterioles and maintain adequate filtration[28]. They should not generally be used in patients with impaired renal function, also if renovascular disease is present or suspected ACE inhibitors are occasionally necessary for severe renal hypertension in such patients when they can only be given with great caution and under specialist supervision. Also, ACE inhibitors may reduce glomerular filtration in patients with severe congestive heart failure or in heart failure patients who have been over treated with diuretics[28].

Patients with peripheral vascular diseases or generalized atherosclerosis may be at high risk because they may have silent renovascular disease renal function should be assessed in all patients prior to administration of ACE inhibitors[28].

Patients with pre-existing renal disease or taking high doses should be observed regularly for proteinuria[28].

Regular white blood cell count may be necessary in patients with peripheral vascular disorders, such as systemic lupus erythematosus and scleroderma, or in patients receiving immuno suppressive therapy, especially as they also have impaired renal function[29].

ACE inhibitors have been reported to produce harmful effects in animal foetuses following large maternal doses and should not be used during pregnancy. Although ACE inhibitors are not teratogenic during the early period of organogenesis (first trimester), continued administration of ACE inhibitors during second and third trimester can cause oligohydrammos, fetal calcorial hypoplasia, fetal pulmonary hypoplasia, fetal growth retardation, fetal death, neonatal anuria, and neonatal death[28].

Despite some reduction in the concentration of aldosterone, significant retention of potassium ion is rarely encountered in patients with normal renal function who are not taking other drugs that cause potassium ion retention.

However, ACE inhibitors may cause hyperkalemia in patients taking K^+ - sparing diureties, K^+ - supplements, β-adrenoceptor blockers, or NSAIDS[27].

An exceedingly rare and reversible side effect of ACE inhibitors is spilage of glucose into the urine in the absence of hyperglycemia[27]. This mechanism is unknown.

Also exceedingly rare and reversible is hepatotoxicity, usually of the cholestatic variety[27]. The mechanism is also unknown.

2.4.7: **Drug Interactions**

Antacids may reduce the bio-availability of ACE inhibitors, capsaicin may worsen ACEI induced cough, NSAIDS may reduce the antihypertesive response to ACE inhibitors and K^+ - sparing diuretics and K^+- supplements may exacerbate ACE inhibitors - induced hyperkalemia. ACE inhibitors may increase plasma levels of digoxin and lithium and may increase hypersensitivity reactions to allopurinol.

2.4.8: **Actions of ACE Inhibitors**

The actions of ACE inhibitors are thought to be primarily due to the inhibition of renin-angiotensin aldosterone system in the circulation, it is now recognized that this mechanism alone cannot readily explain why ACE inhibitors are effective in patients with normal or low plasma renin activity and

even in enephric subjects, why the anti-hypertensive response lasts much longer than the duration of serum - ACE inhibition and why the best pharmacokinetic models incorporate a parameter for binding to non-circulating ACE[30]. It has been known that endogenous renin-angiotensin systems exist in many tissues, with diverse effects on tissue function, and pharmacokinetic studies indicate that response to ACE inhibitors[30]. The clinical implications of tissue ACE inhibition can be illustrated by the functional and structural adaptations associated with long-term ACE inhibitor therapy, including increased arterial wall compliance, improved left ventricular function in heart failure, regression of vascular and left ventricular hypertrophy and delayed progression of diabetic nephropathy[30].

It has been suggested that ACE inhibitors may exercise their anti-hypertensive effects, at least in part by inhibiting calcium-mobilization in vascular tissue. Whether this represents direct calcium channel blocking properties or is mediated via tissue renin-angiotensin systems warrants investigation[30].

2.4.9: **Therapeutic Uses of ACEIS**

i. **In Hypertension**

A significant reduction in blood pressure may be achieved in many hypertensive patients with relatively few adverse reactions, this is especially true when an ACE inhibitor is used concurrently with a diuretic. When used alone, ACE, inhibitors are roughly comparable in their activity to a thiazide diuretic or a β-adrenergic antagonist, and they lower blood pressure significantly in about haif of patients with moderate essential hypertension. When used with a thiazide diuretic, this fraction rises to more than 80%. The concurrent administration of a β-adrenergic blocking agent also enhances the response, but to a lesser extent. This is perhaps because the β-adrenergic blockers owe their efficacy, in part to inhibition of renin release[31].

ii. **In Hypertensive Crises**

The ACE inhibitor, captropril have been suggested as alternative in the management of hypertensive crises, however, it has not generally been recommended for initial use since pressure may fall too abruptly, in addition patients with accelerated hypertension have quite a high prevalence of renovascular

disease, ACE inhibitors may cause severe deterioration of renal function in such patients[32].

iii. **In Diabetic Patients**

ACE inhibitors and calcium channel blockers are generally preferred in diabetic patients with hypertension because of potential adverse effects of diuretics and β-blockers. ACE inhibitors are reported to reduce insulin resistance, they may be particularly effective in patients with nephropathy, as there is evidence of benefit in preserving renal function, they have been reported to decrease protein uria and preserve glomerular filtration rate in diabetic patients independently of changes in systemic blood pressure[32].

iv. **In Hypertension and Renal Disease**

ACE inhibitors are used in patients with hypertension and renal diseases although there are concerns about progression of stenosis and possible harmful effects of blood pressure reduction on the function of the affected kidney[32].

v. **In Myocardial Infarction**

In both the GISS 1 - 3 study and the ISIS - 4 study favourable results were achieved with the ACE inhibitors lisinopril and captopril, respectively, given by mouth and started within 24 hours of the onset of symptoms and in the Chinese Cardiac Study (CSS - 1) benefit was seen with captopril given by mouth within 36 hours of the on-set of symptoms. The authors of ISIS - 4 recommended that early treatment with an ACE inhibitor should be considered in all patients except those with cardiogenic shock or persistent severe hypotension, and the treatment should be reviewed after a few weeks and continued in those with left ventricular dysfunction. Others considered that, until further studies define which patients benefit from early treatment with an ACE inhibitor, their routine use in unselected patients was not warranted[33].

In long term management of myocardial infarction, ACE inhibitors reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Myocardial infarction patients with left ventricular dysfunction benefit from long term oral

administration of ACE inhibitors such as captopril, ramipril or trandolapril started about 3 days or more after infarction[34].

In prevention of myocardal infarction; studies (LVD (SOLVD) trials have indicated that the ACE inhibitor enalapril, might protect against MI, unstable angina, and cardiac death in patients with sysmptomatic or asymptomatic heart failure[34].

vi. <u>In Chronic Congestive Heart Failure</u>

ACE inhibitors are very useful in the management of chronic CHF because they induce systemic arteriolar dilatation, and thereby reduce after load, and also cause venodilatation, lessen fluid retention, and thus, reduce preload. These and other beneficial effects described above lead to increased cardiac out-put, amelioration of signs and symptoms of congestion, increased exercise tolerance, improved clinical status, and prolongation of life for

patients in end-stage CHF. Although, initially indicated for patients inadequately controlled by digitals and diuretics. CEIS are now being used at earlier stages of cardiac decomposition.

Some less common hypertensive conditions in which converting enzyme inhibitors appear to be particularly useful include malignant hypertension, renovascular hypertension, hypertensive crises of scleroderma, and dialysis - resistant hypertension in end-stage renal failure[34].

Captopril is an effective agent for the treatment of hypertensive emergencies as well as urgencies[35, 36, 38].

2.5: CALCIUM AND THE HEART

Ionic calcium is required to sustain the beating of the heart in vitro. This indicate that cardiac cell membrane is calcium-sensitive. Heilbrum ad Wiercumski showed that micro-injections of calcium into muscle cells would initiate contraction. This shows that there is an unusual dependence of heart muscle upon external calcium. Thus, it was evident that excitation contraction coupling involved calcium ions[37].

Regulation of the intracellular free calcium ion concentration plays a central role in the contraction-relaxation cycle of the mammalian heart. Rapid switches in the intracellular free calcium ions concentration to high levels (about 2×10^{-6} MOI/L), induce contraction during systole, and back to low levels (about 2×10^{-7} MOI/L) produce relaxation during diastole. This process

required an apparatus of several Ca^{2+} binding and transport proteins, most of them located on or in the sarcoplasmic reticulum (SR).

Upon depolarization of the sarcolemma extracellular Ca^{2+} enters the cell through voltage-gated Ca^{2+} channels (dihydropyridine receptors), located on the transerse tubules (T-tubules) formed by the sarcolemmal membrane. The Ca^{2+} release channel is also termed as the ryanodine receptor (RyR). In the heart this Ca^{2+} induced Ca^{2+} release from the SR is the main source for the systolic increase of Ca^{2+} concentration. The cardiac SR is an entirely intracellular membrane network that represents the main structure of Ca^{2+} of storage in the cardiomyocyte. It is composed of three main components[38].

(a) The functional region with the terminal cisternae containing the RyR in dose contact with the sarcolemmal T-tubules;

(b) The corbular region which represents terminal cisternae not opposed to the T-tubules, and;

(c) The logitudinal region contains the sarco.(endo) plasmic reticulum Ca^{2+}- ATPase (SR Ca^{2+} - ATPase, SERCA) and its regulatory protein phospholamban. The Ca^{2+} by the SR binds to troponin C, which initiates contraction by activating cross bridge cycling between actin and myosin. Ca^{2+} binding to troponin C causes a conformational change of the troponin-tropomyosin complex and

allows the binding of myosin and actin which is sterically inhibited by tropomyosin during diastole.

Myocardial relaxation is induced by a rapid decrease in cytosolic free Ca^{2+} concentration leading to a dissociation of Ca^{2+} from troponin C, thus, restoring the inhibition of actin-myosin binding by the troponin-tropomyosin complex. In part Ca^{2+} is extruded out of the cell by the sarcolemmal Na^{+} - Ca^{2+} exchanger. The main mechanism for reduction of cytosolic Ca^{2+} against a concentration gradient into the lumen of the SR where it is bound by storage proteins, mainly calsequestrin. The activity of the SR Ca^{2+} - ATPase can be enhanced by phosphorylation of the inhibitory regulatory protein PLN, the mechanism by which catecholamines enhance the rate of myocardial relaxation. The Ca^{2+} reuptake by the SR Ca^{2+} - ATPase contributes to about 70-80% of the Ca^{2+} flux during diastole. This protein is therefore, regarded as a key player in cardiac relaxation. Moreover, the filling state of the SR also determines the force of contraction generated during systole since cardiac contaction is triggered mainly by Ca^{2+} release from SR[36],[40].

Although, calcium has a direct effect on blood vessels, increasing peripheral vascular resistance, it role in clinical hypertension may be a consequence of its ability to increase the release of catecholamines at nerve terminals or from the adrenal medulla[39].

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Increase in intracellular sodium leads to increase in intracellular calcium which increase vascular smooth muscle contractility and thereby raises peripheral resistance. The presence of increased intracellular sodium will raise the concentration of free calcium within the vascular smooth muscle cells[40].

Depolarization in atrial tissue was mediated by two inwardly directed ionic currents. When the transmembrane potential of a cardiac cell reaches threshold, the membrane permeability (conductance) for Na^+, increases rapidly and markedly.

The so called fast channel is responsible for this influx of Na^+ , and it is blocked by tetrodoxin. The time required for the second inward current is determined in large part by the movement of Ca^{2+} or into the cell through a membrane pore that is thus, termed the slow channel and is inhibited by Mn^{2+}, but not by tetrodotoxin and it contributes to the maintenance of the plateau phase of the cardiac action potential.

A derivative of verapamil, D-600 (gallopamil), was subsequently shown to block the movement of Ca^{2+} through the slow channel and thereby alter the plateau phase of the cardiac action potential[41].

From the rather complex process of Ca+ cyling in the myocardium it is evident that close regulation of intracellular Ca^{2}+ homeostasis is essential to

maintain normal myocardial contraction and relaxation, and that alterations in either quantity or function of the proteins involved might significantly affect cardiac performance. Indeed, several studies on experimental animal models with cardiac hepertrophy or failure as well as on myocardium from patients with hypertrophy or end-stage heart failure have shown abnormal intracellular Ca□□ handling under these conditions. The common key observation was a prolonged diastolic Ca^{2}□ transient with a diminished capacity to restore low resting Ca^{2}□ level 41.

Human congestive heart failure is characterized by a combination of reduced contractility during systole and impaired relaxation during diastole more or less independently of the type of the underlying cardiac disease. In particular, diastolic dysfunction, clinically characterized by elevated left ventricular end-diastolic pressure and volume, is regarded as an important clinical and prognostic parameter since it is highly correlated with the clinical performance of the patients. Functional studies on isolated failing human myocardium led to the hypothesis that abnormalities in intracellular Ca^{2+} cycling may in part account for contractile and relaxational dysfunction. Measuring intracellular Ca^{2+} transients with luminescent indicators such as aequorin or fura 2 shows a peak Ca^{2+} transient, a reduced systolic, markedly prolonged diastolic Ca^{2+} decline with an elevated diastolic resting Ca^{2+}

concentration and a reduce SR Ca^{2+} content as estimated from caffeine induced release. Furthermore, the force-frequency relation has been shown to be altered in failing myocardium. The potentiation of contractile force at higher stimulation frequencies seen in non-failing myocardium is absent or even inverted in failing hearts. Given a prolonged SR Ca^{2+} re-uptake, this was interpreted as a consequence of partial SR Ca^{2+} depletion, which is more pronounced at high frequencies. Tension-independent head development was also found to be diminished in failing human heart, reflecting a decrease in the amount of Ca^{2+} released and in the rate of diastolic Ca^{2+} removal. In summary, these results point to a defect in SR Ca^{2+} re-uptake and/or release in human heart failure[41].

The cellular mechanisms of cardiac hypertrophy remain despite tantalizing clues glared from a variety of experimental approaches. There a hypothesis that an increase in cytosolic free ca^{2+} concentration ($[Ca^{2+}]i$) triggers the expression of proto oncogens, which in turn direct the characteristic increase in protein synthesis. New results from perfused ferret hearts are presented demonstrating that $[Ca^{2+}]_i$ increases, that $[Ca^{2+}]_i$ constitutes as a direct consequence of an elevation in perfusion pressure. It therefore seems plausible that there is crucial link between the initial stimulus for hypertensive hypertrophy (elevated perfusion pressure) and the

secondary alterations in gene expression. Nevertheless, further investigation will be required to establish whether changes in $[Ca^{2+}]_i$ are necessary or sufficient to stimulate myocardial cell growth[41].

Acute and chronic hyper-calcemia, perse, cause hypertension and correction of the hyper-calcemia is often followed by return of blood pressure to normal levels. Chronic hypercalcemia may lead to progressive renal failure which in turn, can cause hypertension. Patients with chronic renal failure are more sensitive to the hypertensive effect of hypercalcemia. Acute hypocalcemia, perse, is associated with hypotension in man and in dogs[42].

Hass and Hart Felder reported in 1962 that verapamil, a putative coronary vasodilator, possessed negative inotropic and chronotrophic effects that were not seen with other vasodilatory agents such as nitroglycerin. In 1967, Fleckenstein suggested that the negative inotropic effect resulted from inhibition of excitation-contraction coupling and that the mechanism involved reduction of the movement of Ca^{2+} into cardiac myocytes. A derivative of verapamil gallopamil and other compounds, such as nifedipine also were subsequently shown to block the movement of Ca^{2+} through the slow channel and thereby alter the plateau phase of the cardiac action potential[43].

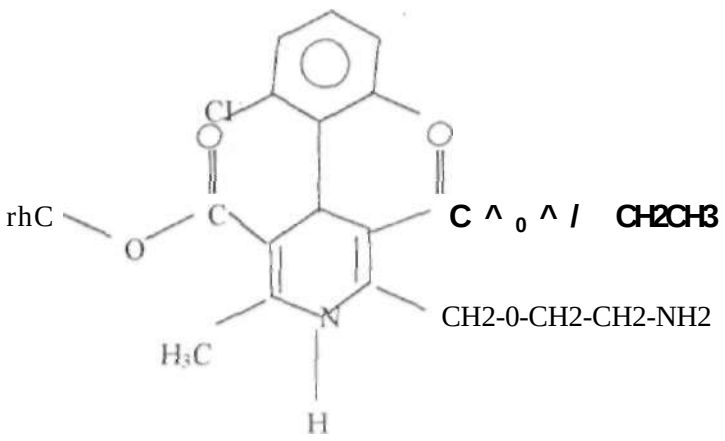
2.6: CALCIUM CHANNEL BLOCKERS

The development of the calcium channel antagonists represents one of the major advances in cardiovascular pharmacotherapeutics of the latter half of the twentieth century. In contrast to other cardio active agents such as antihypertensive, anti-arrhythmias, antiischemic, and positive ionotropic agents, calcium antagonists are unique in that they play an important role in the treatment of a wide variety of cardiovascular disorders[43].

At present there are many calcium channel blockers in use some are hereby named verapamil (a phenylalkylamine), diltiazem (a benzothiazepine), nicardipine, nifedipine, amlodipine, felodipine, and nimodipine (dihydropyridines); and bepridil (a diarylamino propyl amine ether) are approved for use in the United States. These agents have diverse chemical structures (see Figure 2.3).

2.6.1: Pharmacological Properties of Calcium Channel Blockers

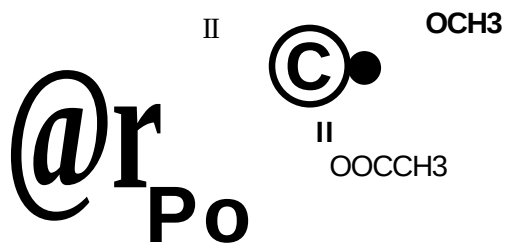
Calcium antagonists or calcium entry blockers are pharmacologic agents which inhibit the entry of calcium into cardiac and smooth muscle cells through calcium-permeable channels in the cell plasma-membrane. The currently available calcium antagonists differ in their molecular structures, their sites and modes of action upon the slow channel, and their effects on various vascular functions. There are, therefore, differences in clinical actions and



rhC O C C ^ 0 ^ / CH2CH3

CH2-0-CH2-CH2-NH2

Amlodipine (Norvasc)



$CH_2CH_2N(CH_3$ -

Diltiazeiii (Care izeni, Dilacor)

u.

- N-

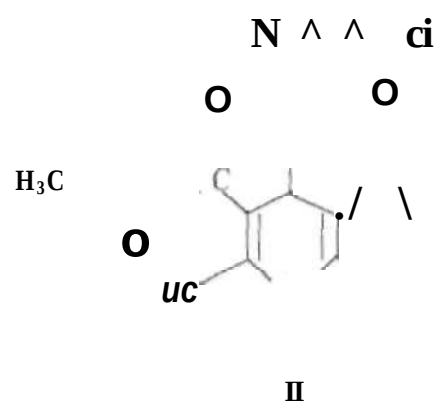
CH2 CH3

<S N-CI I2-CH-CH2-O-CII2-CH

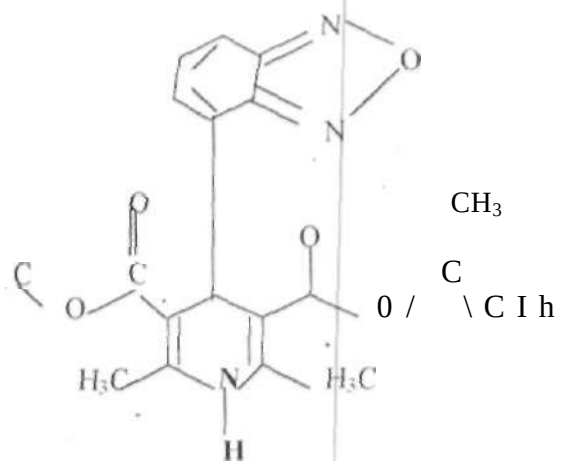
C1I3

' Bcpridil (Vascor).

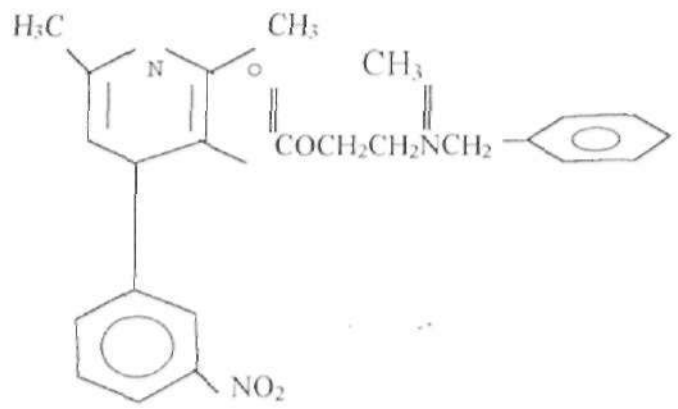
CI



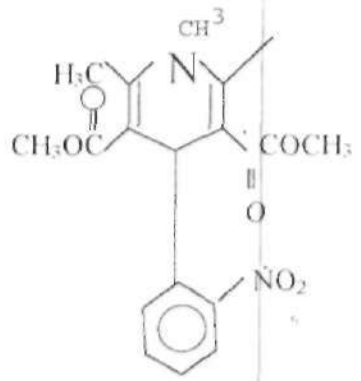
Felodipine (Plcndil)



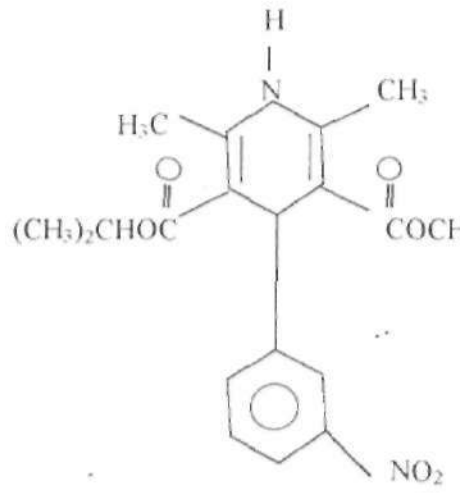
Isradipiuc (Dynacir C)



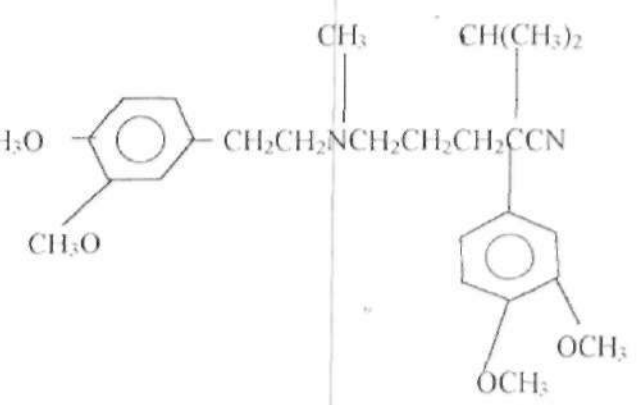
Nicardipine (Cardene)



Nifedipine (Adalat, Procardia)



Nimodipine (Nimlop)



Verapamil (Calan, Isoptin, Verelan)

Figure 2.3: ***Structure of some Calcium Channel Blockers Currently in Use 43***

marked variations in side effects between the three classes of calcium antagonists now available[43].

(a) **Actions in Vascular Tissue**

Although, there is some involvement of sodium ion (Na^+) currents, depolarization of vascular smooth muscle cells is primarily dependent on the influx of Ca^{2+} via at least three distinct mechanisms that may be responsible for contraction of vascular smooth muscle cells[45], first, voltage sensitive calcium-channels upon in response to depolarization of the membrane, and extracellular Ca^{2+} moves down its electrochemical gradient into the cell. After closure of calcium-channels, a finite period of time is required before the channels can open again in response to a stimulus. Second, agonist-induced contractions that occur without deplorization of the membrane result

from the hydrolysis of membrane phosphatidylinositol with the formaton of inositol triphosphate, which acts as a second messenger to release intracellular calcium from the sarcoplasmic reticulum. This receptor mediated release of intracellular calcium may trigger further influx of extracellular calcium.

Third, receptor-operated calcium channel allow the entry of extracellular calcium in response to receptor occupancy[43].

(b) **Actions in Cardiac Cells**

Calcium channel blockers produce a negative inotropic effect. Although, this is true of all classes of calcium channel blockers, the greater the degree

of peripheral vasodilation seen with the dihydropyridines is accompanied by sufficient baroreflex - mediated increase in sympathetic tone to overcome the negative inotropic effect. Diltiazem also may inhibit mitochondrial Na^{2+} - Ca^{2+} exchanger[43].

(c) **Hemodynamic Effects**

All of the calcium - channel blockers that have been approved for clinical use decrease coronary vascular resistance and increase coronary blood flow. The dihydropyridines are more potent vasodilators in vivo and in vitro than is verapamil, which is more potent than diltiazen. The hemodynamic effects of each of these agents vary, depending on the route of administration and the extent of left ventricular dysfunction[43].

2.6.2: **Mechanisms of Action**

Increased concentrations of cytosolic calcium cause increased contraction of cardiac and vascular smooth muscle cells. The entry of extracellular calcium is more important in initiating the contraction of myocardial cells, while the release of calcium from intracellular storage sites also participates in contraction of vascular smooth muscle, particularly in some vascular beds. In addition, the entry of extracellular calcium can trigger the release of additional calcium from intracellular stores[43].

2.6.3: **Absorption, Fate and Excretion of Calcium-Channel Blockers**

Although, the absorption of these drugs is nearly complete after oral administration, their bio-availability is reduced, in some cases markedly because of first pass hepatic metabolism. The effects of these drugs are evident within 30-60 minutes of an oral dose, with the exception of the more slowly absorbed and larger-acting agents amlodipine, isradipine, and felodipine. For comparison, peak effects of verapamil occur within 15 minutes of its intravenous administration. These agents all are bound to plasma proteins to a significant extent (70-98%), their elimination half-lives, during repeated oral administration, bio-availability and half-life may increase because of

saturation of hepatic metabolism. A major metabolite of diltiazem is desacetyl diltiazem with diltiazem's potency as a vasodilator. N-Demethylation of verapamil results in production of nor-verapamil, which is biologically active but much less potent than the parent compound. The half-life of nor-verapamil is about 10 hours. The metabolites of the dihydropyridines are in active or weakly active in patients with hepatic cirrhosis, the bio-availabilities and half-lives of the calcium-channel blockers may be increased and dosage should be decreased accordingly. The half-lives of these agents may also be long in older patients[43].

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2.6.4: **Adverse Effects**

The most common side effects caused by the calcium channel blockers, particularly the dihydropyridines, are due to excessive vasodilation. These effects may be expressed as dizziness, hypotension, headache, flusing, digital dysesthesia, and nausea. Other effects that may be experienced by patient include constipation and peripheral edema[43].

Nimodipine may produce muscular cramps when given in the large doses required for a beneficial effect in patients with sub-arachnoid hemorrhage[43].

Less common side effects include rashes, somnolence, and occasional minor elevations of liver function tests. These side effects usually are benign and may abate with time or with adjustment of the dose[43].

Although, bradycardia, transient asystole, and exacerbation of heart failure have been reported with verapamil, these responses usually have been reported with verapamil these responses usually have occurred after intravenous administration of verapamil, in patients with disease of the SA node or AV nodal conduction disturbances, or in the presence of β-adrenergic blockage[43].

2.6.5: Precautions

Aggravation of myocardial ischaemia has been reported with the dihydropyridines. Verapamil and diltiazem are less likely at therapeutic doses to aggravate myocardial ischemia, because of their lower capacity to induce excessive peripheral arteriolar dilatation and their ability to restrain excessive tachycardia. Thus, calcium channel blockers should be used with caution in this condition[43].

2.6.6: **Contra Indication**

The use of intravenous verapamil with a β-adrenergic receptor antagonist is contra-indicated because of increased propensity for atrio-ventricular block and/or severe depression of ventricular function[43].

Patients with ventricular dysfunction, SA or AV nodal conduction distrubances, and systolic blood pressures below 90mm Hg should not be treated with verapamil or diltiazem, particularly intravenously[43].

2.6.7: **Therapeutic Uses**

All calcium-channel blockers are equally effective when used alone for the treatment of mild to moderate hypertension; and in comparative trials, Ca^{2+} channel blockers are as effective in lowering blood pressure as β-adnergic receptor antagonists or diurectics[44].

Calcium-channel blockers are versatile drugs with proven efficacy in all types of hypertensive patients[44]. They seems to be especially efficacious in low-renin hypertension compared with other classes of anti-hypertensives, there is greater frequency of achieving blood pressure control with calcium-channel blockers as monotherapy in elderly subjects and in African-Americans, population groups in which the low renin status is more prevalent[44].

The efficacy of calcium-channel blockers is enhanced by the concomitant use of an angiotensin converting enzyme inhibitor, methyldopa, or

β-adrenergic receptor antagonists the preferred calcium-channel blocker would be one from the group that is relatively vasoselective, e.g. amlodipine, isradipine, nicardipine. Diuretics also may enhance the efficacy of calcium channel blockers but the data have not been consistent.

Calcium-channel blockers do reduce left ventricular mass but they are less effective than ACE inhibitors and methyldopa[44].

Nifedipine and captopril are the two agents with the most rapid on-set of action and are therefore, useful in the treatment of hypertensive emergencies as well as urgencies[44].

Calcium-channel blockers may be useful for protecting myocardium and improving cardiac function. Since it has been suggested that calcium over load may be one of the major causes of myocardial injury[44].

The calcium-channel blockers reduce cytosolic calcium concentration and are particularly effective in patients with volume dependent forms of hypertension[44].

Calcium-channel blockers and ACE inhibitors are generally preferred in diabetic patients with hypertension because of potential adverse effects of diuretics and β-blockers[44].

In hypertension and renal disease, ACEI and calcium-channel blockers are particularly used[45]. Calcium-channel blockers appears to have a positive

effect on renal function[44]. The use of calcium-channel blockers in pregnancy is still being studied[44].

In pulmonary hypertension, of all the vasodilators studied the most promising agents appear to be calcium-channel blockers and the prostaglandin epoprotenol. Improved survival over a 5-year period has been noted in some patients treated with high dose calcium-channel blockers. However, not all patients respond and because of concern about previously reported adverse effects in patients with primary pulmonary hypertension given these drugs it has been advised that an acute response test should be performed before embarking on long term treatment[44].

In stroke, calcium-channel blockers such as nimodipine can be used. In addtion to increased cerebral blood flow calcium-channel blockers may prevent brain cell necrosis by limiting transcellular calcium influx, but results have been conflicting[44].

Other conditions which calcium-channel blockers are useful are supraventricular tachyarrythmias and ischaemic heart diseases[43,45,44].

2.6.8: Significant Drug - Drug Iteractions

Verapamil can increase plasma concentrations of digoxin. When used with quinidine, calcium-channel blockers may cause excessive hypotension, particularly in patients with idiopathic hypertrophic sub aortic stenosis[44].

In a study with nifedipine, captopril, metoprolol and reserpine + clopamide + dihydroergocristine mesilate (brinerdin). It was shown that captopril and reserpine + clopamide + dihydroergocristine mesilate (brinerdin) were the best tolerated, while side effects were reported most frequently by patients on the calcium antagonists.

Over half of the patients in this group complained of one or more side effects, the most prominent being headache, congestion in the head, flushing and swollen ankles[46].

2.7: AIM OF THE STUDY

The use of calcium channel blockers and ACE inhibitors is increasing everyday the world-over. It therefore becomes necessary that more research be carried out on these two classes of drugs. This research in particular intends to assess the place of these two classes of drugs in Ahmadu Bello University Teaching Hospital, Zaria (a tertiary health institution). That is to find out how often they are being used, which of the different does of the

drugs is most used and most acceptable to patients and also side effects most encountered and the frequency of side effects and so on.

The frequency at which the calcium channel blockers and ACEIS are prescribed relative to other anti-hypertensives will be established, the different doses used will be found and compared, patients acceptability will be determined by compliance. Types of side effects and their frequency of occurrence will be deduced.

2.8: METHODOLOGY

2.8.1: Health Policy

Two complementary approaches have been proposed to control hypertension. In the public health or population approach the goal is to increase population awareness that elevated blood pressure is a major health problem even though it may not be apparent. To achieve this goal, the approach relies exclusively on educating the public, health professionals and patients with elevated blood pressure.

In research, information can be obtained either from records or by field work.

2.8.2: **Deducing Information from Records**

In this method all available records are contacted and studied carefully to deduce the required information. The records could be in form of files or folders carrying patients records in hospital or some documents written and filed in libraries or record sections of hospitals.

2.8.3: ***Field Work***

Field work entails going out to where one can get the required information by studying the specimens. It could be in a hospital, where one goes to hospital to see the patients, interview them or administer questionnaires to them from which the required information can be deduced. The limitation here is that some patients may object to some questions especially questions on their personal life or family history.

CHAPTER THREE

METHOD

3.1: NEED FOR RESEARCH

Research is needed in order to develop and implement control programmes appropriate to each level of health care and relevant to each community's health need. National programmes aimed at controlling high blood pressure are recommended in the countries where hypertension has already been identified as a major health problem or where mean levels of blood pressure in the population are rising in correlation with life style changes. Key elements of such a programme should include:-

- Raising awareness of the problem among the community as a whole, health professionals, individuals with high blood pressure, individuals at risk and policy makers.
- Advising/educating the community and individuals on how to promote and adopt healthy life styles, and the people with hypertension to adhere strictly to long-term therapeutic regimens.
- Ensuring active participation of all sectors of the community in the programme.

- Creating environmental conditions that support the adoption of healthy dietary and behavioural patterns.

Each country should identify specific targets for prevention and treatment and specify the time period for their achievement[1].

3.2: DATA COLLECTION

For a successful research, a method that will yield a reliable result has to be designed. Data can be collected from records or from fieldwork. In this work both methods of data collection were used, including information obtained from patients' folders in the Cardiac Clinic of Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, while other information obtained by interviewing patients and by administering questionnaires to the patients in the Cardiac Clinic.

The investigation was essentially carried out on two groups of patients. The first group of thirty one (31) patients was named as group one (G1). Here information was deduced from the patients folders. The second group of forty nine (49) patients was named as group two (G2). Here information was obtained from patients folders as well as interviewing them and administering an appropriately designed questionnaire, as in Appendix A, (a sample of the questionnaire administered to patients in (G2). First part of the questionnaire

related to personal data such as name, sex, age, height, weight and the diagnosis. These are relevant since they all have bearing on hypertension as a disorder and can help in its diagnosis and management. The diagnosis will reveal if there is a co-existing illness which has to be taken into account in the treatment of hypertension. The first question seeks to know for how long the patient has been a hypertensive and this gives an idea of the duration/long standing nature of the hypertension and thus helps in choosing the appropriate drug or drug combination to be used. The second and third questions will reveal the type of drugs used and which are ACE inhibitors or CCBS. Question four and five gives an idea of availability and cost of the ACEIS and CCBS prescribed, while question six and seven will reveal the patients compliance. Questions eight to seventeen together aim at evaluating patients response to the treatment that is whether the drug/drugs are really vitiating the elevated systemic blood pressure or not and whether the patient is experiencing any side effects or not. The rest of questions will also reveal the non-drug measures such as dietary restrictions (e.g. low salt diet) in the aetiology and management of hypertension as a disorder.

3.3: ANALYSIS DATA

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The data obtained was transformed into a spread-sheet from the bulky information compiled from the records of patients and the questionnaire. Two

different spread-sheets were prepared for each group of patients that is one for group one labelled group one and the other for on two labelled as Group Two. .Tables were formed from these spread-sheets using frequency count, seven tables were formed. The first one, table GI. 1 contains the result of analysis of group one that is comparing calcium channel blockers and angiotensin converting enzyme inhibitors with other anti-hypertensives in terms of frequency of prescribing, tables G2.1.1, G2.1.2, G2.1.3. G2.2.1, G2.2.2 and G2.2.3, contains the result analysed from group two patients with G2.1.1, G2.1.2, and G2.1.3, on calcium channel blockers while G2.2.1, G2.2.2 and G2.2.3 are on angiotensin converting enzyme inhibitors. Three pie charts were constructed on tables G2.1, G2.1.1 and G2.2.1, and six bar charts from tables G2.1.2, G2.1.3, G2.1.4, G2.2.1, G2.2.2and G2.2.3.

3.4: LIMITATIONS OF THE QUESTIONNAIR SURVEY

Since a particular period was specifically used for the survey that is November 1997 to November 1998, it means new patients were not included. Also only old cases who attended the clinic for the period were included. This was necessary because, time limit is an important factor that determines the relevance of information obtained in an investigation.

Some patients especially females shy away from question on their life styles and family history even though the purpose of the question was to establish if they are hypertensives, there is relationship between life styles and family history and high blood pressure. A knowledge of their style and family is therefore important to the overall successful management of their condition. An extra effort was therefore made to explain this fact to these patients and this resulted in the obliging answers to the relevant questions. .

APPENDIX A

QUESTIONNAIRE

NAME:_____

SEX:_____ AGE (YEARS):_____

HEIGHT:_____DIAGNOSIS:_____ WEIGHT:_____

1. Since when have you been diagnosed as a hypertensive patient?_____

2. Anti-hypertensives prescribed? _____

_____

3. How many of them are calcium channel blockers or ACE inhibitors?

_____

4. Are they easily available? Yes ☐ No ☐

5. Are they cheap/costly? Cheap ☐ Costly ☐

6. Are you regular with drugs? Yes ☐ No ☐

7. Why? _____

8. Which of your drugs do you like most?_____

9. Why? _____

10. Have your drugs ever been changed? ☐ Yes No ☐

11. If yes, how many times?_____

12. If no, would you like them to be changed? Yes ☐ No ☐

13. Why? _____

14. Which do you prefer, the present or previous treatment?

_____

15. Why? _____

16. Would you like the present treatment to be changed again?

_____

17. Why? _____

18. Are you on any diet restriction? Yes ☐ No ☐

19. Are you on any exercise? Yes ☐ No ☐

CHAPTER FOUR

RESULTS

Table GI.1 shows the frequency of prescribing of calcium channel blockers, ACE inhibitors and other anti-hypertensives from group one which was a group containing thirty one patients. Eleven out of thirty one (or 35.5%)of patients in this group were on calcium channel blockers, while only six patients (19.4%) were on ACE inhibitors, and only two (6.5%) patients received a combination of the two drugs, while twelve that is 38.71% of the patients were on other anti-hypertensives.

Tables G2.1.1 shows the distribution of patients on calcium channel blockers. It was deduced form the data on group two, which was a group of fourty nine patients with 35 on CCBS, thirty one (31) out of the thirty five (35) patients on CCBS that is 88.57% were all on Nifedipine retard, while only three (3) were on lacidipine and only one (1) was on amlodipine.

Table G2.1.2 shows the distribution of patients on the different doses of calcium channel blockers it was also deduced from group two data. It shows that four (4) patients (11.43%) were on Nifedipine® 20mg daily, twenty six (26) patients that is 74.28% were on Nifedipine 20mg bd, only one (1) patient that is 2.86% was on Nifedipine 20mg tid, while three (3) patients that is 8.5%

were on lacidipine 4mg daily and only one (1) patient (2.86%) was on amlodipine 10mg daily.

Tables G2.1.3 shows the patients response to different doses of calcium channel blockers. It can be seen that out of the four patients on Nifedipine 20mg one daily only one (1) that is 25% showed positive response, and from twenty six (26) patients on Nifedipine 20mg twice daily, seventeen that is 65.38% showed positive respond while the only patient on Nifedipine® 20mg three times daily did not response and only one out of the three patients on lacidipine 4mg once daily responded and the only patient on amlodipine 10mg once daily showed a positive response.

Table G2.1.4 shows the frequency of appearance of side effects due to calcium channel blockers. None out of the four patients on Nifedipine® 20mg once daily showed a side effect. Also, no patient showed side effect due to Nifedipine® 20mg three time daily, lacidipine and amlodipine. And, only one (1) patient out of the twenty six (26) patients on Nifedipine showed side effect (persistent severe headache).

Table G2.2.1 shows the distribution of patients on ACE inhibitors. It was also deduced from group two data out of which eighteen patients were on ACE inhibitors. Seventeen out of eighteen patients were on captotril while only one was on lisinopril.

Table G2.2.2 shows the distribution of patients on different doses of ACE inhibitors. Two patients out of eighteen that is 11.11% were on captopril 6.25mg once daily, five (27.77%) were on captopril 6.25mg twice daily, five also (27.77%) were on Captopril 6.25mg three times daily, two (1.11%) were on Captopril 12.5mg twice daily while one each on Captopril 12.5mg three times daily, Captopril 25mg twice daily, captopril 25mg three times daily and lisinopril 2.5mg once daily.

Table G2.2.3 shows patients response to different doses of ACE inhibitors. All the two patients of Captopril 6.25mg once daily showed positive response, two out of the five patients on captopril 6.25mg twice daily showed positive response, while four out of the five patients on captopril 6.25mg three times daily showed positive response and all the two patients on captopril 12.5mg twice daily showed positive response, also the only patients on captopril 12.5mg three times daily, captopril 25mg twice daily, and lisinopril 2.5mg once daily all responded positively, while the only patient on captopril 25mg three times daily did not respond.

Table G2.2.4 shows frequency of appearance of side effects due to ACE inhibitors. One one patient each showed side effects out of two, five, two and one patients on captopril 6.25mg once daily, captopril 6.25mg twice daily, captopril 12.5mg twice daily and captopril 12.5mg three times daily

respectively, and two patients showed side effect out of the five patients on captopril 6.25mg three times daily, while all the one, one patients on captopril 25mg twice daily, captopril 25mg three times daily and lisinopril 2.5mg once daily did not show any side effect.

Also from the spread sheet on group two data, it can be seen that only four patients on captopril showed bad compliance and only six patients out of the thirty one (31) patients on Nifedipine® were not regular with drugs while two out of the three patients on lacidipine were not regular with drugs. Also out of all the patients in group two only two were on diet restriction (low salt diet), one of which was on Nifedipine and the other on combination of both Nifedipine and captopril.

TABLE-G1.1: Distribution of patients on Calcium Channel Blockers, ACE, Inhibitors and Other Classes of Anti-hypertensives

Antihypertensive	Frequency	Frequency %
CalciumChannel Blockers	11	35.5
ACE Inhibitors	6	19.3
Both	2	6.5
Others	12	38.7
TOTAL	31	100.0

TABLE-G2.2.1: Distribution of Patients on Caclium Channel Blockers

Calcium Channel Blockers	Frequency	Frequency %
Nifedipine®	31	88.57
Lacidipine	3	8.57
Amlodipine	1	2.86
TOTAL	35	100.00

TABLE-G2.1.2: Distribution of Patients on Different doses of Calcium Channel Blockers

Calcium Channel Blockers	Dose (mg)	Frequency	Frequency %
Nifedipine®	20mg od	4	11.43
Nifedipine®	20mg bd	26	74.28
Nifedipine®	20mg tid	1	2.28
Lacidipine	4mg od	3	8.57
Amlodipine	10mg od	1	2.86
		35	100.00

TABLE-G2.1.3: Patients Response to Different Doses of C.C.B.S

Calcium Channel Blockers	Dose (mg)	Frequency	Positive Response	Frequency%
Nifedipine®	20mg od	4	1	25
Nifedipine®	20mg bd	26	17	65.38
Nifedipine®	20mg tid	1	0	0
Lacidipine	4mg od	3	1	33.33
Amlodipine	10mg od	1	1	100

TABLE -G2.1.4 Frequency of Appearance of Side Effects Due to CCBS

Calcium Channel Blockers	Dose(mg)	Frequency	Frequency of Side Effect	Frequency %
Nifedipine®	20mg od	4	0	0
Nifedipine®	20mg bd	26	1	3.84
Nifedipine®	20mg tid	1	0	0
Lacidipine	4mg od	3	0	0
Amlodipine	10mg bd	1	0	0

TABLE-G2.2.1 Distribution of Patients on ACE Inhibitors

ACE Inhibitor	Frequency	Frequency %
Captopril	17	94.44
Lisinopril	1	5.56

TABLE- G2.2.2 Distribution of Patients on Different Doses of ACE Inhibitor

ACE Inhibitor	Dose (mg)	Frequency	Frequency %
Captopril	6.25mg od	2	11.11
Captopril	6.25mg bd	5	27.77
Captopril	6.25mg tid	5	27.77
Captopril	12.5mg bd	2	11.11
Captopril	12.5mg tid	1	5.55
Captopril	25mg bd	1	5.55
Captopril	25mg tid	1	5.55
Lisinopril	2.5mg od	1	5.55
		18	

TABLE-G2.2.3: Patients Response to Different Doses of ACE Inhibitor

ACEI	Dose	Frequency	TVC Response	Frequency %
Captopril	6.25mg od	2	2	11.11
Captopril	6.25mg bd	5	2	11.11
Captopril	6.25mg tid	5	4	22.22
Captopril	12.5mg bd	2	2	11.11
Captopril	12.5mg tid	1	1	5.55
Captopril	25mg bd	1	1	5.55
Captopril	25mg tid	1	0	0
Lisinopril	2.5mg od	1	1	5.55

TABLE G2.2.4: Frequency of Appearance of Side Effect Due to ACEI

ACEI	Dose	Frequency	Frequency of S.ES	Frequency % of S.ES
Captopril	6.25mg od	2	1	50
Captopril	6.25mg bd	5	1	20
Captopril	6.25ng tid	5	2	40
Captopril	12.5mg bd	2	1	50
Captopril	12.5mg tid	1	1	100
Captopril	25mg bd	1	0	0
Captopril	25mg tid	1	0	0
Zestil	2.5mg od	1	0	0

Table G. 1.1.1: Derived From Table G.1.1

ANTIHYPERTENSIVE	FREQUENCY	FREQUENCY %	ANGLE ON THE CHART
Calcium Channel Blockers	11	35.5	$\frac{35.5}{100} \times 360 = 127.8^0$
A. C. E. Inhibitors	6	19.3	$\frac{19.3}{100} \times 360 = 69.5^0$
Both	2	6.5	$\frac{6.5}{100} \times 360 = 23.4^0$
Others	12	38.7	$\frac{38.7}{100} \times 360 = 139.3^0$
TOTAL	**31**	**100**	**360**

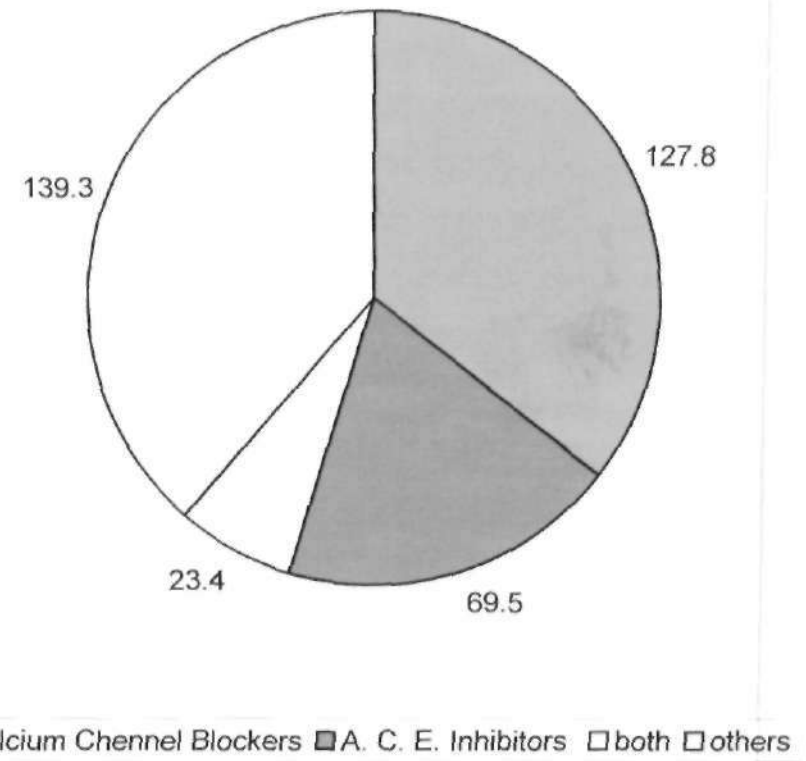


Fig. 4.1: A Pie Chart on the Distribution of Patients on Calcium Channel Blockers, ACEIS and other classes of antihypertensives.

Table G2. 1.1.1: Derived From Table G2.1.1

CALCIUM CHANNEL BLOCKERS	FREQUENCY	FREQUENCY %	ANGLE ON THE CHART
Nifedipine	31	88.57	$\frac{88.57}{100} \times 360 = 318.9^0$
Lacidipine	3	8.57	$\frac{5.56}{100} \times 360 = 30.8^0$
Amlodiphine	1	2.86	$\frac{2.86}{100} \times 360 = 10.3^0$
TOTAL	**35**	**100**	**360**

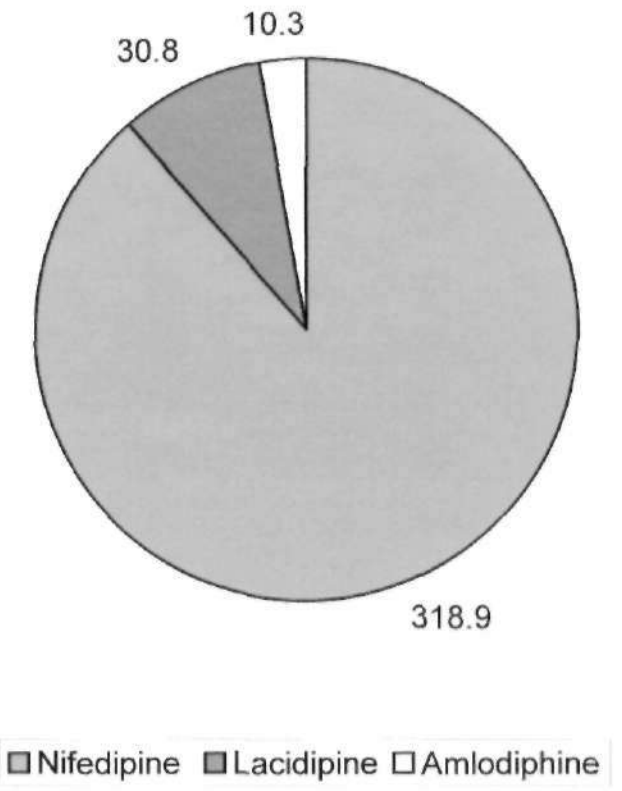


Fig. 4.2: A Pie Chart on the Distribution of Patients on Calcium Channel Blockers.

Table G2 2.1.1: Derived From Table G2.2.1

ACEI	FREQUENCY	FREQUENCY %	ANGLE ON THE CHART
Captopril	17	94.44	$\frac{94.44}{100} \times 360 = 339.98^0$
Lisinopril	1	5.56	$\frac{5.56}{100} \times 360 = 20.02^0$
TOTAL	**18**	**100**	**360**

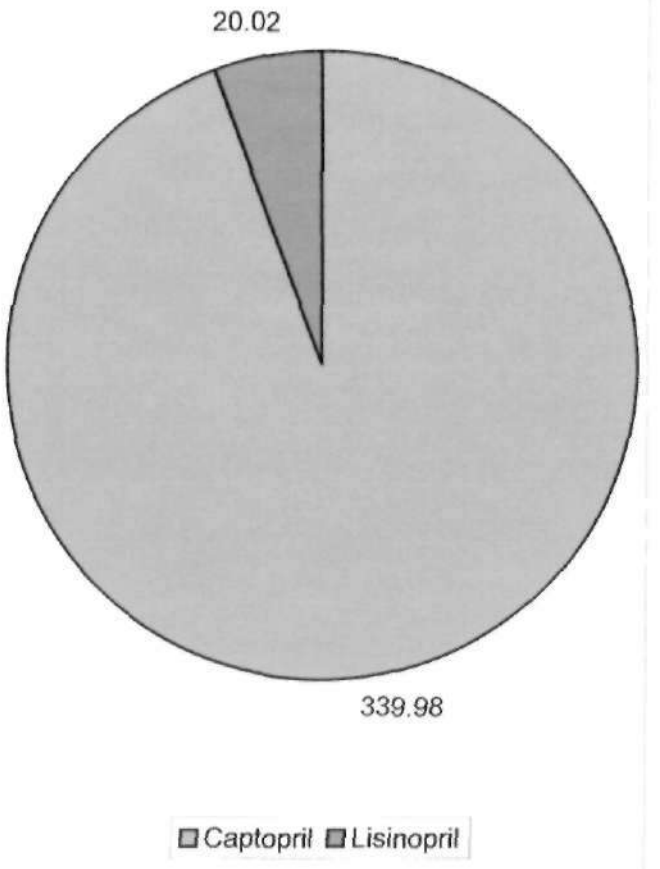


Fig. 4.3: A Pie Chart on the Distribution of Patients on ACE Inhibitors.

Fig. 4.4: Graph of Distribution of Patients on Different Doses of CCBS

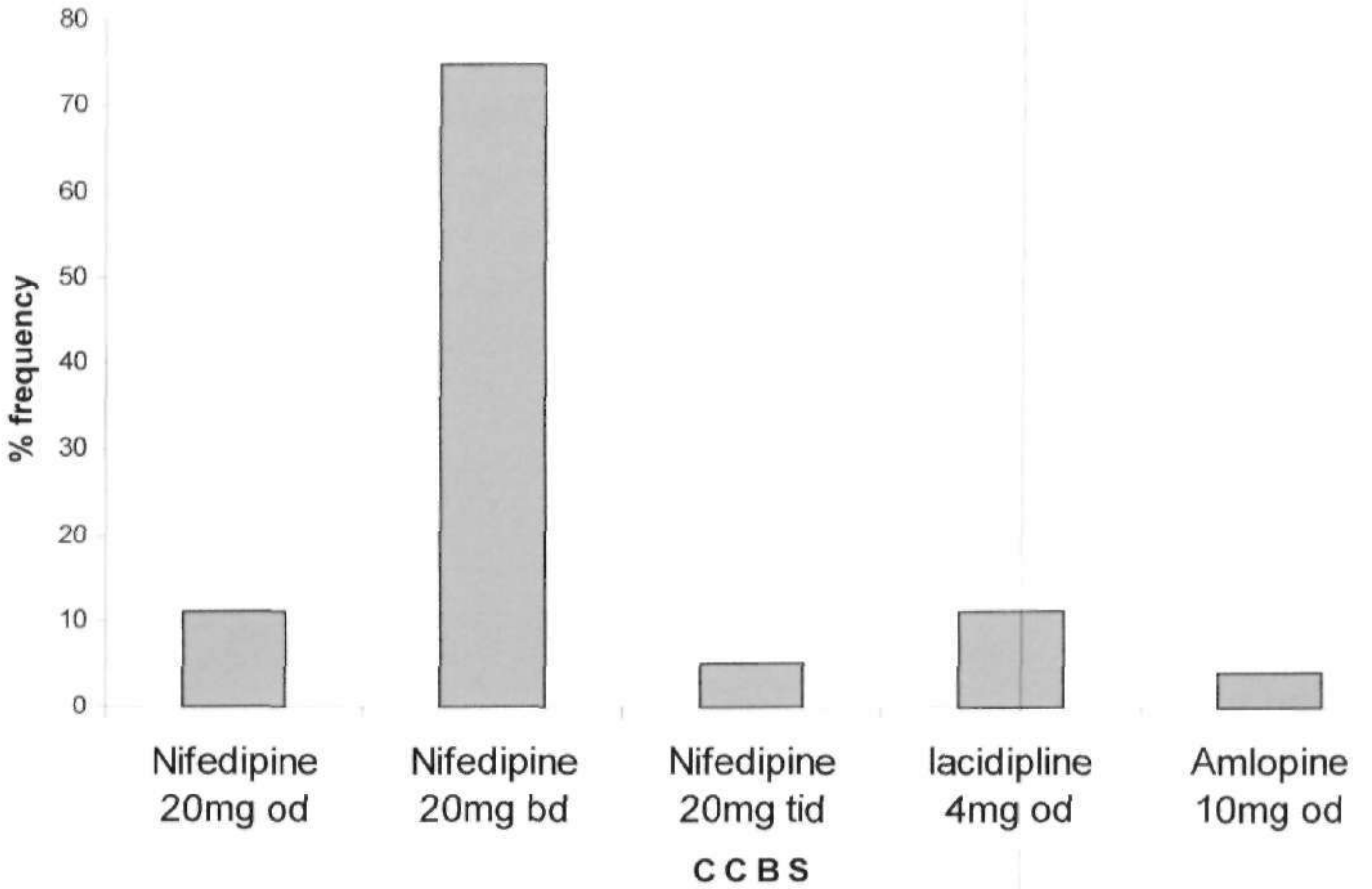


Fig. 4.5: Graph Patients Response to Different Doses of CCBS.

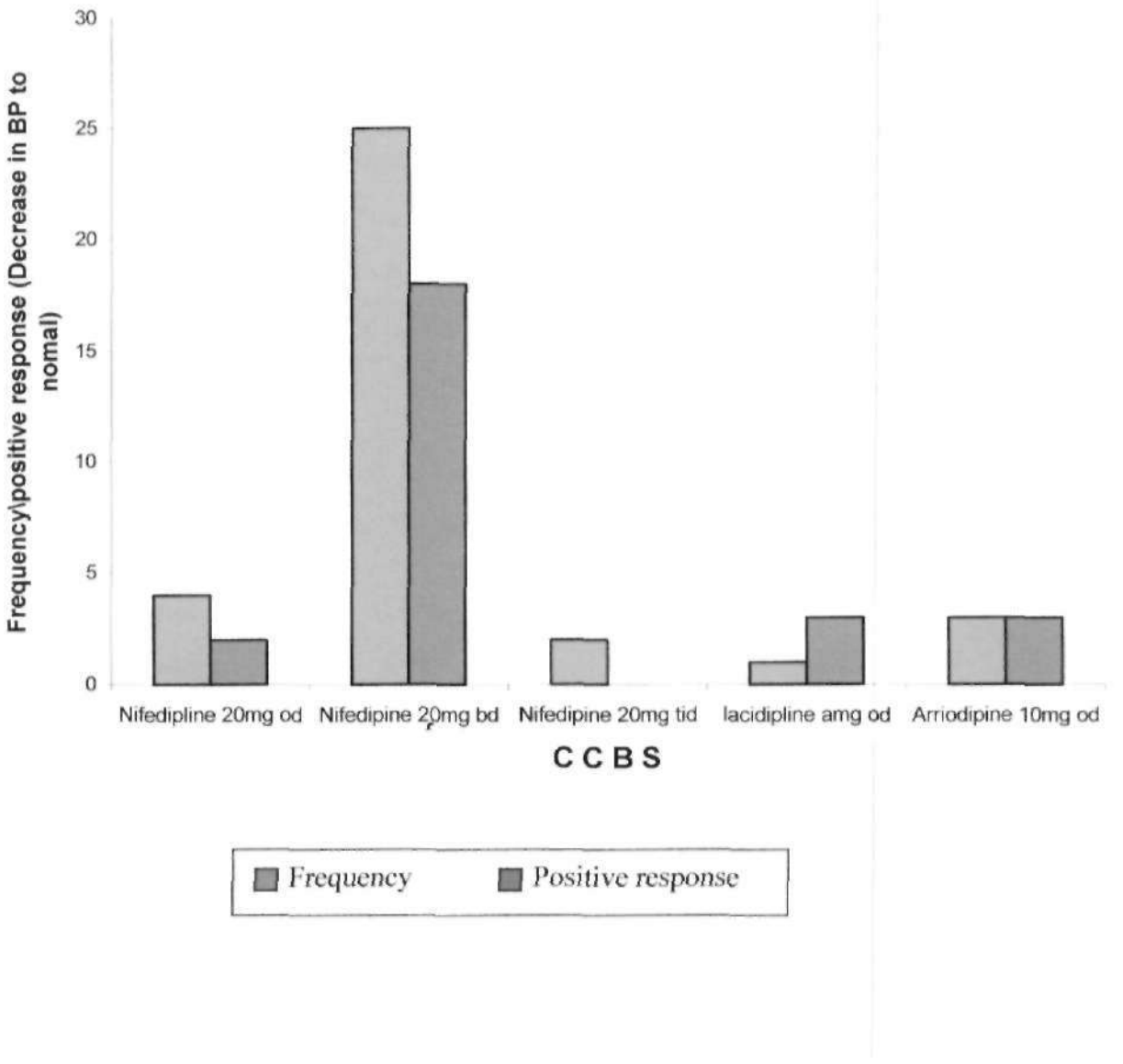
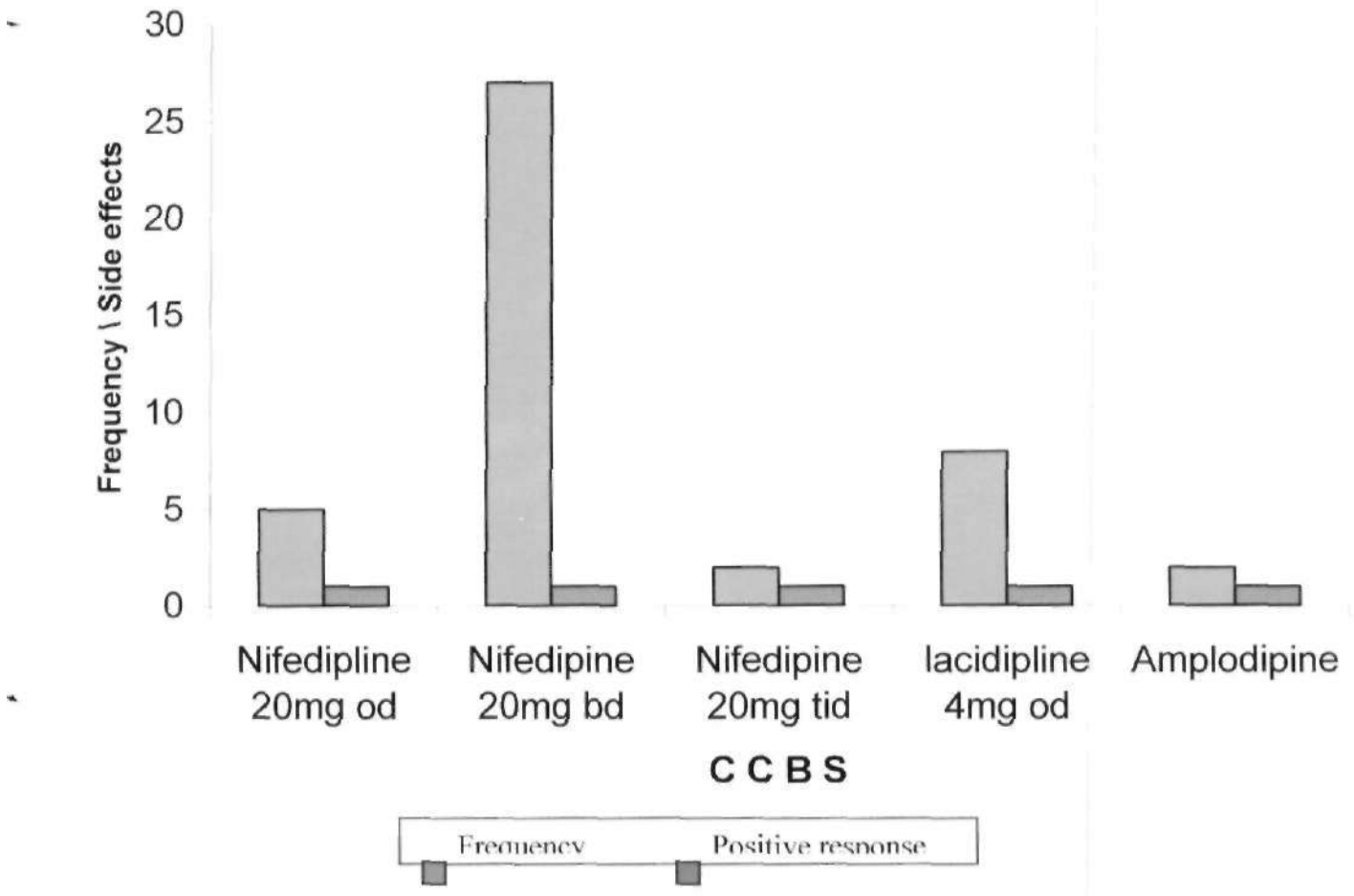


Fig. 4.6: Graph of Frequency of Appearance of Side Effects Due to CCBS



Frequency stands for number of patients placed on the different doses of CCBS

Side effects here the number of patients that presented with side effects is indicated

Fig. 4.7: Graph of Distribution of Patients on Different Doses of ACEIS

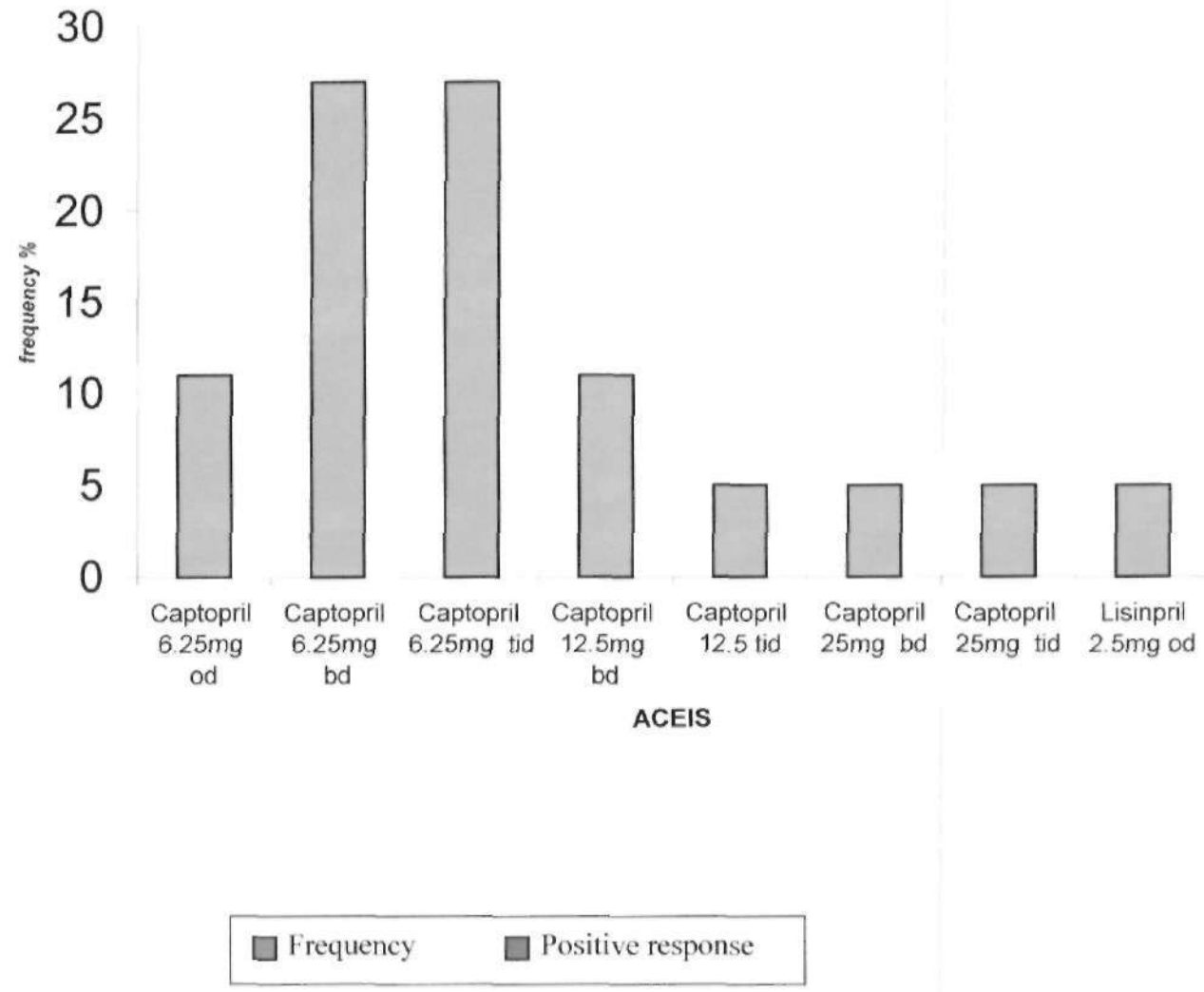


Fig. 4.8: Graph of Frequency of Appearance of Side Effects Due to ACEIS

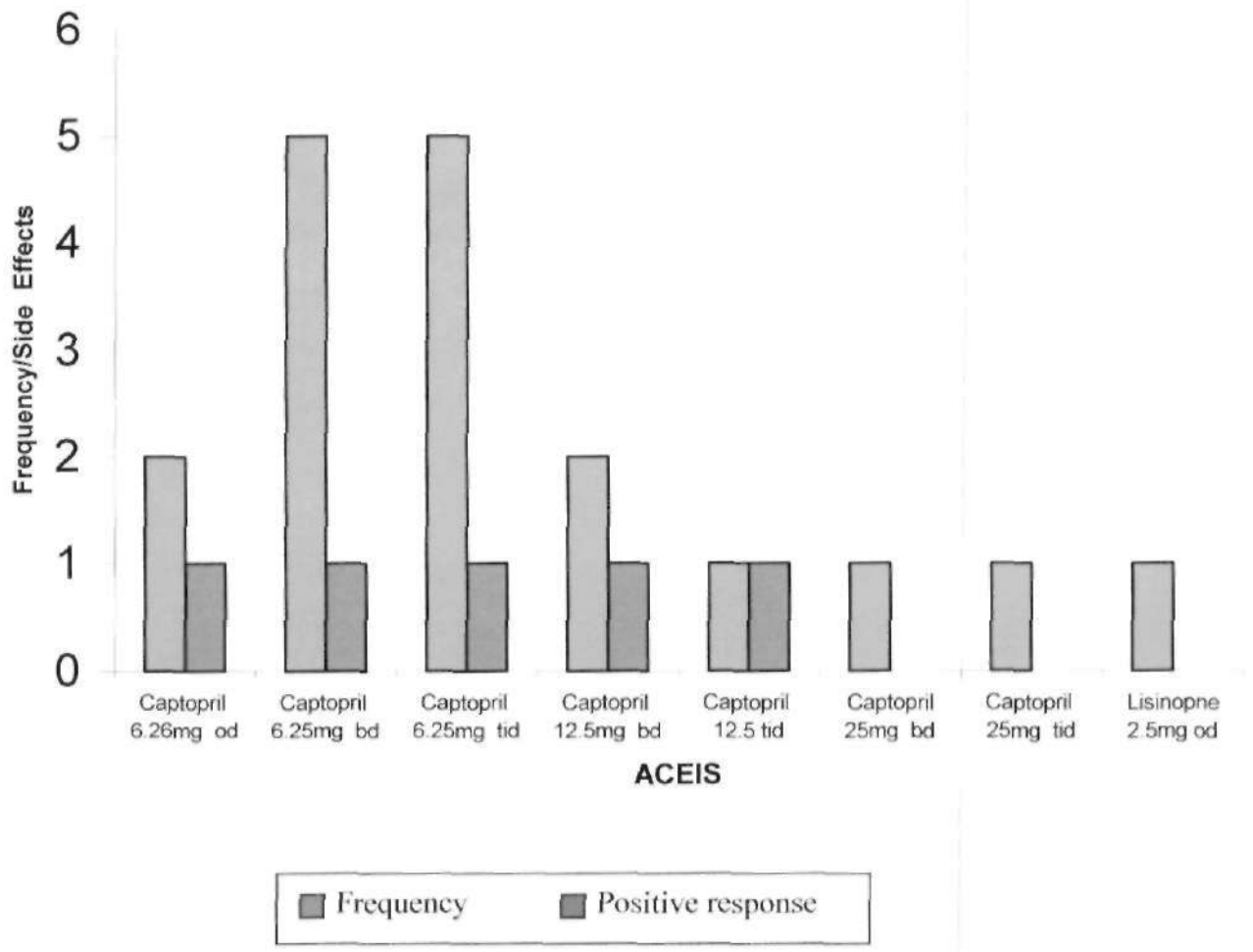
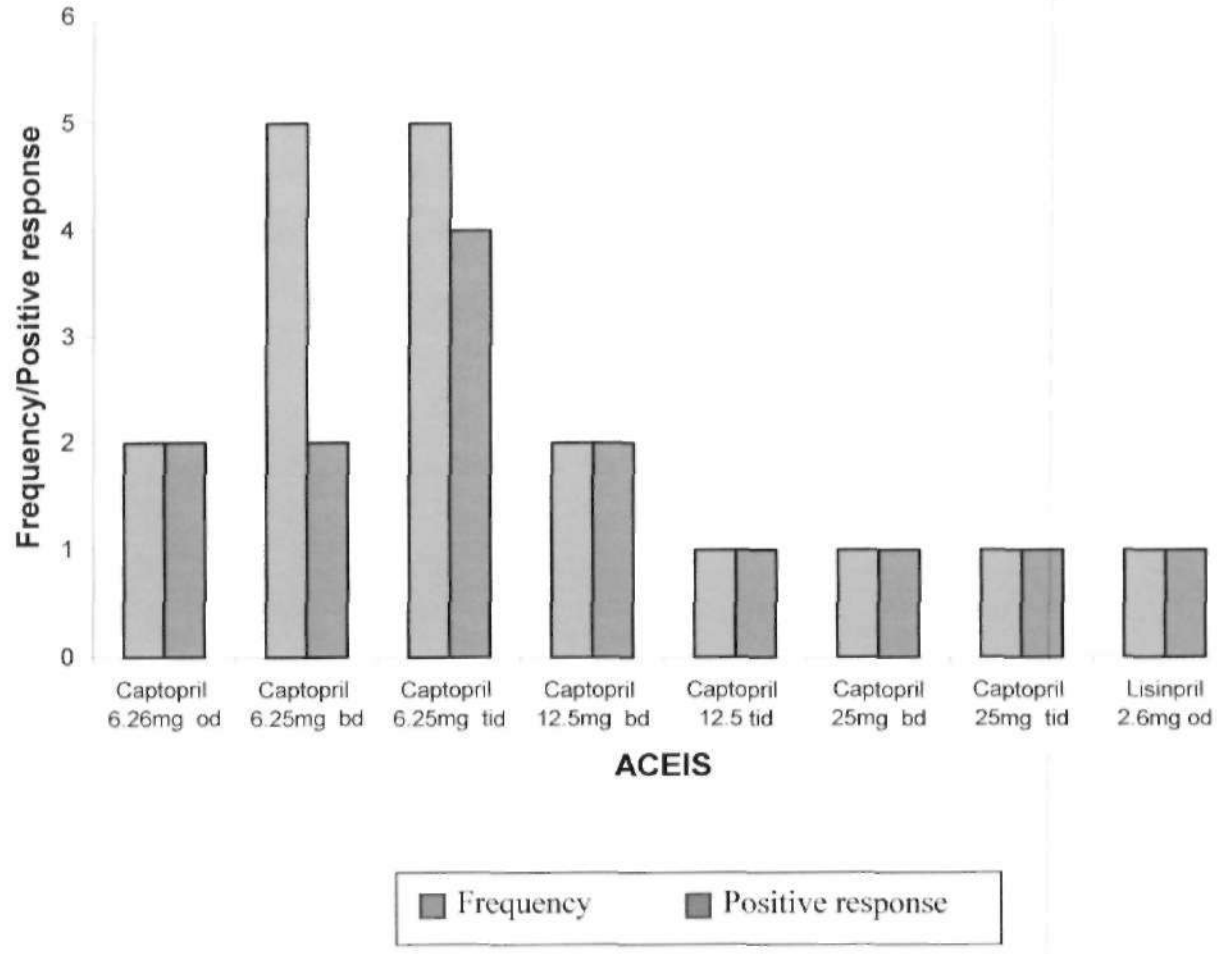


Fig. 4.9: Graph of Patients Response to Different Doses of ACEIS



CHAPTER FIVE

DISCUSSION AND CONCLUSION

5.1: DISCUSSION

The 1993 national and international guidelines from joint national committee[47] generally considered calcium channel blockers, ACE inhibitors and alpha blockers to be alternative first line drugs to diuretics (particularly thiazides) and beta blockers, the ultimate choice depending on the presence or absence of contra indications, on adverse effects, and co-existing disease. There is increasing reliance on ACE inhibitors and calcium channel blockers because of their general effectiveness in lowering blood pressure, low incidence of adverse effects and potential specific benefit in patients with renal disease[47]. In this research, it was discovered that calcium channel blockers and ACE inhibitors are more frequently prescribed thar other anti-hypertensives with calcium channel blockers as the most frequently prescribed followed by ACE inhibitors and lastly the combination of calcium channel blocker with ACE inhibitors. This can be easily seen on the pie chart in figure 4.1. which was constructed using the table G1.1.1 it can be seen that even the calcium channel blockers alone occupies almost the same size of the circumstance as that of other anti-hypertensives altogether. And the combination of the two classes drugs is the least commonly prescribed. The

fact that calcium channel blockers are prescribed almost as high as all the other anti-hypertensives could be because as it was seen from literature that calcium antagonists play an important role in the treatment of a wide variety of cardiovascular disorders[47]. Also, calcium channel blockers are versatile drugs with proven efficiency in all types of patients[48]. ACE inhibitors are less prescribed than calcium channel blockers because, as it was seen in the literature there are many precautions to be taken while or even before using them compared to calcium channel blockers e.g. they should not generally be used in patients with impaired renal function, also if renovascular disease is present or suspected, ACE inhibitors are occasionally necessary for severe renal hypertension in such patients when they can only be given with great caution and under specialist supervision[48]. Also, ACE inhibitors may reduce glomerular filtration in patients with severe congestive heart failure, or in heart failure patients who have been over treated with diuretics, patients with pre-existing renal disease or taking high does should be observed regularly for proteinuria and many others. It was seen in the literature that the efficacy of calcium channel blockers is enhanced by the concomitant use of an angiotensin converting enzyme inhibitor, methyldopa, or β-adrenergic receptor antagonists[48]. In this analysis, it was observed that CCBs are not frequently co-prescribed with ACE-Is, this is because both of them are highly

effective in that their combination will result in over reducing of the high blood pressure that is why as it can be seen from the spread sheet prepared with group two data only two incidences were seen, one of the drugs was stopped in the subsequent part of the treatment in four patients, and in three of the cases, it was the ACE inhibitor that was stopped, it was only in the last patient that CCB was stopped.

It was also discovered that Nifedipine and Captopril are the most frequently prescribed members of each of the groups, as it can be seen on the pie charts in figure 4.2 and 4.3, Nifedipine occupies (88.57%) of the circumference while captopril occupies (94.44%) of the chart. This was also seen in the literature that, Nifedipine and captopril are the commonest, in fact captopril is referred to as the prototype in its group in some books[49]. Other drugs prescribed are lacidipine and Amlodipine are less common. Isradipine was prescribed only once but the patient was unable to procure the drug due to non-availability in Zaria. Lisinopril is the next (in terms of frequency of prescribing) to captopril but it is very much less common (prescribed only once).

The dose of Nifedipine that is most frequently prescribed is 20mg twice daily followed by 20mg once daily and lastly 20mg three times daily. This proves the high effectiveness of the CCBS seen in literature. Lacidipine

4mg once daily is even more frequently prescribed than nifedipine 20mg three times daily. This is because, as was seen in the literature during repeated oral administration of calcium channel blockers, bio-availability and half life may increase because of saturation of hepatic metabolism, also the half lives of this agents may be long in older patients[48]. Also, it can be seen from the records that there was the greatest response by patients to the nifedipine 20mg three times daily and all the other doses including lacidipine and Amlodipine 20mg three times daily did not respond at all. And, there was very low incidence of side effects due to calcium channel blockers, only one patient showed a side effect among all the patients placed on all the calcium channel blockers in this work. This also complies with what was seen in the literature.

The doses of captopril that are most frequently prescribed are 6.25mg twice daily and 6.25mg three times daily with five, five patients out of eighteen each. This proves the high effectiveness of ACEIs seen in literature. But there was greater response and more incidence of side effects due to captopril 6.25mg three times daily than 6.25mg twice daily. The percentage frequency of prescribing for captropril 6.25mg once daily is about half (11.11%) of that of 6.25mg twice daily and thrice daily (27.77%) , the same thing with that for captopril 12.5mg twice daily for captopril 12.5mg thrice daily, captopril 25mg twice daily and lisinopril 2.5mg once daily was all the

same with one one patient each out of eighteen, that is 5.55%. And the response for captopril 6.25mg once daily and captopril 12.5mg twice daily is the same with that of captopril 6.25mg twice daily that is two patients each out of eighteen (11.11%) and is half of that for captopril 6.25mg thrice daily and lisinopril 2.5mg once daily responded positively while the one on captopril 25mg twice daily did not respond. Also, there was a low incidence of side effects with ACE inhibitors that due to calcium channel blockers this also complies with what was seen in literature.

All this can easily be seen on the bar charts in figure 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9. Generally, there was good patient compliance of medication to both the calcium channel blockers and the ACE inhibitors but it was better with the ACE inhibitors.

5.2: CONCLUSION

It can be concluded that in cardiac clinic of Ahmadu Bello University Teaching Hospital Zaria, calcium channel blockers are more frequently prescribed (35.5%) than ACE inhibitors with the rate of prescribing CCBs (35.5%) almost equal to that of other antihypertensives all together (38.7%) and that of ACE inhibitors (19.3%) about half that of CCBs. The most frequently prescribed CCB is Nifedipine retard 20mg daily (88.57%) while the

most frequently prescribed ACEI is captopril 6.25mg twice daily and thrice daily (94.44%). Other CCBs prescribed are lacidipine and amlodipine while the only other ACEI prescribed is lisinopril.

The was generally good therapeutic response to both CCBs and ACEIs with response to CCBs being more than that for ACEIs and also good compliance to the two classes of antihypertensives but the compliance was better for ACEIs than for CCBs.

There was also generally low incidence of side effects due to both calcium channel blockers and ACE inhibitors with calcium channel blockers having the lowest incidence of side effect than the angiotension converting enzyme inhibitors. The side effect due to CCBS (nifedipine in particular) was persistent severe headache and it was observed in only one patient. While those due to ACEIs (captopril in particular) were hypotension and dizziness and were observed in six patients.

There were four incidences of bad compliance to captopril while there was six incidences of bad compliance to nifedipine and two incidences of non-compliance to lacidipine.

About half (22 out of 46) of the patients on calcium channel blockers and ACEIs have a co-existing disease along with hypertension 11 out of the 22 have CHF, 8 have HY, 3 have stroke, 2 have renal failure, one have diabetes

mellitus, I have post partum hypertension. It has been seen in the literature that calcium channel blockers and ACE inhibitors are good choices for all the conditions mentioned above.

Lastly, I would like to suggest that a further work be carried out on this particular topic because of the importance of these two classes of drugs (CCBs and ACEIs) in the treatment of hypertensive patients.

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